Saint Petersburg Medico-Social Institute

POLYAKOVA
Anastasiya Alekseevna

THE DIAGNOSTIC VALUE OF MOLECULAR BIOMARKERS TO PREDICT AND COMPREHENSIVELY EVALUATE DENTAL IMPLANT OUTCOMES

3.1.7. Dentistry

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Scientific supervisor:
Doctor of Medical Sciences, Professor
N.A. Sokolovich

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CONTENTS

INTRODUCTION

Study Rationale

Dental implantology is a major area of contemporary prosthetic dentistry. Despite recent sophisticated technical advancements, dental implant procedures are reported to be associated with early or long-term risks of complications, as an increasing number of research publications claims. Different investigators report the implant rejection rate to vary from 3 to 10%. At the early post–implant procedure stage, inflammatory complications following intraosseous implant prosthetics are showing a steadily high incidence rate of 0.5 to 13.3%. Publications report the incidence rate of mucositis and peri-implantitis standing at 80% and 28 to 56% respectively in patients with implant-supported dentures. Identifying predictors of dental implant complications is a pivotal task for modern dental implantology. However, today a generally accepted list of biomarkers is still missing, as well as a clear-cut procedure to apply such biomarkers in early diagnostics of complication risks and bone-implant osseointegration monitoring. This undermines early prevention, as well as adequate and prompt treatment efforts that would otherwise prevent implant rejection.

Research Aim

The research pursues enhanced prediction and evaluation of successful dental implant survival based on the patient's molecular profiling results.

Research objectives

1. To identify periodontal indices of explanatory value allowing to assess dental implant success rate in 1 and 6 months after a dental replacement procedure.
2. To evaluate the correlation between molecular biomarker expression level in buccal epithelium and potential dental implant complications in young and middle-age patients.
3. To identify molecular biomarkers of diagnostic significance, as well as the best assessment times to predict risks of peri-implant inflammation.
4. To consider options for comprehensive dental status assessment based on a efficient biomarker assay allowing to predict dental implant complications and severity of peri-implantitis.

Practical significance of research

The study results provide a profound insight into the correlations between individual dentist's clinical assessment of dental implant success and evidence obtained from cellular molecular markers.

Provisions presented for defense

1. The epithelium lining of the buccal mucosa is a highly informative tissue allowing to assess molecular biomarker expression associated with peri-implant inflammation.
2. As a screening procedure required prior to dental implant placement, molecular profiling allows to identify patients at a high-risk of complications before dental prosthetics, thus improving evidence-based peri-implant tissue assessment 6 months after the procedure.

Research materials and methods

The study was performed using the facilities of the St. Petersburg State Autonomous Healthcare Establishment 'City Dental Outpatient Clinic No. 22'. The study involved 78 patients who underwent dental implant procedure to restore a damaged dental row. All patients were split into 3 groups by their treatment outcomes - successful dental implant procedure; moderate peri-implantitis; and severe peri-implantitis. Prior to implant procedure, patient's oral cavity was examined in daylight using a conventional dental examination kit; periodontal indices were assessed 1 and 6 months after the procedure. The 36-item Short Form Health Survey (SF-36), a renowned generic health-related questionnaire, was filled in by patients before implant placement and 6 months after the procedure. Patients underwent buccal epithelium immunocytochemistry and computer-assisted morphometry using video-mixed microscopic images to assess α-tubulin, β-tubulin, COX-1, COX-2, COX-3, VEGF and VEGFR, melatonin, MT1 and MT2 receptors, NeuN, NO, NSE, CLDN1 and E-cadherin the expression prior to implant placement and 6 months after the procedure. Mathematical and static analysis of the obtained data was performed (we analyzed temporal dynamics for selected markers, compared statistic differences for the assessed parameters across the three groups, conducted the cross-group comparison for all biomarkers, followed by a correlation analysis between the obtained quantitative variables to build decision trees).

Conferences, congresses and symposiums where the research results were reported

The research findings were reported at the 27th International Biomedical Conference for Young Researchers 'Fundamental Science and Clinical Medicine - Humans and Their Health' (St. Petersburg, 2024), the 2nd Russian Congress for Medical University Residents 'Science and Practical Training of Medical Residents as a Basis for Public Health' (St. Petersburg, May 29-30, 2024).

The findings of the dissertation are reported in 8 research papers, including 1 published in a peer-reviewed journal approved by the State Commission for Academic Degrees and Titles and 2 publications in the Scopus database.

The key results and findings are reported in the following publications:

1. Polyakova A.A. The role of VEGF and VEGF receptor in dental implant success [11].
2. Polyakova A., Trotsyuk D., Medvedev D. [et al.] The method of cell biology in the implementation of clinical tasks: assessment of implant survival in elderly patients [217].
3. Polyakova A.A., Medvedev D.S., Polyakova V.O. Developing a diagnostic biomarker assay to predict dental implant survival in old-age patients [10].
4. Polyakova A.A., Medvedev D.S., Kozlov K.L. [et al.]. Signaling molecules as biomarkers for predicting implant survival in people of different ages [13].
5. Polyakova A., Medvedev D., Semiglazova J. [et al.]. Buccal epithelium: as an object of non-invasive diagnostics of implant survival in people of different ages [45].
6. Polyakova A.A., Medvedev D.S. Fluorescence diagnostics as a method assess implant survival in patients of different age groups [12].
7. Polyakova A.A. Buccal epithelium and its role in noninvasive diagnostics of implant survival [8].
8. Polyakova A.A. Biomarkers among cyclooxygenases and their significance for dental implant procedure planning [7].

Dissertation scope and structure

The dissertation follows a conventional structure comprising 3 chapters, a conclusion and 9 appendices. The work has 199 pages, including 66 figures and 20 tables. References comprise 234 positions - 14 published in Russian and 220 in foreign languages.

CHAPTER 1. CURRENT VIEWS ON PERI-IMPLANT DISEASES

1.1 Key concepts and basic medical and hygiene information

Dental implant procedures are widely used to repair single or multiple tooth loss. Dental implants are a safest missing tooth replacement option, regardless of the cause of tooth loss. The procedure has proved high efficacy with a 90-95% survival rate over more than 5 years [23]. Despite the favorable results of dental implant procedure and long-term survival rates, the occurrence of peri-implant diseases is a common phenomenon that poses a significant problem and requires the development of preventive intervention programs [178].

Survival rates, however, shall be distinguished from treatment success rates. A dental prosthesis supported by a sufficient number of implants and no mobility (positive survival rate) might fail in case of twisting or persistent soft tissue inflammation surrounding the implant (unsuccessful treatment). Implant-associated complications are a cause of significant economic burden affecting patient's perception of treatment [170, 179]. With the incrementally growing number of patients in demand of dental implants, prevention and treatment of concomitant complications is a critically urgent challenge [207, 216, 230].

Peri-implant mucositis is associated with limited inflammation affecting the peri-implant tissue, without marginal bone loss. Peri-implant mucositis is completely reversible in case of early treatment. Peri-implantitis is inflammation of mucous membrane surrounding the implant and is associated with loss of marginal bone tissue. Peri-implantitis is a more severe advanced stage of peri-implant disease. In this case the inflammation extends beyond the soft tissues, affecting the bone foundation of the dental implant. Advanced peri-implantitis causes manifest bone loss, eventually leading to implant rejection if left untreated [174]. Surgical treatment is often required to remove the implant-surrounding infected tissue and deposits. Antimicrobial therapy is prescribed as well. Severe cases presented with significant bone loss and implant

damage require implant removal as the only solution [174]. Considering its complicated treatment, peri-implantitis demands efficient early detection and prevention to avoid disease development [177].

At an early stage peri-implant diseases are caused by dysbiotic biofilms on the implant surfaces that induce local inflammation involving peri-implant mucosa (i.e. mucositis) and peri-implant bone tissue (i.e. peri-implantitis) at an advanced stage [17, 108, 135]. However, knowledge regarding the etiology and physiopathology of peri-implant diseases is still insufficient. They are currently known to originate from infections and come in two forms - mucositis and peri-implantitis [183]. Peri-implantitis is characterized by destructive inflammatory lesion of polymicrobial origin affecting both soft and hard tissues and leading to progressive bone loss exacerbated by periodontal pocket formation in case of extensive inflammation after the implant placement [24]. Thus, increased periodontal pocket depth, accompanied by bleeding and sometimes pus formation a pathognomonic sign of peri-implantitis [25].

The build-up of plaque is a mayor cause of peri-implant diseases, as well as periodontal disease [37, 181]. Gum health depends on a variety of factors, including oral hygiene, genetic and epigenetic factors, general health status and nutrition [185, 186]. Tissues affected by peri-implantitis and periodontitis often contain gram-negative anaerobic bacteria. As different from periodontitis, peri-implantitis is characterized by greater microbial diversity. When compared to periodontitis, peri-implantitis histology presents double size lesions with numerous blood vessels and infiltrates in connective tissue, exceeding that of healthy gums by 78% in case of chronic periodontitis [36]. In addition, peri-implantitis affected tissue contains extracellular matrix antibodies [165]. Peri-implantitis is characterized by faster disease progression leading to more rapid and severe bone loss, as different from periodontal diseases. Over time peri-implantitis leads to nonlinear bone loss presumably associated with different types of microorganisms at the implant placement sites, immunity, or periodontal ligament loss [19, 37].

Peri-implant diseases vary in prevalence and incidence depending on research design and population cohorts. The incidence rate depends on a variety of factors, including patient-related characteristics such as oral hygiene and general health, as well

as implant-related factors such as prosthetic design. Understanding the prevalence and incidence of peri-implant diseases is paramount for public health, as well as efficient prevention and treatment strategies [128].

Peri-implant mucositis ranges in prevalence from 19 to 65% of implant placement sites [30, 136]. According to the recent meta-analysis, the patient- and implant-level prevalence of peri-implantitis is approximately 20% and 11.5% respectively [181]. The observed data variance may depend on various factors, including the follow-up timeframe. Discordant data regarding the prevalence of peri-implantitis presumably reflects variable clinical parameters selected for disease diagnosis in different studies; this particularly true regarding the scope of adjacent supporting bone loss and probing depth, as well as the heterogeneity of patient cohorts or individual risk factors. Individual risk factors can significantly augment the prevalence of peri-implantitis; those include patient history of periodontal disease, smoking, poor oral hygiene, diabetes mellitus and genetic factors [35, 66, 139].

1.1.1 Risk factors

Potential risk factors contributing to peri-implant tissue damage include an array of parameters [72, 75, 180]. Those are smoking [105, 124], diabetes mellitus [35, 48, 101, 194], periodontitis [157], insufficient supportive peri-implant maintenance [196], irregular efforts to prevent biofilm formation [42], depleted keratinized mucous membrane after implant placement [27, 119, 204], and specific implant design [116, 154, 174].

Other investigators refer to the following risks of peri-implant diseases - plaque, smoking, history of periodontitis, implant design and rough transmucous surface, residual cement, implant angled >30 degrees, radiation therapy, and diabetes mellitus as indicators of the [182, 185, 188]. Other factors associated with peri-implantitis are occlusal overload [191, 216], patient's daily habits, and incorrect implant position [180, 193].

The 2023 co-authored systematic review on peri-implantitis reports a set of risk factors [181]:

- poor glycemic control (by the glycated hemoglobin HbA1c value) in diabetes mellitus or prediabetes. Howeever, the HbA1c upper limit was not established due to cross-country differences and concomitant pathologies that obscure the evaluation of glycemic control as 'good' or 'poor'. The preventive measures implied improved or efficient glycemic control;
- smoking status (a current smoker) and habit (evaluated by the number of cigarettes smoked per day or type of device, i.e. traditional cigarettes, electronic cigarettes, hookah). The prevention includes efforts to facilitate smoking cessation, using any strategy according to recommendations;
- customized periodontal / peri-implant maintenance protocols and compliance. The prevention implied fostering patient's adequate / regular commitment. The review included studies comparing the efficiency of different protocols;
- the amount of the keratinized mucosa width after implant placement and periimplant soft tissue thickness. The thin peri-implant mucosa was considered a risk factor. The preventive surgery was required to expand the soft tissue margin;
- oral hygiene (including proper teeth brushing technique and frequency). Prevention was aimed at encouraging optimal / improved patient behavior to achieve proper oral hygiene;
- bruxism / oral parafunction. The prevention included therapy to achieve appropriate bruxism and oral parafunction control.

Peri-implant mucositis is associated with an increased risk of peri-implantitis. Moreover, peri-implant mucositis is considered a predictor of peri-implantitis due to the potential ongoing progression, as is the case for gingivitis progressing to periodontitis [40, 162, 213]. However, evidence allowing to consider any systemic condition as risk factor of peri-implant placement mucositis is scarse. Data suggest a presumable relative correlation between alcohol consumption and periimplant diseases.

Poor oral hygiene. Poor oral hygiene poses a major risk of peri-implant diseases. Failure to efficiently manage plaque formation surrounding dental implants leads to

accumulation and proliferation of harmful bacteria, as well as biofilm formation. Inflammation onset is a direct consequence of destructive microbial activity. Proper oral hygiene, including regular and thorough cleaning of implant-supported dentures, is essential for peri-implant disease prevention [195, 201].

Smoking. Smoking is a well-known significant risk factor of peri-implant diseases. Smoking unarguably undermines the immune response, reducing blood supply to implant-surrounding tissues. Smokers are therefore more susceptible to infections and inflammation with an elevated risk of peri-implant complications. Cessation of smoking and counseling are critically required for efficient treatment and prevention of peri-implant diseases in such patients [190, 192].

Evidence reveals significant clinical differences between former smokers, e-cigarette or hookah users, and active smokers. As opposite to other groups, former smokers presented down-regulated inflammatory response in the mucous membrane, lower PPD (peri-implant pocket depth) and less manifest MBL (marginal bone level) changes following implant installation. The study found that in contrast to e-cigarette users, active smokers presented higher expression of proinflammatory markers, including matrix metalloproteinase-8 (MMP-8), IL-1b [58, 233], IL-6 interleukins and tumor necrosis factor alpha (TNF-alpha) in the peri-implant sulcus fluid [182].

Systemic diseases. Particular systemic diseases, such as diabetes mellitus and immunosuppressive conditions augment the risk of peri-implant complications. To reduce the risk of peri-implant placement disease, dentists should cautiously and closely monitor patients with systemic diseases, emphasizing the importance of careful oral hygiene and timely intervention [72, 216].

Patients with diabetes mellitus and poor glycemic control (HbA1c > 8%) have an elevated risk of peri-implantitis and BL (bone loss) exacerbation over time, compared to patients with diabetes mellitus, but appropriate glycemic control. Though consistent, the research evidence is limited, with the average implant survival rate considered acceptable in both groups (95.6% and 99%, respectively). The results for dental implants were presented as well [15]. The study groups presented differences in BL. This confirms that bone loss is a major clinical manifestation of peri-implantitis

following implant procedure [172]. Prediabetic patients should also be considered at risk of peri-implantitis.

Systemic diseases such as scleroderma, ectodermal dysplasia, lichen planus, osteoporosis, rheumatoid arthritis, or Sjogren's syndrome may exacerbate peri-implantitis, undermining dental implant health [132, 188].

Moreover, family history, stress, dietary challenges, and other lifestyles pose potential risks of peri-implant disease onset [139]. The published research findings of lack uniformity and therefore report discordant risk rates, depending on the parameter in focus. The available data do not allow us to identify the true risk factors (specific for peri-implant diseases), due to the lack of long-term prospective longitudinal studies assessing the potential causal relationship between exposure (risk factor) and outcome (after implant placement).

Dental prosthesis design affecting the course of peri-implant placement diseases. Dental prosthesis design, including the crown and abutment type may critically affect the risk of peri-implant disease [131]. Prosthesis structure, materials, and margins can promote microbial colonization, cause mechanical impact and soft tissue damage [21]. It is therefore pivotal to understanding how prosthetic design parameters affect the oral cavity environment in order to make informed decisions and minimize the risk of peri-implant complications. Orthopedic and prosthetic dentists must be extremely careful in selecting the appropriate prosthetic structure in order to reduce such risks and improve long-term implant health [75]. Implant-abutment connections fall into three types: platform switched, butt-joint, and no interface [193]. Butt-joint connections are prone to marginal bone loss of about 1.5–2.0 mm due micro cracks in implant sealing, causing bacterial leakage, proliferation and colonization. Although platform switching prevents or reduces marginal bone loss [129, 142] contaminated connections can eventually cause peri-implantitis and implant rejection. Moreover, a convex emergence profile poses extra risk of implant failure implants at the bone level [145].

The residual cement remaining on the implant after crown setting triggers a potential risk of peri-implantitis due the adverse effect on the implant-surrounding tissues [88, 123]. The implant position, i.e. an excessively apical, over-inclined, or over-

contoured crown is associated poor accessibility and failure to clean the subgingival space from residual cement. Implants splinted with both mesial and distal adjacent implants are associated with a higher risk of peri-implantitis [91]. Cement surface roughness is favorable for bacteria colonization, which in turn triggers inflammatory response to foreign bodies, leading to peri-implantitis. Cement removal performed using minimally invasive dental endoscopy or open flap surgery resolves inflammation within a few days or weeks [63]. Therefore, to reduce the risk of peri-implant disease associated with excessive cement, the recommendation is to ensure that the crown edge matches the edge of mucous membrane, ensuring sufficient access and soft tissues maturation, as well as early follow-up assessment after the restoration [88, 104].

Biomechanical stress (occlusal overload) is also considered the main cause of implant screw loosening or fracture of the implant and its fixture. Excessive biomechanical stress exacerbates the implant neck exposure to overload [23, 25]. In addition, overload and long exposure time causes fatigue micro-injuries, leading to bone resorption and therefore peri-implantitis progression [24]. Moreover, overload exposure drives bone metabolism around dental implants. Mutually protected occlusal schemes and excessive contact prevention, reducing cantilevers, a narrow occlusal table, multiple tooth-replacing implants, tubercle slope reduction , increasing the number of contact points and management of parafunctional habits mitigate peri-implantitis severity [134].

Dental prosthesis design includes considerations regarding the denture manufacturing and configuration, especially if supported by dental implants. These considerations include the choice of materials, the crown and abutment design, as well as the overall prosthesis geometry. These parameters play a key role in functional and aesthetic success of implant repair, as well as the peri-implant tissue health [106].

The prosthesis components and their significance for peri-implant health. Prosthesis components are of paramount importance for peri-implant health due to close contact with the oral cavity environment. The choice of materials and design considerations during prosthetic rehabilitation via implant placement can profoundly impact implant long-term stability and the health of implant-surrounding tissues.

Awareness of such complexity is indeed fundamental to achieve implant survival and efficient prevention of peri-implant diseases [142].

Choosing materials for every prosthesis component is pivotal for peri-implant health. Biocompatible corrosion and wear resistant materials mitigate adverse reactions and tissue irritation, thus preventing complications from implant-surrounding tissues. The choice of materials for crowns, abutments, and other components shall rely on profound understanding of compatibility with the patient's oral environment and health status [78].

In addition, prosthesis design, i.e. the emergence profile, contouring, and occlusion pattern, critically affects peri-implant tissue health. Accurate design choice ensure unchallenged and adequate oral hygiene around the implant-supported prosthesis. Poor prosthesis design provokes food jamming and bacterial colonization, making the patient more susceptible to peri-implant mucositis and peri-implantitis, subsequently [36].

Prosthesis design overview. Occlusion forces play a significant role for dental implant success. Dentists must unarguably take into account the distribution of occlusion forces applied to the crown. Poor crown design exposed to imbalanced distribution of forces leads to stress overburden at particular points of the implant—bone interface. Locally applied forces can potentially damage the surrounding bone and soft tissues, augmenting the peri-implant complications risk [115]. Platform switching is an efficient strategy to mitigate the impact of occlusal forces. Platform shifting implies using an abutment that has a smaller diameter than the implant platform. This maintains horizontal mismatching of the implant / abutment interface associated with favorable redistribution of occlusal forces. Platform switching also allows a well-designed crown to guarantee a balance distribution of occlusal forces affecting the implant, thus significantly reducing the risk of overload-related complications [183]. The platform switching technique is crucial for the overall success of dental implant treatment.

Emergence profile. The emergence profile, i.e. the emergence of the crown from circumscribed soft tissues, is another important parameter of the crown architecture. An adequate emergence profile helps to maintain healthy soft tissue contours and facilitates

oral hygiene. On the contrary, inadequate emergence profiles undermine proper oral hygiene due to food traps and bacterial colonization. Later inflammation and infection provoke the development of peri-implant mucositis and eventually peri-implantitis [27, 118].

Crown-to-implant ratio. The crown-to-implant ratio plays a critical role in peri-implant health. Negligence of this parameter leads to imbalanced distribution of forces, in particular in case of excessive crown height space. This may cause biomechanical complications and implant—bone interface overexposure to stress, exacerbating bone loss and peri-implant disease [78].

The abutment design and correlation with peri-implant diseases. Emergence profile. The abutment-dependent emergence profile plays a key role in the peri-implant health. The way implant-supported restorations emerge from soft tissues has both functional and aesthetic significance. An adequate emergence profile ensures healthy and natural soft tissue contours surrounding the implant, thus improving the restoration aesthetics and helping to maintain healthy soft tissues around the implant. On the contrary, poor abutment design can lead to inadequate or unfavorable emergence profile. These disorders challenge oral hygiene maintenance due to exacerbated food trapping and bacterial biofilm. This, in turn, may provoke peri-implant mucositis - the early stage of peri-implant disease. A flawed emergence profile exacerbates food particle trapping and bacteria proliferation, impregnated with risks of soft tissue complications [215, 225].

Soft tissue contours. The abutment design directly affects the soft tissue contours surrounding the implant restoration. Ideally, abutments should promote the formation of well-adapted and healthy soft tissues around the implant. Abutment design failure to maintain favorable soft tissue contours can lead to soft tissue recession. This in turn is conducive of implant pocket or crevice formation for unchallenged bacteria accumulation. Bacterial biofilm inside these depressions increases the risk of inflammation and infection, which is a characteristic feature of peri-implant disease. Thus, the abutment design maintaining healthy soft tissue contours is critical for peri-implant health [143].

Access to oral hygiene. Efficient and regular oral hygiene is the cornerstone of peri-implant disease prevention. Poor abutment design can undermine patient's efforts to clean the surface of the implant-supported prosthesis. The underlying causes include an array of factors. Flawed abutment contours impede access to particular implant-surrounding areas, making it a challenge for the patient to clean them. In addition, prosthesis undercuts or areas that are hard to approach using dental instruments turn into food traps, posing even greater problems for ideal cleaning. Patient's failure to maintain adequate oral hygiene due to flawed design significantly augments the risk of peri-implant mucositis and peri-implantitis. Inadequate cleaning leads to the build-up of microbial biofilm, inflammation and peri-implant disease progression [121, 196].

Prosthesis-to-material interaction and implications. Biocompatibility is a crucial factor for the choice of prosthesis materials. Biocompatible materials stand out for good tolerance and absence of side effects and / or inflammatory response. Biocompatibility significantly mitigates the risk of complications such as local irritation, improper host reactions and implant rejection. Profound understanding of material biocompatibility is paramount to prevent such complications and improve the overall peri-implant health. Biocompatible materials are especially important in implant procedures since their long-term direct contact with oral cavity tissues [220].

Corrosion resistance. The intraoral environment is highly demanding and is exposed to varying pH, temperature, or different chemical agents. The choice of prosthesis materials must consider corrosion and potential deterioration over time. Corrosion is associated with ions and particles released into the surrounding tissues, potentially causing inflammation and adverse reactions. The choice of corrosion-resistant materials is vital to ensure long-term stability and health of the implant-surrounding tissues. Resistance to intraoral impacts helps to minimize the risk of corrosion-associated complications [85].

Aesthetic aspects. Aesthetics plays is of overarching importance, especially for the front teeth where implant-supported dentures must seamlessly blend with natural dentition. Aesthetic materials enhance patient's satisfaction and confidence, improving the overall quality of life. However, it extremely important to balance aesthetics against

material properties. Biocompatibility and durability must not be sacrificed in to satisfy aesthetic considerations. The choice of materials that both ensure aesthetic appeal and are compatible with oral tissues is fundamental for patient satisfaction and long-term health of the implant-surrounding tissues. The reasonable balance ensures that implant-supported restorations look natural, maintain structural integrity, and effectively support the surrounding tissues [97].

Prosthesis design and its impact on peri-implant disease.

Microbial colonization and biofilm formation is a major driver of peri-implant diseases and must not be overlooked by dental implantologists. The prosthesis design can significantly impact the ability of harmful microorganisms to attach to the implant surface and prosthesis components which is indeed crucial for peri-implant disease management and prevention [113].

Surface roughness. Prosthesis surface roughness can significantly exacerbate microbial colonization. Uneven and rough surfaces have niches for bacteria to adhere and form a biofilm. On the contrary, smooth prosthesis materials are less prone to the adherence of bacteria and subsequent biofilm formation. Prosthesis design and production should pursue minimized surface roughness to eventually prevent microbial colonization and reduce the risk of peri-implant diseases [185].

The emergence profile formed by prosthesis components - such as abutments - significantly affects microbial colonization. A healthy emergence profile should ensure a smooth implant-to-crown interface, with minimum space left for bacteria to adhere. Poorly designed emergence profile is susceptible to crevice and pocket formation that function as a shelter for bacteria to adhere and exacerbate biofilm formation. Biofilms can cause inflammation and peri-implant mucositis, conducive to peri-implantitis, if left unmanaged [86].

Mechanical stress and its impact on implant surrounding tissues Mechanical stress caused by occlusal forces during biting and chewing can affect the development of peri-implant disease. Prosthesis design and occlusal scheme can significantly affect the distribution of mechanical forces applied to the implant and surrounding bone.

Understanding the mechanical stress affecting the implant-surrounding tissues is crucial for healthy peri-implant tissue in the long-term [56].

Distribution of occlusal forces. The distribution of occlusal forces travelling through the implant and surrounding bone is crucial for peri-implant disease prevention. In case of flawed prosthesis design or unbalanced occlusal scheme, the patient is at risk of focal stress concentration. Such focal stress concentration can lead to excessive mechanical stress on the implant—bone interface, resulting in bone loss. Appropriate prosthesis design should provide for uniform distribution of occlusal forces in order to reduce the risk of mechanical complications [161].

Prosthesis design parameters significantly influence the management and distribution of occlusal forces in implant-supported restorations. These parameters include the crown design, the implant angle, and the choice of materials. Careful crown design in cemented prostheses is crucial to ensure resistance to and even distribution of occlusal forces. In addition, implant angle alignment with patient's natural occlusion is vital to prevent any misdirected forces. The choice of materials also becomes crucial, since it is necessary to consider the material strength and ability to withstand mechanical loads.

Screw-fixed prostheses imply similar principles. The crown design is of paramount importance for efficient management of occlusal forces. Here, the choice of materials may rely on factors related to the screw and abutment design. The implant angle should be aligned with patient's natural occlusion to reduce the risk of misdirected forces. A comprehensive understanding of how these factors interact is necessary to minimize the risk of bone loss and implant damage [126].

Prosthesis contours and their impact on soft tissue health. Food traps and oral hygiene. Poorly contoured prosthetic components can form spaces and crevices where food particles are trapped. This may pose a challenge for patients performing oral hygiene procedures, as such areas are inaccessible for cleaning with a standard toothbrush or floss. The accumulation of debris and poor oral hygiene contribute to the bacterial biofilm formation - a key factor inducing peri-implant mucositis [50].

The emergence profile, defined as the contour of a prosthesis component as it emerges from the gingiva, is a critical for soft tissue health. An adequate emergence profile ensures natural and healthy soft tissue contours, providing a tight fit of the soft tissues to the implant and the components of the prosthesis. Poorly designed emergence profiles can lead to unattractive black triangles, soft tissue recession and insufficient papilla preservation, damaging the aesthetics and oral hygiene. Such unappealing contours can render the patient predisposed to peri-implant complications [110].

Soft tissue thickness. The peri-implant soft tissue thickness is also affected by prosthesis contours. Properly designed contours help to maintain sufficient soft tissue thickness, providing better papilla support and minimizing the risk of recession. Insufficient soft tissue thickness renders the implant more vulnerable to bacterial infiltration and peri-implant mucositis [134].

1.1.2 Diagnosis of peri-implant diseases

Peri-implantitis can be asymptomatic or clinically manifest as mucous membrane erythema, edema, increased probing depth (PD), bleeding on probing (BOP), followed by suppuration and nonlinear progressive bone loss (BL) [127]. A consensus report of the 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions presented a new classification of periodontal and peri-implant diseases; in the absence of previous examination data diagnosis of peri-implantitis can be based on the combination of bleeding on probing (BOP) and/or bleeding during implant procedure, suppuration, probing depth ≥6 mm and supporting bone loss ≥3 mm [17, 169].

Biomarkers and dental implant survival is considered as a secondary outcome [178]. Diagnosis of peri-implantitis, especially in its early stages, is of key importance for disease progression prevention, since there is currently no one common treatment protocol for all clinical cases [68]. In addition, diagnosing peri-implantitis is not an easy task [180]. According to the consensus report, BOP cannot always predict the disease

development; moreover, BOP alone is not enough the diagnosis [104]. In addition, implant probing may be useful for BL monitoring, but without radiographic data this may be insufficient to determine the BL scope and cause of BL over time [171].

The most commonly used definition of peri-implantitis considers it as "an inflammatory reaction associated with the loss of supporting bone tissue around the implant" [23]. S. Renvert et al. proposed a different definition of peri-implantitis based on concomitant peri-implant inflammation and BL radiographic measurements after primary healing [170].

However, radiographic data regarding the peri-implant bone level does not always lend to unambiguous interpretation, considering a few limitations, including that periapical and panoramic radiographic data allow to evaluate only mesial and distal BL. Special software is required to measure bone level changes, whereas the length of the implant is a good strategy to overcome radiographic data inaccuracies. However, radiographic data is unable to identify all lesions and therefore lacks sensitivity [145].

Moreover, with all the clinical parameters and changes in the bone tissue level brought together, this body of data may still be insufficient to forecast the patient's risk of peri-implantitis and further development of early inflammation [210].

Before implant installation, a basic clinical and radiographic examination is required. The obtained data will guide the dentist's assessment of physical or pathological changes in the implant-surrounding tissues over time. As a rule, healthy implant-surrounding tissue shows no signs of inflammation, bleeding on probing (BOP), or increased depth of probing (PD) , when compared to the initial or baseline examination.

Peri-implant health diagnosis is based on the absence of soft implant-surrounding soft tissue inflammation (redness, swelling or heavy bleeding on probing) and the absence of excessive bone loss after wound healing [170]. Elevated PD may indicate loss of attachment and supportive bone loss. Adequate diagnosis is extremely important for an appropriate treatment plan and successful treatment of peri-implant diseases.

According to the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (2017) [170], peri-implant mucositis can be diagnosed based on: (1) the presence of peri-implant inflammation (redness or swelling around the

gum line or bleeding in 30 seconds after probing), together with (2) absence of extra bone loss after primary healing. The diagnosis of peri-implantitis is established based on the signs of peri-implant inflammation, depleted bone tissue confirmed by radiograhy after the primary wound healing, as well as increased depth on probing after the prosthetsis installation compared to the baseline measurement. In the absence of earlier radiographs, radiographic measurement of the bone level ≥3 mm with BOP and PD ≥6 mm suggests peri-implantitis.

1.1.3 Peri-implant disease prevention strategies

The European Federation of Periodontology (EFP) emphasizes the importance of periodontitis prevention [17, 46] suggesting a set of recommendations for dentists that include management of major risk factors for periodontitis [169].

Indeed, risk assessment is part of professional preventive care. An efficient personalized prevention based on the patient's risk profile is required, considering all the potentially affected local and systemic risk factors of peri-implant diseases. Such personalized prevention also requires specific patient learning and motivation to change habits, in order to assume responsibility for their own health under the guidance and support of oral care professionals [22]. Preventive measures can be taken even before the implant is installed to prevent exposure to risk factors and ultimately reduce the incidence of new diseases. Primary prevention is the earliest effort to avert the main risk factors and conditions contributing to the onset of the disease [128]. A possible mainstreaming effort is promotion of healthy behaviors, such as to stop tobacco smoking, engage in regular physical exercise to prevent non-communicable diseases such as type 2 diabetes mellitus, or disembark from destructive habits that increase the risk of peri-implantable diseases [153].

After the dental implant is installed, peri-implant tissue health maintenance is a collateral for a long-term perspective. These efforts are fundamental for primary prevention, aimed at peri-implant tissue health and risk management to prevent disease

manifestations [128]; these efforts should include individual patient training and motivation to observe proper oral hygiene and avoid the biofilm build-up around dental implants and their restorations. Treatment of peri-implant mucositis is a preventive measure - although a secondary one - in case of peri-implantitis.

The maintenance protocols and their role in periimplant disease prevention. Efficient care protocols for implant-supported prosthesis rely on regular medical visits. They present a proactive strategy for periimplant health monitoring and protection. Routine visits allow dentists to carefully assess tissue condition around the implant and detect any minor changes or manifestations of problems at an early stage. This includes monitoring the implant stability and any deviations from normal function or mobility. Early detection at this stage is crucial because it allows timely intervention and potentially prevents the progression of peri-implant mucositis to severe peri-implantitis. Early identification of disease allows doctor to initiate appropriate treatment and provide the recommendations to mitigate complications in order to maintaining the durability and functionality of the implant-supported prosthesis [56].

Deep dental cleaning of dental implants. Professional care and its relevance for maintenance protocols cannot be overestimated. These clinical interventions, including tartar removal and root planing play an important role in maintaining implant surfaces and prosthesis components clean and healthy. Deep dental cleaning allows to remove microbial biofilm and tartar deposits that can accumulate over time. Regular oral hygiene performed by patients at home fails to remove the deposits completely, thus making deep dental cleaning is necessary to maintain health around the implant [95]. Professional cleaning greatly helps to prevent diseases around the implant by rendering the implant surface and surrounding tissues free of harmful bacterial deposits. Apart from hygiene, as dental cleaning maintains a healthy implant environment and contributes to the long-term success of restoration.

Peri-implant health assessment. Regular assessment of peri-implant tissues represents a comprehensive diagnostic approach based on maintenance protocols. This includes a thorough clinical examination, often complemented by radiographic data. Such examinations are an integral part of soft tissue disease prevention, early detection

of bone level depletion, inflammation or infection. Dentists often use probes to measure the depth of pockets around implants to obtain valuable diagnostic information. Such efforts allow dentists to detect complications around the implant at an early stage, even prior to clinical manifestations. Early detection is indeed essential for prompt intervention, management and prevention of complication or disease transformation into more serious and challenging conditions. Regular assessment of the peri-implant tissue condition enables doctors to make informed decisions and provide timely treatment, thus preserving the health and functionality of the implant-supported prosthesis in the long run [146].

Adjustments of prosthesis components. Adjustments of prosthesis components is part of a proactive approach to treat peri-implant diseases. These adjustments include a thorough examination of crown and abutment contours and materials in order to facilitate oral hygiene and reduce the risk of bacterial colonization. This process often involves changing the shape or design of prosthesis components to eliminate potential areas prone to food traps or microbial biofilm. Smooth and well-defined prosthetic components help dentists to minimize debris trapping and enable patients to perform efficient oral hygiene themselves. These modifications contribute to the overall maintenance of peri-implant health and prevent peri-implant disease development and progression, creating a favorable environment for long-term stability of implant-supported restoration [176].

Minimizing mechanical stress. Prosthetic adjustments aimed at minimizing mechanical stress are crucial to ensure biomechanical balance between the implant and bone. When unbalanced, occlusal forces are identified as potential contributors to peri-implant disease, requiring mandatory correction. The adjustments herein pursue a more even distribution of forces to reduce the risk of further tissue damage. Occlusion scheme adjustment allows dentists to maintain harmony, reducing excessive pressure on the implant and surrounding tissues. Biomechanically favorable conditions ensure the implant structural integrity and minimize the risks of complications affecting peri-implant health [176].

Comprehensive treatment approach. Prosthesis adjustments and modifications report utmost efficiency provided that those are integrated into a comprehensive peri-implant disease treatment strategy. Such an integral concept envisions the peri-implant health from a variety of perspectives, recognizing its multifactorial nature. In addition to prosthetic modifications, this approach includes other therapeutic measures, like deep dental cleaning, antimicrobial therapy, and patient education. By combining these interventions, dental professionals can develop a holistic strategy that controls peri-implant disease progression and mitigates its detrimental effects on peri-implant health. This unifying approach highlights the importance of comprehensive care, emphasizing the need for multidimensional interventions to ensure the long-term success and stability of an implant-supported prosthesis [75].

Strategies for patient education and long-term maintenance of oral hygiene. Training is pivotal for peri-implant disease prevention. Dental professionals should provide patients with important information about proper oral hygiene practices. This includes educating patients about the importance of effective cleaning around the implant-supported prosthesis, which may require specific skills and equipment. Patients should understand that their active involvement in oral care is crucial for the long-term success of implants. In addition, patients should be informed about the risk factors associated with peri-implant disease and be aware of potential signs such as bleeding gums or discomfort. With this knowledge, patients are able to recognize early warning signs and take timely action. In addition, it is important to emphasize the need for regular dental checkups and professional cleaning. Such systematic monitoring ensures that the condition of the periimplant is monitored and professionally maintained [179]. The cooperation of the patient and the doctor is invaluable for achieving and maintaining the health of the periimplant [155].

Individual oral hygiene strategies. Patient education goes hand in hand with the development of customized long-term strategies for maintaining oral hygiene. These strategies should be tailored to patient-specific needs and circumstances. It is noteworthy that patient’s abilities, preferences, and any existing conditions should be considered as well. For example, patients with dexterity difficulties may benefit from

special oral hygiene products such as interdental brushes, adaptive floss holders, or water irrigators. These tools help facilitate effective cleaning around implant-supported prostheses, ensuring that patients maintain proper oral hygiene despite potential problems [82].

Oral hygiene plans. An individual oral hygiene plan is essential for peri-implant health maintenance. The plan should consider patient-specific needs and their oral cavity health. This may include scheduling regular checkups and deep dental cleaning procedures, or any additional efforts, such as antimicrobial mouthrinse or prescription toothpaste. Patients should actively participate in the development of their oral hygiene plans, ensuring that strategies match their abilities and preferences. A well-structured and tailored plan reinforces patient's commitment to oral health and encourages active participation in peri-implant health maintenance [73].

Potential advances in prosthesis design to prevent of peri-implant diseases. Cutting-edge prosthesis materials are a most promising approach to mitigating peri-implant disease risks. Research in materials science is extensively exploring the boundaries of biocompatibility and corrosion resistance. These advances allow to enhance the compatibility of materials with the oral environment, minimizing the risk of adverse reactions or sensitivity. Improved material properties can also contribute to implant restoration durability, minimizing the need for replacement or revision. Integration of new materials can lead to implant-supported prostheses of long-term durability and enhanced tolerance by host tissues [120].

Digital technologies and precision prosthetics. The integration of digital technologies such as CAD/CAM (computer-aided design/computer-aided manufacturing) is transforming the field of prosthetic design. These technologies allows to design precise and customized prosthesis components. Advanced imaging techniques and computer-assisted modeling allows doctors to design restorations with optimized fitting surface, function, and aesthetics of implant-supported prosthesis. The result is a personalized approach to prosthesis design, patient comfort and satisfaction. A high-precision prosthesis fit minimizes gaps and crevices that would otherwise induce food trapping and bacterial colonization, augmenting the risk of peri-implant disease [21].

Innovative solutions in prosthetics and their assessment. Any advancement in prosthetics relies on deep understanding of how new prosthesis materials and digital technologies affect peri-implant health. Regular clinical trials are necessary to evaluate the safety and efficiency of innovative solutions. In-depth assessments can help identify any potential risks or benefits associated with new materials or design. The data can help clinicians to select the most suitable prosthetics options for their patients [30].

Multidisciplinary teams of dentistry professionals. In implantology, a multidisciplinary team often consists of a periodontist, an orthodontist, a dental surgeon, and an oral hygienist, each contributing their unique expertise. Only joint efforts of a multidisciplinary team can guarantee comprehensive satisfaction of patient's needs. For example, a periodontist takes care of support structure health, while an orthodontist focuses on prosthetics, and a dental surgeon manages the implant surgery. Oral hygienists play a crucial role in maintaining oral health, including the tissues around the implant. Such cooperation leads to more effective treatment planning and delivery, allowing every specialist to contribute their expertise to achieve adequate patient treatment outcomes [26].

Cross-disciplinary approach. Many systemic diseases, such as diabetes mellitus or immunosuppressive disorders can affect the outcome of implant placement therapy. By working closely with internal medicine practitioners, dentists can coordinate care, eliminate potential complications, and optimize treatment plans. This approach considers the patients general health, with every specific medical consideration included in the implant treatment plan [106]. Cross-disciplinary team allow to approach every patient individually, providing both clinically effective and patient-focused treatment [103].

1.1.4 Peri-implantitis treatment

Peri-implant diseases share similar clinical features and origin with periodontal diseases, suggesting similar treatment approaches. The mucositis treatment is more

predictable, than that of peri-implantitis. The latter allows to mitigate its risk through supportive therapy at initial stage [117, 168]. Supportive peri-implant therapy increases implant survival rate. The treatment should consider local and systemic factors [87]. Long-term supportive therapy is recommended for peri-implant diseases to achieve infection control, prevention of disease progression, and lost bone restoration. This protocol emphasizes the need for regular patient monitoring, regular assessment for plaques, stones, depth on probing measurement and radiological data of bone loss in order to evaluate the disease severity. State-of-the-art protocols refer to different treatment approaches depending on clinical and radiographic data [139].

Conservative treatment. Various non-surgical treatments of peri-implant diseases include mechanical or chemical intervention, antibiotics, laser therapy, and oral hygiene procedures [175, 208].

Mechanical methods. Mechanical treatment reduces inflammation by removing microbial plaque from the implant surface. Mechanical plaque debriding tools include plastic curettes, metal ultrasonic scaler tips, metal curettes, an air abrasive system, and metal (titanium) brushes [224]. Piezoelectric ultrasonic scalers and hand scalers also ensure effective BOP reduction. Ultrasonic metal scaler tips and metal curettes can effectively remove supragingival deposits of up to 0.83 microns in size, as well as bacteria [225]. However, careful manipulation is required, since improper handling can result in scratches on the implant surface [232]. On the other hand, plastic curettes are unable to completely remove debris or biofilm. Mechanical plaque removal methods can be administered in combination with antibiotics or surgery to achieve a better result. A randomized trial by S. Toma et al. [224] compares three mechanical methods to treat peri-implantitis (an air abrasive system, titanium brush, and plastic curettes). The research showed that an air polishing system device and titanium brush outperformed other options; however, overall success was poor.

A single-blind longitudinal randomized trial by G.R. Persson et al. [40, 147] evaluated mechanical debridement results on the implant-surrounding microbiota in peri-implantitis lesions. The research findings demonstrated that mechanical

debridement alone may not be efficient enough to eliminate bacteria and should therefore be combined with other treatment options (antiseptic agents and surgery).

Antiseptic agents. Antiseptic agents for local irrigation are mainly aimed at reducing the number of bacteria. Chlorhexidine gluconate (CHX) is commonly used in periodontitis and peri-implant diseases. CHX slows down bacterial colonization; CHX 0.12% effectively mitigates peri-implantitis [140]. Therefore, CHX is a useful antiseptic agent to treat peri-implantitis. In addition, local controlled-released CHX chips promote periodontal osseoreintegration, although clinical studies are scarce. Therefore, further clinical studies are required on CHX osseointegration properties in peri-implantitis. CHX disadvantages include the ability of 2% CHX - which is routinely used in clinical practice - to stop cell migration abruptly and significantly reduce the fibroblast, myoblast and osteoblast survival in *vitro* [65].

Antibiotics and antimicrobials. Adjuvant antibiotics are added to mechanical therapy to suppress or kill infectious agents. Both local routes and systemic applications of antibiotic administrations have been explored. In peri-implantitis, the most common topical antibiotics are minocyclinum (MNO), doxycycline, gentamicin, and cefazolin [50, 201].

Local doxycycline or MNO following antiseptic agent administration and irrigation has showed efficiency in moderately deep lesions in implant-surrounding tissue. Repeat local MNO administration combined with surgical treatment provides improved clinical results and radiographic bone recovery measurements, as well as enhanced treatment success rate in the short-term. In addition, various polymer films containing antibiotic agents, such as tetracycline hydrochloride, polylactic acid, poly(e-caprolactone), and polymer / tetracycline solutions mitigate the development of peri-implantitis and its pathogens [109]. Local antibiotics such as MNO, doxycycline, or CHX are effectively combined with the mechanical treatment of peri-implantitis, especially in lesions of mild to moderate severity. MNO and doxycycline showed better results, as opposite to CHX. Moreover, the best treatment results were yielded for the combination of systemic antibiotics (such as ceftriaxone or gentamicin) and local antibiotics (tobramycin or gentamicin) [209].

O. Carcuac et al. [19] analysed adjuvant systemic antibiotics and topical CHX for implant surface disinfection in peri-implantitis. Treatment success was achieved in 45% of implants, with unmodified implants (79%) outperforming surface-modified implants (34%) in terms of success rate. Topical application of CHX had no overall effect on treatment outcomes. Although adjuvant systemic antibiotics did not contribute to the treatment success of unmodified implants, a positive effect was observed in the treatment of surface-modified implants. Thus, adjuvant systemic antibiotics might seem promising in surface-modified implants, though the observed success rate was fairly low. Therefore, following careful consideration, antibiotics can be recommended in patients with peri-implantitis.

Antimicrobial photodynamic therapy has been viewed as a promising alternative that promotes the elimination of bacteria and crest bone remodeling in peri-implantitis [33]. Likewise, bioactive glass (BAG), 45S5 and S53P4 Bioglass in particular, is an efficient antimicrobial agent, making it an ideal bone substitute in peri-implant infection treatment [42].

Surface disinfection. Non-surgical mechanical therapy produces predictable results in peri-implant mucositis. However, complications arise in case of exposed implant surfaces due to peri-implantitis. Mechanical treatment alone does not ensure complete plaque debridement, since implant threads are unaccessible for dental tools [142].

Chemical methods. Chemical methods include local administration of antibacterial agents. The most common chemical agents administered in peri-implant diseases are presented below.

Citric acid (CA). Although normally used to clean implants, CA is a highly promising chemotherapeutic agent in biofilm debridement from contaminated surfaces [225].

Ethyldiaminetetraacetic acid (EDTA). In dentistry, EDTA is commonly used as a chelating agent to eliminate the smear layer for periodontal regeneration and peri-implantitis.

Hydrogen peroxide. Hydrogen peroxide efficiently inactivates microorganisms (bacteria and fungi)[215]. Implant exposure to locally applied 3% hydrogen peroxide for 1 minute significantly reduces the number of *E. coli lipoproteins.* on the surface of a sandblasted titanium implant and HA-coated strips when compared to untreated samples [225]. Similarly, another study showed that in humans, 10% hydrogen peroxide inactivates biofilm eliminating 99.9% of bacteria from the implant surface [214].

Saline solution. Cleaning of the implant surface with curettes and saline solution gives clinically stable results in peri-implantitis [154].

Laser treatment. Laser radiation has shown a positive healing result in peri-implantitis and can be used as an adjuvant option to standard mechanical therapy [26]. In some specific cases, the advantages of such treatment include comfort, pain relief and better outcomes [34, 133]. Peri-implantitis is also treated using an erbium-doped yttrium aluminium garnet laser (Er:YAG laser), a diode laser, or a carbon dioxide ($_{CO2}$) laser [29, 55]. In peri-implantitis, laser therapy combined with non-surgical or surgical treatment showed poor benefits measured by the depth on probing, the clinical attachment level, recession and plaque index [99]. As an adjunct to conservative therapy, lasers can lead to a greatly mitigate bleeding at probing in the short term.

Elevated levels of adenosine triphosphate stimulate macrophages, fibroblasts, mast cells, endothelial cells, bradykinin, nerve cells, and growth factors that stimulate collagen synthesis, leading to tissue regeneration [14, 140, 142]. A clinical trial by Chambrone, L.F. Palma [51] demonstrated successful treatment of peri-implantitis-associated deep (≥6 mm) defects using an Er:YAG laser to disinfect the implant surface, remove granulomatous tissue and bone transplantation defects. Similarly, T. Yoshino et al. [231] showed that antibiotic therapy significantly reduces the number of bacteria in peri-implantitis lesions, while laser therapy combined with bone expansion, promotes bone regeneration in peri-implant bone defects.

Low-intensity diode laser accelerates soft tissue repair. In a set of cases, J.B. Pai et al. [20] confirmed the clinical benefits of laser therapy, once combined with other of peri-implantitis treatment methods.

In addition, a systematic review showed that laser mitigates bleeding on probing in the short term, compared to other conventional mechanical treatment [57]. On the contrary, G.A. Kotsakis et al. [32] recommended to use laser therapy for peri-implantitis within stage I treatment. Evidence suggests, that if used in combination, non-surgical methods, including curettage of granulation tissue, laser detoxification, irrigation with chlorhexidine solution and MNO ointment administration, contributed to bone regeneration as well [76]. Therefore, a combination of treatment options is essential for a successful outcome. Similarly, $_{CO2}$ lasers can be used to treat peri-implantitis [29].

Surgical treatment. Based on four reviews [87], the 2019 consensus report [85] suggests that surgery to treat peri-implantitis is indicated in cases where conservative treatment failed to yield success and was associated with recurrent bleeding and suppuration [207].

Air-abrasive uses compressed air to propel abrasive particles and remove biofilm [22]. Abrasive powder effectively cleans contaminated implant surfaces [146, 192, 195]. Promoted by improved clinical characteristics, significant bone regeneration for reintegration (39-46%) was achieved using abrasive implant cleaning in peri-implantitis, if combined with surgery [22]. The treatment results varied depending on the powder, exposure time, as well as surgical or non-surgical powder application [195].

Air-abrasive systems facilitate the mechanical biofilm removal; however, there is a risk of incurring microscopic damages to the implant surface. V.H. Matsubara et al. [146] studied the cleaning efficiency of various abrasive powders and how those affect the surface of titanium implants.

Resective surgery is aimed at reducing the pocket depth through bone grafting and/or osteoectomy, allowing to improve the bone defect and ensure adequate flap adjustment [167].

Implantoplasty. Implantoplasty, or implant surface modification, allows to remove the exposed infected implant surface. Implantoplasty involves disinfection of the implant surface to render it smooth surface and reduce plaque adhesion [25]. Evidence suggests that burs are a most efficient tool to smoothen the implant surface

[206]. A study showed, however, that implantoplasty significantly reduces the failure strength of narrow implants, without affecting wide implants [116].

Regenerative surgery. The regenerative surgery pursues bone regeneration in the areas surrounding the peri-implantitis lesion. The materials are bone grafts with or without membranes, or just membranes. Biological agents, i.e. growth factors or bone morphogenic proteins, are another option [89].

Various bone grafts with or without collagen membranes are often used for bone regeneration and expansion. Despite wound healing, the immersion technique failed to improve the clinical parameters [68]. Y. Sasada et al. [183] studied the regenerative capacity of autologous growth factors and xenogenic bone grafts to identify a 4 mm PD decrease within 1 year's follow-up [212].

The study showed that recombinant human platelet growth factor resulted in increased bone regeneration (40%) due to its osteoconductive properties, which subsequently increased the level of clinical attachment compared to β-tricalcium phosphate [67]. A bone graft with a membrane is a feasible solution as it promotes bone regeneration, thus yielding extra space.

In some cases, however, surgery may not be the best option to treat peri-implantitis. In case of significant bone loss occurs in peri-implant lesions (measuring at half the implant length), the implant success is scarcely likely [17]. Inaccurate implant installation undermines treatment results. In addition, the implant mobility is the evidence of bone loss (>60%) or a lack of implant osseointegration. In such cases, implant removal is to be recommended [60]. Following the implant removal, the next implant installation procedure would require the dentist to use an implant of a larger diameter [178].

1.2 Diagnostic biomarkers

Early diagnosis of inflammation, peri-implantitis, or unhealthy implant mobility are are pivotal for implant success. The diagnosis lends to verification by analyzing

immunology biomarkers, such as chemokines, cytokines, bone markers, and enzymes involved in tissue metabolism around the implant [48]. Pro-inflammatory cytokines (i.e. TNF-α, interleukins IL-1b, IL-6, and IL-17) are commonly associated with inflammatory response. Bone turnover markers, including osteoprotegerin (OPG) and soluble receptor activator for nuclear factor kappa β ligand (sRANKL), as well as osteoclastogenic cytokines and chemokines (granulocyte colony-stimulating factor (G-CSF), MMP-8, monocyte chemoattractant protein (MCP-1)) are considered to be associated with the profile of immune and inflammatory response in peri-implantitis [43].

Nevertheless, a few promising molecules are pending analysis of their ability to signal dental implant success.

1.2.1 α-Tubulin

Tubulin plays a key role in osteogenesis and bone remodeling [92]. In case of healthy functionality, tubulin microtubules are involved in the actin cytoskeleton dynamics in osteoclasts and osteoblasts. Moreover, microtubule dysregulation may disrupt bone mineralization and resorption.

Evidence showed that the expression level of cytoskeletal proteins, including tubulin [54], is directly associated with successful osseointegration of dental implants. Upregulated tubulin expression in peri-implant cells was associated with improved implant osseointegration into bone tissue, which indicates the promising use of tubulin as a prognostic marker of efficient implant placement.

Microtubule stability is known to be essential for the signal transduction and eventually mesenchymal stem cell differentiation into osteoblasts. Destabilization of microtubules impedes osteogenic differentiation, undermining dental implant success [196].

The level of α-tubulin expression in the implant surrounding tissue can be used as a predictor of implant placement success. Upregulated α-tubulin expression was

associated with favorable implant outcomes and fewer complications after surgery [234].

Growth factors, including BMP-2 (bone morphogenetic protein 2) promote α-tubulin synthesis and accelerated osseointegration, thus improving dental implant health. These findings confirm the importance of α-tubulin in bone tissue regeneration, making it a promising agent in dental implant installation procedures [92].

Overall, the analyzed data underscore the α-tubulin predictive value in dental implant success through its capacity to enhance osteogenesis, bone remodeling and osseointegration. Nevertheless, further studies, including clinical trials and large patient cohort studies, are required to obviate α-tubulin prognostic significance.

1.2.2 β-Tubulin

By regulating microtubulin properties, β-tubulin plays a role in coordinating cellular functions, including those associated with dental implant survival. Thus, as a regulator of cell adhesion, migration, and differentiation, β-tubulin should be considered in predicting implant success.

Studies show that a high β-tubulin expression is associated with successful osseointegration [49, 94]. It is noteworthy that β-tubulin is involved in microtubule formation, the latter playing a key role in cell migration and division, in particular in osteoblasts responsible for bone tissue regeneration. The more active are these processes, the more likely is the successful bone tissue integration with the implant surface. On the contrary, low β-tubulin may suggest attenuated or disfunctional osteogenesis and elevated risk of implant failure. Microtubule deficit can hinder normal osteoblast functions, underminig bone regeneration and bone-implant integration. Downregulated β -tubulin is impregnated with higher risk of implant failure [112].

β-Tubulin is a cytoskeleton component, critically important for cell adhesion to the implant surface. Implant surface modification may promote β-tubulin expression and, ultimately, cell adhesion and implant integration [198].

β-Tubulin is also favorable for osteogenesis. β-Tubulin regulation enables osteoblast precursor differentiation, ensuring successful implant osseointegration [49].

β-Tubulin participates in various signaling pathways, such as Wnt/β-catenin, which can affect osteoangiogenesis in the implant placement area. By interacting with signaling molecules, β-tubulin can enhance implant integration [92].

Overall, β-tubulin is a promising predictor of dental implant success because of its ability to promote healing and osseointegration at the cell level.

1.2.3 Cyclooxygenases

Cyclooxygenases (COX) acts on arachidonic acid to produce prostaglandins and thromboxane, responsible for pain associated with inflammation. These enzymes also mediate other conditions and diseases, making it extremely important in dentistry to consider the factors that elevate their levels. Upregulated COX expression is observed in inflammation and malignant lesions of the oral cavity, such as periodontitis, pulpitis, or oral cancer [38, 83]. In addition, dental materials provoke unfavorably upregulated COX expression, which may directly affect pulp health [81].

Cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and cyclooxygenase-3 (COX-3) are three enzyme isoforms, with each encoded by different genes [7, 107].

Until lately, little was known about a third COX isoform [203]. COX-1 is referred to as a 'constitutive isoform', and is considered to be expressed in most tissues ensuring their the normal cell function; in contrast, COX-2 is referred to as an ‘inducible isoform’ [64]. Both isoforms mediate various normal and pathological conditions, the latter including inflammation and cancer. In addition, COX-1 and COX-2 proteins participate in prostaglandin E2 (PGE2) biosynthesis mediating various cardinal features of inflammation, including vasodilation, increased pain, and nociceptor activation [200].

COX-1 plays a pivotal role in inflammation and tissue regeneration and cannot be overlooked in dental implant installation. Upregulated COX-1 expression is associated with critically poor implant survival, in contrast to low COX-1 expression level [122].

Increased COX-1 activity can extend implant healing, contributing to poor bone tissue regeneration [79]. Nonsteroidal anti-inflammatory drugs can be administered to inhibit COX-1 activity and improve treatment outcomes [111].

The presented evidence suggests considering COX-1 as a potential predictor of dental implant success.

Increased COX-2 expression is associated with various conditions such as periodontitis, pulpitis, toothache, or oral cancer. In addition, dental materials provoke unfavorably upregulated COX expression, which may directly affect pulp health [81].

COX-2 overexpression in periodontal tissues is associated with chronic periodontitis, bleeding index, inflammatory infiltrate, progressive loss and loosening of connective tissue attachment to the plate, radiographic alveolar bone mass depletion, and inflammation [150, 233]. COX-mediated bone resorption is one of the many factors involved in orthodontic tooth movement which is be assessed to predict treatment success in enhancing or inhibiting tooth movement, as well as attenuating bone and root resorption [81].

COX-2 expression is associated with periodontitis severity; drug-initiated suppression of the enzyme may be beneficial to mitigate periodontitis progression [218]. In patients with decreased gingival index, pocket depth probing, decreased loss of attachment, plaque index, gingival fluid volume, bleeding during probing, redness, and bone loss, evidence suggests clinical improvement administering COX inhibitors to treat periodontal diseases [39, 81].

Since cyclooxygenase-synthesized inflammatory mediators are promote periodontitis progression, the enzyme can be potentially useful as a biomarker of periodontal disease progression; elevated COX may therefore be a predictive marker of implant placement success [9]. By modifying COX-2 production in pulp inflammation, dentists can facilitate disease prediction and forecast the endodontic treatment results.

COX-3 can affect specific inflammatory processes, pain response, end eventually the implant placement outcome. COX-3 is involved in prostaglandin production that regulate inflammation. Genetic predisposition to unstable COX levels or COX inhibition may affect implant healing and integration [100, 211].

COX-3 can also affect pain perception following implant placement. A positive correlation was revealed between COX-3 expression and pain perception after treatment. COX-3 inhibition can attenuate postoperative pain, thus improving quality of life post-op [44, 211].

COX-3 overexpression is impregnated with a higher risk of inflammatory response and infection following dental implant procedure [111].

Upregulated COX-3 genotypes were associated with poor probability of successful implant integration [196]. Evidence of COX-3 polymorphisms facilitates prediction of implant success, allowing to choose a most optimal treatment protocol.

Higher COX-3 is associated with early implant rejection, upregulated inflammatory response and poor bone-implant integration. An early COX-3 assessment can be useful in making decisions on prevention and treatment adjustment, minimizing the probability of failure [38].

Thus, COX-3 may be a potential predictor of dental implant success due to its ability to affect both inflammatory response and pain control.

Pre-op COX-2 and COX-3 assessment allows to identify patients at high risk of inflammation following 3 and 6 months after the procedure [7, 9].

1.2.4 Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a heparin-binding protein with angiogenic activity, delivering a mitogenic and antiapoptotic effect on endothelial cells, increasing vascular permeability and cell migration. VEGF is therefore actively involved in normal and pathological angiogenic regulation.

In humans, the VEGF family comprises VEGF-A (with various isoforms), VEGF-B, VEGF-C, VEGF-D, VEGF-E (viral VEGF), VEGF-F (snake venom VEGF), placental growth factor (PlGF), and the endocrine gland-derived vascular endothelial growth factor (EG-VEGF) - a novel mediator of endocrine-specific angiogenesis. VEGF binds to cellular tyrosine kinase receptors (VEGFRs) VEGFR-1, VEGFR-2 and

VEGFR-3. VEGFR-1 and VEGFR-2 are expressed primarily in vascular endothelial cells, while VEGFR-3 is expressed in lymphatic endothelial cells. VEGFR-2 shows the strongest proangiogenic and higher tyrosine kinase activity than VEGFR-1. Endothelial cells also express co-receptors, such as neuropilin-1 (NP-1) and neuropilin-2 (NP-2) that modulate tyrosine kinase receptor activity. Both VEGF and VEGFRs are expressed both in endothelial cells and in non-endothelial cells [226].

For a long time, VEGF was mainly considered a powerful vascular endothelial mitogenic factor, able to transform angiogenesis, vascular permeability, as well as impact tissue inflammatory response. Lately, evidence was reported showing VEGF-dependent bone regeneration, skeletal growth, and recovery after fractures, as well as bone-forming osteoblast proliferation and differentiation [11, 67]. VEGF expression is high in osteoblast progenitor cells, and it is now known to stimulate bone formation [62, 229].

VEGF (vascular endothelial growth factor) is a key molecule associated with angiogenesis and healing of tissues after dental implant procedure. VEGF promotes new blood vessels formation around the implant, improving oxygen and nutrient delivery to the bone tissue [227]. Elevated VEGF helps control inflammatory processes. VEGF is also associated with restored vascular permeability and mitigated risk of infections, required for tissue healing around the implant [93, 228].

In implant placement, VEGF assessment in peri-implant fluids can predict implant survival. A post-hoc meta-analysis [158] revealed a link between VEGF expression and clinical outcome observed as better implant integration and no complications.

A pre-op mini-invasive procedure was used to show that VEGF and VEGFR are promising predictors of dental implant complications [11].

In elderly patients, decreased VEGF, VEGFR-1 and VEGFR-2 expression results in impaired tissue vascularization and innervation, impeding recovery after the implant procedure and eventually lower implant placement success [10, 217].

VEGF promotes angiogenesis and new blood vessel formation of around the implant, improving blood supply and healing VEGF expression was associated with better implant healing, confirming its important role in dental implant success [223].

Fibrin-based NanoSol scaffold incorporating VEGF- and bFGF-loaded nanoparticles accelerated angiogenesis and improved wound vascularization, essential for faster and effective wound healing [84].

These results show that VEGF and other growth factors play a key role in tissue healing and regeneration.

1.2.5 Vascular Endothelial Growth Factor Receptor

VEGFR is a receptor that binds to vascular endothelial growth factor (VEGF) and is essential in angiogenesis (formation of new blood vessels). Angiogenesis is important to ensure adequate blood supply to the implant area and successful bone-implant integration. VEGFR is regulates angiogenesis and may predict the dental implant success. By interacting with VEGF, VEGFR expression can significantly impact osseointegration.

VEGFR plays a key role in the formation of new blood vessels, which, in turn, is critical for tissue healing after implant placement.

Some studies demonstrated that VEGFR overexpression is associated with better vessel formation around the implant and faster healing [197]. VEGFR expression showed correlation with tissue vascularization in the implant area [199]. VEGFR affects osteoblast activity and bone remodeling. In the implant-surrounding area, upregulated VEGFR was associated with improved osteogenic response and successful integration of implants in the bone tissue [114]. Higher VEGFR expression ensures better bone regeneration and reduces the risk of implant rejection [228].

A few clinical studies confirmed that upregulated VEGFR involved higher dental implant success rate [102]. A retrospective analysis found that elevated VEGFR expression was a valuable marker of successful osseointegration [160]. Elevated

VEGFR expression correlated with better clinical outcomes after implant placement, suggesting that VEGFR is feasible predictive biomarker of successful osseointegration.

A systematic review and meta-analysis showed that VEGFR expression is closely related to clinical outcomes after implant placement [189]. Upregulated VEGFR correlates with better clinical outcomes, including attenuated inflammation and stronger implant-bone juncture.

Thus, as a key driver of angiogenesis and osseointegration, VEGFR can serve as a biomarker of dental implant success.

1.2.6 Melatonin and its receptors

Melatonin (MT) and its metabolites have been effectively used to combat oxidative stress [138, 149] and stimulate antioxidant enzymes. Its antioxidant activity allows to mitigate the impact of oxidative stress by protecting cells from common pathology-caused disorders [148, 184].

Studies show that implant-related osteogenesis is affected by an arrray of substances, including platelet-derived growth factor [96], morphogenetic proteins [62] and melatonin [18]. The role of melatonin (MT) in osteoblast differentiation and bone formation is especially noteworthy [90, 151, 219].

J.L. Calvo-Guirado et al. (2010) showed that one month after prosthetics, melatonin and collagen combination stimulated bone formation, mitigating bone destruction of the alveolar ridge, in contrast to bone structures that were not exposed to melatonin administration [18]. In chronic experiments with laboratory animals, it has been established that with the extra-intestinal route of melatonin administration in the early recovery period after implant placement, an increase in the activity of osteoclast formation processes is observed. In animal models, melatonin and fibroblast growth factor-2 (FGF-2) improved bone growth in the implant area [80]. Considering its extensive healing potential, melatonin is a promise in treating certain oral cavity diseases [16, 164].

In humans, melatonin and its receptors (MT1 and MT2) are expressed by dental pulp odontoblasts and connective tissue cells. Melatonin inhibits COX-2 and IL -1β transcriptional activation in pulp fibroblasts and therefore can attenuate inflammation in acute pulpitis by exerting immunomodulatory effect through melatonin receptors expressed by dental pulp cells [125].

Thus, at the pre-treatment stage melatonin and its type 1 receptor are promising predictors of complications after dental implant procedure [8].

1.2.7 Neuron specific nuclear protein

As a marker used in neuroscience to delineate CNS neuron borders with precision, neuron specific nuclear protein (NeuN) has recently gained focus in dental implantology. Although mainly associated with nerve tissue, NeuN is currently assumed to promote implant healing and osseointegration.

NeuN can affect tissue regeneration, as its expression is associated with neurons that can participate in the recovery processes after implant placement. NeuN-associated neurogenic factors improve healing, thus contributing to dental implant success [5, 70]. NeuN expression in peri-implant tissue may refer to elevated neurogenic activity, better biocompatibility and healing. Preliminary results show that NeuN expression correlates with unchallenged bone tissue healing [71]. Elevated NeuN expression correlates with successfully recovered sensitivity of gum cells following dental implant procedure [59, 156]. A systematic review and meta-analysis have confirmed the NeuN value in predicting implant success [3]. NeuN expression correlated with restored sensitivity and successful implant integration.

Thus, NeuN can be a potential predictor of dental implant success by indirectly exerting neural regeneration and repair in implant-surrounding tissues.

1.2.8 Nitric oxide

Nitric oxide (NO) is a vasodilating and anti-inflammatory signaling molecule, essential for vascular homeostasis. Produced by endothelial cells, nitric oxide is a critical modulator of important homeostatic functions, with endothelial dysfunction defined as a reduced capacity for nitric oxide production and decreased nitric oxide sensitivity [159]. Ultimately, this leads to vascular homeostasis disorders. Endothelial dysfunction underlies pathologies. In the pulp and periodontal tissue of animal models immobilized by the NO-synthase enzyme blocker, odontoblasts and vascular endothelium showed lesions with cell apoptosis. Hemodynamic disorders were accompanied by extensive hemostasis, hemorrhages of various size, edema, leukodiapedesis, and macrophage reaction [4].

NO is synthesized from L-arginine in the presence of the nitric oxide synthase (NOS) enzymes. In mammals, the enzyme comes in three isoforms: the calcium-calmodulin controlled isoenzymes eNOS (endothelial NOS) and nNOS (neuronal NOS), as well as the calcium-calmodulin independent induced isoform (iNOS) in physiological concentrations. The iNOS-mediated NO production critically depends on the substrate expression and availability, resulting in higher NO levels compared to eNOS and nNOS. iNOS-derived NO is associated with the pathogenesis and progression of numerous diseases, including liver diseases, insulin resistance, obesity, and cardiovascular disorders. Available evidence strongly suggest that iNOS-derived NO is a pivotal player in the regulation of biochemical pathways and energy metabolism, including glucose and lipid metabolism in inflammatory conditions [31].

With its ability to influence inflammatory processes and osseointegration, NO can be considered a predictor of dental implant success. NO plays an important modulator of inflammatory responses, which is critical for successful healing after implant procedure. NO also promotes osteoblast proliferation and differentiation, enhancing osteogenesis and implant-bone integration.

High NO level in the oral fluid may suggest successful implant installation [221]. NO is assumed to improve microcirculation in implant surrounding tissue, associated with better bone tissue nutrition and regeneration.

Low NO levels were evidently associated with increased pro-inflammatory cytokine expression, including IL-6 and TNF-α, indicative of an increased risk of peri-implantitis [4]. Thus, low NO levels presume a higher risk rate of peri-implantitis and implant rejection [221].

1.2.9 Neuron-specific enolase

Neuron-specific enolase (NSE) is a glycolytic enzyme found in neuronal and neuroendocrine tissues. NSE is involved in the glycolytic glucose metabolism and energy-generating process of the neuron. NSE is detectable in blood and is a useful biochemical marker to estimate neuronal damage in brain lesions, especially in strokes and brain tumors. NSE measure may therefore correlate with the health and healing of tissues after dental implant installation. As a neural activity biomarker, NSE can indicate disorders in dental and surrounding tissues. NSE levels are useful to assess the patient's health that, in turn, affects the dental implant health [166].

Elevated pre-op NSE measure can suggest a higher implant procedure success rate. Elevated NSE indicates healthy tissue regeneration, rapid wound healing and bone-implant integration [228]. On the contrary, in patients, low NSE is associated with a higher risk of complications. Overall, NSE can be a useful predictor of both successful implant installation and potential complications [59].

1.2.10 Vascular cell adhesion molecule-1

Vascular cell adhesion molecule-1 (VCAM-1) or cluster of differentiation 106 (CD106) is a cell adhesion protein that plays an important role in inflammatory

response and angiogenesis. VCAM-1 can be a useful predictor of dental implant survival, considering that inflammation and vascular disorders in the implant-surrounding area impede osseointegration and long-term implant stability.

Recent studies have demonstrated the role of VCAM-1 as a predictor of dental implant success. The findings showed that periodontal ligament stem cells that highly express VCAM-1 have a high capacity for osteogenic differentiation suggesting that elevated VCAM-1 can predict successful osseointegration following dental implant placement [227].

A different study analyzed peri-implant VCAM-1 and ICAM-1 expression throughout early dental implant healing, concluding that elevated expression was apparently associated with inflammatory response and successful osseointegration [151].

Some studies report that adhesive molecules, including VCAM-1, are critical for implant success because of their play in the regulation of inflammatory response and angiogenesis [157].

As a protein affecting inflammatory response and osseointegration, VCAM-1 can therefore be a useful predictor of dental implant health [156].

1.2.11 Claudine-1

Claudins are a transmembrane protein family that regulate epithelial barrier function. By interacting with other transmembrane proteins, cytosolic scaffold proteins and the actin cytoskeleton, claudins form a tight junction barrier. Claudins exert specific activity on the scaffold proteins of dense junctions, regulating their interaction with the cytoskeleton. This mechanism can regulate tight joint assembly and function [141].

Claudins comprise almost two dozen transmembrane proteins that are a key part of the dense compound barrier regulating the trafficking solutes through polarized epithelial cells. Dense junctions consist of a few different protein classes interacting with one another to form epithelial barriers [52, 53]. Claudins are represented by proteins of four transmembrane domains, two extracellular loops, a short cytosolic N-

terminus, and a longer cytosolic C-terminus. Claudins may serve also as signaling nodes via specific interactions with various scaffold proteins [14].

CLDN1 (claudin-1) plays a critical role in tight junctions by regulating paracellular barrier permeability, integrity and homeostasis. The recently published research is an attempt to tap the potential of claudins in dental implant procedure.

As a regulator of cell barrier permeability and cell interactions, CLDN1 can influence implant healing. CLDN1 expression may serve as a measure of efficient osseointegration, potentially predicting dental implant success [28].

Claudin family, including CLDN1, are involved in inflammatory responses that may affect implant outcomes. Efforts to optimize the CLDN1 level can attenuate specific inflammatory response, contributing to improved implant installation outcome [6].

Upregulated CLDN1 may be associated with better biocompatibility of implant materials, suggesting a greater chance of successful treatment [2].

In leukoplakia and squamous cell carcinoma of the oral mucosa, high cell proliferation correlated with suppressed claudin-1 expression, whereas failure detect claudin-1 on the cell surface was implicated with manifest cellular neoplasia [6].

Fellow investigators revealed attenuated claudin-1 and claudin-10 expression after dental implant placement, with elevated claudin-7. Fluctuating claudin expression may imply a pathological process, including successful implant installation, especially in elderly patients [13].

1.2.12 E-cadherin

Cadherins are transmembrane or membrane-bound glycoproteins that mediate $Ca2^{+}$-dependent intercellular adhesion [46]. Cadherins play essential roles in tissue morphogenesis, including polarity of simple epithelial cells, cell-fate specification, organ architecture, cell-cell contact stabilization and resistance to mechanical forces, as well as tissue organization and cohesion [41, 47]. Cadherin expression is regulated by

multiple developmental factors and cell signals [46]. E-cadherin mediates strong homotypic adhesion between neighboring epithelial cells, thus preserving the epithelial barrier integrity [61]. E-cadherin is essential for stable epithelial cell-cell contacts, whereas its downregulation leads to dysfunctional weak cell-to-cell adhesion and formation of desmosomes [77]. E-cadherin sustains epithelial integrity through homophilic interaction; E-cadherin's cytoplasmic tail interacts with various catenins, further enforcing extracellular adhesive contact to regulate numerous intracellular signal transduction pathways, including the epithelial-to-mesenchymal transition program [74, 202].

Some bacteria (e.g. *F. nucleatum, L. monocytogenes, S. pneumoniae*) use E-cadherin to enter their target cells. Other bacteria affect the expression of this molecule on the cell surface either by modulating the transcription of the *CDH1* gene (for example, *C. trachomatis, H. pylori*), or by inducing cleavage of the E-cad molecule (for example, *C. perfringens, S. aureus, C. burnetii*) through proteases [77, 205].

Thus, E-cadherin expression is indicative of the peri-implant soft tissue health. Downregulated E-cadherin can be associated with damaged epithelial integrity, potentially suggesting an ongoing inflammation or implant rejection.

Evidence shows that E-cadherin suppression correlates the severity of inflammation in the implant area, serving as a promising diagnostic biomarker of peri-implantitis [205]. The possibility of using E-cadherin as a marker for early diagnosis of inflammatory processes around implants is being considered, which makes it possible to take the necessary measures in time to prevent complications [205].

E-cadherin is critical for for teeth development, including the enamel, crown, pulp and roots [61].

CHAPTER 2. RESEARCH MATERIALS AND METHODS

2.1 Research design

The study was performed using the facilities of the St. Petersburg State Autonomous Healthcare Establishment 'City Dental Outpatient Clinic No. 22'. Every patient signed a voluntary informed consent to participate in the research study (see Appendix A).

Inclusion criteria:

- age 18 to 59 y.;
- 1 tooth missing.

Exclusion criteria:

- diabetes mellitus;
- oncologic conditions;
- blood and hematopoietic disorders;
- > 1 tooth missing;
- anatomical limitations for implant placement;
- pregnancy and lactation.

Patient stratification into groups. The study enrolled 78 patients. All patients were stratified into groups:

Group 1 comprised 15 patients (19.2%) with successful implant placement.

Group 2 comprised of 31 patients (39.8%) with moderate peri-implantitis.

Group 3 comprised 32 patients (41%) with severe peri-implantitis.

2.2 Dental examination protocol

All patients underwent an oral cavity examination under overcast daylight condition with a standard dental examination toolkit featuring a dental

probe, mirror and tweezers. The examination and all parameters were evaluated before, 1 month, and 6 months after implant placement.

Patient admission procedure included:

– patient survey;
– visual mouth examination;
– local health status of the oral cavity;
– palpation;
– probing;
– panoramic radiography of teeth (OPTG).

The following periodontal indices were calculated: GI (gingival or tongue hygiene index, see H. Loe, J. Silness, 1964), CPI (community periodontal index), PMA (papillary marginal alveolar index, as modified by S. Parma, 1960), PI (periodontal index, see A. Russel, 1956); hygiene indices: OHI-S (simplified oral hygiene indices, oral hygiene index; see J.C. Green, J.R. Vermillion, 1964), PHP (patient hygiene performance index, see Podshadley, Haley, 1968); the Muhlemann-Son Sulcus Bleeding Index (see H.R. Muhlemann, 1971) as modified by Cowell (I. Cowell, 1975).

All indexes were evaluated prior to, 1 month, 6 months after the implant placement.

2.3 Dental implant surgery protocol

Dental implant surgery is a procedure replacing missing teeth with artificial titanium implants to support a crown or a dental prosthesis. A standard single-tooth dental surgery protocol a set of steps that ensure a safe and durable result.

1. Consultation and treatment planning. The first stage includes consultation with a dental surgeon or an implantologist. The doctor examines the oral cavity to assess the condition of the remaining teeth, gums and bone tissue. Information about the patient's health status, allergies, and medications is also collected.

Diagnostics. The X-ray examination includes a panoramic jaw imaging (orthopantomogram) and / or computed tomography to assess bone tissue volume and density.

Modeling. A plaster model of jaws is obtained to simulate the implant positioning.

Computer simulation Sophisticated software is used to perform virtual simulation of dental implant treatment.

2. Pre-surgery preparation. Before surgery, the patient is prescribed antibiotics and anti-inflammatory drugs to reduce the risk of infectious complications. Nutrition and lifestyle guidance is required shortly before surgery.

The patient should stop smoking or alcohol drinking a few days before surgery.

The patient is recommended to avoid eating harder, solid foods

and follow the doctor's instructions regarding the prescribed medication.

3. Surgery. The surgery is performed under local anesthesia or, less commonly, under general anesthesia. The procedure lasts approximately 30 to 60 minutes.

Stages of dental implant surgery:

- gum incision — the gum is cut to access the bone tissue;
- the implant bed is formed — the surgeon drills a hole of appropriate size and shape in the bone tissue;
- implant installation — the implant is screwed into the bed;
- Wound suturing — the gum is sutured over the implant to protect and accelerate healing.

4. Wound healing. After surgery, the wound healing lasts from 3 to 6 months. This timespan allows the implant to integrate with the bone tissue (i.e. osseointegration).

Wound Care:

1) mouthwash with antiseptic solutions;
2) administration of antibiotics and painkillers as prescribed by a doctor;
3) aviod hard solid foods or hot drinks;
4) regular doctor appointments to monitor the wound healing.

5. Gum shaper should be be installed. Once osseointegration is completed in 3 to 6 months following the implant installation, a gum shaper is installed. A gum shaper is a temporary element installed in the implant during the final period of osseointegration to form the gum around the future tooth.

Installation procedure:

- plug removal — the plug covering the implant is removed;
- installing the gum shaper — the shaper is screwed in instead of the plug;
- suturing — the gum can be sewn around the shaper.

6. Crown manufacturing and installation. Once the gum formation is complete, the gum shaper is replaced with the abutment to connect the crown to the gum. A permanent crown is then made to be attached to the abutment.

Crown fabrication and installation procedure:

- dental plaster cast — plasters casts of teeth are obtained to fabricate the crown;
- crown fabrication — the crown is made in a dental laboratory;
- fitting and adjustment — the crown is fitted with adjustments made if required;
- crown attachment — the finished crown is fixed to the abutment using cement or screws.

7. Patient follow-up and guidance. Once the procedure is completed, the patient should be provided with recommendations regarding the new tooth and implant care. Regular appointments with the dentist are a collateral to monitor the implant status and prevent complications.

Aftercare recommendations:

1) brushing the teeth twice a day with a soft-bristled toothbrush and toothpaste;
2) using a dental floss and irrigator to clean interdental spaces;
3) regular dental checkups every 6 months.

The standard protocol for single dental implant procedure includes a few stages, with every step ensuring a successful outcome. Proper and thorough performance of

every step, including compliance with the dentist's recommendations will ensure a long service life of the implant and a high quality of life for the patient.

2.4 SF-36 Quality of life questionnaire

All patients responded to the SF-36 questionnaire (The Short Form-36; see Appendix I) prior to and 6 months after the dental implant procedure. Patient answers underwent a standard scoring procedure to obtain the results (Table 1).

Table 1 — The SF-36 index calculator

Items	Questions	Minimum and maximum values	Score range
Physical functioning (PF)	3a, 3b, 3v, 3g, 3d, 3e, 3zh, 3z, 3i, 3k	10–30	20
Role (physical) functioning (RP)	4a, 4b, 4v, 4g	4–8	4
Pain (P)	7, 8	2–12	10
General health (GH)	1, 11a, 11b, 11v, 11g	5–25	20
Vitality (VT)	9a, 9d, 9zh, 9i	4–24	20
Social functioning (SF)	6, 10	2–10	8
Role emotional (RE)	5a, 5b, 5v	3–6	3
Mental health (MH)	9b, 9v, 9g, 9e, 9z	5–30	25

In points 6, 9a, 9d, 9g, 9z, 10, 11, the score is obtained by reverse count.

Requirements to result presentation:

1) specified number of observations per parameter;
2) descriptive statistics — M ± SD, Me (LQ; UQ), % (n/N);

3) score accuracy (p-value); CI (for key survey results) and p-value;
4) report the utilized statistical methods (parametric and nonparametric) and software.

2.5 Buccal epithelium sampling

Buccal epithelium (BE) was sampled for immunocytochemistry. BE was obtained from the oral cavity (the mucous membrane of the inner cheek) no earlier than 4 hours after food intake, prior to sampling the oral cavity was rinsed with saline solution. BE was collected using sterile single-use synthetic swabs; after sample collection the swab head was cut-off and placed in a sterile single-use Eppendorf tube with transport medium. Smear slides were prepared using a fully automated system for liquid-based cytology: the Novoprep (France).

2.6 Immunocytochemistry

All patients enrolled in the study were stratified into groups (Table 2). Groups 2 and 3 were comparable by patient number, gender and age. Buccal epithelium was collected from patient representing all the three groups to assess the expression of signaling molecules prior to the dental implant procedure, after 1 and then 6 month's follow-up.

Every patient enrolled in the study underwent BE collection to assess the expression of signaling molecules prior to the dental implant procedure, after 1 and the 6 month's follow-up.

Table 2 — Characteristics of collected samples

Sample characteristics	Patients with dental implant success	Patients with mild peri-implantitis	Patients with moderate peri-implantitis
	Group 1	Group 2	Group 3
Number of patients	15	31	32
Including males	8	15	15
Including females	7	16	17

2.7 Confocal immunofluorescence microscopy

Immunocytochemistry of BE samples was performed using primary monoclonal antibodies (Table 3).

Alexa Fluor® 647-conjugated secondary antibodies (Abcam, England, 1:1000) were used for immunofluorescence.

Cells were incubated for 30 minutes in the dark at room temperature. Hoechst 33258 (Sigma, USA) staining was used for visualization of cell nuclei. Immunofluorescent cell cultures were visualized using Zeiss LSM 980 confocal microscopy.

The conventional BE immunocytochemical staining procedure with fluorochrome-conjugated secondary antibodies is provided below.

1. Fix the cells in 4% paraformaldehyde (Sigma, USA) prepared in phosphate-salt buffer (PBS) — 15 minutes.
2. Rinse in PBS three times, 5 minutes / wash.

Table 3 — Primary monoclonal antibodies

Antibodies	Brand	Dilution
α-Tubulin	Dako	1:100
β-Tubulin	Dako	1:100
COX-1	Dako	1:100
COX-2	Dako	1:100
COX-3	Dako	1:100
Melatonin	Abcam	1:120
MT1 Melatonin receptor	Abcam	1:50
MT2 Melatonin receptor	Abcam	1:100
VEGF	Abcam	1:100
VEGFR	Abcam	1:50
NeuN	Abcam	1:100
NO	Abcam	1:100
Neuron-specific enolase	Abcam	1:50
VCAM 1	Abcam	1:75
E-cadherin	Abcam	1:100
Claudine-1	Abcam	1:75

3. Permeabilize cells with 0.1% TritonX-100 solution (Biolot, Russia) — 15 minutes.

4. Rinse in PBS three times, 5 minutes / wash. Change PBS between washes.

5. Incubate in 1% bovine serum albumin (Biolot, Russia) — 30 minutes.

6. Primary antibody incubation — 1 hour.

7. Rinse in PBS three times, 5 minutes / wash. Change PBS between washes.

8. Incubate with secondary antibodies conjugated with Alexa Fluor 567 fluorophore (1:1000, Abcam, USA) or Alexa Fluor 488 fluorophore (1:1000, Abcam, USA) or Alexa Fluor 555 fluorophore for 30 minutes in the dark at room temperature.

9. Rinse in PBS three times, 5 minutes / wash. Change PBS between washes.

10. Apply the Hoechst 33258 (Sigma, USA) marker dye to the cell nuclei — 1 minute.

11. Rinse in PBS, 5 minutes / wash.

12. Place the specimen on the glass coverslip and apply it over the Dako Fluorescent Mounting Medium (Dako, USA).

2.8 Computer-assisted morphometric microscopic image analysis

Computer-assisted morphometric microscopic image analysis is performed to evaluate the immunocytochemical staining results, using a ZEISS LSM 980 microscope, ZEISS digital camera, desktop computer, and ImageJ software. From each section, 5 microscopic visual fields were selected for analysis at ×200.

Measuring the area percentage of marker expression. The marker expression area was assessed using the ratio between immunopositive area to the total area of cells in the visual field; the result was quantified in percentages for biomarkers in cytoplasmically stained cells or as the proportion of immunopositive nuclei to the total nuclei in the visual field for nuclear markers.

2.9 Statistical processing of obtained results

Statistical processing was performed using the Excel 2010 Microsoft Office (Microsoft Corporation) and Statistica 10.0 (Statsoft Inc., Tulsa) software. The Shapiro-Wilk test was applied to test that the data were normally distributed; the Levene test was applied to assess the equality of variances. Normally distributed continuous variables were represented as (M ± Se), where M is the arithmetic average and Se is the standard error of the average value. Medians (25-75 percentiles) were used when normal sample distribution was missing.

The Kruskal-Wallis test (H-test) was used to compare the analyzed continuous variable across the three groups. The H-test was used to compare the variable across the three groups at a time to detect whether the variable would change between the three groups. All values were grouped together and aggregated in a common row. Then, the sum of the ranks was calculated per every sample. In case of random differences, high and low ranks split uniformly among samplings. If high ranks dominate in one group, with low ranks dominating in the other group, the differences are not random. The critical confidence level of the null hypothesis (no significant effect or relationship between the variables) was assumed to be 0.05; 0.01; 0.001.

The Spearman's rank correlation test was performed to analyze the correlation. P-values <0.05 were considered statistically significant. Correlation was analyzed to identify age-specific dependencies.

To validate absence of bias in the obtained results, as well as the informative value of the analysed parameters, the Kullback-Leibler metric [1] was used as follows:

$$J\left(x_i\right)=10\lg\frac{P_1}{P_2}\cdot 0,5\cdot\left(P_1-P_2\right), \quad (1)$$

(Translator's note: 0,5 should be considered 0.5)

where$J$ — the informative value of the biological indicator under consideration;

P_1 — the relative average expression of the studied protein prior to the dental implant procedure;

P_2 — the relative average expression of the studied protein 6 months after the dental implant procedure.

The differential value of information (i.e. parameters utilized to compare the samplings (Group 1 and Group 2)) allowed to select the most informative parameters out of the initially tested characteristics. To this end, the Kullback-Leibler (KL) information measure is used [1]. Our research uses the Kullback-Leibler measure to compare samplings for different groups prior to and 6 months after the dental implant placement.

The parameter is considered informative, if $J \geq 0.5$. The parameters is regarded highly informative, if the value is ≥ 3 ($J(x_i) \geq 3$).

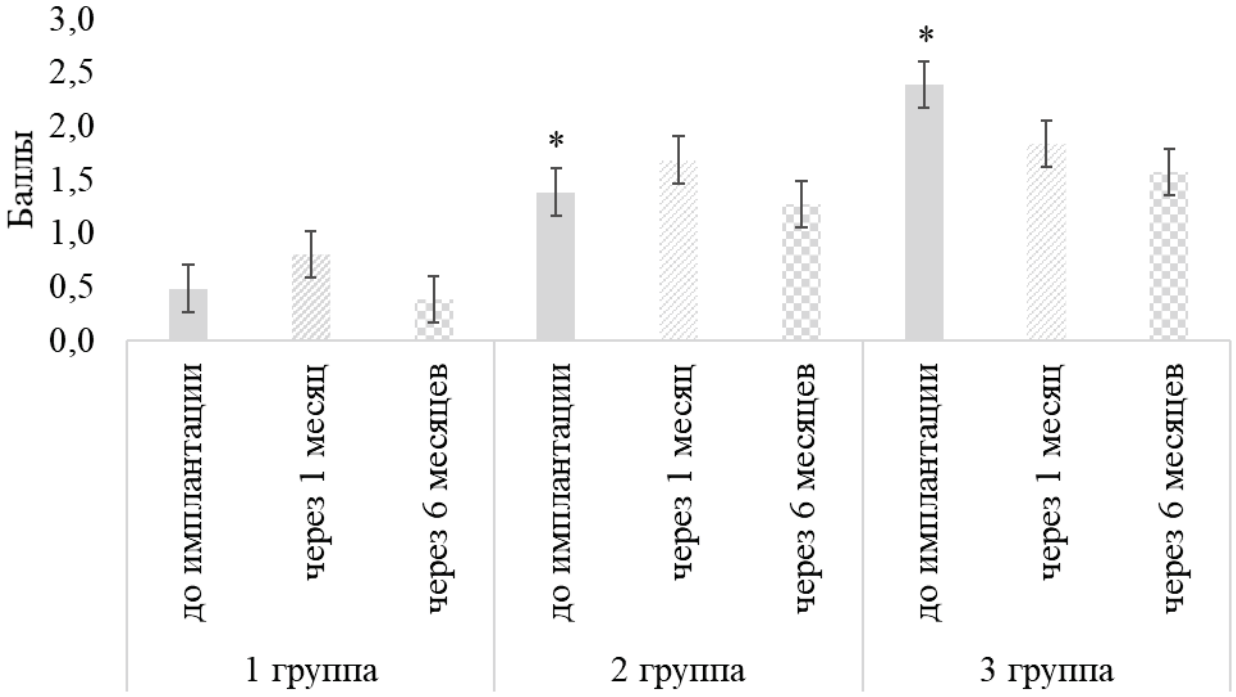
Mathematical and static analysis of the obtained data was performed (we analyzed temporal dynamics for selected markers, compared statistic differences for the assessed parameters across the three groups, conducted the cross-group comparison for all biomarkers, followed by a correlation analysis between the obtained quantitative variables to build decision trees).

CHAPTER 3. THE STUDY RESULTS

Periodontal indices are an important tool to assess the general oral cavity status, personal hygiene quality, and predict the dynamics of inflammation and damage.

3.1 Gingival index

See Figure 1 for the mean GI values across the groups.



Left to right: score (*top – down* 3.0; 2.5; 2.0; 1.5; 1.0; 0.5; 0.0); Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 1 — GI dynamics.

* — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

In Group 1, GI average increased significantly ($p < 0.05$) by 1.6 times 1 month after the dental implant procedure vs. prior to implant placement. After 6 months of follow-up, however, the GI average dropped almost to baseline level, observed prior to implant placement.

Following 1 month after implant placement, Group 2 average GI index showed an upward trend, as different from baseline prior to the procedure. After 6 months of follow-up, the average GI index in this group decreased at the trend level, without reaching the level of statistically significant differences.

In Group 3, the average gingival index GI at 1 month and 6 months after implant placement significantly decreased by 1.3 and 1.5 times, respectively, compared with this indicator prior to the implant placement ($p < 0.05$).

In Groups 2 and 3, the calculated gingivitis localization and severity measures prior to implant procedure were significantly ($p < 0.05$) higher (2.9- and 4.9-fold for Group 2 and Group 3 respectively), than in Group 1.

In Groups 2 and 3, the average GI index 1 month after the implant placement was equally significantly ($p < 0.05$) elevated (2.1- and 2.3-fold for Group2 and Group 3, respectively), as different from Group 1.

The average GI index 6 months after the implant placement was also significantly ($p < 0.05$) high in Group 2 and Group 3 (3.3- and 4.1-fold, respectively) compared to Group 1.

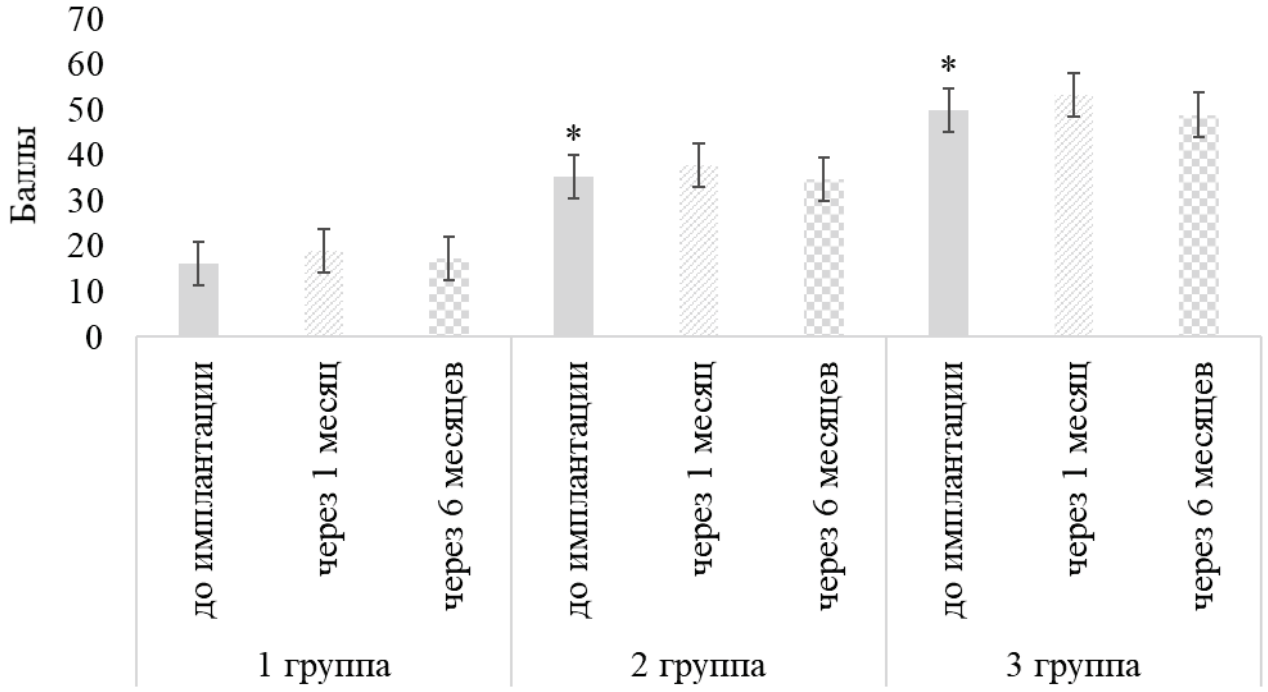
3.2 Papillary marginal alveolar index

Figure 2 shows the papillary marginal alveolar (PMA) index useful to assess gingivitis extent and severity.

The average PMA index in Group1 fluctuated slightly 1 and 6 months after implant placement compared to pre-implant baseline.

In Group 2, the average PMA index showed an upward trend after 1 month after the procedure vs. pre-implant baseline. After 6 months of follow-up, however, the average PMA index showed a downward trend, as different from 1 month after the surgery, dropping down almost to reach the pre-surgery baseline.

In Group 3, patterns similar to the second group were observed.



Left to right: score; Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 2 — PMA index dynamics. * — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

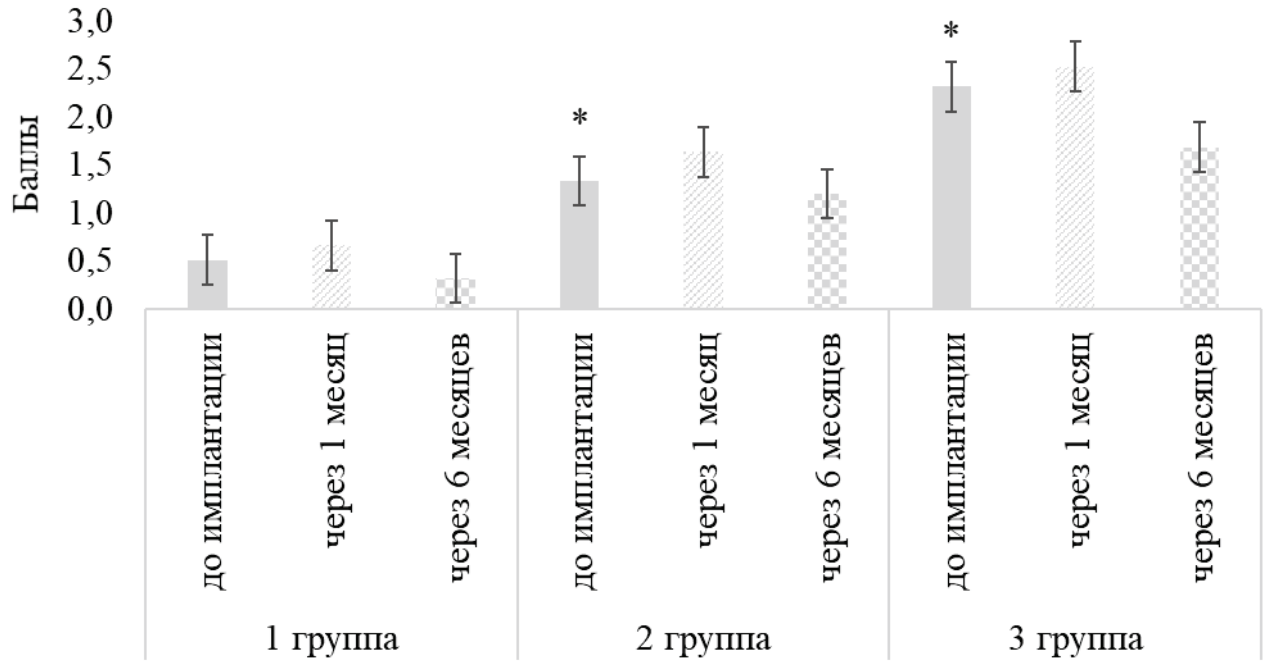
For the PMA index prior to implant placement, Group 2 and Group 3 showed significantly ($p < 0.05$) higher values (2.1- and 3.0-fold, respectively) than Group 1.

For the average PMA index 1 month after the implant placement, Group 2 and Group 3 showed significantly ($p < 0.05$) higher values (2.0- and 2.8-fold, respectively) than Group 1.

For the average PMA index 6 months after the implant placement, Group 2 and Group 3 showed significantly ($p < 0.05$) higher values (2.0- and 2.8-fold, respectively) than Group 1.

3.3 Communal periodontal index

Figure 3 shows the CPI bar chart to assess the extent and severity of periodontal disease



Left to right: score (*top – down* 3.0; 2.5; 2.0; 1.5; 1.0; 0.5; 0.0); Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 3 — The CPI dynamics. * — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

In Group 1, the average CPI index showed a slightly upward trend 1 month after the implant placement, decreasing insignificantly 6 months after the implant placement, as different from pre-treatment baseline.

In Group 2, the average CPI showed an upward trend 1 month after the implant placement, as different from pre-treatment baseline. After 6 months, the average CPI decreased without any statistically significant difference, when compared to pre-treatment baseline.

In Group 3, the average CPI showed an upward trend 1 month after the implant placement, as different from pre-treatment baseline. After 6 months, the average gingival CPI in this group significantly ($p < 0.05$) decreased by 1.4 times compared with pre-treatment baseline.

In Group 2 and Group 3, the average pre-treatment CPI showed significantly ($p < 0.05$) higher values (by 2.6 and 4.5 times for Group 2 and Group 3, respectively) as different from Group 1.

Likewise, 1 month after the implant placement, the average CPI showed was significantly ($p < 0.05$) higher in both groups (by 2.4 and 3.8 times in Group 2 and Group 3, respectively), as different from Group 1.

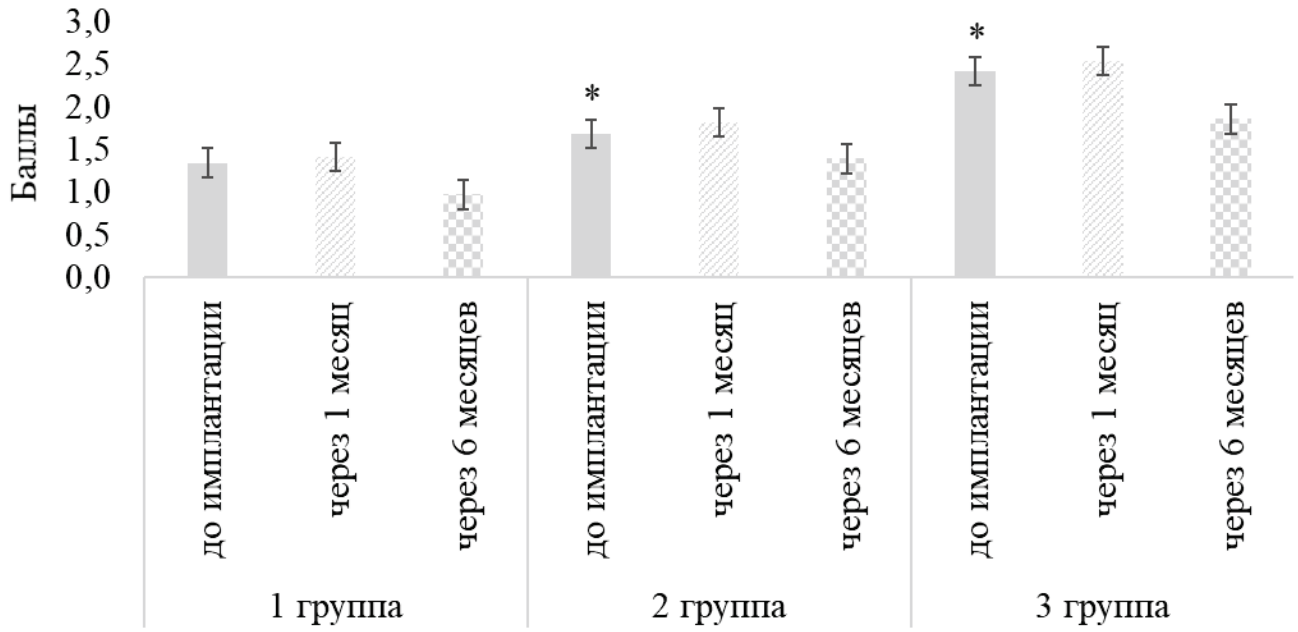
Ultimately, 6 months after the implant placement, the average gingival CPI was significantly ($p < 0.05$) higher in both groups (by 3.7 and 5.2 times in Group 2 and Group 3, respectively), as different from Group 1.

3.4 Simplified oral hygiene index

In Group 1, the average OHI-S remained virtually unchanged 1 month after the implant placement (see Figure 4). After 6 months, the average OHI-S decreased significantly ($p < 0.05$) by 1.3 times vs. the pre-treatment value.

In Group 2, the average OHI-S showed an upward trend 1 month after implant placement, as different from pre-treatment baseline. After 6 months, however, the average OHI-S decreased significantly ($p < 0.05$) by 1.2 times vs. the pre-treatment value.

In Group 3, the average OHI-S showed an upward trend 1 month after implant placement, as different from pre-treatment baseline. After 6 months, however, the average OHI-S decreased significantly in Group 3 ($p < 0.05$) by 1.3 times vs. the pre-treatment value.



Left to right: score (*top – down* 3.0; 2.5; 2.0; 1.5; 1.0; 0.5; 0.0); Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 4 — The OHI-S dynamics. * — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

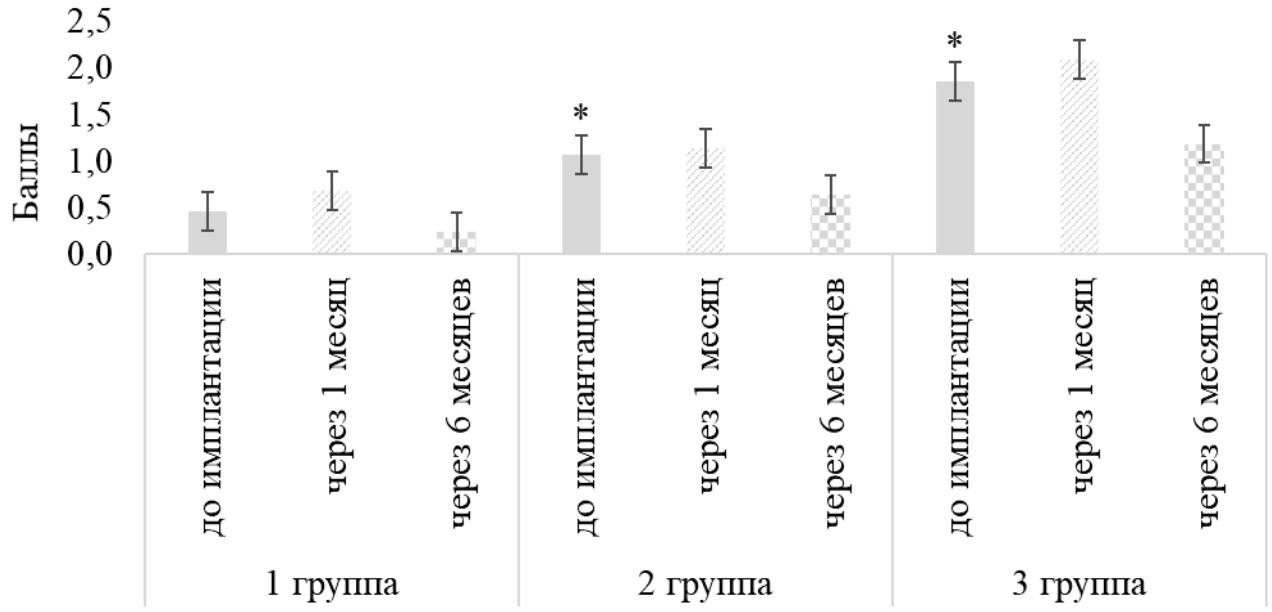
In Group 2 and Group 3, the pre-treatment OHI-S showed significantly ($p < 0.05$) higher values (1.2- and 1.7-fold for Group 2 and Group 3, respectively) as different from Group 1.

For the average OHI-S 1 month after the implant placement, Group 2 and Group 3 showed significantly ($p < 0.05$) higher values (1.3- and 1.8-fold, respectively) in comparison to Group 1.

Ultimately, 6 months after the implant placement, the average gingival OHI-S was significantly ($p < 0.05$) higher in both groups (1.4- and 1.9-fold in Group 2 and Group 3, respectively), as different from Group 1.

3.5 Periodontal index

Figure 5 shows periodontal index values for three study groups before treatment, 1 month and 6 months after dental implant placement.



Left to right: score (*top – down* 2.5; 2.0; 1.5; 1.0; 0.5; 0.0); Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 5 — The periodontal index (PI) dynamics.

* — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

In Group 1, the average PI showed a slightly upward trend 1 month after the implant placement. After 6 months, the average PI decreased significantly ($p < 0.05$) by 2.0 times vs. the pre-treatment value.

In Group 2, the average PI remained virtually unchanged 1 month after the implant placement compared to the pre-treatment value. After 6 months, however, the average PI in this group decreased significantly ($p < 0.05$) by 1.7 vs. the pre-treatment value.

In Group 3, the average PI showed an upward trend 1 month after implant placement, as different from pre-treatment baseline. After 6 months, however, the average PI decreased significantly ($p < 0.05$) by 1.5 times vs. the pre-treatment value.

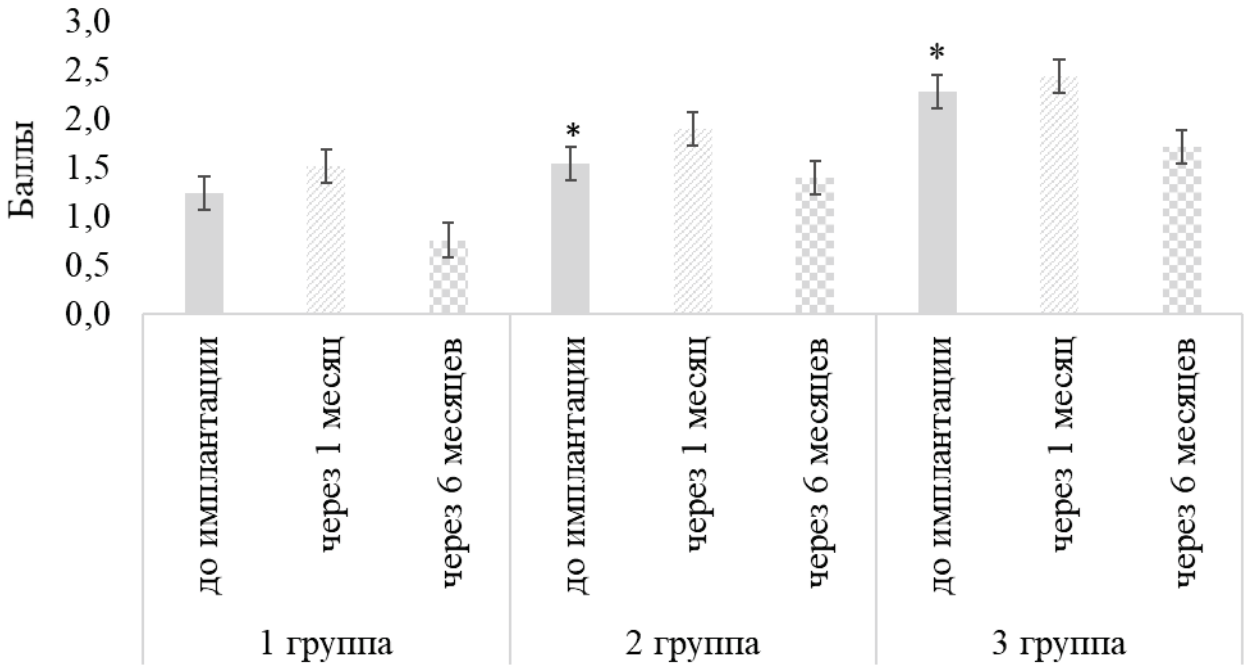
In Group 2 and Group 3, the average pre-treatment PI showed significantly ($p < 0.05$) higher values (by 2.3 and 4.0 times for Group 2 and Group 3, respectively) as different from Group 1.

Likewise, 1 month after the implant placement, the average PI was significantly ($p < 0.05$) higher in both groups (by 1.6 and 3.0 times in Group 2 and Group 3, respectively), as different from Group 1.

Ultimately, 6 months after the implant placement, the average gingival PI was significantly ($p < 0.05$) higher in both groups (by 2.7 and 5.1 times in Group 2 and Group 3, respectively), as different from Group 1.

3.6 PHP index

In Group 1, the average PHP index increased significantly ($p < 0.05$) by 1.2 times 1 month after implant placement compared to the pre-treatment baseline. After 6 months, however, the average PHP in this group decreased significantly ($p < 0.05$) by 1.6 times vs. the pre-treatment value (Figure 6).



Left to right: score (*top – down* 3.0; 2.5; 2.0; 1.5; 1.0; 0.5; 0.0); Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 6 — The PHP dynamics.

* — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

In Group 2, the average PHP increased significantly ($p<0.05$) by 1.2 times 1 month after the implant placement compared to the pre-treatment value. After 6 months,

the average PHP in Group 2 showed a downward trend, when compared to the pre-treatment baseline.

In Group 3, the average PHP showed an upward trend 1 month after implant placement, as different from the pre-treatment baseline. After 6 months, however, the average PHP decreased significantly in Group 3 ($p < 0.05$) by 1.3 times vs. the pre-treatment value.

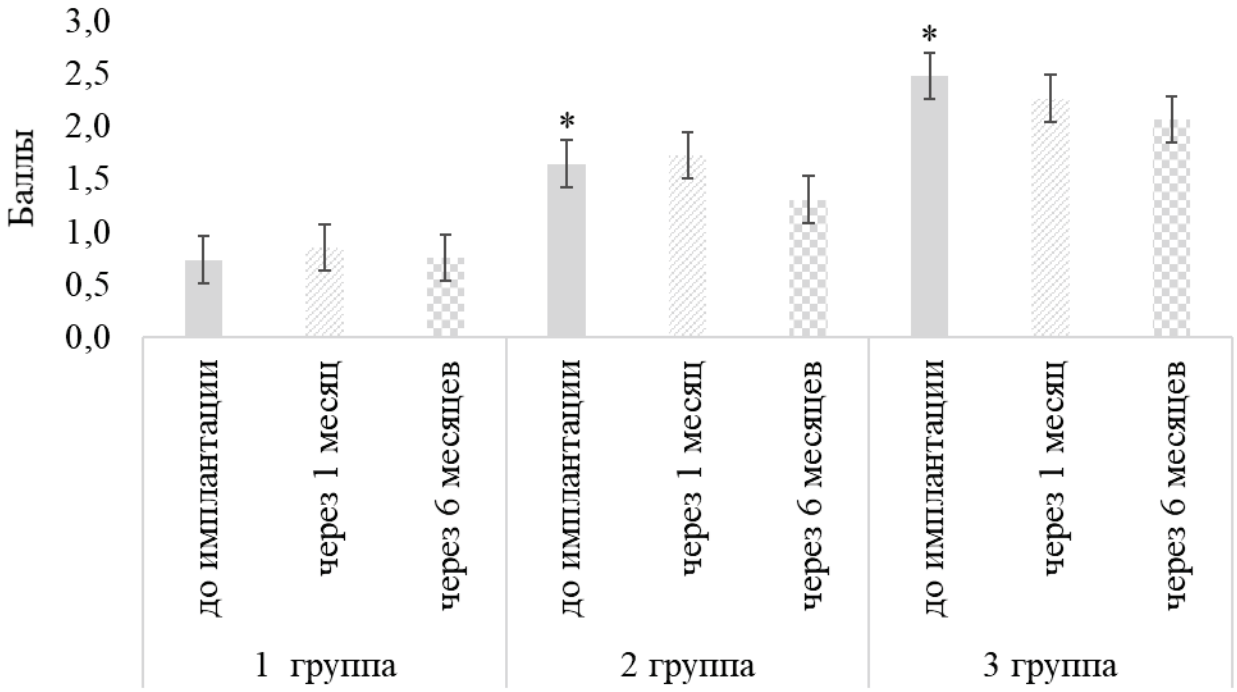
In Group 2 and Group 3, the average pre-treatment PHP showed significantly ($p < 0.05$) higher values (by 1.2 and 1.8 times for Group 2 and Group 3, respectively) as different from Group 1.

Likewise, 1 month after the implant placement, the average PHP showed was significantly ($p < 0.05$) higher in both groups (by 1.2 and 1.6 times in Group 2 and Group 3, respectively), as different from Group 1.

Ultimately, 6 months after the implant placement, the average gingival PHP was significantly ($p < 0.05$) higher in both groups (by 1.8 and 2.2 times in Group 2 and Group 3, respectively), as different from Group 1.

3.7 The Muhlemann-Son sulcus bleeding index

The Muhlemann-Son sulcus bleeding index is used to assess the bone tissue quality prior to dental implant installation. This index helps to measure the jaw bone density as it is essential for successful implant integration. The obtained results are presented in Figure 7.



Left to right: score (*top – down* 3.0; 2.5; 2.0; 1.5; 1.0; 0.5; 0.0); Group 1: at pre-treatment baseline, after 1 month, after 6 months; Group 2: at pre-treatment baseline; after 1 month; after 6 months; Group 3: at pre-treatment baseline; after 1 month; after 6 months.

Figure 7 — The Muhlemann-Son sulcus bleeding index dynamics.

* — compared to Group 1 prior to dental implant procedure ($p < 0.05$)

In Group 2, the average Muhlemann-Son sulcus bleeding index remained virtually unchanged 1 month after the implant placement compared to the pre-treatment value. After 6 months, however, the average Muhlemann-Son sulcus bleeding index decreased significantly in Group 2 ($p < 0.05$) by 1.3 times vs. the pre-treatment value.

In Group 3, the average Muhlemann-Son sulcus bleeding index slightly decreased 1 month after the implant placement, as different from the pre-treatment baseline. Likewise, after 6 months, the average Muhlemann-Son sulcus bleeding index decreased significantly in Group 3 ($p < 0.05$) by 1.2 times vs. the pre-treatment value.

In Group 2 and Group 3, the average pre-treatment Muhlemann-Son sulcus bleeding index showed significantly ($p < 0.05$) higher values (by 2.2 and 3.4 times for Group 2 and Group 3, respectively) as different from Group 1.

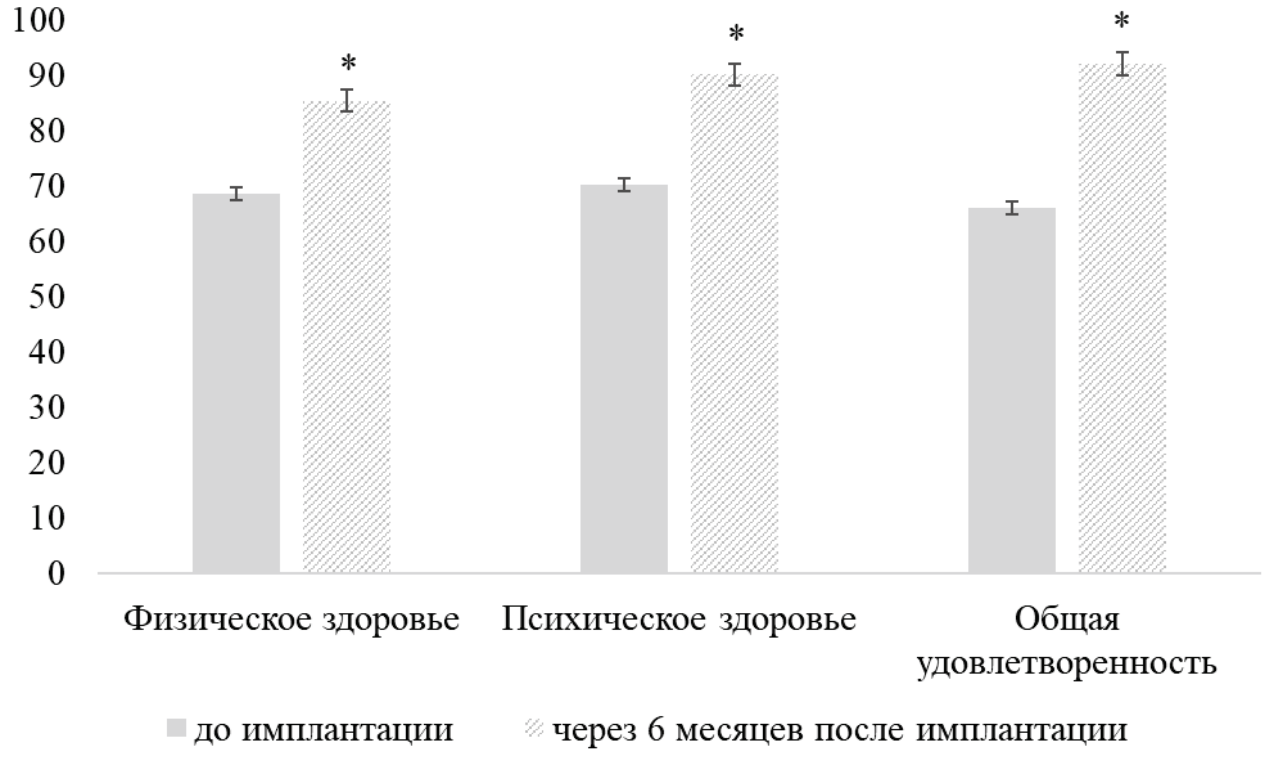
Likewise, 1 month after the implant placement, the average Muhlemann-Son sulcus bleeding index was significantly ($p < 0.05$) higher in both groups (by 2.0 and 2.6 times in Group 2 and Group 3, respectively), as different from Group 1.

Ultimately, 6 months after the implant placement, the average gingival Muhlemann-Son sulcus bleeding index was significantly ($p < 0.05$) higher in both groups (by 1.7 and 2.7 times in Group 2 and Group 3, respectively), as different from Group 1.

3.8 SF-36 score as a measure of health-related quality of life (SF-36)

In group 1, the SF-36 showed a significant improvement in physical and mental health (by 1.3 times) 6 months after the implant placement, as different from the pre-treatment baseline (Figure 8).

Overall satisfaction increased 1.4-fold compared to the pre-treament baseline. Thus, we can assume that even a single missing tooth impairs the overall quality of life, as well as mental and physical health perception.



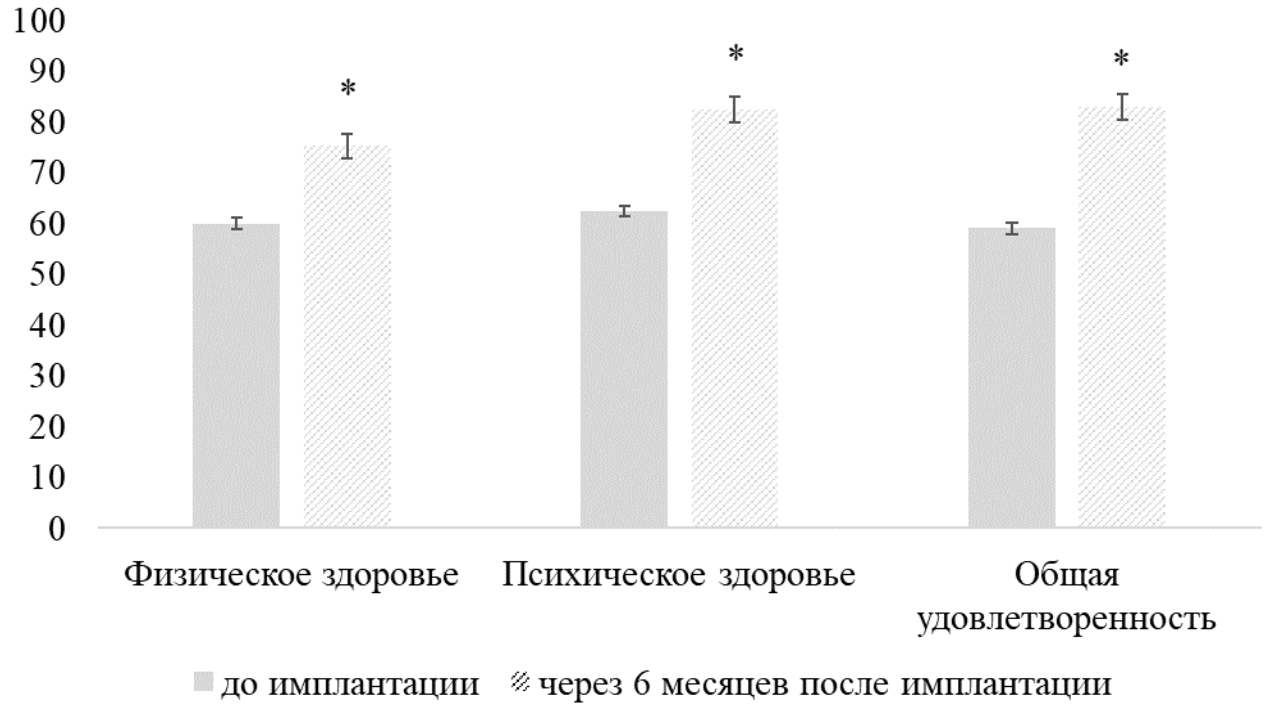
Top left to right: physical health; mental health; total satisfaction
Bottom left to right: at pre-treatment baseline; 6 months after the dental implant placement.

Figure 8 shows the SF-36 questionnaire results for Group 1 at pre-treatment and 6 months after the implant placement. * — compared to the pre-treatment baseline ($p < 0.05$)

The Group 2 results are shown in Figure 9.

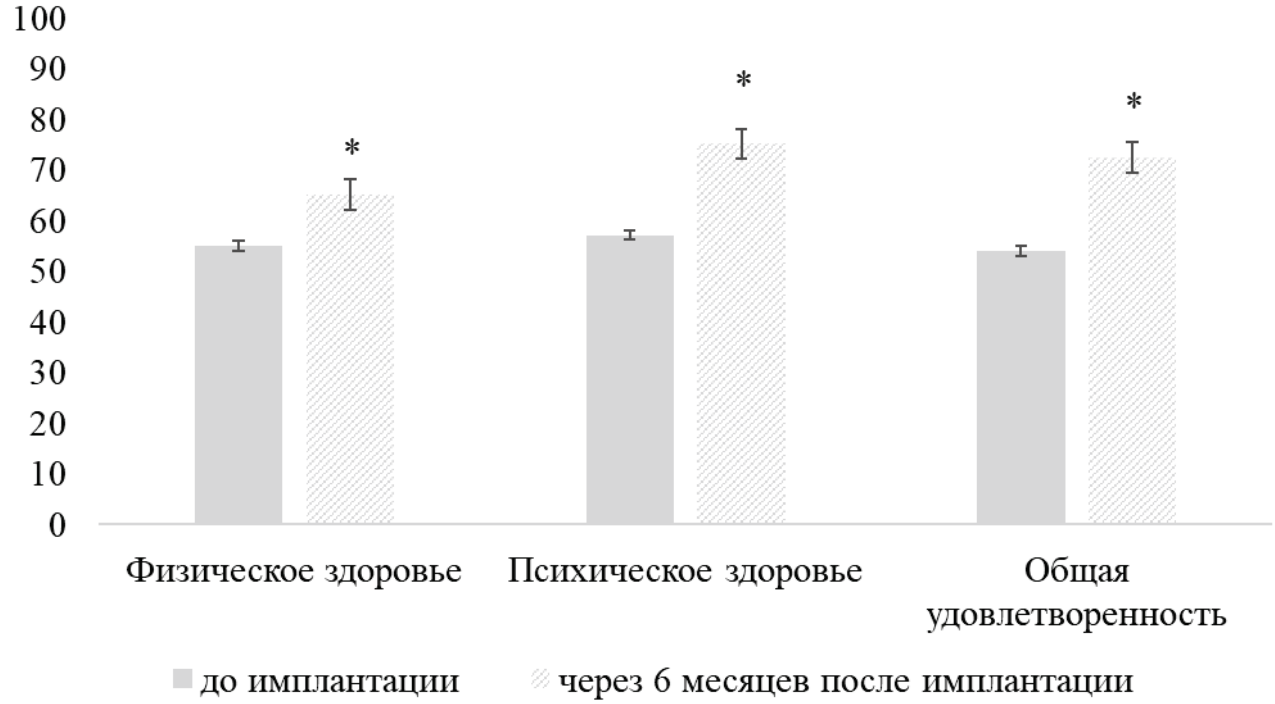
Group 2 showed similar trends to Group 1. The survey results showed a significant improvement in physical and mental health (by 1.2 and 1.3 times, respectively) 6 months after the implant placement, as different from the pre-treatment baseline (see Figure 9). The overall satisfaction saw a 1.3-fold increase 6 months after the dental implant placement against the pre-treatment baseline, with social satisfaction increasing 1.4-fold against the baseline.

In Group 3, the SF-36 showed a 1.2-fold and 1.3-fold improvement in the physical and mental health status, as different from the pre-treatment baseline (Figure 10).



Top left to right: physical health; mental health; total satisfaction
Bottom left to right: at pre-treatment baseline; 6 months after the dental implant placement.

Figure 9 shows the SF-36 questionnaire results for Group 2 at pre-treatment and 6 months after the implant placement. * — compared to the pre-treatment baseline ($p < 0.05$)

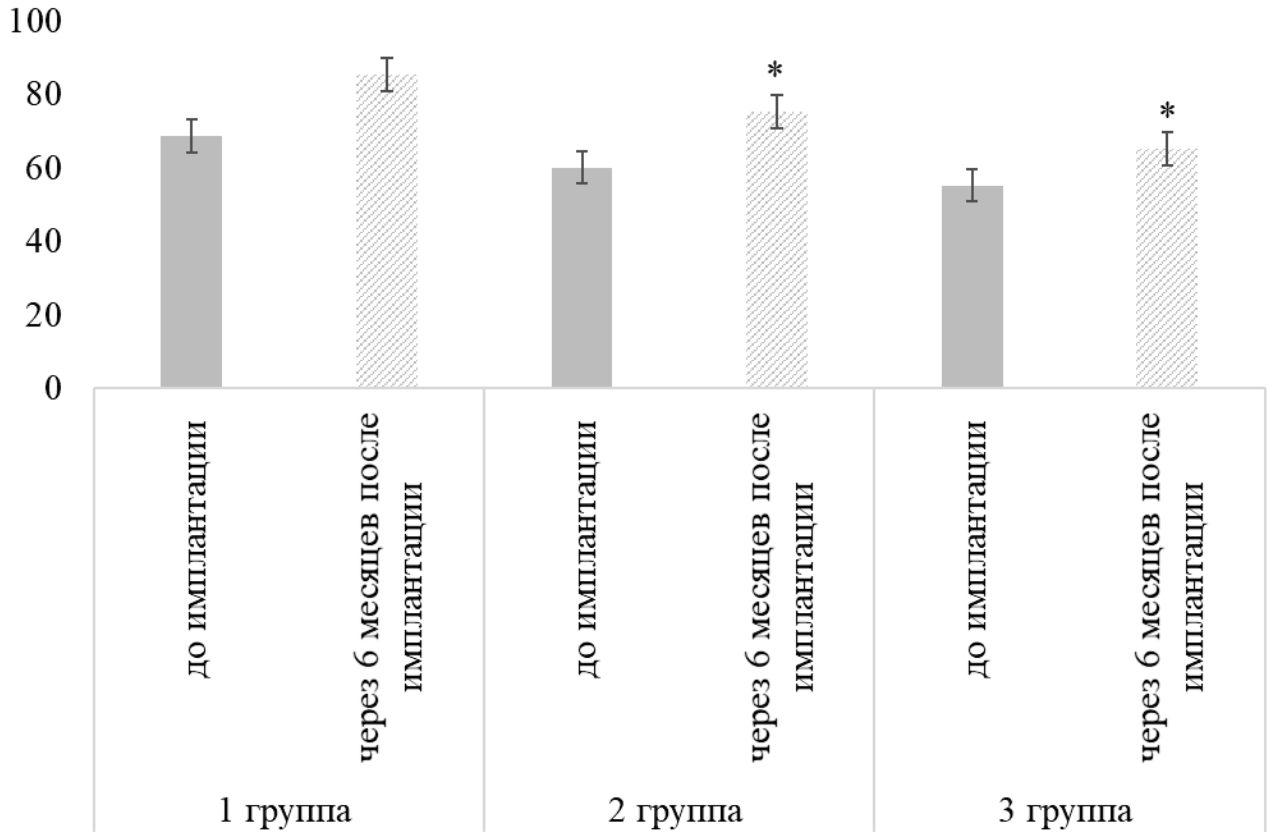


Top left to right: physical health; mental health; total satisfaction
Bottom left to right: at pre-treatment baseline; 6 months after the dental implant placement.

Figure 10 shows the SF-36 questionnaire results for Group 3 at pre-treatment and 6 months after the implant placement. * — compared to the pre-treatment baseline ($p < 0.05$)

The toral satisfaction and social satisfaction increased 1.3 times 6 months after implant placement compared to pre-implant placement levels.

Physical health analysis revealed (Figure 11) a significant discrepancy across all the groups at the pre-treatment stage and 6 months after the implant placement.

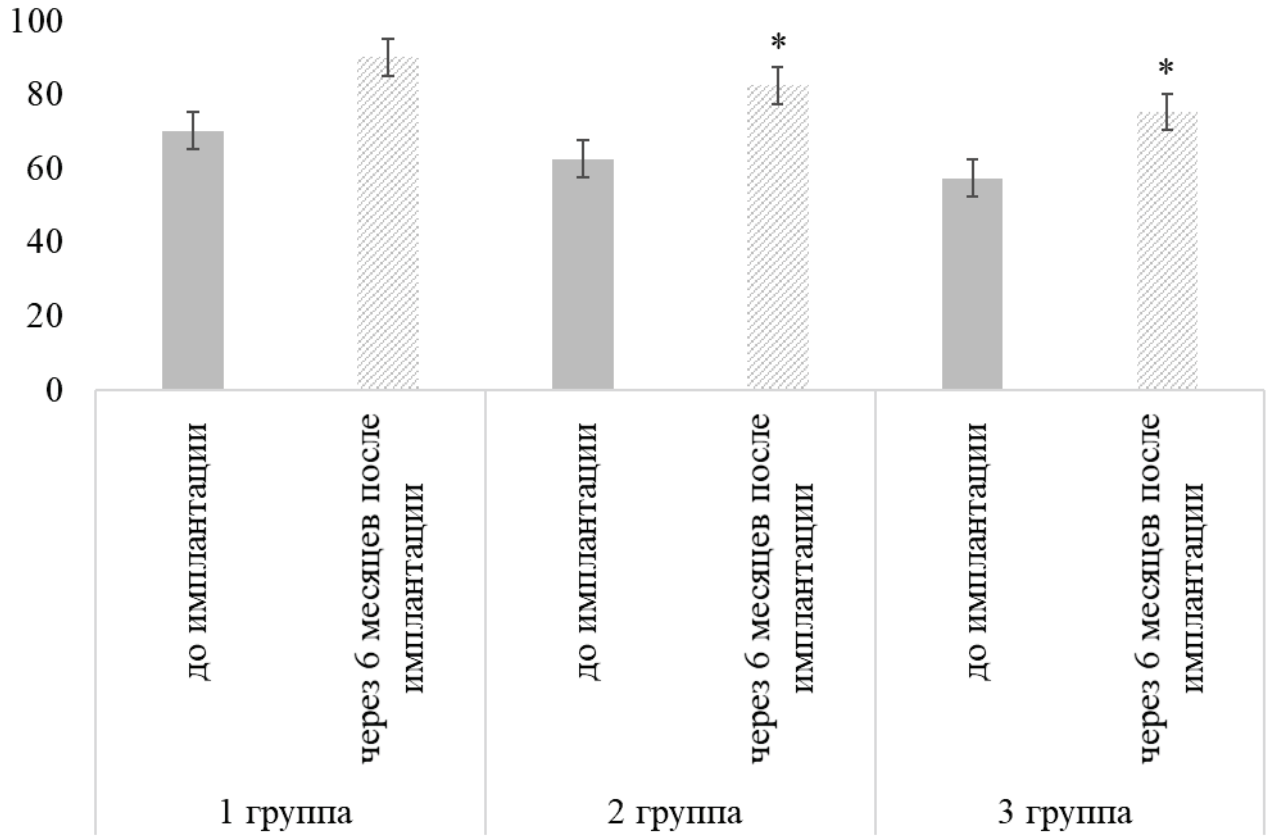


Top left to right: at pre-treatment baseline, 6 months after the dental implant placement; at pre-treatment baseline, 6 months after the dental implant placement; at pre-treatment baseline, 6 months after the dental implant placement.
Bottom left to right: Group 1; Group 2; Group 3.

Figure 11 shows the SF-36 results for physical health. * — compared to Group 1 6 months after the dental implant procedure ($p < 0.05$)

Mental health showed a similar trend as physical health. The results are presented in Figure 12.

Groups 2 and 3 demonstrated significantly deteriorated physical health, as different from Group 1, with Group 3 showing the worst measures before treatment and 6 months after the implant placement.



Top left to right: at pre-treatment baseline, 6 months after the dental implant placement; at pre-treatment baseline, 6 months after the dental implant placement; at pre-treatment baseline, 6 months after the dental implant placement.

Bottom left to right: Group 1; Group 2; Group 3.

Figure 12 shows the SF-36 results for mental health. * — compared to Group 1 6 months after the dental implant procedure ($p < 0.05$)

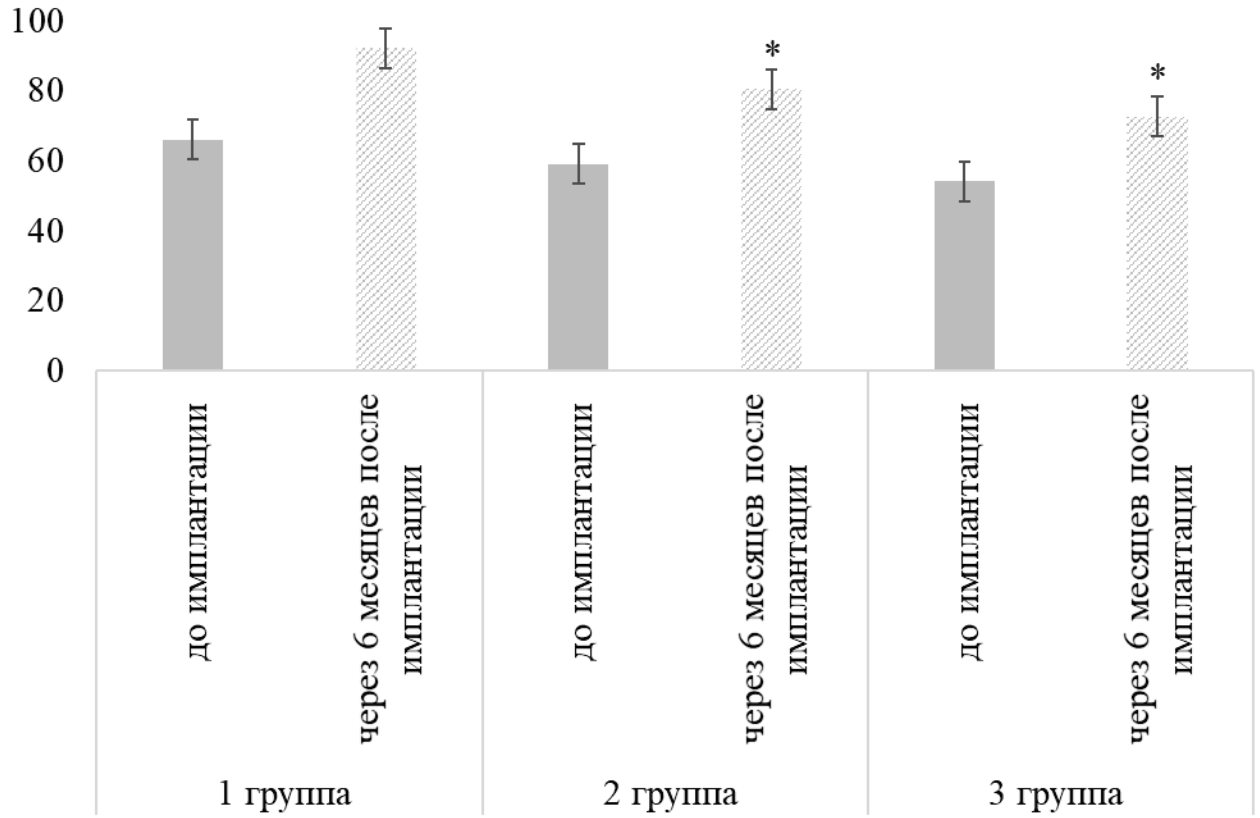
Group 3 showed the lowest mental health measures at pre-treatment baseline.

The overall satisfaction was also the worst in Group 3 at pre-treatment baseline (Figure 13).

Remarkably, 6 months after the dental implant procedure, the overall satisfaction with the quality of life in Group 3 reaches the measures, showed by to Group 1 at pre-treatment baseline.

Thus, we can conclude, that the restoration of even a single missing tooth improves the quality of life in patients. A single missing tooth can cause discomfort and

chronic stress. Implants solve these problems by recovering the patient's control of their own health, thus improving the overall satisfaction with the quality of life.



Top left to right: at pre-treatment baseline, 6 months after the dental implant placement; at pre-treatment baseline, 6 months after the dental implant placement; at pre-treatment baseline, 6 months after the dental implant placement.

Bottom left to right: Group 1; Group 2; Group 3.

Figure 13 shows the SF-36 results for the overall satisfaction among the three groups. * — compared to Group 1 6 months after the dental implant procedure ($p < 0.05$)

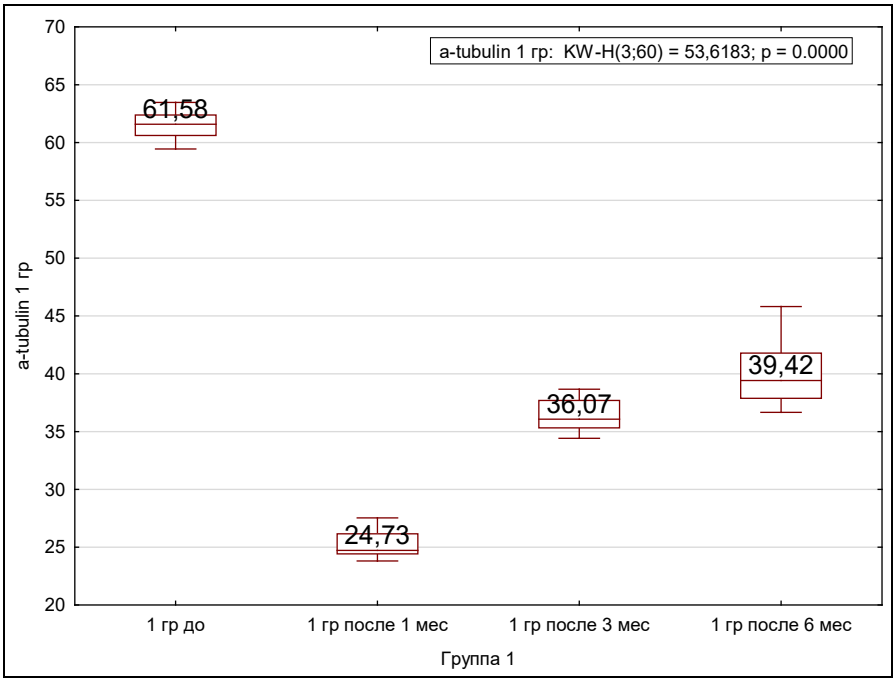
3.9 α-Tubulin

Table 4 shows the results obtained for the α-tubulin biomarker using Kullback informative measures in the three study groups. The α-tubulin measures were informative in all the three study groups, with Group 1 showing the highest informative measure.

In Group 1, the expression of α-tubulin showed statistically significant differences ($p < 0.01$) between EB samples obtained 1 and 3 months after the implant placement (Figure 14). Group 1 showed no statistically significant differences in α-tubulin expression levels between pre-treatment baseline and 6 months after the implant placement ($p = 0.06$).

Table 4 — α-Tubulin expression informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	61.52 ± 1.23	39.93 ± 2.65	20.26
Group 2	30.28 ± 1.10	25.81 ± 0.94	1.55*
Group 3	12.74 ± 0.87	9.21 ± 0.62	2.49*
* p 0.01 between the groups.			

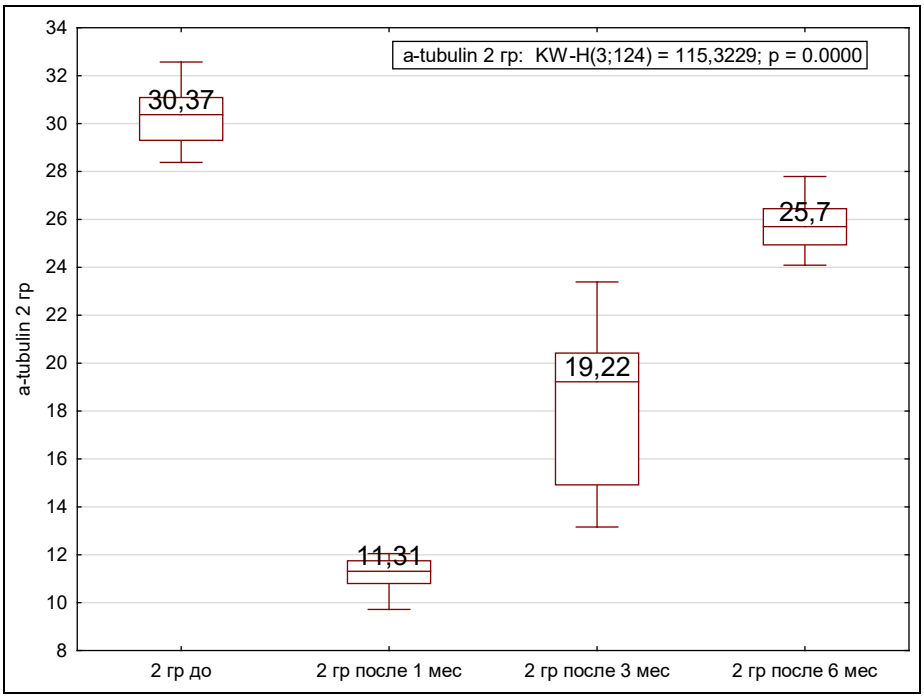


Left to right: Group 1 (*top right and vertical left);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 14 — Diagram showing the relative α-tubulin expression area in Group 1

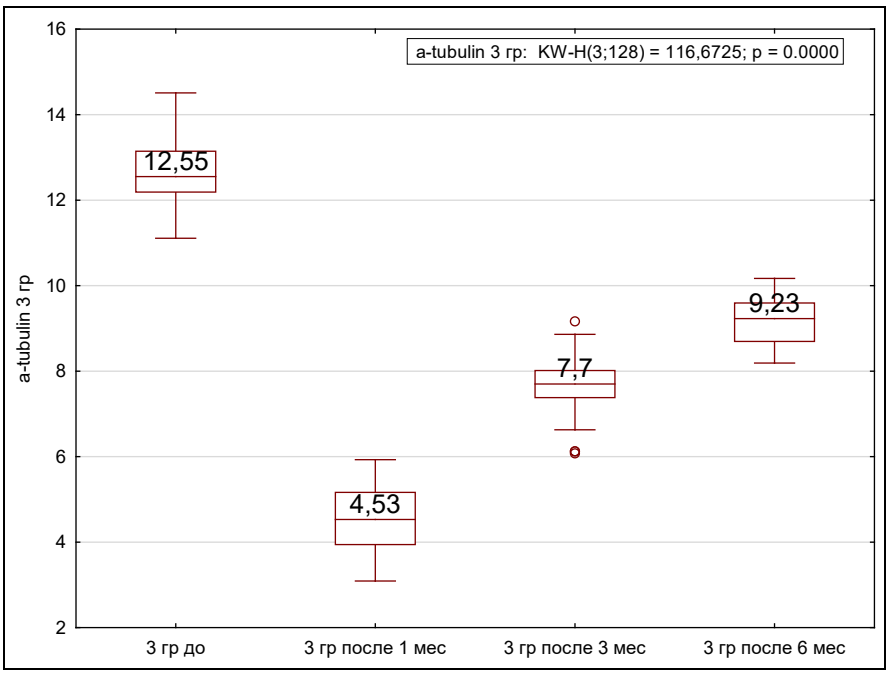
In Group 2, comparative analysis of α-tubulin expression at 1, 3, and 6 months after the implant placement revealed significant differences ($p \leq 0.01$) from the pre-treatment baseline (Figure 15).

In Group 3, α-tubulin expression at 1, 3, and 6 months after the implant placement also revealed significant differences ($p \leq 0.01$) from the pre-treatment baseline (Figure 16).



Left to right: Group 2 (*top right and vertical left);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 15 — Diagram showing relative α-tubulin expression area in Group 2



Left to right: Group 3 (*top right and vertical left);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 16 — Diagram showing relative α -tubulin expression area in Group 3

3.10 β-Tubulin

Table 5 shows the results obtained for the β-tubulin biomarker using Kullback informative measures in the three study groups, with Group 1 showing the highest informative measure.

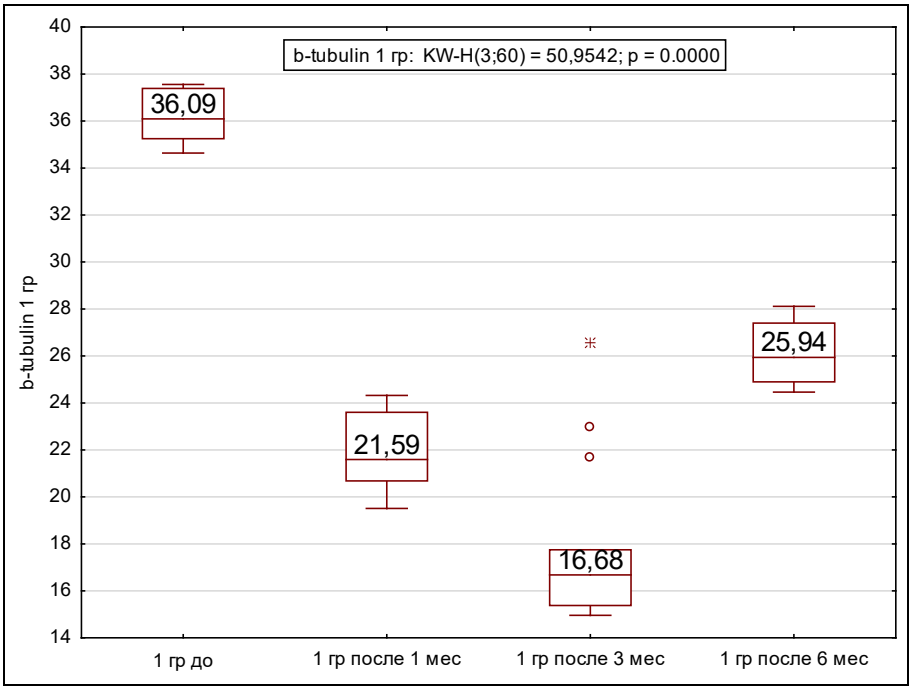
Table 5 — β-Tubulin informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	36.16 ± 1.04	26.18 ± 1.22	7.00
Group 2	18.87 ± 1.43	14.32 ± 0.92	2.73*
Group 3	8.90 ± 0.57	6.54 ± 0.59	1.58*

* p 0.01 between the groups.

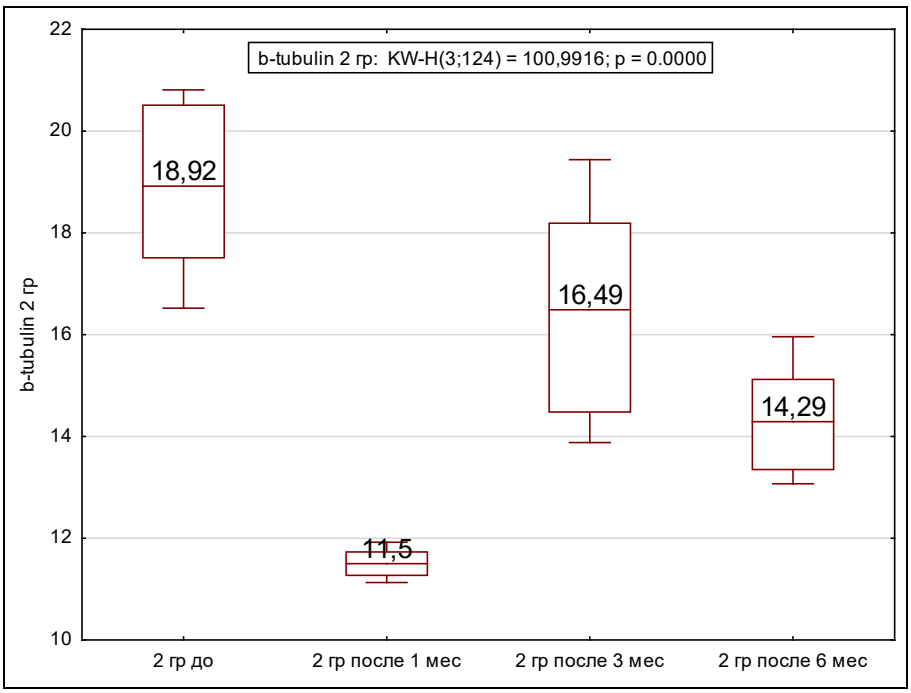
In Group 1, comparative analysis of β-tubulin expression at 1 and 3 months after the implant placement revealed significant differences (p≤0.01) from the pre-treatment baseline (Figure 17). However, Group 1 showed no statistically significant differences (p = 0.09) in β-tubulin expression at 6 months after the implant placement and the pre-treatment baseline. Likewise, Group 1 showed no statistically significant differences (p = 0.7) in β-tubulin expression between 1 month and 3 months after the implant placement.

In Group 2, however, omparative analysis of β-tubulin expression 1, 3, and 6 months after the implant placement showed significant differences (p≤0.01) as different from the pre-treatment baseline (Figure 18).



Left to right: Group 1 *(top right and vertical left);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

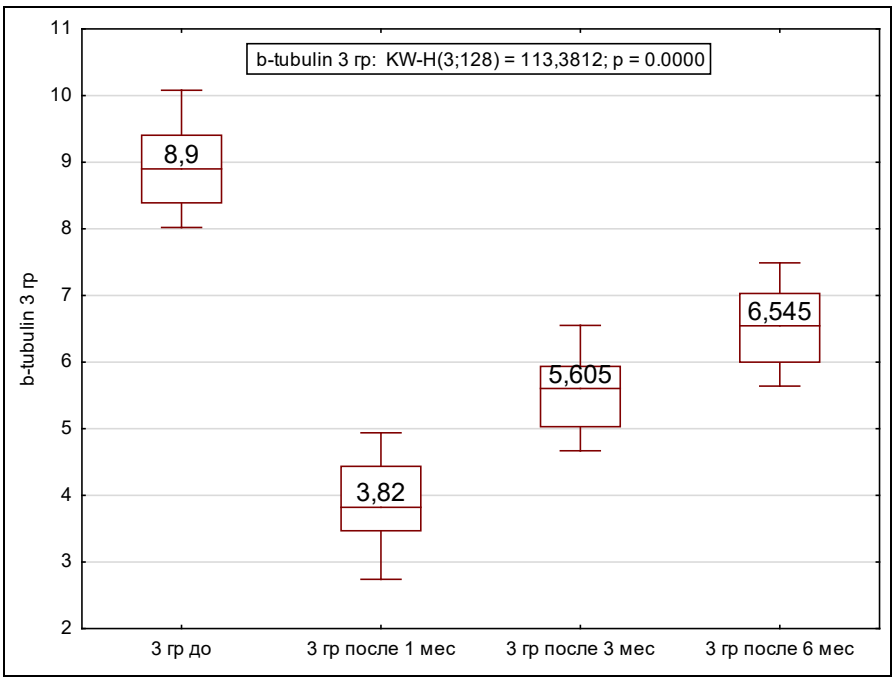
Figure 17 — Diagram showing the relative β--tubulin expression area in Group 1



Left to right: Group 2 (*top right and vertical left);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 18 — Diagram showing the relative β--tubulin expression area in Group 2

In Group 3, β-tubulin expression differed significantly ($p \leq 0.01$) 1, 3, and 6 months after the implant placement as different from the pre-treatment baseline (Figure 19).



Left to right: Group 3 (*top right and vertical left);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 19 — Diagram showing the relative β--tubulin expression area in Group 3

3.11 Cyclooxygenase-1

Table 6 shows the results obtained for the COX-1 biomarker using Kullback informative measures in the three study groups. COX-1 indicators were informative in all patient groups, with Group 3 showing being the most informative.

Table 6 — COX-1 informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	13.65 ± 0.86	17.10 ± 0.70	1.69
Group 2	20.76 ± 1.01	24.35 ± 1.18	1.24*
Group 3	54.77 ± 0.35	62.18 ± 1.51	2.04*
* p 0.01 between the groups.			

In Group 1, statistically significant differences ($p \leq 0.01$) in COX-1 expression were found 1 and 3 months after implant placement as different from the pre-treatment baseline (Figure 20). In Group. 1 no statistically significant differences were found between COX-1 levels at the pre-treatment baseline and 6 months after implant placement ($p = 0.11$). In Group 1, no statistically significant differences were found between COX-1 expression levels 1 and 3 months after implant placement ($p = 0.11$).

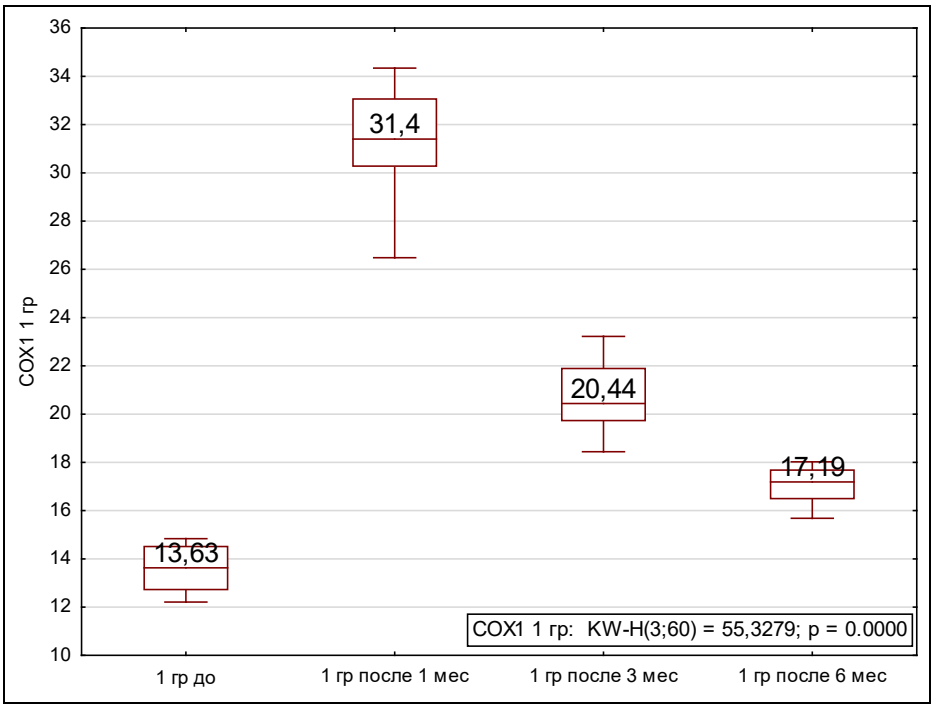
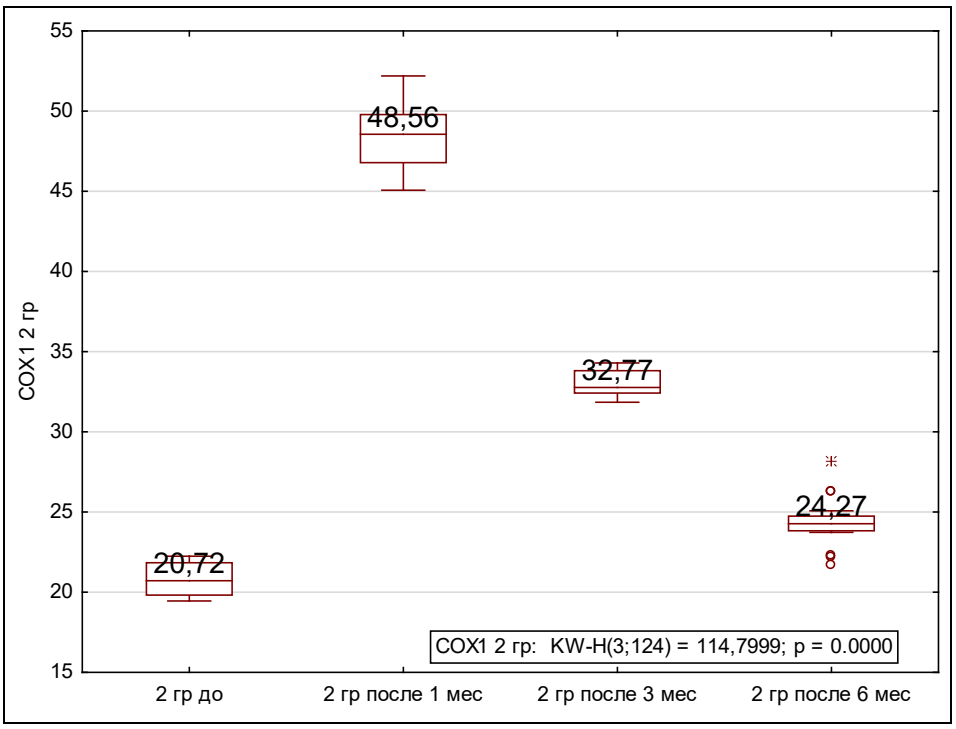


Figure 20 — Diagram showing the relative COX-1 expression area in Group 1

Left to right: Group 1 (*vertical left, bottom right);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

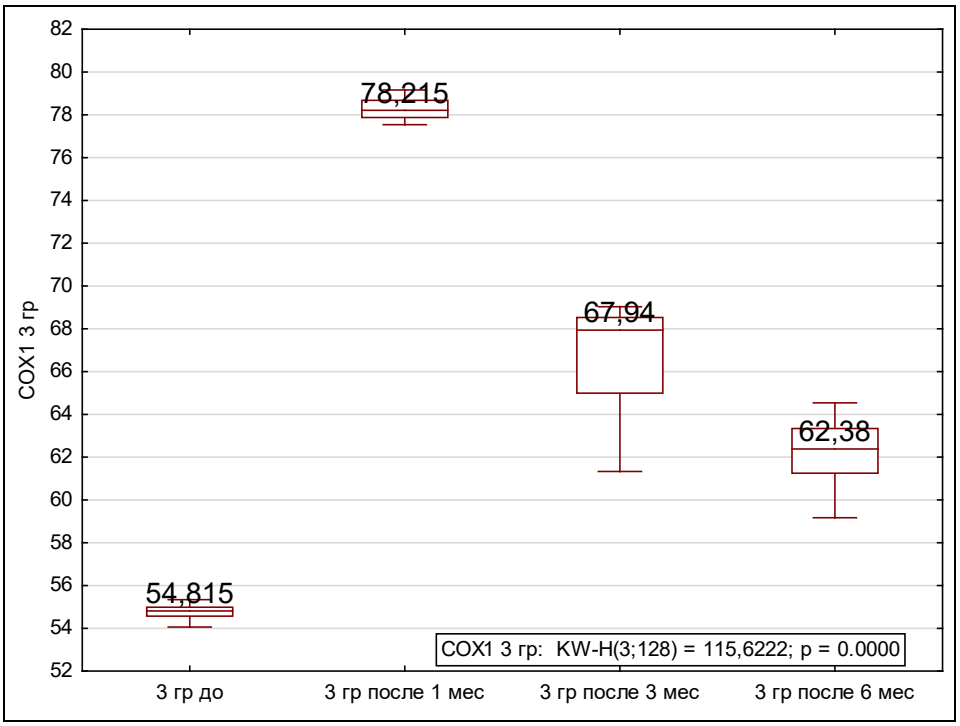
In Group 3, β-tubulin expression differed significantly ($p \leq 0.01$) 1, 3, and 6 months after the implant placement as different from the pre-treatment baseline (Figure 21).

Group 2 revealed statistically significant differences ($p \leq 0.01$) in COX-1 expression 1, 3, and 6 months after implant placement (Figure 22) as different from the pre-treatment baseline.



Left to right: Group 2 (*vertical left, bottom right);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 21 — Diagram showing the relative COX-1 expression area in Group 2



Left to right: Group 3 (*vertical left, bottom right);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 22 — Diagram showing the relative COX-1 expression area in Group 3

3.12 Cyclooxygenase-2

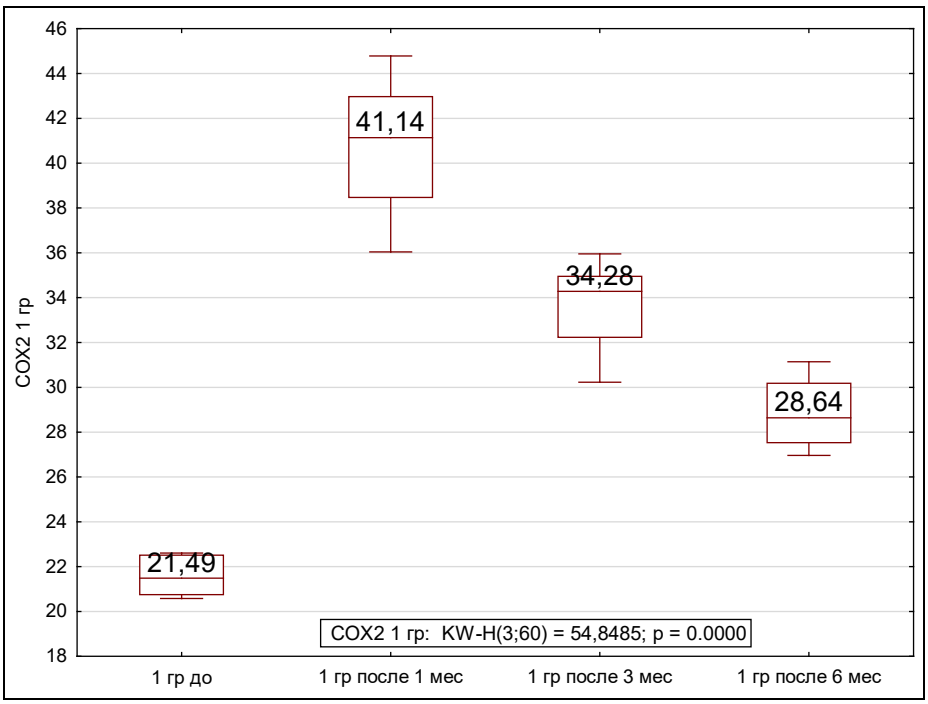
Table 7 shows the results obtained for the COX-2 biomarker using Kullback informative measures in the three study groups. In Group 1, COX-2 measure was the most informative.

Table 7 — COX-2 informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	21.61 ± 0.78	28.95 ± 1.44	4.66
Group 2	30.70 ± 1.98	35.31 ± 1.18	1.40*
Group 3	66.78 ± 3.07	72.77 ± 1.76	1.12*
* p 0.01 between the groups.			

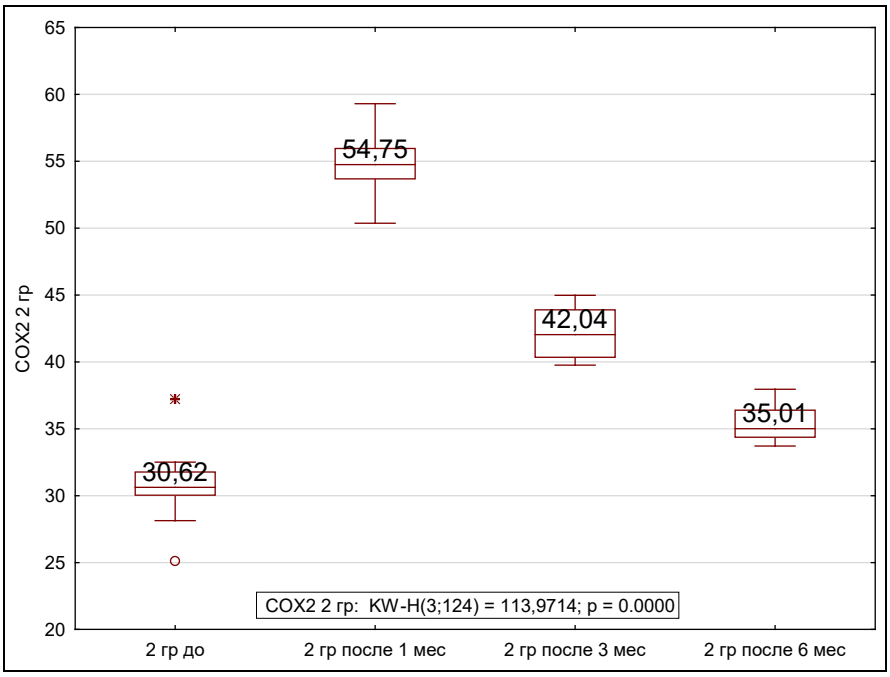
In Group 1, significant differences ($p < 0.01$) were revealed in COX-2 expression 1 and 3 months after implant placement, as different from the pre-treatment baseline(Figure 23). However, no statistically significant differences in COX-2 expression levels were observed after 6 months and the pre-treatment baseline ($p = 0.15$). In Group 1, no statistically significant differences in COX-2 expression 1 and 3 months after implant placement were revealed ($p = 0.10$).

In Group 2, significant differences in COX-2 expression were revealed between 1, 3 and 6 months after implant placement vs. the pre-treatment baseline ($p \leq 0.01$) (Figure 24).



Left to right: Group 1 (*vertical left, bottom right);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

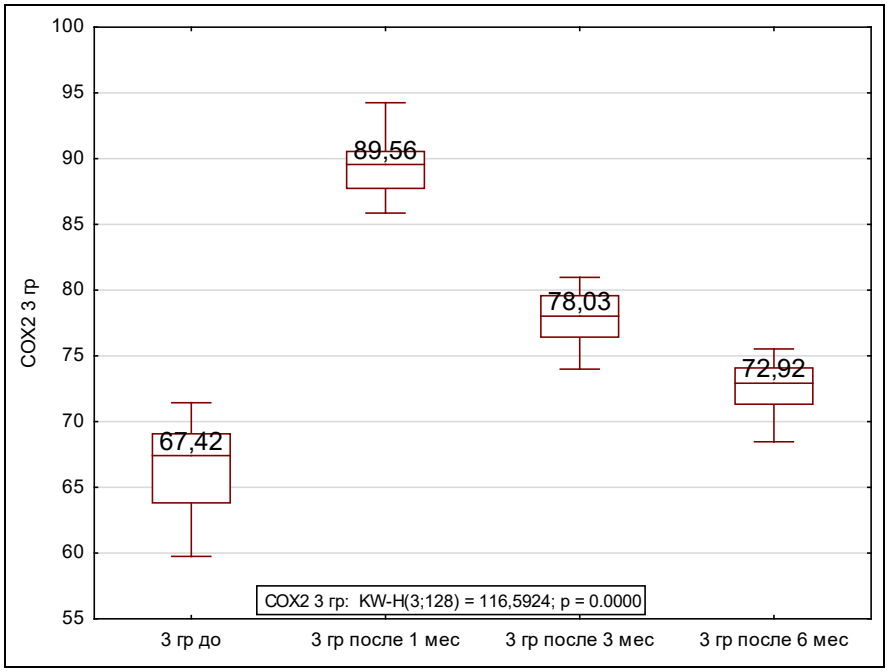
Figure 23 — Diagram showing the relative COX-2 expression area in Group 1



Left to right: Group 2 (*vertical left, bottom right);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 24 — Diagram showing the relative area of COX-2 expression area in Group 2

In Group 3, significant differences in COX-2 expression were revealed between 1, 3 and 6 months after implant placement vs. the pre-treatment baseline ($p \leq 0.01$) (Figure 25).



Left to right: Group 3 (*vertical left, bottom right);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 25 — Diagram sowing the relative COX-2 expression area in Group 3

3.13 Cyclooxygenase-3

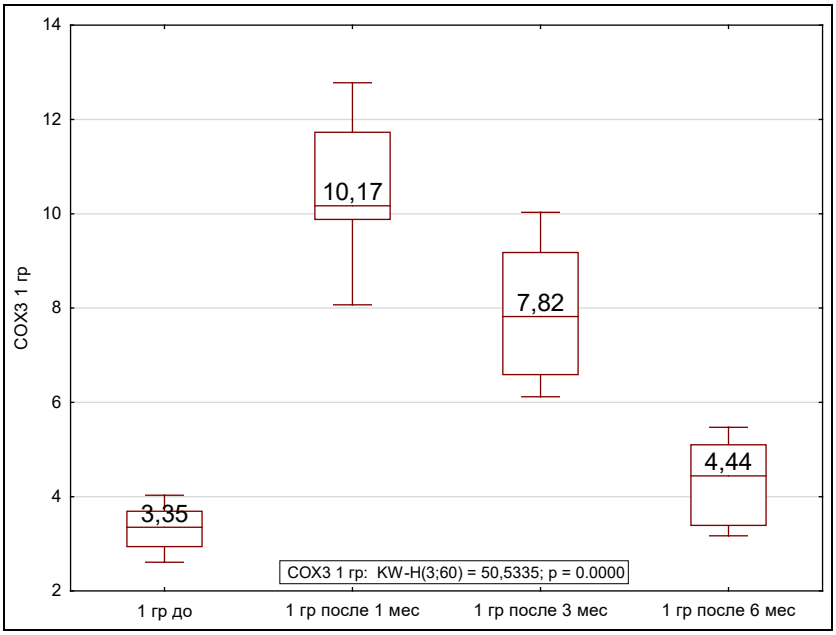
The results of the conducted study on the COX-3 marker by evaluating the informative value of the Kullback in the study groups are presented in Table 8. In Group 2, COX-3 measure was the most informative.

Table 8 — COX-3 informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	3.37 ± 0.44	4.27 ± 0.78	0.46

Group 2	7.21 ± 0.74	8.66 ± 0.93	0.58
Group 3	12.99 ± 0.89	13.76 ± 0.76	0.10

In Group 1, significant differences ($p \leq 0.01$) were revealed in COX-3 expression 1 and 3 months after implant placement vs. the pre-treatment baseline (Figure 26). No statistically significant differences in COX-3 expression was observed between 6 months after the implant placement and the pre-treatment baseline ($p = 0.75$). Group 1 showed showed no statistically significant differences ($p = 0.29$) in COX-3 expression 1 and 3 months after the implant placement.



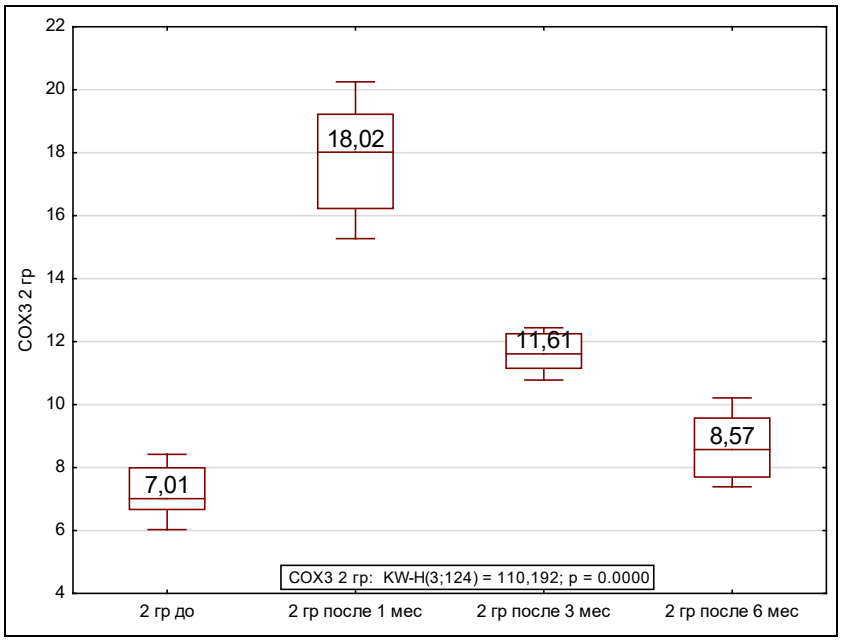
Left to right: Group 1 (*vertical left, bottom middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 26 — Diagram showing the relative COX-3 expression area in Group 1

In Group 2, significant differences were found in COX-3 expression at 1, 3, and 6 months after the implant placement vs. the pre-treatment baseline ($p \leq 0.01$) (Figure 27). However, no statistically significant differences in COX-3 expression levels were observed after 6 months and the pre-treatment baseline ($p = 0.07$).

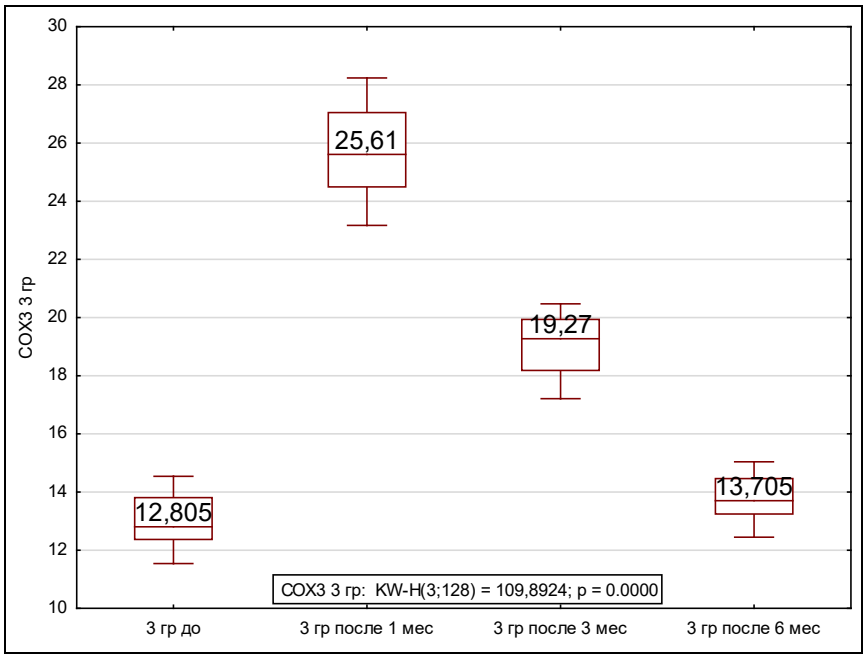
In Group 3, significant differences were found in COX-3 expression at 1, 3, and 6 months after the implant placement vs. the pre-treatment baseline ($p \leq 0.01$) (Figure 28).

However, Group 3 showed no statistically significant differences in COX-3 expression at baseline and 6 months after the implant placement (p = 0.59).



Left to right: Group 2 (*vertical left, bottom middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 27 — Diagram showing the relative COX-3 expression area in Group 2



Left to right: Group 3 (*vertical left, bottom middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 28 — Diagram showing the relative COX-1 expression area in Group 3

3.14 Vascular endothelial growth factor

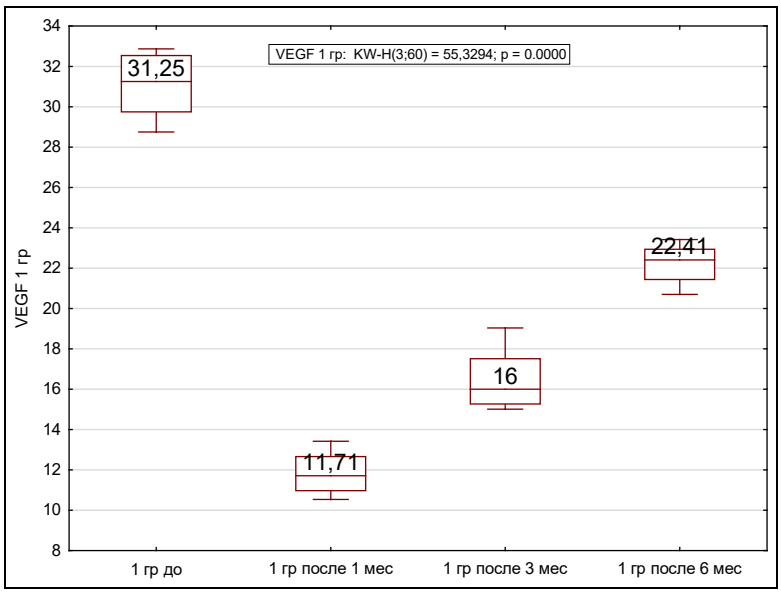
Table 9 shows the results obtained for the VEGF biomarker using Kullback informative measures in the three study groups. In Group 1 and 2 VEGF was the most informative. Meanwhile, VEGF was highly informative in Group 1 as well.

Table 9 — VEGF informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	31.08 ± 1.37	22.19 ± 0.88	6.51
Group 2	18.87 ± 1.06	15.54 ± 0.69	1.40*
Group 3	10.42 ± 1.25	9.09 ± 0.66	0.39
* p 0.01 between the groups.			

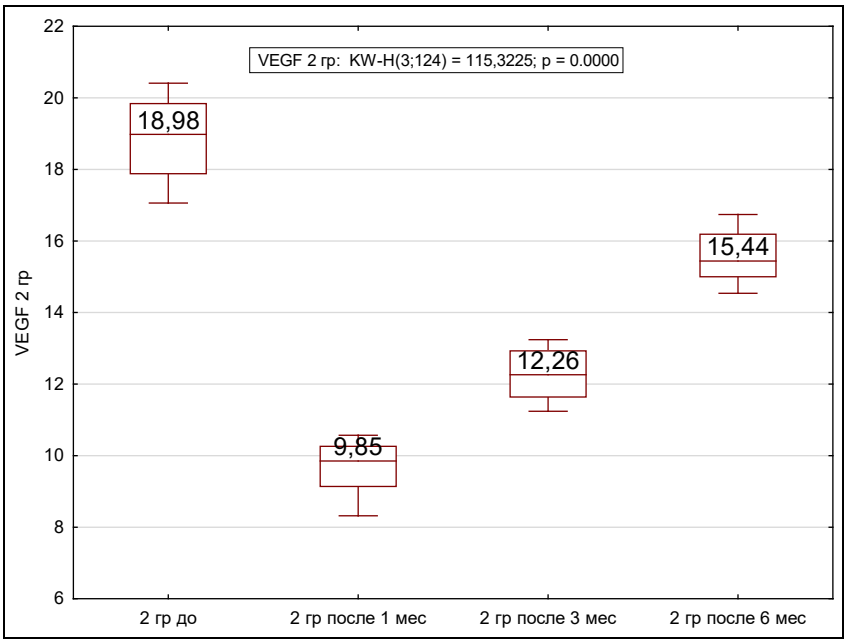
In Group 1, significant differences ($p \leq 0.01$) in VEGF expression were revealed 1 and 3 months after the implant placement vs. the pre-treatment baseline (Figure 29). Group 1 showed no statistically significant differences in VEGF expression at baseline and 6 months after the implant placement ($p = 0.11$). Likewise, Group 1 showed no statistically significant differences in VEGF expression 3 months after the implant placement vs. 1 and 6 months of follow-up ($p = 0.11$).

Group 2 showed significant differences ($p \leq 0.01$) in VEGF expression 1, 3, and 6 months after the implant placement vs. the pre-treatment baseline (Figure 30).



Left to right: Group 1 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

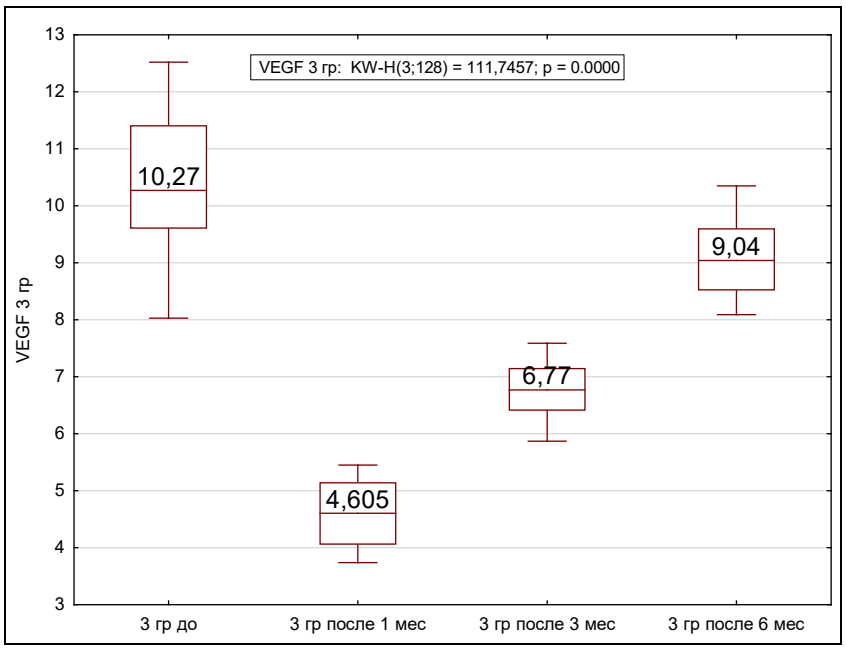
Figure 29 — Diagram showing the relative VEGF expression area in Group 1



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 30 — Diagram showing the relative VEGF expression area in Group 2

Group 3 revealed significant differences ($p \leq 0.01$) in VEGF expression 1 and 3 months after the implant placement vs. the pre-treatment baseline (Figure 31). In Group 3, VEGF expression at baseline and 6 months after the implant placement revealed no statistically significant differences ($p = 0.19$).



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 31 — Diagram showing the relative VEGF expression area in Group 3

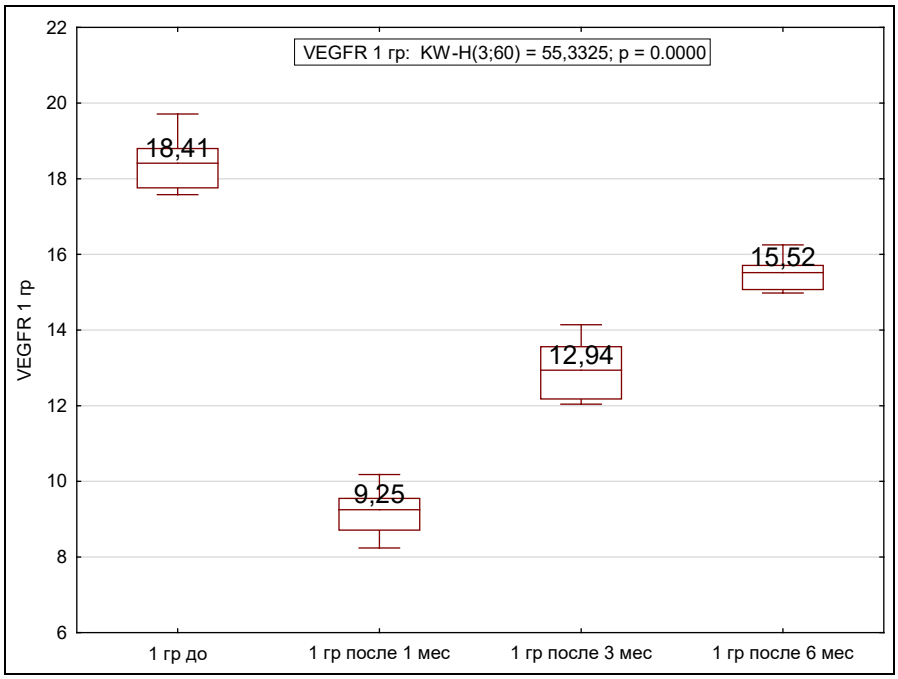
3.15 Vascular Endothelial Growth Factor Receptor

Table 10 shows the results obtained for the VEGFR biomarker using Kullback informative measures in the three study groups. VEGFR expression was informative in all the study groups.

Table 10 — VEGFR informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	18.35 ± 0.67	15.51 ± 0.40	1.04
Group 2	11.05 ± 0.55	8.67 ± 0.40	1.26*
Group 3	4.59 ± 0.25	3.06 ± 0.20	1.35*
* p 0.01 between the groups.			

Group 1 showed significant differences (p ≤0.01) in VEGFR expression 1 and 3 months after the implant placement vs. baseline (Figure 32). No statistically significant differences in VEGFR levels were revealed between the pre-treatment baseline and 6 months after the implant placement (p = 0.11). Likewise, no statistically significant differences in VEGFR levels were revealed between 1 and 6 months after the implant placement vs. 3 months after the implant placement (p = 0.11).

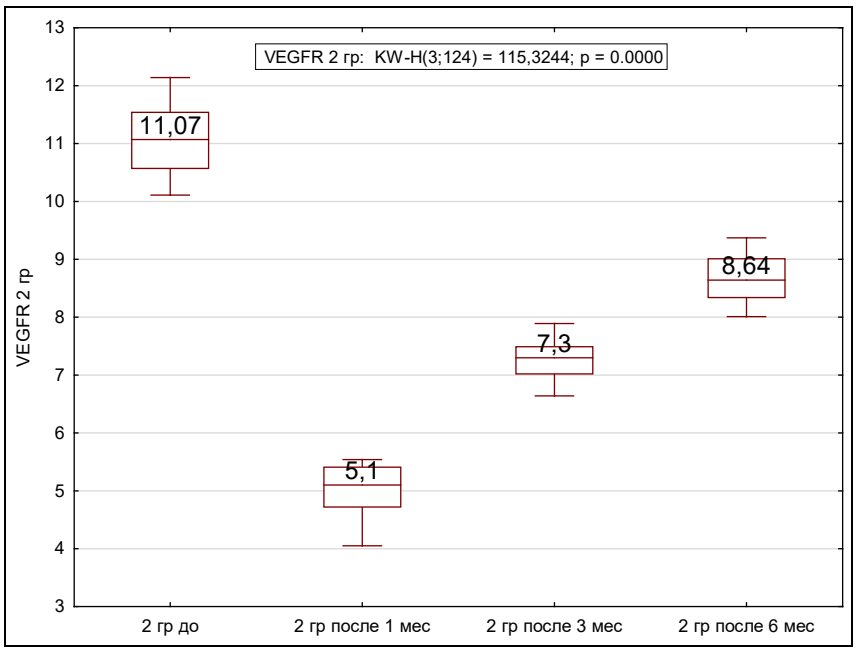


Left to right: Group 1 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 32 — Diagram showing the relative VEGFR expression area in Group 1

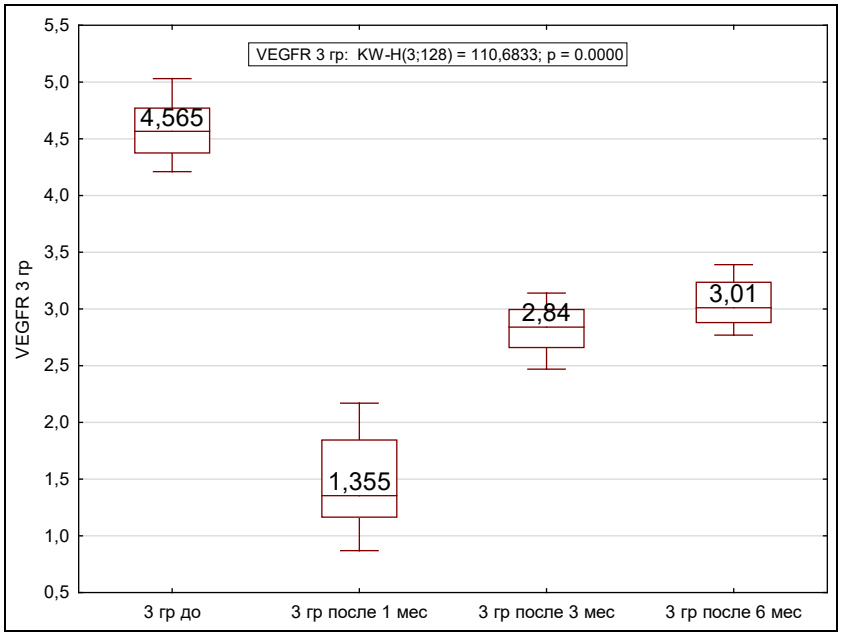
Group 2 showed significant differences (p≤0.01) in VEGF expression at 1, 3, and 6 months after the implant placement vs. the pre-treatment baseline (Figure 33).

Likewise, Group 3 showed significant differences (p≤0.01) in VEGF expression at 1, 3, and 6 months after the implant placement vs. the pre-treatment baseline (Figure 34). No statistically significant differences in VEGFR levels were revealed at 3 and 6 months after the implant placement (p = 0.37).



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 33 — Diagram showing the relative VEGFG expression area in Group 2



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 34 — Diagram showing the relative VEGFR expression area in Group 3

3.16 Melatonin

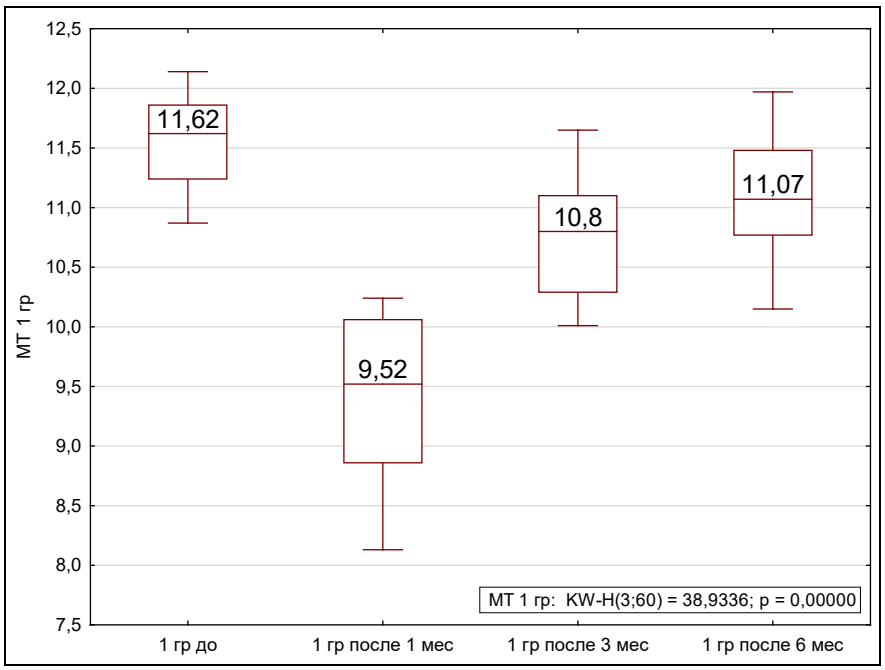
The MT expression evaluated based on the Kullback informative measure is presented in Table 11. Informative MT levels were identified in Groups 2 and 3. In Group 1, the MT index did not demonstrate informative value.

Table 11 — MT expression Kullback informative measure

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	11.54 ± 0.39	11.12 ± 0.49	0.03
Group 2	7.41 ± 0.72	4.90 ± 0.48	2.26*
Group 3	3.00 ± 0.08	2.02 ± 0.22	0.83*
* p 0.01 between the groups.			

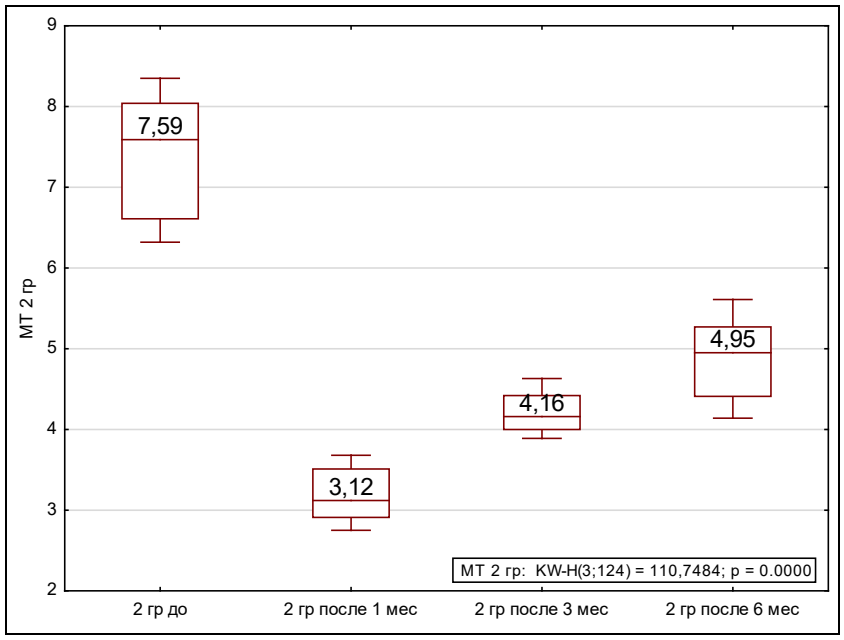
Group 1 showed significant differences ($p \leq 0.01$) in MT expression 1 month after the implant placement vs. the pre-treatment baseline and 3 months after the implant placement (Figure 35). No statistically significant differences in MT expression at the the pre-treatment baseline and 6 months after the implant placement ($p = 0.47$) were observed, as well as between 3 and 6 months after the implant placement ($p = 1.00$).

Group 1 showed significant differences ($p \leq 0.01$) in MT expression among all three timepoints (1, 3, and 6 months) after the implant placement, revealing significant differences ($p \leq 0.01$) against the pre-treatment baseline (Figure 36). No statistically significant differences in MT expression between 3 and 6 months after the implant placement were found ($p = 0.05$).



Left to right: Group 1 (*vertical left, bottom right);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

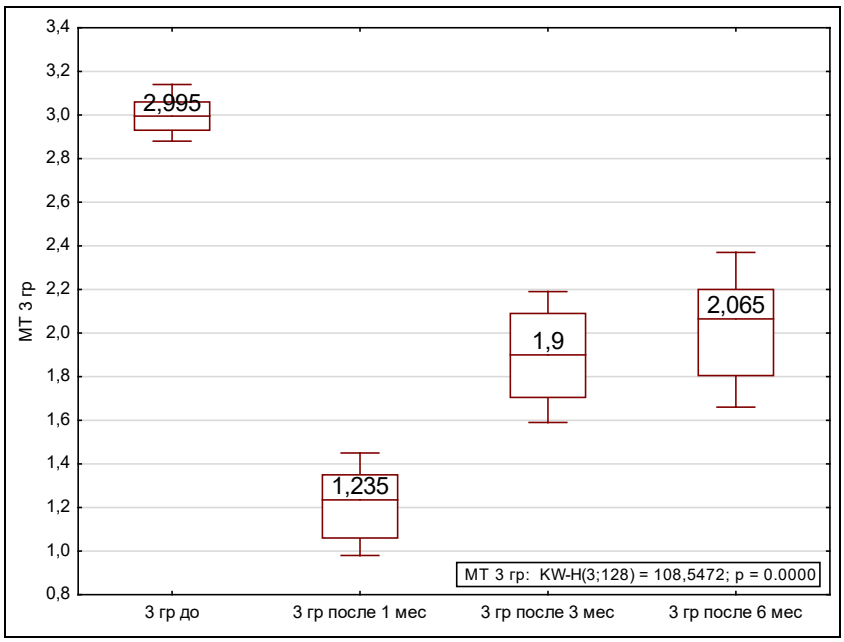
Figure 35 — Diagram showing the relative MT expression area in Group 1



Left to right: Group 2 (*vertical left, bottom right);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 36 — Diagram showing the relative MT expression area in Group 2

Group 3 showed significant differences ($p \leq 0.01$) in MT expression 1, 3, and 6 months after implant placement vs. the pre-treatment baseline (Figure 37). No statistically significant differences in MT expression between 3 and 6 months after the implant placement were found ($p = 1.00$).



Left to right: Group 3 (*vertical left, bottom right);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 37 — Diagram showing the relative MT expression area in Group 3

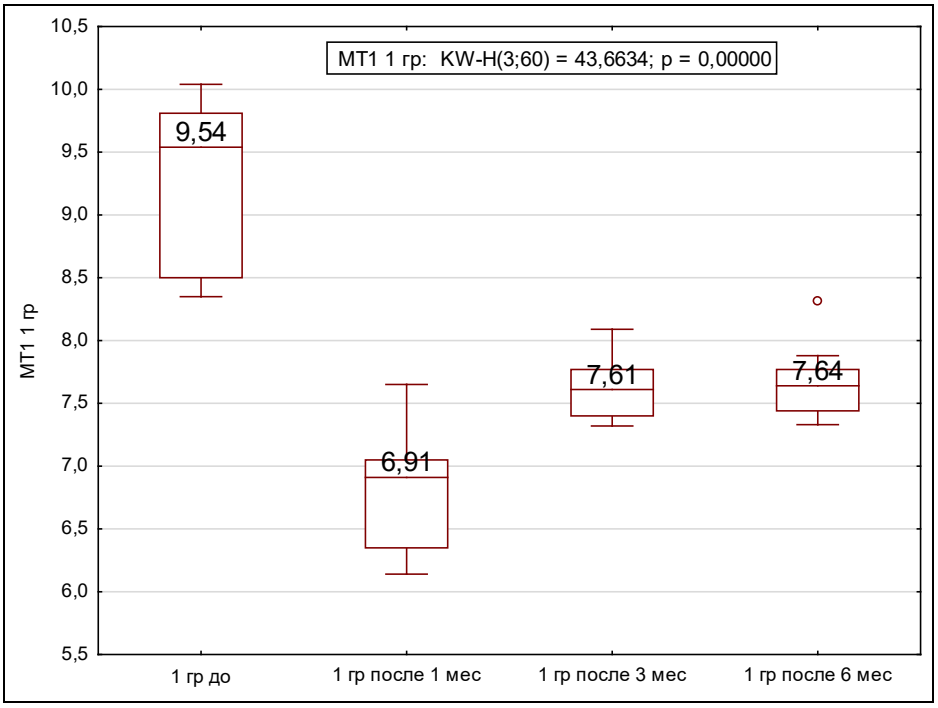
3.17 Melatonin receptor 1

The MT1 expression evaluated based on the Kullback informative measure is presented in Table 12. Informative MT1 levels were identified in Groups 1 and 2, although without high informative value.

Table 12 —MT1 informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	9.25 ± 0.62	7.64 ± 0.25	0.67*
Group 2	4.59 ± 0.46	3.48 ± 0.31	0.68*
Group 3	1.81 ± 0.16	1.55 ± 0.19	0.09*
* p 0.01 between the groups.			

In Group 1, when comparing the level of MT1 expression at all three reference points with the level of MT1 expression before implant placement, statistically significant differences (p <0.01) were revealed (Figure 38). There were no statistically significant differences (p = 1.00) between MT1 expression levels 3 and 6 months after implant placement.

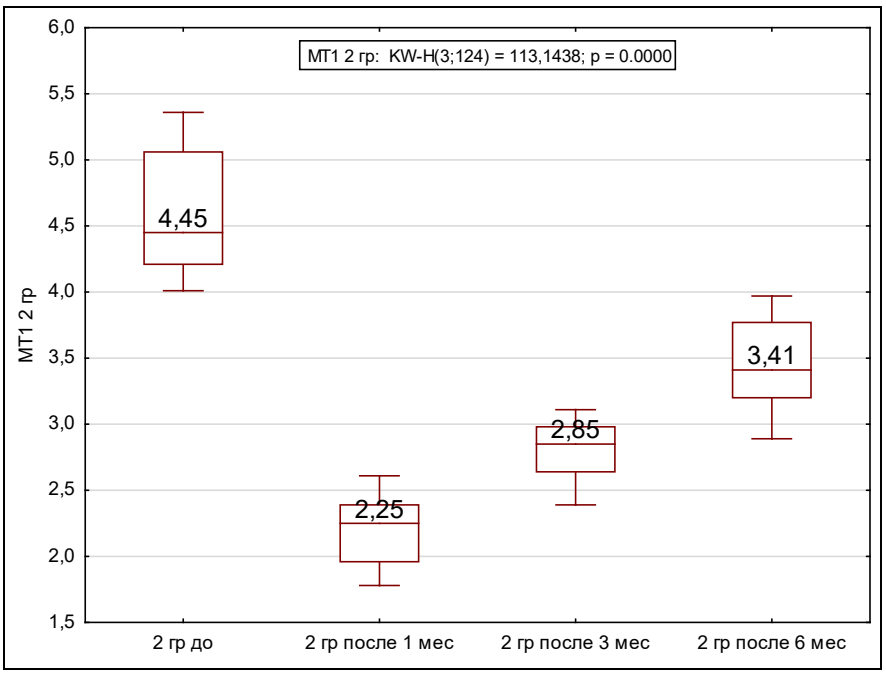


Left to right: Group 3 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 38 — Diagram showing the relative MT1 expression area in Group 1

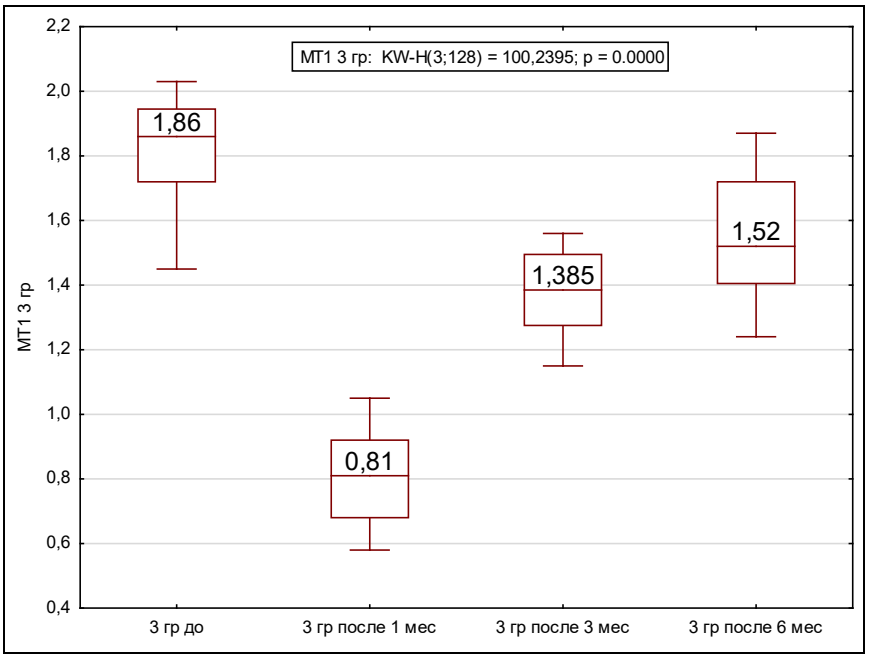
Significant differences (p <0.01) were found when comparing MT1 values at all three reference points after implant placement with the level of this marker before implant placement in patients of the second group (Figure 39).

Significant differences (p<0.01) were found when comparing the level of MT1 expression at all three reference points after implant placement with the level of expression of this marker before implant placement in patients of the third group (Figure 40). There were no statistically significant differences (p = 0.24) in the level of MT1 expression 3 and 6 months after implant placement in this group.



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 39 — Diagram showing the relative MT1 expression area in Group 2



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 40 — Diagram showing the relative MT1 expression area in Group 3

3.18 Melatonin receptor 2

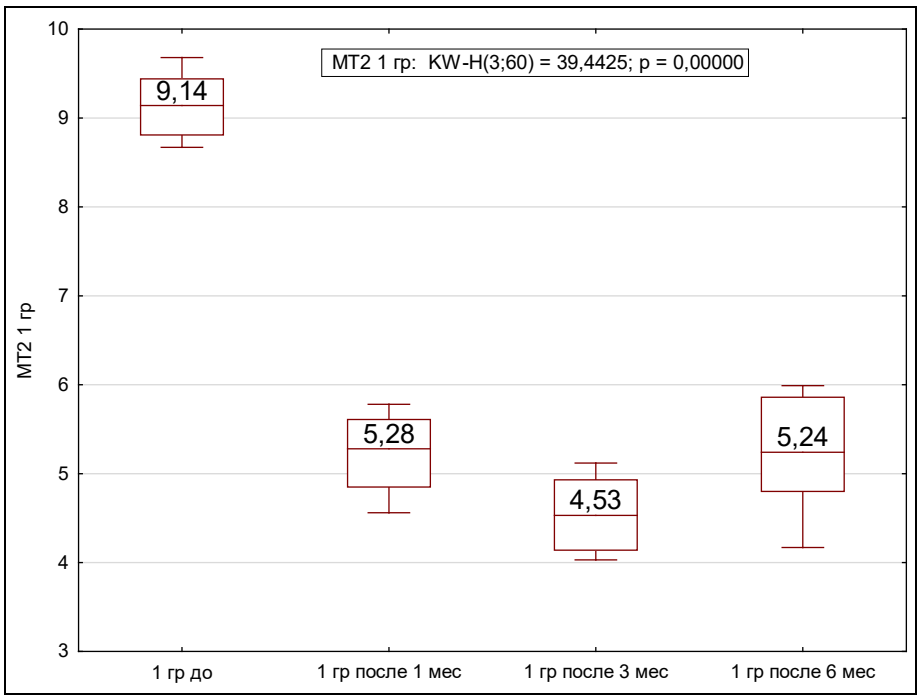
The results of the conducted research on the MT2 marker by evaluating the informative value of the Kullback for the studied groups are presented in Table 13. Informative MT2 levels were detected in all groups, but high information content was demonstrated only in Group 1.

Table 13 — MT2 informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	9.12 ± 0.32	5.18 ± 0.60	4.85*
Group 2	5.12 ± 0.43	3.87 ± 0.13	0.77*
Group 3	2.01 ± 0.17	1.11 ± 0.15	1.17*
* p 0.01 between the groups.			

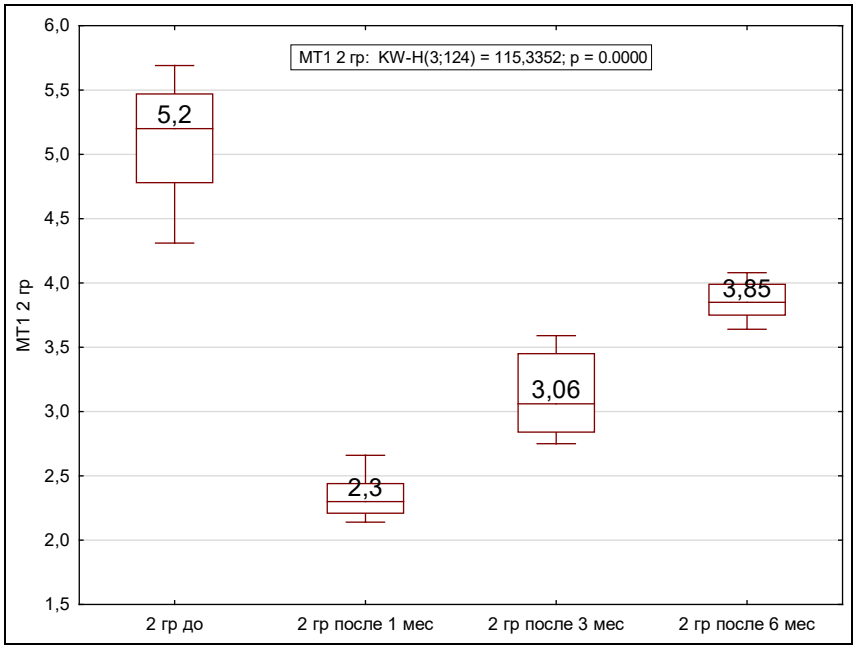
In Group 1, significant differences ($p < 0.01$) were revealed when comparing the level of MT2 expression 1, 3, and 6 months after implant placement with the level of this marker before implant placement (Figure 41). There were no statistically significant differences in the level of MT2 expression in Group 1 between the other periods ($p \geq 0.05$).

Statistically significant differences ($p < 0.01$) were revealed when comparing the level of MT2 expression at all three reference points after implant placement with the level of this marker before implant placement in patients of the second group (Figure 42).



Left to right: Group 1 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

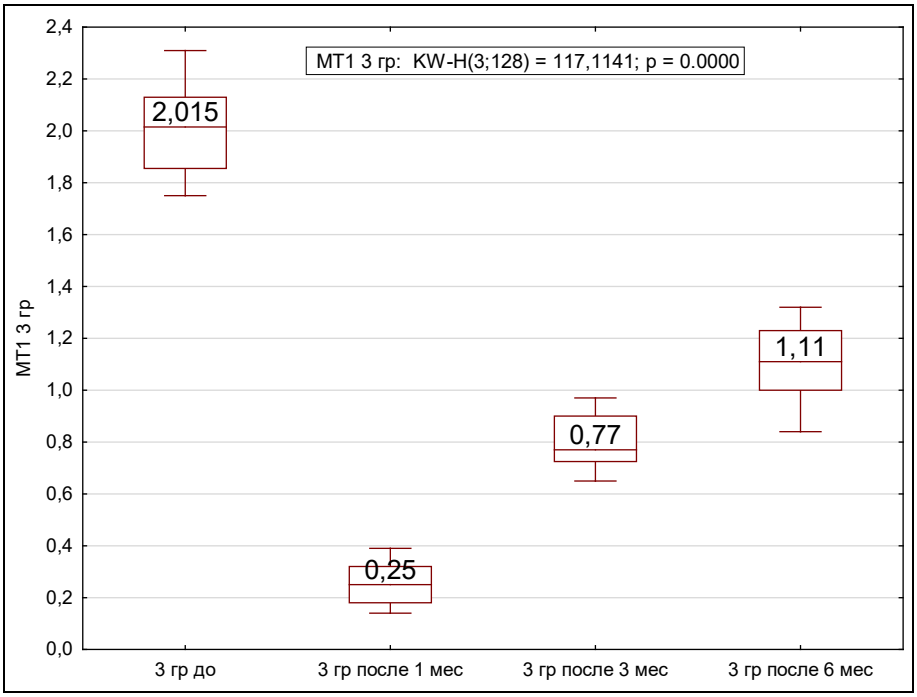
Figure 41 — Diagram showing the relative MT2 expression area in Group 1



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 42 — Diagram showing the relative MT2 expression area in Group 2

Statistically significant differences (p <0.01) were found when comparing the level of MT2 expression 1, 3, and 6 months after implant placement with the level of expression of this marker before implant placement (Figure 43).



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 43 — Diagram showing the relative MT2 expression area in Group 3

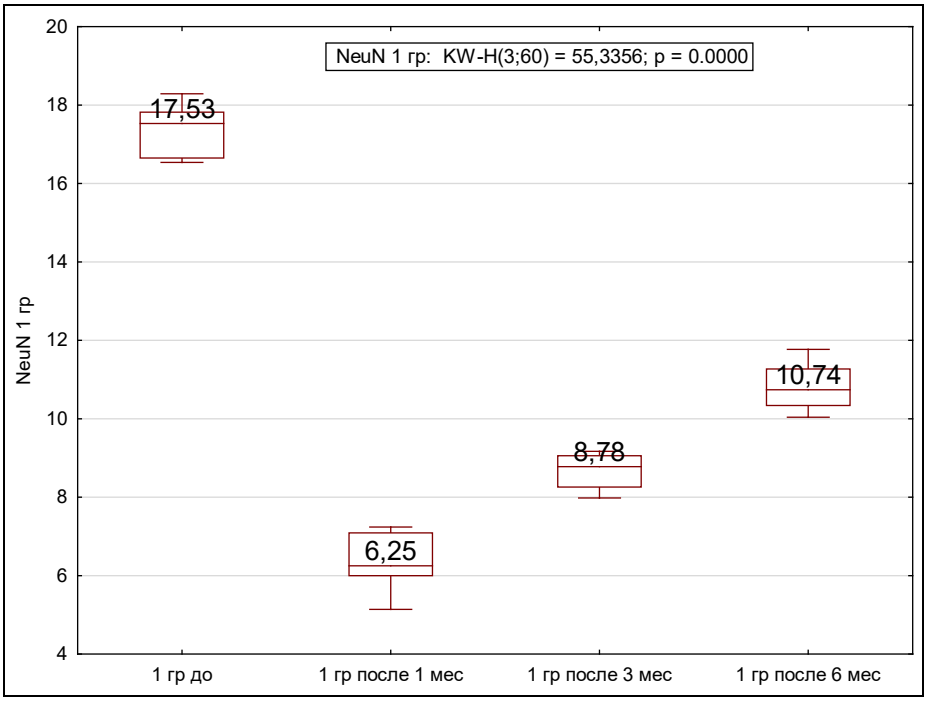
3.19 Neuron specific nuclear protein

The results of the conducted study on the NeuN marker by evaluating the informative value of the Kullback in the study groups are presented in Table 14. The NeuN marker demonstrated high informative value for the first and especially for the second group.

Table 14 —NeuN informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	17.35 ± 0.61	10.81 ± 0.55	6.73
Group 2	13.60 ± 0.71	6.10 ± 0.38	13.05*
Group 3	6.84 ± 0.43	6.11 ± 0.56	0.18
* p 0.01 between the groups.			

In Group 1, significant differences (p <0.01) were revealed when comparing the level of NeuN expression in patients before implant placement and the level of NeuN expression 1 and 3 months after implant placement (Figure 44). There were no statistical differences in Group 1 between the level of NeuN expression before implant placement and the level of expression of this biomarker 6 months after implant placement (p = 0.11).

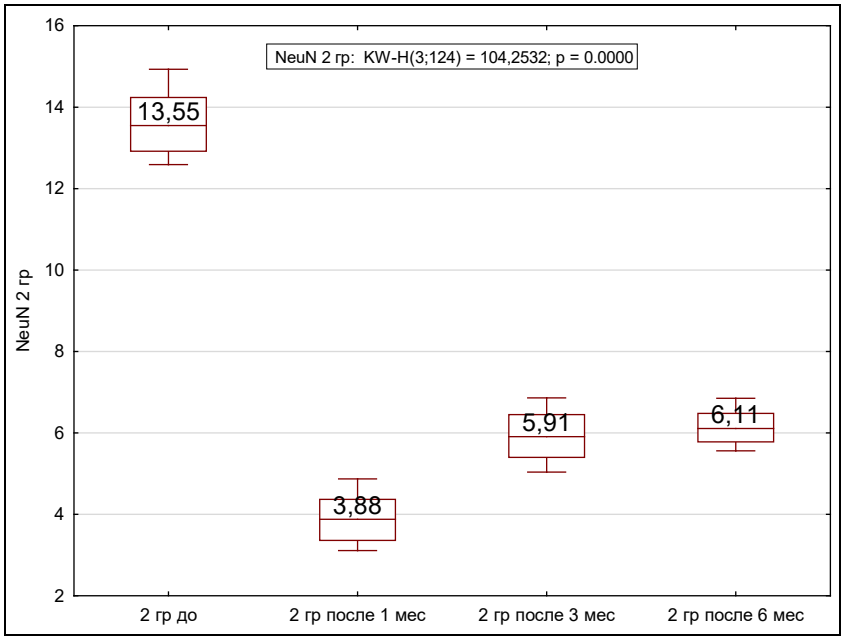


Left to right: Group 1 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 44 — Diagram showing the relative NeuN expression area in Group 1

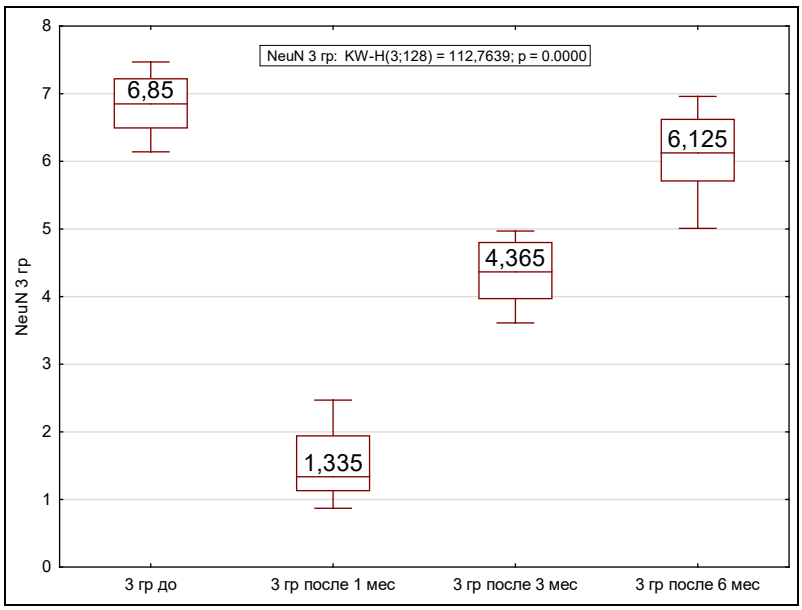
In the second group, significant differences (p <0.01) were found in the level of NeuN expression 1, 3, and 6 months after implant placement and the level of NeuN expression before implant placement (Figure 45). There were no statistical differences in the second group in terms of NeuN expression level 3 months after implant placement and 6 months after implant placement (p = 1.00).

In the third group, significant differences (p <0.01) were found in the level of NeuN expression 1 and 3 months after implant placement and the level of NeuN expression before implant placement (Figure 46). There were no statistical differences between the levels of NeuN expression before implant placement and 6 months after implant placement (p = 0.11).



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 45 — Diagram showing the relative NeuN expression area in Group 2



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 46 — Diagram showing the relative NeuN expression area in Group 3

3.20 Nitric oxide

The results of the conducted study on the NO marker by evaluating the informative value of the Kullback in the study groups are presented in Table 15. The NO marker demonstrated high informativeness for all the studied groups.

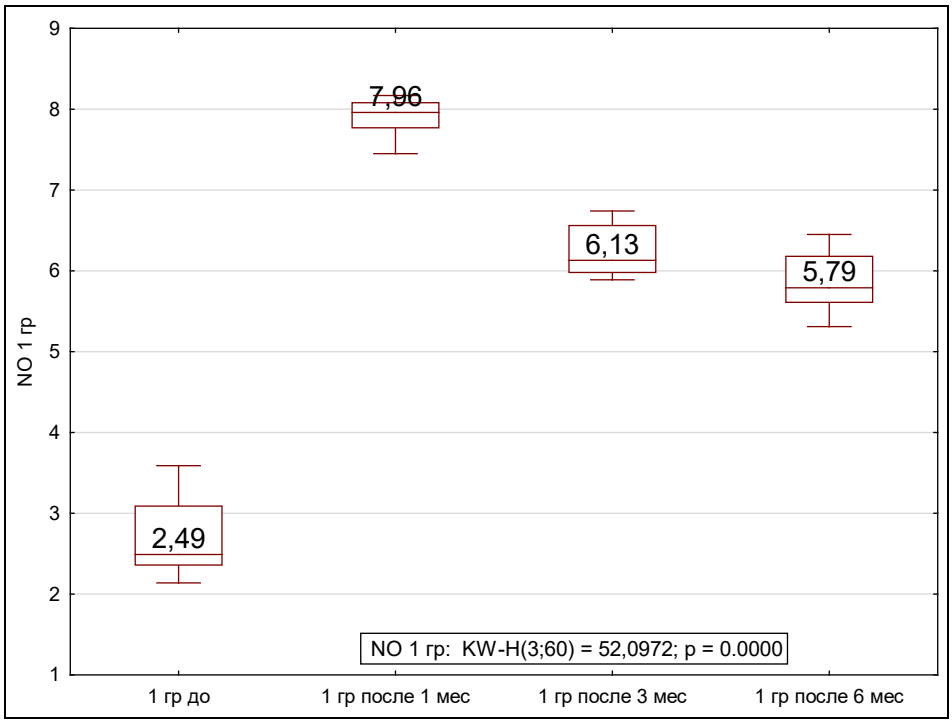
Table 15 —NO informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	2.70 ± 0.48	5.83 ± 0.32	5.25*
Group 2	6.05 ± 0.49	9.62 ± 0.63	3.59*
Group 3	8.20 ± 0.47	14.79 ± 0.52	8.46*
* p 0.01 between the groups.			

In Group 1, significant differences (p <0.01) were revealed when comparing the NO values before implant placement compared with the NeuN expression levels after 1, 3 and 6 months (Figure 47). A comparison of expression levels 3 months after implant placement and 6 months after implant placement revealed no statistically dependent differences (p = 0.78).

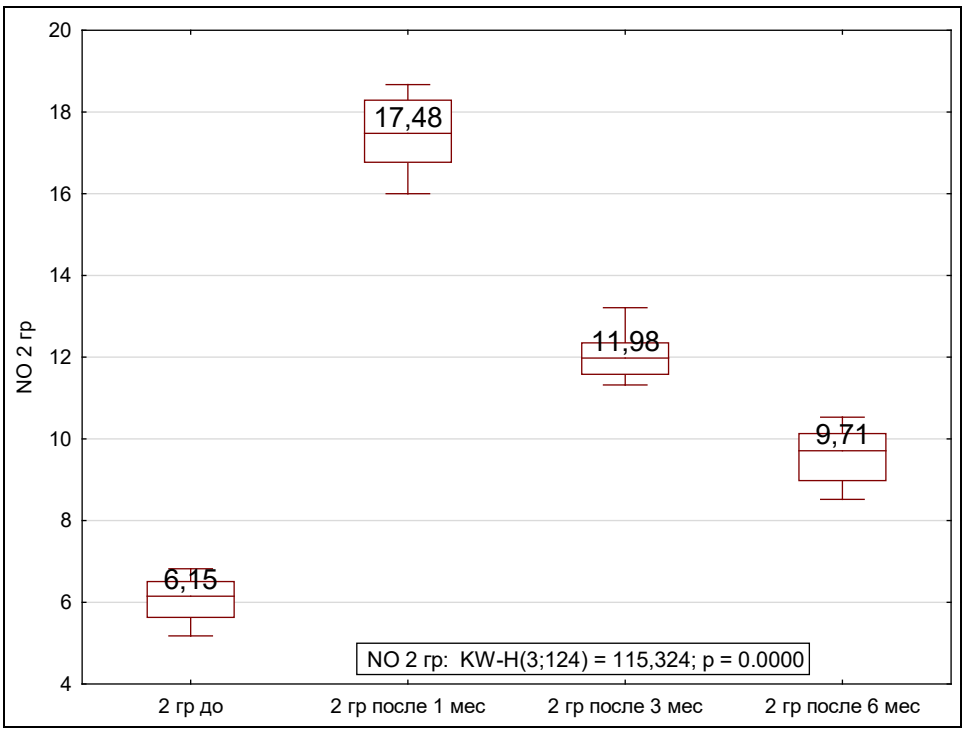
In the second group, significant differences (p <0.01) were found when comparing the level of NO expression 1, 3, and 6 months after implant placement with the level of NO expression before implant placement (Figure 48).

In the third group, significant differences (p <0.01) in the level of NO expression were detected 1, 3, and 6 months after implant placement and the level of NO expression before implant placement (Figure 49)).



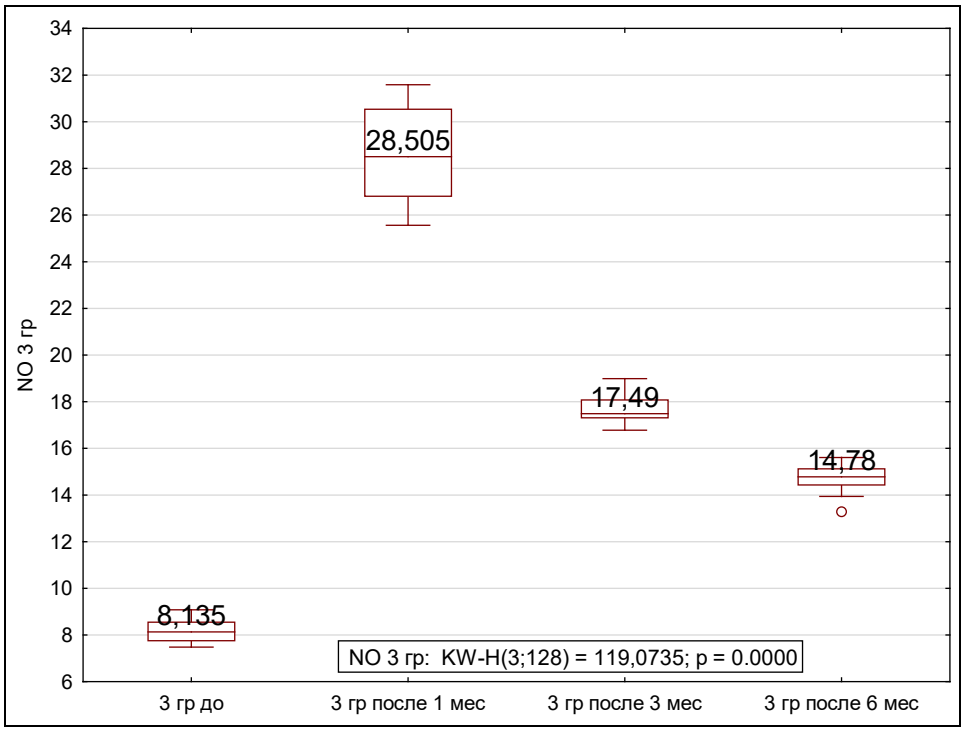
Left to right: Group 1 (*vertical left, bottom middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 47 — Diagram showing the relative NO expression area in Group 1



Left to right: Group 2 (*vertical left, bottom middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 48 — Diagram showing the relative NO expression area in Group 2



Left to right: Group 3 (*vertical left, bottom middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 49 — Diagram showing the relative NO expression area in Group 3

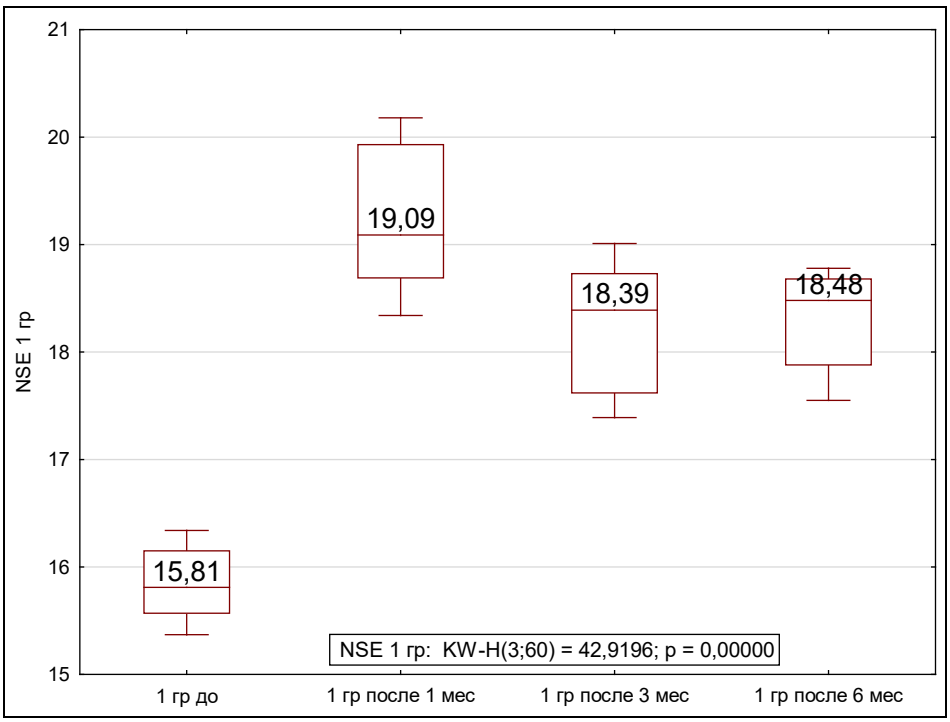
3.21 Neuron-specific enolase

The results of evaluating the informativeness of the NSE level using Kullback's informativeness measures are presented in Table 16. The NSE marker demonstrated high information content only for the third group, however, NSE is also informative for the first and second groups.

Table 16 — NSE informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	15.83 ± 0.31	18.29 ± 0.44	0.77*
Group 2	18.83 ± 0.83	24.16 ± 0.84	2.89*
Group 3	18.72 ± 0.50	24.44 ± 0.16	3.30*
* p 0.01 between the groups.			

In Group 1, significant differences ($p < 0.01$) were revealed when comparing the NSE values in the group before implant placement compared with this indicator 1, 3 and 6 months after implant placement (Figure 50). There were no statistically dependent differences between NSE expression levels in Group 1 1, 3, and 6 months after implant placement ($p \geq 0.05$).

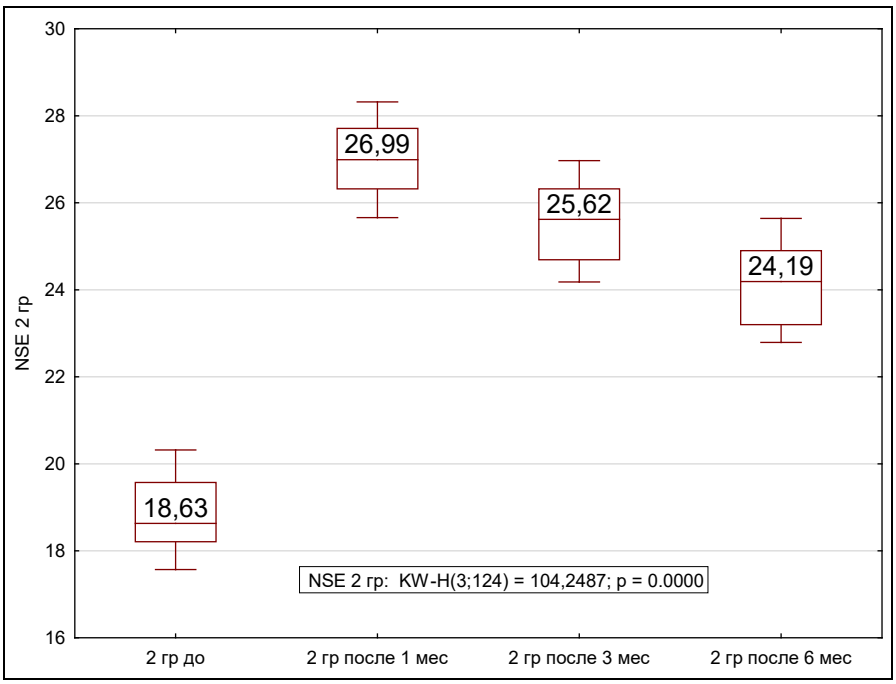


Left to right: Group 1 (*vertical left, bottom middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 50 — Diagram showing the relative NSE expression area in Group 1

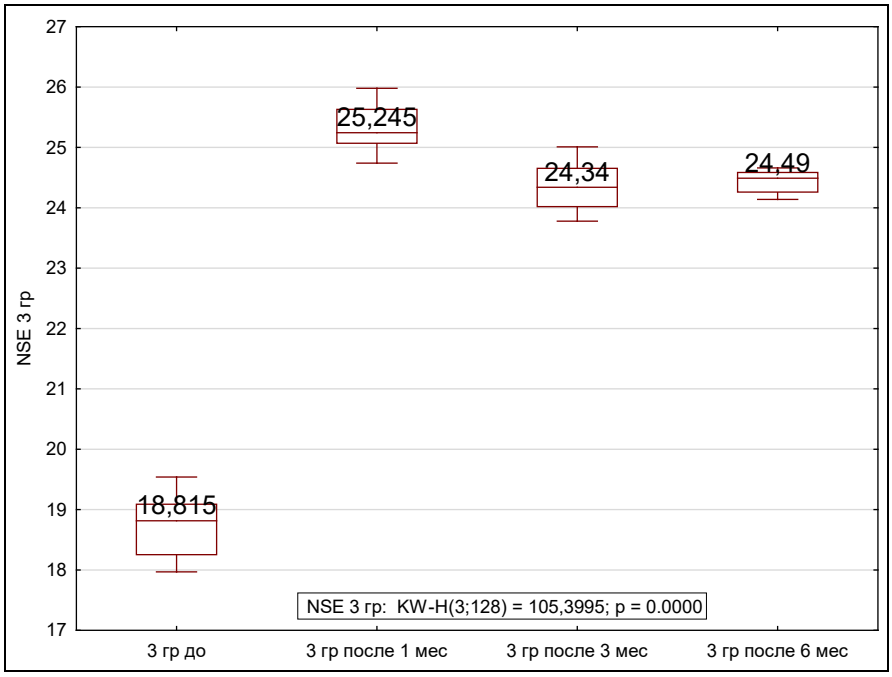
In the second group, significant differences ($p < 0.01$) were revealed when comparing the level of NSE expression at 1 month, 3 months, and 6 months after implant placement (Figure 51).

In the third group, significant differences were found when comparing the NSE values in all patients 1, 3, and 6 months after implant placement ($p < 0.01$) (Figure 52). In patients of the third group, there were no statistical differences between NSE expression levels 3 and 6 months after implant placement ($p = 1.00$).



Left to right: Group 2 (*vertical left, bottom middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 51 — Diagram showing the relative NSE expression area in Group 2



Left to right: Group 3 (*vertical left, bottom middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 52 — Diagram showing the relative NSE expression area in Group 3

3.22 Vascular cell adhesion molecule-1

The results of the conducted study on the VCAM1 marker by evaluating the informative value of the Kullback in the study groups are presented in Table 17. The VCAM1 marker demonstrated high information content only for the third group, however, VCAM1 is also informative for the first and second groups.

Table 17 —VCAM1 informative value assessed using Kullback measures

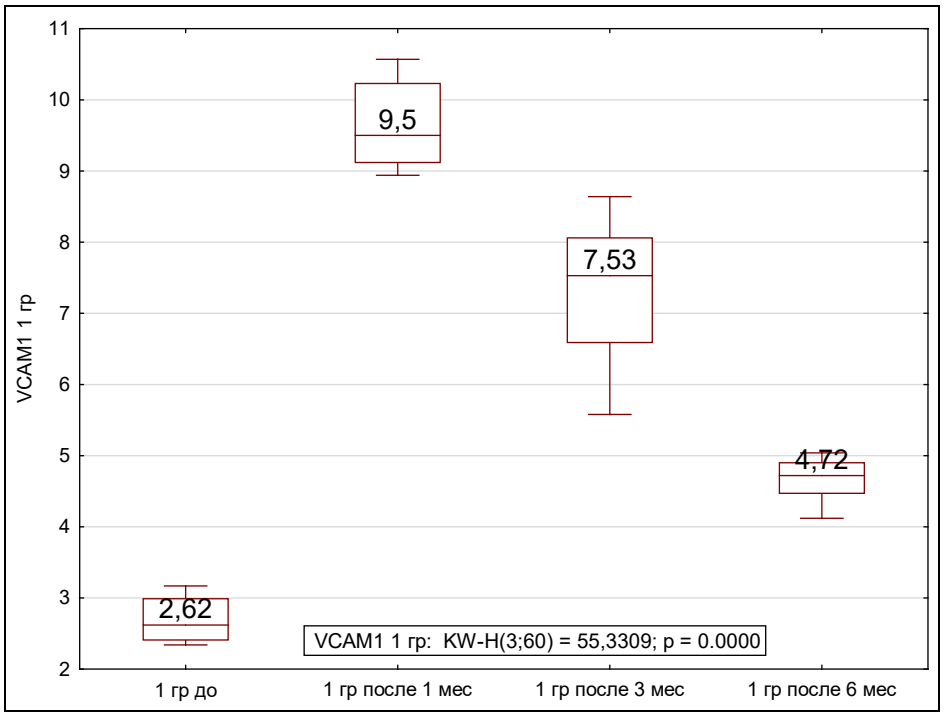
Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	2.67 ± 0.27	4.68 ± 0.27	2.45
Group 2	6.71 ± 0.62	8.63 ± 0.86	1.05*
Group 3	8.92 ± 1.27	14.11 ± 0.54	5.18*
* p 0.01 between the groups.			

In Group 1, significant differences ($p < 0.01$) were found when comparing VCAM1 values before implant placement and 1 and 3 months after implant placement, but the expression levels did not differ between each other 1 and 3 months after implant placement ($p = 0.11$) (Figure 53). There were no statistical differences between the expression level of VCAM1 before implant placement and this indicator 6 months after implant placement ($p = 0.11$).

In the second group, significant differences ($p < 0.01$) were found when comparing VCAM1 expression levels before implant placement and after 1, 3, and 6 months (Figure 54).

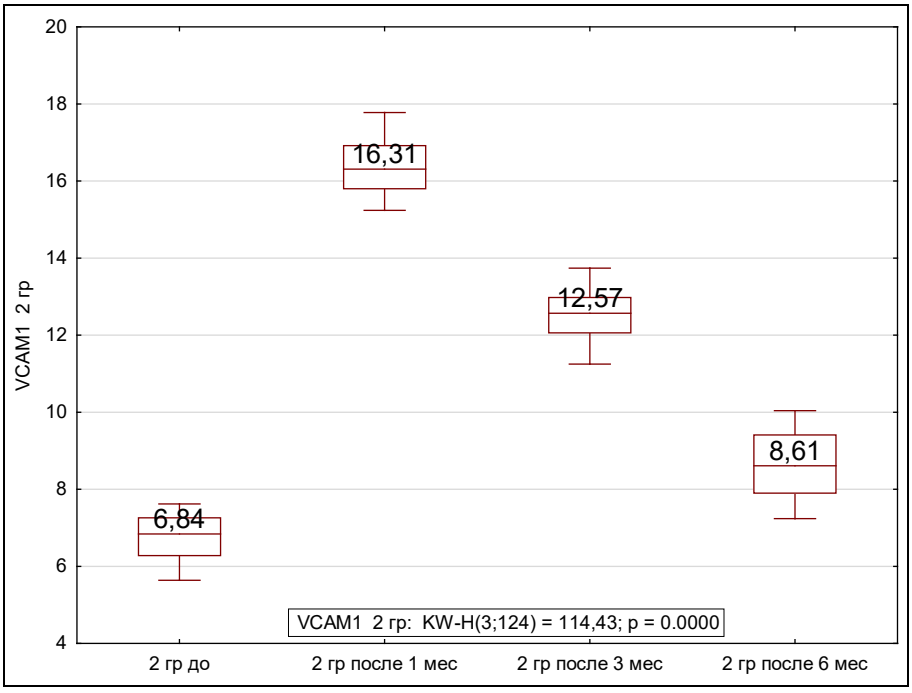
In the third group, significant differences ($p < 0.01$) were revealed when comparing VCAM1 expression levels 1, 3, and 6 months after and before implant placement. Comparison of VCAM1 expression levels in the third group 3 and 6 months

after implant placement and VCAM1 expression levels before implant placement revealed no statistically dependent differences (p = 1.00) (Figure 55).



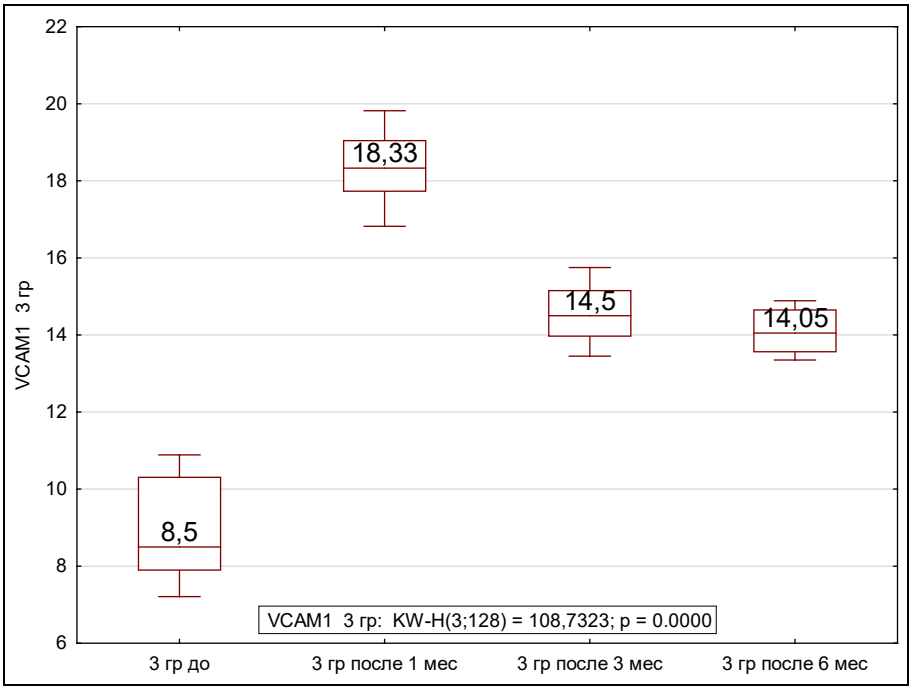
Left to right: Group 1 (*vertical left, bottom middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 53 — Diagram showing the relative VCAM1 expression area in Group 1



Left to right: Group 2 (*vertical left, bottom middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 54 — Diagram showing the relative VCAM1 expression area in Group 2



Left to right: Group 3 (*vertical left, bottom middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 55 — Diagram showing the relative VCAM1 expression area in Group 3

3.23 Claudine-1

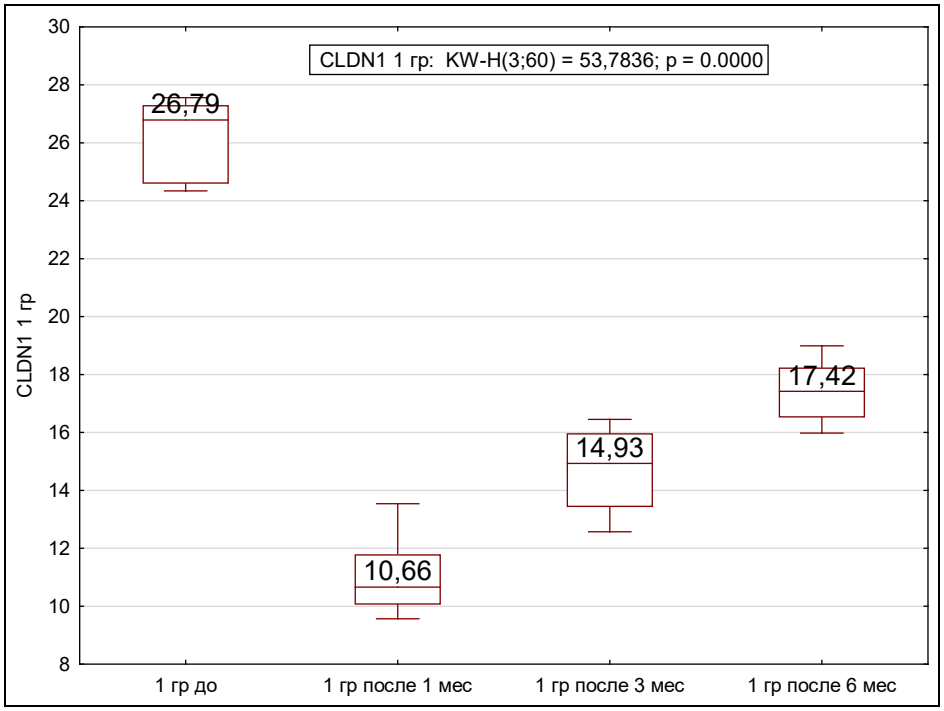
The results of the conducted study on the evaluation of the informative value of the CLDN1 marker are presented in Table 18. The CLDN1 marker was highly informative for all groups.

Table 18 — CLDN1 informative value assessed using Kullback measures

Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	26.21 ± 1.30	17.38 ± 1.00	7.89
Group 2	18.98 ± 1.08	13.80 ± 0.88	3.58*

Group 3	11.23 ± 1.14	6.87 ± 0.40	4.66*
* p 0.01 between the groups.			

In Group 1, when comparing the expression level of CLDN1 1 and 3 months after implant placement with the expression level of this marker before implant placement, significant differences were found (p <0.01) (Figure 56). The levels of CLDN1 expression did not differ significantly at 1 and 3 months after implant placement (p ≥0.05). There were no statistical differences (p ≥0.05) between the expression level of CLDN1 6 months after implant placement and the expression level of this marker before implant placement in Group 1.

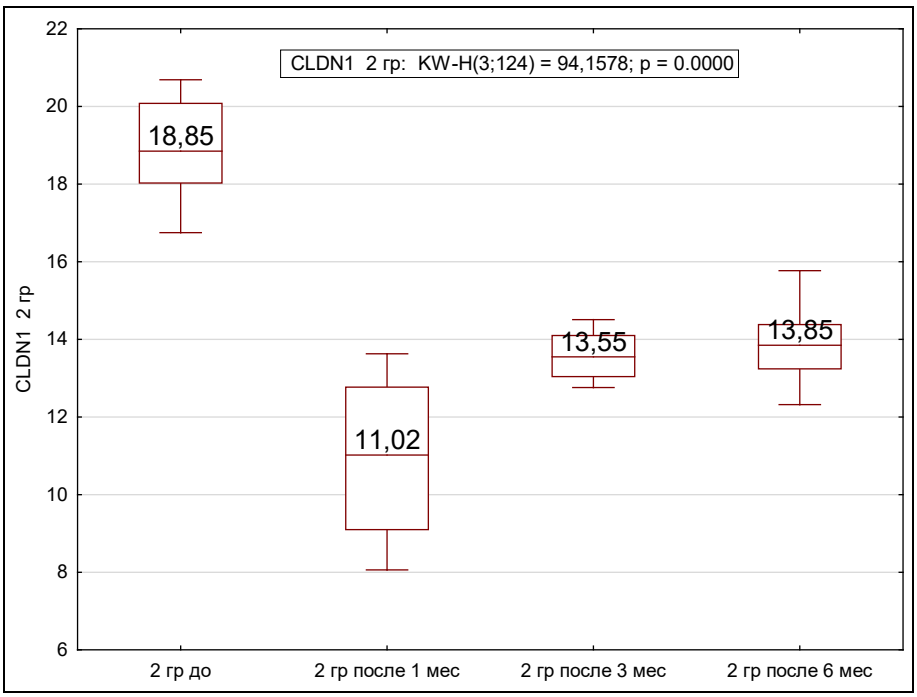


Left to right: Group 1 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 56 — Diagram showing the relative CLDN1 expression area in Group 1

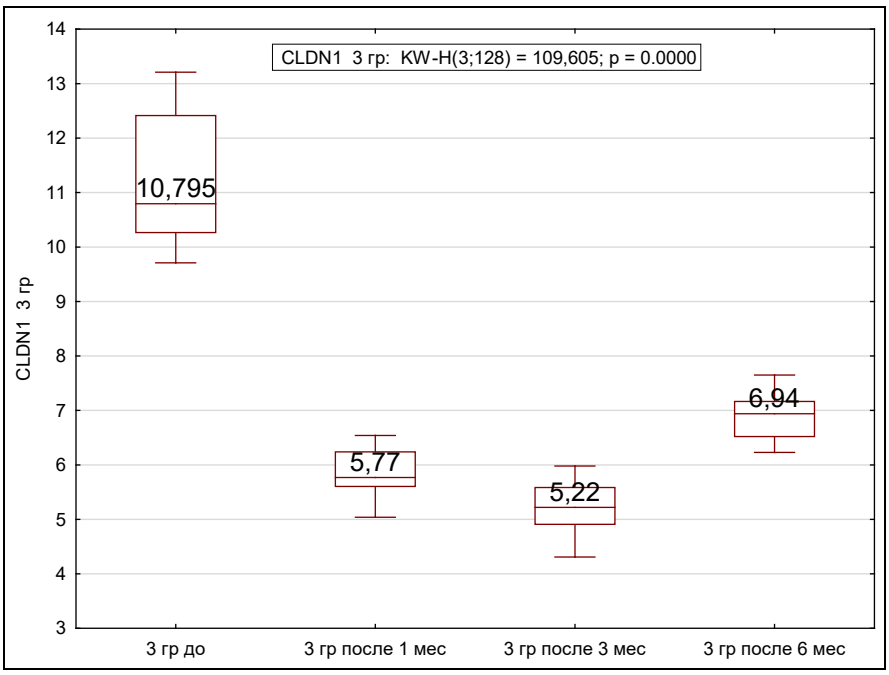
Statistically significant differences were found when comparing CLDN1 values at all three reference points after implant placement (p <0.01) in patients of the second group, except for the expression level of this marker 3 and 6 months after implant placement (p = 1.00) (Figure 57).

In the third group of patients, significant differences (p <0.01) were found when comparing the level of CLDN1 expression among themselves at all three reference points after implant placement, except for the level of expression of this marker 1 and 3 months after implant placement (p = 0.08) (Figure 58).



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 57 — Diagram showing the relative CLDN1 expression area in Group 2



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 58 — Diagram showing the relative CLDN1 expression area in Group 3

3.24 E-cadherin

The results of the conducted study on the E-cadherin marker using the Kullback information assessment are presented in Table 19. The E -cadherin marker demonstrated informative value for all groups, but high informative value of this protein was observed only in Group 1.

Table 19 — E-cadherin informative value assessed using Kullback measures

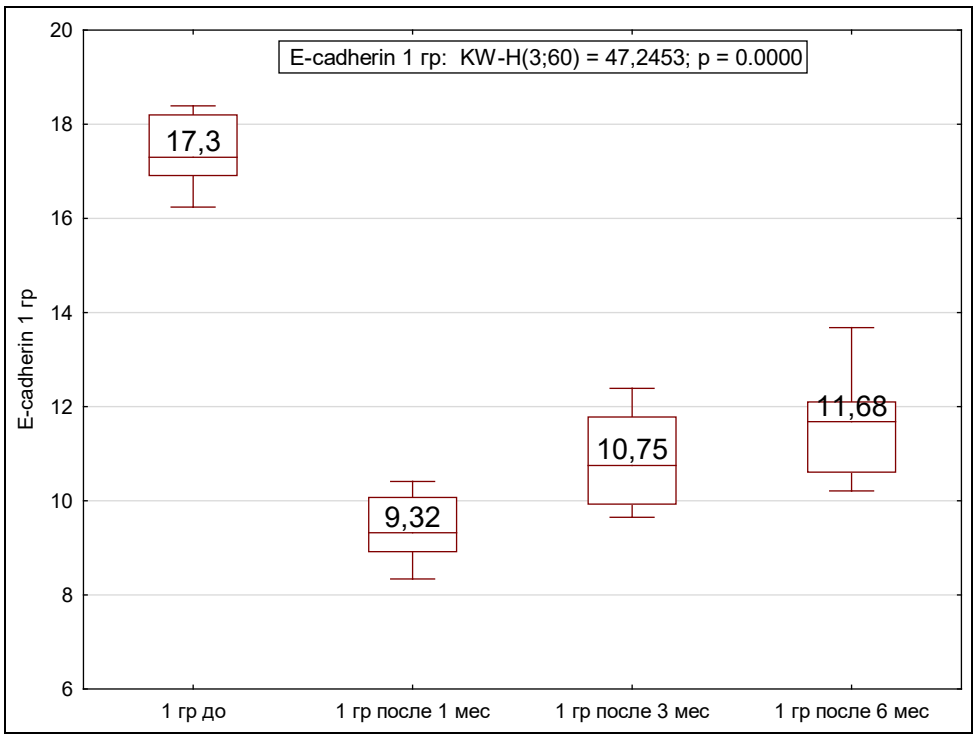
Group number	Prior to implant placement	6 months after implant placement	$J(x_i)$
Group 1	17.44 ± 0.72	11.60 ± 1.12	5.16*
Group 2	9.45 ± 0.36	6.57 ± 0.39	2.28*
Group 3	4.66 ± 0.61	2.89 ± 0.40	1.84*

* p 0.01 between the groups.

In Group 1, significant differences (p <0.01) in E-cadherin expression were revealed among the three timepoints after the implant placement, except between 3 and 6 months after the implant placement (p = 1.00) (Figure 59).

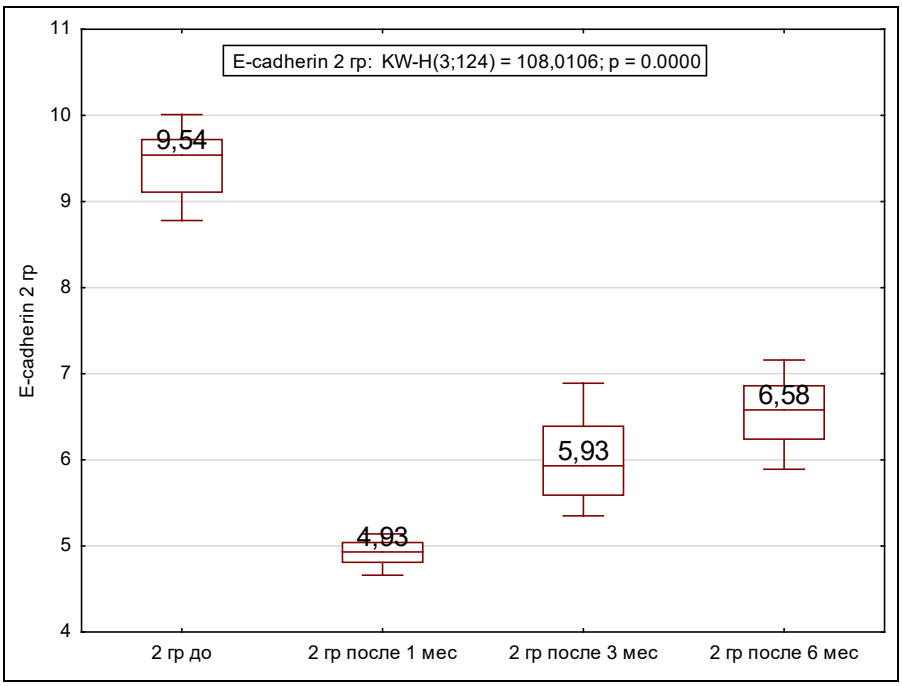
In Group 2 of patients, significant differences (p <0.01) in the level of E-cadherin expression were revealed when comparing the values at all three reference points after implant placement, except for the level of expression of this marker 3 and 6 months after implant placement (p = 0.24) (Figure 60).

In Group 3, statistically significant differences (p <0.01) were revealed when comparing the E-cadherin indices when comparing the indices at all three reference points after implant placement, except for the expression level of this marker 3 and 6 months after implant placement (p = 0.07) (Figure 61).



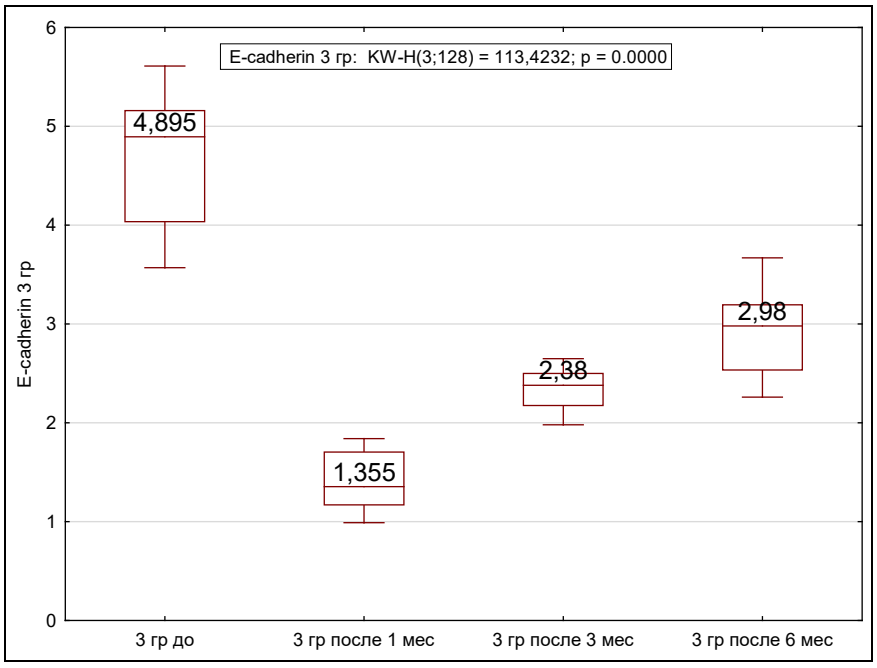
Left to right: Group 1 (*vertical left, top middle);* Group 1 at baseline; Grop 1 after 1 mnth; Group 1 after 3 mnths; Group 1 after 6 mnths

Figure 59 — Diagram showing the relative E-cadherin expression area in Group 1



Left to right: Group 2 (*vertical left, top middle);* Group 2 at baseline; Grop 2 after 1 mnth; Group 2 after 3 mnths; Group 2 after 6 mnths

Figure 60 — Diagram showing the relative E-cadherin expression area in Group 2



Left to right: Group 3 (*vertical left, top middle);* Group 3 at baseline; Grop 3 after 1 mnth; Group 3 after 3 mnths; Group 3 after 6 mnths

Figure 61 — Diagram showing the relative E-cadherin expression area in Group 3

3.25 Analysis of the temporal biomarker dynamics

This part of research has resolved the following tasks:

1) to assess the extent to which all the studied groups differ in biomarkers depending on the age category and timespan (pre-treatment, after a month, three months and six months of treatment);
2) to evaluate the biomarker expression differences among the three groups at the pre-treatment baseline.

Statistical analysis by age categories.

α-Tubulin

For age-based comparative analysis, the Shapiro-Wilk test was first used to test the hypothesis that the dataset follows a normal distribution. The normal distribution, also known as the Gaussian distribution, is one of the most common distributions in statistics. The Shapiro-Wilk test compares the observed data with the expected values of a normal distribution. The hypotheses for this test are formulated as follows: Null hypothesis (H_0): the data follows a normal distribution. Alternative hypothesis (H_1): The data do not follow a normal distribution.

When conducting the Shapiro-Wilk test, if the p-value (the probability of obtaining the same or more extreme results under the null hypothesis) is less than the specified significance level (usually 0.05), then the null hypothesis is rejected in favor of the alternative hypothesis, indicating that the data do not follow a normal distribution.

Each group in the dataset was divided into age categories labelled as ‘Young’ (18-44 years old) and ‘Old’ (45-70 years old). For all groups, the normality test yielded a p-value >0.05, which supports the assumption of a normal distribution for each group.

The analysis of the quantiles, as shown in Figure 62 using the example of the first group, suggests that the data are normally distributed

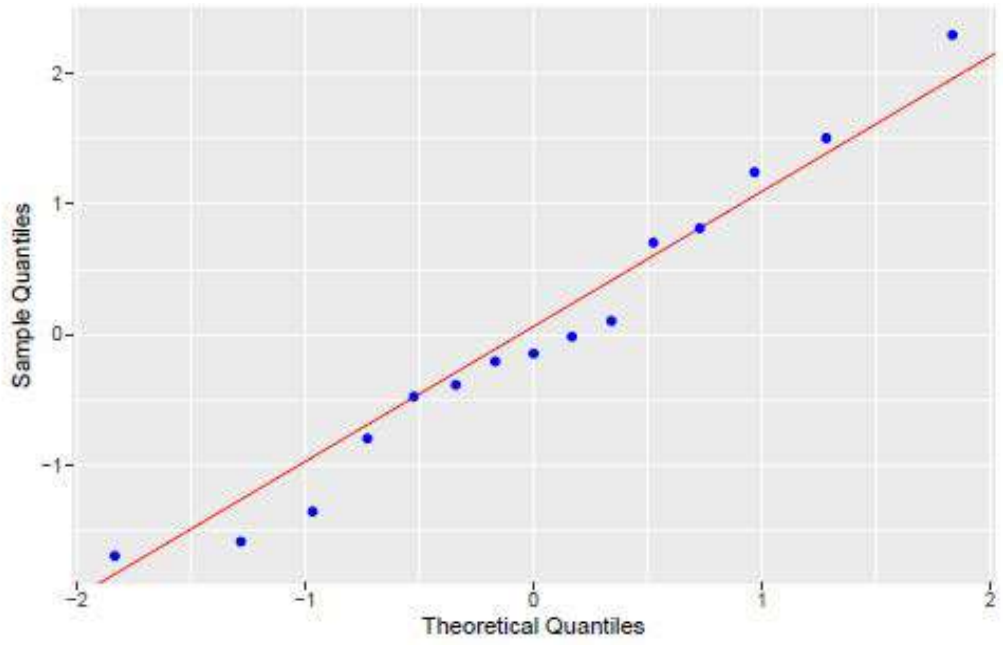
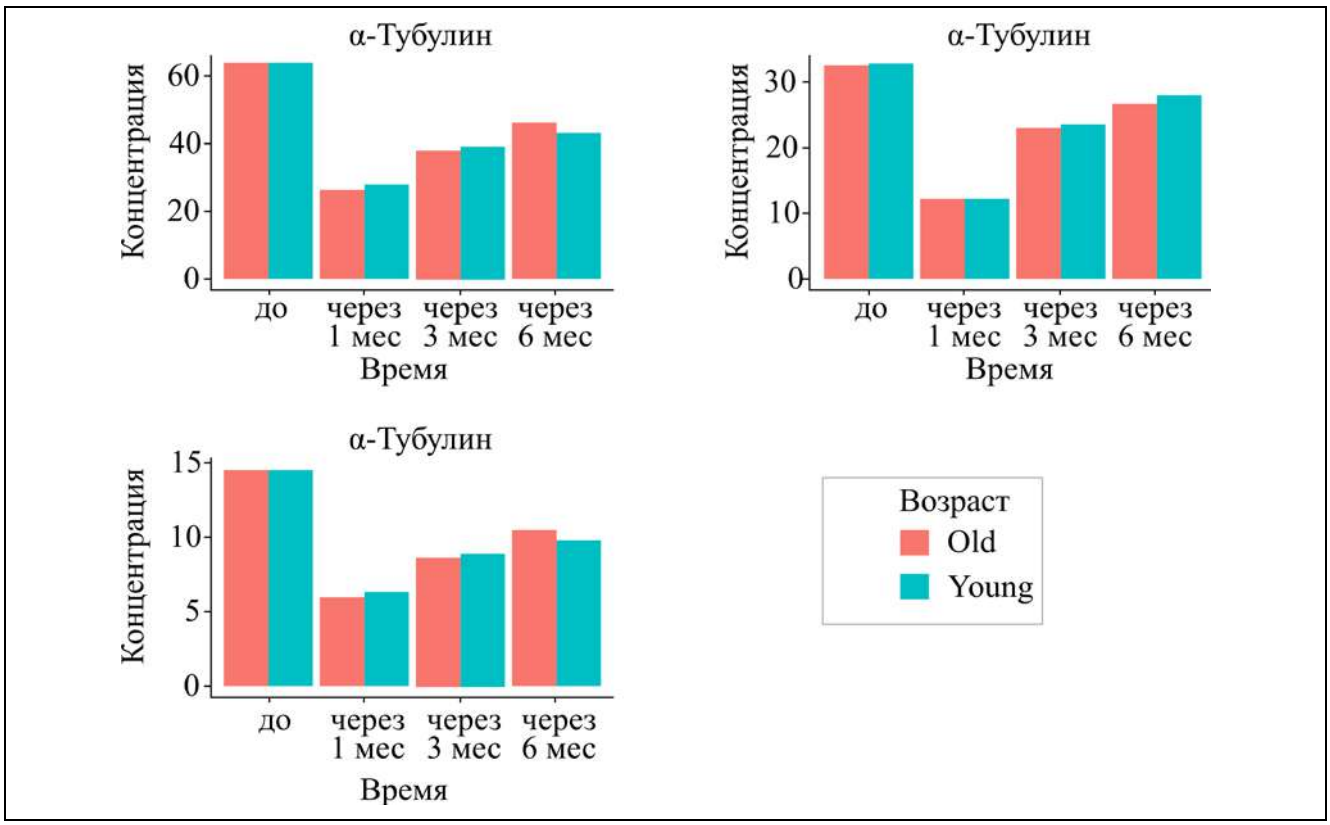


Figure 62 is a QQ graph comparing the quantile values from the data sample with theoretical quantiles that would correspond to the assumed distribution. The data for the first group is shown in the time interval before the start of treatment

since the data points lie along the diagonal. The same analysis was performed for all other groups and for each time interval (data not shown due to excessive bulk).

The data for the first group are shown for the time interval before the start of treatment.

The next step was an in-group comparison (for each group) of biomarker data across different time intervals (Figure 63).



Top left chart. Left to right: concentration (*vertical*); α-Tubulin (*top middle above the chart*); *Row 1 bottom horizontal*: pre-treatment, 1 month after, 3 months after, 6 months after; *Row 2 bottom horizontal:* Time	*Top right chart. Left to right*: concentration (*vertical*); α-Tubulin (*top middle above the chart*); *Row 1 bottom horizontal*: pre-treatment, 1 month after, 3 months after, 6 months after; *Row 2 bottom horizontal:* Time
Bottom left chart. Left to right: concentration (*vertical*); α-Tubulin (*top middle above the chart*); *Row 1 bottom horizontal*: pre-treatment, 1 month after, 3 months after, 6 months after; *Row 2 bottom horizontal:* Time	Age

Figure 63 — Histograms comparing all three groups (I, II, III) by age at 4 timepoints (pre-treatment, 1 month, 3 months, and 6 months after treatment). The significance levels (p-values) for all three groups ranged from 0.06 to 0.90.

Analysis of variance (ANOVA). One-factor analysis of variance (ANOVA) can be considered an extension of the t-test when testing more than two groups. No significant age-specific differences between the groups were detected across all time spans (see Figure 63).

3.26 Statistical comparison of the differences among the three groups by the measured factors

To assess the significance of the marker when comparing the three groups of patients, an ANOVA was performed to identify intergroup differences in the factor for the time interval before treatment. The groups were statistically different from each other (p-value <2×10-16).

Although ANOVA is a powerful parametric method for analyzing approximately normally distributed data with more than two groups (called ‘treatments’), it does not provide detailed insights into patterns or comparisons between specific groups. A multidimensional test should be followed by a more detailed examination of specific groups to understand the extent of differences or similarities. This subsequent step is called post-hoc analysis, which is an important part of hypothesis testing. One common method for post-hoc analysis is the Tukey test (Figure 64).

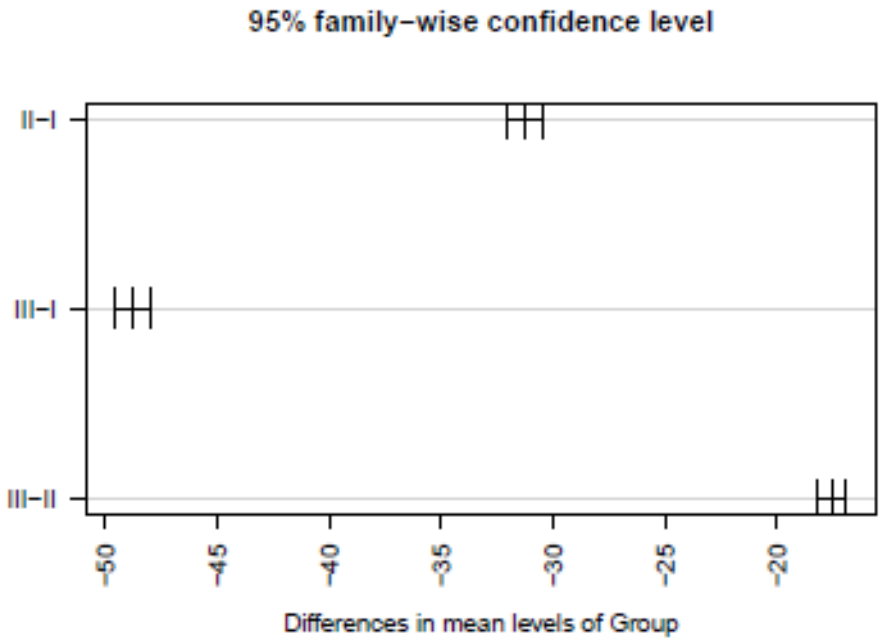


Figure 64 — Visualization of the Tukey test.

The difference in averages across the groups does not overlap (p-value <2×10-16).

I, II, III — Group 1, Group 2, Group 3

Figure 64 shows that no average value CI among the study groups has yielded a zero value suggesting a statistically significant difference in average losses among all three groups. This is consistent with the fact that all p-values are below 0.05 (also consistent the ANOVA results).

3.27 Cross-group biomarker comparison

Similarly, as described in the previous sections, the analysis included all other biomarkers. No statistical differences in the age-specific distribution of biomarkers were detected. Cross-group comparison results are shown in Table 20.

Table 20 — cross-group p-values (ANOVA, Tukey test) by biomarker at pre-treatment

(I)	(II)	(III)	p-value	(I)	(II)	(III)	p-value
α-Tubulin			<2 ×10^{-16}	MT1			<2 ×10^{-16}
β-Tubulin				MT2			
COX-1				NeuN			
COX-3				NO			
COX-2				NSE			0.78 (groups III–II) <2 ×10-16 (groups I–II, I–III)
VGEF				VCAM1			1 ×10-14 (groups III–II) <2 ×10-16 (groups I–II, I–III)
VGEFR				CLDN1			<2 ×10^{-16}
MT				E-cadherin			

3.28 A model for predicting dental implant placement efficiency

The decision tree method is one of the most popular machine learning methods used for classification and regression tasks. It involves building a decision tree, where each node represents a test for a certain feature and each branch corresponds to a possible outcome of that test. After the decision tree is built, predictions are made by passing data through the tree from the root to the corresponding leaf node. The classification tree predicts the class label for a new sample based on the majority class of the samples in the corresponding leaf node (Figure 65).

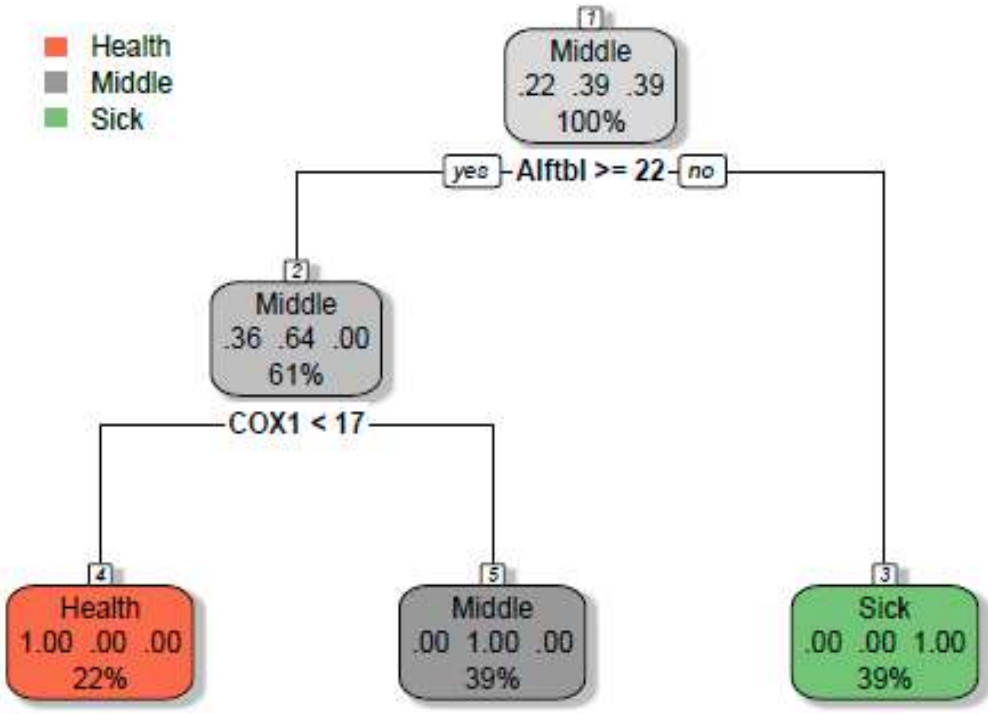


Figure 65 is a decision tree for a training sample. Health, Middle, and Sick are groups divided by treatment success: healthy, average success, and complete failure. The rectangles (gray, green, and red) show the percentage of data from the sample, and the middle row shows the probability of belonging to a particular group.

In R, several packages can be used for decision tree methods. One of the most popular packages is **rpart**, which provides the ability to build decision trees. In our case, we used the classifier method. It was found (as expected) that several features are

sufficient to classify all three groups with high accuracy. Seventy percent of the data was used for training the model and 30% for testing it. Figure 65 shows the results based on the training data, demonstrating that factors such as α-tubulin and COX-1 are sufficient to accurately separate all three categories.

When the model was tested on the sample data, it showed perfect accuracy, along with high specificity and sensitivity. However, to further validate the model, it should be tested on non-homogeneous data.

3.29 Correlation analysis

Next, the pre-treatment data obtained for the three groups were analyzed. The dependent variable was considered to be the success of treatment (i.e., group membership), which was categorized as Health (successful treatment), Middle (average treatment outcome), and Sick (treatment failure). To examine how all quantitative independent variables are related to each other, a correlation analysis was performed. This analysis helps determine the strength and nature of the relationships between variables.

Since classical correlation analysis is applicable to numerical variables (with the treatment success variable being categorical and analyzed using ANOVA as described above), we excluded the treatment success variable from this analysis. In R, the *cor()* function was used to calculate a matrix of correlations between all pairs of numeric variables in the dataset (Figure 66).

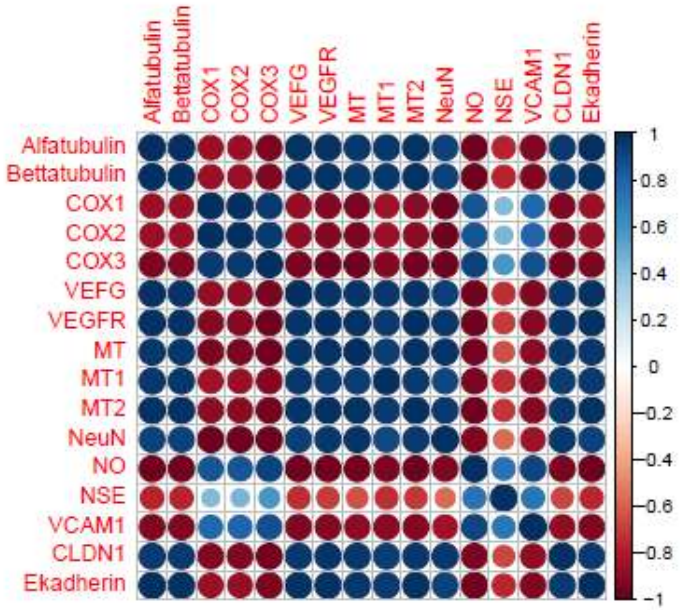


Figure 66 — Correlation analysis matrix between the studied quantitative variables

As shown in Figure 66, strong correlations exist among most variables (indicating that the variables are interdependent), except for enolase (NSE). This suggests that treatment predictions should be based on one or more independent measurements rather than all available biomarkers.

CONCLUSION

Prediction and evaluation of dental implant success is a collateral in dental practice, helping dentists in making informed decisions regarding patient-tailored treatment choices.

Peri-implantitis after dental implant placement is a common problem leading to tissue destruction and implant loss. Inflammation around a dental implant can occur due to various factors, which can be broadly categorized into three groups: local, systemic, and postoperative. These factors play an important role in the development of inflammatory processes around dental implants and should therefore be considered and mitigated to ensure successful treatment.

The main risk factors for peri-implantitis include smoking, diabetes mellitus, prior history of periodontitis, insufficient supportive therapy, depleted keratinized layer of the mucous membrane after implant placement, occlusive overload, radiation therapy, bruxism and other parafunctional habits, malocclusion, incorrect implant position, poor oral hygiene, and alcohol consumption. Systemic diseases such as scleroderma, ectodermal dysplasia, lichen planus, osteoporosis [137], rheumatoid arthritis, or Sjogren's syndrome may exacerbate peri-implantitis, undermining dental implant health [69, 132, 188]. Moreover, family history, stress, dietary challenges, and other lifestyles pose potential risks of peri-implant disease onset [139].

Plaque accumulation and biofilm formation play an important role in peri-implantitis on-set and progression. Prosthetics-induced disorders such as residual cement and overload can also lead to peri-implantitis. Routine maintenance therapy reduces the risk of peri-implantitis [130].

Peri-implantitis treatment depends on the disease severity. Initially, non-surgical mechanical therapy could be effective. Antibiotics can also contribute to the peri-implantitis treatment success. Laser therapy can remove early supragingival biofilm, while low-intensity laser treatment accelerates soft tissue regeneration. Regenerative treatment options can ensure modest regeneration, although complete osseointegration could still be challenging. Conservative treatment outcomes in peri-implantitis are

negatively affected by loss of adjacent periodontal support, poor basic oral hygiene, and large diameter implants (≥4.5 mm) [178]. Implantoplasty or an additional barrier membrane can slow down the mucous membrane recession around the implant after peri-implantitis is resolved [187].

Surgical treatment is an option when conservative methods are ineffective, with the patient showing ongoing recurrent bleeding and purulent discharge. Different surgical treatment options include air abrasion, resection surgery, implantoplasty and regenerative surgery. However, surgery may not be always the most optimal solution. In case of significant bone loss (over half of the implant length), surgery may be ineffective. Incorrect implant position can also limit the treatment success. If the dental implant becomes mobile, indicating significant bone loss or a lack of osseointegration, implant removal is often preferable. IIn such cases, re-implant placement can be performed using a larger diameter implant.

Traditionally, the forecast is based on clinical data, including bone tissue condition, the patient's overall health, and the presence of concomitant diseases. Before implant placement, basic clinical and radiographic examinations are conducted, serving as a baseline for monitoring tissue health around the implant. The health of peri-implant tissues is assessed by the absence of inflammation, bleeding on probing, and increased probing depth compared to initial measurements.

At the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases, the following criteria were proposed for diagnosing peri-implantitis: bleeding on probing (BOP) and/or bleeding during implant placement, suppuration, probing depth ≥6 mm, and supporting bone loss ≥3 mm. These criteria are based on a combination of clinical and radiographic data, emphasizing the need for an integrated diagnostic approach.

Diagnosing peri-implantitis requires careful evaluation of the clinical presentation, radiographic findings, and additional studies [144]. The main symptoms include redness and swelling of the mucosa, bleeding on probing, purulent discharge, and progressive bone loss [152]. However, these symptoms may not appear immediately, making early-stage diagnosis challenging

One of the main difficulties in diagnosing peri-implantitis is the ambiguity of its criteria, particularly in the early stages. For instance, bleeding on probing does not always indicate peri-implantitis, and this symptom alone is insufficient for diagnosis. Implant probing can help monitor bone loss, but it may not accurately reflect its extent and nature without radiographic assessment.

Radiographic methods remain the primary tool for evaluating bone loss around implants, though they have limitations, as they primarily detect mesial and distal bone loss while other areas may go unnoticed, reducing sensitivity.

Recent studies suggest that analyzing a patient's molecular profile can significantly enhance the accuracy of prognosis and implant success evaluation. Several promising molecular markers have been identified in scientific literature, allowing for a more detailed assessment of dental implant outcomes.

Thus, improving prognosis and evaluating the success of dental implants through molecular profiling represents a promising advancement in modern dentistry. The use of molecular markers enhances predictive accuracy, individualizes treatment approaches, and ensures the long-term stability of implants. A comprehensive assessment of the dental status and a panel of biomarkers makes it possible to predict implant rejection, the development of peri-implantitis, and bone loss. In the presence of peri-implantitis, a biomarker panel can be used to assess the severity of the disease, the activity of inflammation, the degree of bone destruction, and the effectiveness of treatment.

The study was performed using the facilities of the St. Petersburg State Autonomous Healthcare Establishment 'City Dental Outpatient Clinic No. 22'. The study enrolled 78 patients. All patients were divided into three groups: Group 1 — 15 patients (19.2%) with successful implant placement; Group 2 — 31 patients with moderate peri-implantitis; Group 3 — 32 patients with severe peri-implantitis.

The comprehensive assessment of dental status included an assessment of the condition of teeth, gums, and oral mucosa, as well as checking for caries, periodontal pockets, dental mobility, and other pathologies, calculating periodontal indices, while taking into account the patient's medical history, including chronic diseases, medication, allergies, and prior surgeries.

All patients underwent an oral cavity examination under overcast daylight condition with a standard dental examination toolkit featuring a dental probe, mirror and tweezers. The examination and all parameters were evaluated before, 1 month, and 6 months after implant placement. The calculation of periodontal indices was carried out; gingival index GI, communal periodontal index CPI, PMA (modified by S. Parma, 1960), PI, hygienic index OHI-S, oral hygiene efficiency index PHP, Mulemann gum index modified by Cowell (Cowell I., 1975). All indexes were evaluated prior to, 1 month, 6 months after the implant placement. The 36-item Short Form Health Survey (SF-36), a renowned generic health-related questionnaire, was filled in by patients before implant placement and 6 months after the procedure.

Based on the literature analysis, a panel of biomarkers was selected that can be used to predict complications after dental implant placement and assess the severity of peri-implantitis: α-tubulin, β-tubulin, COX-1, COX-2, COX-3, VEGF and its VEGFR receptor, melatonin and its MT1 and MT2 receptors, NeuN, NO, NSE, CLDN1, and E-cadherin.

An increased level of α-tubulin may indicate the activation of inflammatory processes, since inflammation is accompanied by an increase in the number and activity of cells of the immune system, which are associated with the activity of microtubules. In conditions of inflammation caused by bacterial infection or other factors, osteoclasts are activated, destroying bone tissue. These cells also depend on microtubules, so a high level of α-tubulin may correlate with increased osteoclast activity and accelerated bone resorption around the implant. α-Tubulin level analysis can be used to diagnose the early stages of peri-implantitis or other inflammatory conditions associated with the implant.

High levels of β-tubulin are associated with osteoclast activation, which leads to bone resorption around the implant, so an increase in β-tubulin levels may indicate inflammation and cell damage. On the contrary, low β-tubulin may suggest attenuated or disfunctional osteogenesis and elevated risk of implant failure [196, 234].

Upregulated COX expression is observed in inflammation and malignant lesions of the oral cavity, such as periodontitis, pulpitis, or oral cancer. In addition, dental

materials provoke unfavorably upregulated COX expression, which may directly affect pulp health [81].

COX-1 plays a pivotal role in inflammation and tissue regeneration and cannot be overlooked in dental implant installation. Upregulated COX-1 expression is associated with critically poor implant survival, in contrast to low COX-1 expression level [122]. Increased COX-1 activity can extend implant healing, contributing to poor bone tissue regeneration [79].

COX-2 overexpression in periodontal tissues is associated with chronic periodontitis, bleeding index, inflammatory infiltrate, progressive loss and loosening of connective tissue attachment to the plate, radiographic alveolar bone mass depletion, and inflammation [150, 233]. COX-mediated bone resorption is one of the many factors involved in orthodontic tooth movement which is be assessed to predict treatment success in enhancing or inhibiting tooth movement, as well as attenuating bone and root resorption [81].

Higher COX-3 is associated with early implant rejection, upregulated inflammatory response and poor bone-implant integration.

The relationship between VEGF levels and clinical outcomes, such as implant integration and absence of complications, has been revealed [158]. VEGF promotes angiogenesis and new blood vessel formation of around the implant, improving blood supply and healing 10217VEGF expression was associated with better implant healing, confirming its important role in dental implant success [].

VEGFR expression showed correlation with tissue vascularization in the implant area [197]. VEGFR affects osteoblast activity and bone remodeling. In the implant-surrounding area, upregulated VEGFR was associated with improved osteogenic response and successful integration of implants in the bone tissue [114]. Higher VEGFR expression ensures better bone regeneration and reduces the risk of implant rejection [228].

High levels of melatonin and adequate expression of its MT1 and MT2 receptors indicate a good state of antioxidant protection, anti-inflammatory potential, and favorable conditions for bone tissue regeneration. This may indicate a low risk of

complications and a high probability of successful implant integration. On the contrary, a decrease in melatonin levels or a malfunction of its receptors may indicate an increased risk of inflammatory and infectious complications, slowing down the healing process and increasing the likelihood of unsuccessful dental implant placement.

NeuN expression correlated with restored sensitivity and successful implant integration [3, 156].

With its ability to influence inflammatory processes and osseointegration, NO can be considered a predictor of dental implant success. NO plays an important modulator of inflammatory responses, which is critical for successful healing after implant procedure. NO also promotes osteoblast proliferation and differentiation, enhancing implant-bone integration.

Elevated NSE indicates healthy tissue regeneration, rapid wound healing and bone-implant integration. NSE can be a useful predictor of both successful implant installation or potential complications [59].

VCAM-1 expression correlates with the activity of osteogenic differentiation, which indicates a potential link between the level of this protein and successful osseointegration during dental implant placement. The level of VCAM-2 is elevated in the periimplant tissue, which indicates a possible link between inflammatory reactions and the successful process of osseointegration [227]. VCAM-1 plays an important role in the regulation of inflammatory processes and angiogenesis, which affects the success of dental implant placement [157].

CLDN1 expression may serve as a measure of efficient osseointegration, potentially predicting dental implant success [28]. Efforts to optimize the CLDN1 level can attenuate specific inflammatory response, contributing to improved implant installation outcome [6]. Increased expression of CLDN1 may be associated with improved biocompatibility of implant materials, which may also be an indicator of the success of their use [2].

E-cadherin suppression correlates the severity of inflammation in the implant area, serving as a promising diagnostic biomarker of peri-implantitis [205]. The possibility of using E-cadherin as a marker for early diagnosis of inflammatory

processes around implants is being considered [205]. E-cadherin is critical for for teeth development, including the enamel, crown, pulp and roots [61].

Buccal epithelium (BE) was sampled for immunocytochemistry [45]. BE was obtained from the oral cavity (the mucous membrane of the inner cheek) no earlier than 4 hours after food intake, prior to sampling the oral cavity was rinsed with saline solution. Every patient enrolled in the study underwent BE collection to assess the expression of signaling molecules prior to the dental implant procedure, after 1 and then 6 month's follow-up. To evaluate the results of immunocytochemical staining, a morphometric study was performed using a computer analysis system of microscopic images.

The combination of the immunocytochemical method and confocal microscopy provides unique opportunities for assessing the expression of inflammatory markers in the tissues around the implant, the degree of vascularization using vascular endothelial growth factor, analyzing the condition of nerve endings, and determining the degree of destruction of the epithelial barrier [12].

Mathematical and static analysis of the obtained data was performed (we analyzed temporal dynamics for selected markers, compared statistic differences for the assessed parameters across the three groups, conducted the cross-group comparison for all biomarkers, followed by a correlation analysis between the obtained quantitative variables to build decision trees).

The GI and PHP indexes are widely used to assess periodontal health and oral hygiene. Their high information content confirms the importance of monitoring these parameters after dental implant placement. The OHI-S index and the Russell periodontal index are also important, but judging by the results of our study, they show differences only in the second and Group 3s 1 month after implant placement. This indicates that both indexes may have limited predictive value in this context. The lack of prognostic significance of the remaining indices highlights the need for careful selection of indicators to assess the condition of patients after dental implant placement.

The SF-36 questionnaire is a standard tool for assessing the quality of life. The positive dynamics of indicators of psychological and social well-being, social

functioning and general satisfaction after dental implant placement indicates the positive impact of this type of treatment on the lives of patients. This is an important conclusion that highlights the importance of aesthetics and functionality of dental implants.

The expression of α-tubulin and cyclooxygenase-1 is associated with inflammatory processes and regenerative abilities of tissues. Assessment of their level before dental implant placement can help predict the risk of inflammation in peri-implant tissues after 6 months. Predicting complications allows you to take preventive measures and adjust the treatment plan, which will increase the chances of successful implant placement.

Absence of age-specific differences in young and middle age groups suggests that the studies approach can be comprehensively used regardless of the patient age.

Buccal epithelium swabs are a simple technique to obtain biosamples, as this region is easily accessible and does not require invasive procedures. Highly informative correlations between the studied biomarker expression and complications after the dental implant placement confirm the benifits of using these biomarkers to predict treatment outcomes.

An integrated approach combining clinical assessment of dental status with analysis of molecular biomarkers proves effecient in predicting complications and stratifying patients according to the severity of peri-implantitis. Such approach provides more accurate diagnosis and individual selection of treatment methods, leading to improved dental implant placement results and increased patient satisfaction.

CONCLUSION

1. The GI and PHP were proved to be the most informative periodontal indices for all the three study groups 1 and 6 months after the dental implant placement. In Group 2 and Group 3, the OHI-S and PI were significant different 1 month after the dental implant placement, while the other indices showed no prognostic significance throughout the studied timespan.

2. In all the study groups, the SF-36 questionnaire revealed significant quality of life improvement in the domains of physical health, mental health, social functioning and general satisfaction after the dental implant placement.

3. Significant correlation was demonstrated between molecular biomarker expression in buccal epithelium and potential complications after the dental implant placement, with no age-specific differences in young and middle-aged patients.

4. In order to predict the risk of peri-implant inflammation 6 months after the dental implant placement, comparative evaluation of α-tubulin and COX-1 expression with the pre-treatment baseline is recommended.

5. Comprehensive evaluation of the dental status and biomarker expression under consideration allows to predict complications and perform an evidence-based patient stratification based on peri-implantitis severity risk.

PRACTICAL RECOMMENDATIONS

Risk assessment of dental implant complications is essential for professional preventive care. Efficient personalized prevention based on the patient's risk profile is required, considering all the potentially affected local and systemic risk factors of peri-implant diseases. [98]. Such personalized prevention also requires specific patient learning and motivation to change habits, in order to assume responsibility for their own health under the guidance and support of oral care professionals [163]. Preventive measures can be taken even before the implant is installed to prevent exposure to risk factors and ultimately reduce the incidence of new diseases. Primary prevention is the earliest effort to avert the main risk factors and disorders contributing to disease onset [190, 222]. A possible mainstreaming effort is promotion of healthy behaviors, such as to stop tobacco smoking, engage in regular physical exercise to prevent non-communicable diseases such as type 2 diabetes mellitus, or disembark from destructive habits that increase the risk of peri-implantable diseases. After the dental implant is installed, peri-implant tissue health maintenance is a collateral for a long-term perspective. These efforts are fundamental for primary prevention, aimed at peri-implant tissue health and risk management to prevent disease manifestations [128]; these efforts should include individual patient training and motivation to observe proper oral hygiene and avoid the biofilm build-up around dental implants and their restorations. Treatment of peri-implant mucositis is a preventive measure - although a secondary one - in case of peri-implantitis [206].

Efficient care protocols for implant-supported prosthesis rely on regular medical visits. They present a proactive strategy for periimplant health monitoring and protection. Routine visits allow dentists to carefully assess tissue condition around the implant and detect any minor changes or manifestations of problems at an early stage [173]. This includes monitoring the implant stability and any deviations from normal function or mobility. Early detection at this stage is crucial because it allows timely intervention and potentially prevents the progression of peri-implant mucositis to severe peri-implantitis. Early identification of disease allows doctor to initiate appropriate

treatment and provide the recommendations to mitigate complications in order to maintaining the durability and functionality of the implant-supported prosthesis [75].

LIST OF ABBREVIATIONS AND SYMBOLS

BE	—	buccal epithelium
PI	—	periodontal index
COX	—	cyclooxygenase
BL	—	bone loss
BOP	—	bleeding on probing
CHX	—	chlorhexidine gluconate
CLDN1	—	claudin-1
COX	—	cyclooxygenase
CPI	—	community periodontal index
GI	—	gingival index
HbA1c	—	glycated hemoglobin
IL	—	interleukin
MMP-8	—	matrix metalloproteinase-8
MNO	—	minocyclinum
MT	—	melatonin
MT1	—	Type 1 melatonin receptors
MT2	—	Type 2 melatonin receptors
NeuN	—	neuronal nuclei
NO	—	nitric oxide
NSE	—	neuron-specific enolase
OHI-S	—	oral hygiene indices - simplified
PD	—	probing depth
PHP	—	patient hygiene performance index
PMA	—	papillary-marginal-alveolar index
SF-36	—	The Short Form-36 (questionnaire)
TNF-α	—	tumor necrosis factor alpha
VCAM-1	—	vascular cell adhesion molecule-1
VEGF	—	vascular endothelial growth factor

VEGFR — receptors for vascular endothelial growth factor

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APPENDIX A. PATIENT INFORMED CONSENT FORM

By signing this informed consent form, I confirm that I have read and understood the purpose, procedure, methods, and possible inconveniences of participating in the study. I have had the opportunity to ask all the questions that interest me. I have received satisfactory answers and clarifications to all my questions related to this study. I give my consent to participate in the study.

____ I agree to be recorded on video

Participant's Signature Date: '_____' _____202___

By signing this informed consent form, I confirm that the participant has read and understood the purpose, procedure, methods, and possible inconveniences of participating in the study. The participant has had the opportunity to ask all questions of interest. The participant has received satisfactory answers and clarifications to all questions related to this study. The participant gives their consent to participate in the study.

_____

Investigator's full name and signature Date: '_____' _____202___

I have explained the above informed consent form to the respondent and answered all of their questions regarding participation in the study. Their decision to participate in the study was not influenced by anyone and was made consciously and voluntarily, as confirmed by their consent.

By signing this informed consent form, I confirm that the participant has read and understood the purpose, procedure, methods, and possible inconveniences of participating in the study. The participant has had the opportunity to ask all questions of interest. The participant has received satisfactory answers and clarifications to all questions related to this study. The participant gives their consent to participate in the study.

_____

Investigator's full name and signature Date: '_____' _____202___

_____

Investigator's full name and signature Date: '_____' _____202___

APPENDIX B. OHI-S INDEX AT BASELINE

Table B.1

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
1	1.2	1.4	1.0	1.5	1.6	1.0	2.7	2.9	2.1
2	1.4	1.5	1.2	1.9	2.0	0.8	2.6	2.7	1.8
3	1.4	1.5	0.7	1.4	1.6	1.2	2.7	2.6	1.8
4	1.3	1.4	1.0	1.9	2.0	1.4	2.5	2.6	1.5
5	1.1	1.2	0.9	1.5	1.9	1.6	2.9	3	1.6
6	1.3	1.3	1.0	1.5	1.7	1.5	2.1	2.3	2.0
7	1.5	1.6	1.1	1.4	1.8	1.4	2.0	2.2	2.1
8	1.1	1.2	1.2	1.8	2.1	1.5	2.6	2.6	1.6
9	1.4	1.3	0.9	1.6	1.9	1.9	2.6	2.8	1.9
10	1.3	1.3	0.9	2.0	2.1	1.2	2.2	2.3	1.9
11	1.4	1.5	0.8	1.9	2.0	1.1	2.1	2.4	2.0
12	1.4	1.6	0.9	1.6	2.0	1.5	2.4	2.5	1.7
13	1.5	1.5	0.8	1.5	1.3	1.6	2.2	2.3	1.8
14	1.3	1.4	1.0	1.8	1.6	1.7	2.1	2.1	1.8
15	1.5	1.5	1.1	1.9	1.9	2.1	2.6	2.7	1.6
				1.9	1.9	1.5	2.3	2.4	1.9
16				1.3	1.5	1.7	2.7	2.8	2.0
17				1.6	1.9	1.4	2.8	2.9	1.9
18				1.4	1.5	1.1	2.7	2.8	2.1
19				1.8	1.9	1.2	2.2	2.3	1.6
20				1.5	1.5	1.3	2.1	2.2	1.6

21				1.8	1.9	1.4	2.3	2.4	1.8
22				1.6	1.7	1.6	2.2	2.3	1.7

Table B.1 (continued)

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
23				1.7	1.7	1.5	2.1	2.2	1.9
24				1.6	1.8	1.7	2.4	2.6	2.0
25				1.7	1.9	1.4	2.5	2.5	2.1
26				1.8	1.9	1.2	2.1	2.3	1.8
27				1.5	1.7	1.7	2.3	2.4	1.6
28				1.8	1.9	1.1	2.3	2.5	1.7
29				1.6	1.7	1.4	2.9	3	1.8
30				1.9	2	1.1	2.5	2.6	2.2
31				1.9	2.1	0.8	2.4	2.6	2.1
32				1.675	1.8125	1.39375	2.6	2.7	2.2

APPENDIX V. PRIMARY DATA ON THE PMA INDEX

Table V.1

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
1	29	32	30	30	33	31	42	45	41
2	26	28	25	45	46	44	44	46	45
3	15	19	18	40	43	42	48	53	46
4	18	19	17	41	42	40	39	42	41
5	10	13	11	38	39	37	51	56	55
6	11	15	14	32	35	30	56	58	54
7	15	17	15	31	34	31	59	60	58
8	8	10	8	30	32	31	62	64	60
9	11	14	13	31	35	33	49	57	50
10	14	18	17	34	37	35	50	53	52
11	7	11	9	38	39	35	52	55	49
12	21	23	24	41	42	39	49	51	45
13	24	26	23	40	43	38	53	56	53
14	18	19	17	42	45	39	45	48	45
15	16	20	18	35	38	38	44	47	44
				34	39	36	48	51	47
16				30	33	31	51	55	50
17				32	35	33	50	52	47
18				40	43	41	56	58	48
19				41	43	39	59	60	49

20				38	41	35	49	54	47
21				32	38	36	47	51	47
22				33	35	31	45	49	45

Table V.1 (continued)

	1			2			3		
	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement
23				35	37	36	51	56	46
24				36	38	35	53	57	54
25				33	36	33	60	61	60
26				31	33	31	57	59	54
27				32	34	32	55	58	56
28				30	34	31	49	53	47
29				31	34	29	47	52	49
30				38	39	30	46	49	45
31				36	38	30	42	47	43
32							43	48	44

APPENDIX G. CPI SCORE AT BASELINE

Table G.1

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
1	0.3	0.5	0.2	1.2	1.8	1.4	2.6	1.5	1.5
2	0.2	0.7	0.3	1.4	1.6	1.2	2.3	1.1	1.6
3	0.1	0.8	0.1	1.1	1.9	1.6	1.8	2.1	1.1
4	0.8	1.1	0.6	1.6	2.0	1.8	2.0	1.7	1.6
5	0.6	0.9	0.6	1.8	2.1	1.9	2.4	1.9	1.5
6	0.5	0.7	0.3	1.5	1.9	1.7	2.7	1.6	2.0
7	0.4	0.8	0.3	1.7	2.2	1.9	2.7	2.6	1.7
8	0.7	1.1	0.5	0.8	1.6	1.1	2.6	1.8	1.8
9	0.2	0.4	0.3	0.7	1.7	0.9	2.8	2.2	1.4
10	0.6	0.8	0.4	0.6	1.3	0.8	2.5	1.9	1.1
11	0.8	1.2	0.6	1.3	1.4	1.2	2.3	1.9	1.6
12	0.7	0.9	0.4	1.8	1.7	0.9	2.1	1.8	1.3
13	0.3	0.6	0.5	1.4	1.8	1.4	2.6	2.3	1.7
14	0.7	0.9	0.4	1.3	1.5	0.8	2.1	2.4	1.7
15	0.3	0.6	0.2	1.8	1.2	0.9	2.7	1.3	1.2
				1.7	1.9	1.8	2.3	2.4	1.9
16				1.5	1.8	1.4	2.7	1.5	1.3
17				1.4	2.3	1.3	1.8	1.2	1.7
18				0.9	1.6	1.2	2.6	1.4	1.6
19				0.9	1.7	1.1	1.9	1.3	1.9
20				0.8	1.5	1.4	1.8	1.6	1.8

21				1.2	1.6	1.1	2.3	1.2	1.7
22				1.1	1.5	1.0	2.7	2.1	1.6

Table G.1 (continued)

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
23				1.3	1.5	1.3	2.6	1.4	1.8
24				1.5	1.4	1.1	2.2	2.1	1.2
25				1.7	1.5	1.3	2.6	2.4	1.4
26				1.9	1.6	1.1	2.3	2.5	1.8
27				1.7	1.8	1.6	2.0	1.5	1.7
28				1.6	1.5	0.9	2.5	2.2	1.7
29				1.6	1.4	1.1	2.2	2.3	1.4
30				1.9	1.8	1.2	2.8	1.1	1.7
31				1.6	1.7	1.3	2.4	1.4	1.5
32							2.8	2.6	1.6

APPENDIX D. THE MUHLEMANN-SON SULCUS BLEEDING INDEX AT BASELINE

Table D.1

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
1	0.1	0.3	0.3	1.1	1.7	1.2	2.3	2.0	2.4
2	0.9	0.9	0.5	1.9	2	1.3	2.8	2.6	1.9
3	0.7	0.8	0.4	1.7	1.8	1.1	2.9	2.3	2.0
4	0.6	0.8	0.7	1.3	1.5	1.3	2.6	2.8	2.1
5	0.4	0.5	0.3	1.4	1.5	1.2	2.1	1.9	2.1
6	0.9	1.0	0.6	1.3	1.6	1.4	2.4	2.2	1.8
7	1.0	1.1	0.8	1.6	1.7	1.2	2.6	2.1	1.5
8	0.8	0.9	0.7	1.8	1.9	1.5	2.7	2.5	1.4
9	0.7	0.8	0.8	2.0	2.1	1.6	2.3	2.1	2.2
10	0.5	0.7	0.4	1.9	1.7	1.0	2.5	2.5	2.6
11	0.9	1.0	0.7	1.7	1.8	1.4	2.3	2.4	2.4
12	0.7	0.8	0.6	1.5	1.6	1.3	2.3	2.3	2.3
13	0.8	1.0	0.7	1.3	1.4	1.1	2.9	2.6	2.0
14	0.9	1.0	0.6	1.2	1.3	1.1	2.4	2.0	2.5
15	1.0	1.1	0.8	1.5	1.6	1.4	1.9	1.8	2.1
				1.8	1.7	1.3	1.8	1.7	1.9
16				1.4	1.5	1.5	2.5	2.3	1.9
17				1.7	1.8	1.4	2.1	1.9	2.2
18				1.8	1.9	1.5	3.0	2.3	2.1
19				1.8	1.6	1.3	2.7	2.2	1.7

20				1.9	2.0	1.5	2.7	2.5	1.6
21				1.6	1.8	1.2	2.3	2.1	1.8

Table D.1 (continued)

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
22				1.7	1.7	1.1	2.1	2	1.9
23				1.9	2.0	1.2	2.1	2.2	2.2
24				1.8	1.8	1.6	2.3	2.1	2.4
25				1.5	1.6	1.4	2.2	1.9	2.2
26				1.4	1.5	1.1	3.0	2.4	2.0
27				1.8	1.9	1.3	2.7	2.5	1.8
28				1.6	1.7	1.5	2.8	2.5	2.0
29				1.7	1.8	1.2	2.6	2.4	2.1
30				1.8	1.7	1.5	2.4	2.2	2.3
31				2.0	1.8	1.1	2.5	2.4	2.4
32							2.7	2.6	2.3

APPENDIX E. CPI SCORE AT BASELINE

Table E.1

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
1	0.7	0.9	0.6	1.1	1.4	1.2	2.2	3.0	2.1
2	0.8	1.1	0.4	1.2	1.5	1.1	2.1	2.8	1.7
3	0.3	0.7	0.1	1.1	1.8	0.9	1.8	2.1	1.9
4	0.5	0.8	0.5	1.4	1.7	0.8	1.9	2.3	1.8
5	0.2	0.4	0.1	1.5	1.7	1.4	1.7	2.1	1.8
6	0.4	0.4	0.2	1.4	1.9	1.3	2.3	2.4	2.0
7	0.4	0.6	0.4	1.3	2.2	0.8	3.0	2.9	1.8
8	0.5	0.7	0.2	1.5	1.9	1.4	2.5	2.6	1.4
9	0.7	0.3	0.5	1.6	1.8	1.5	2.6	2.7	1.6
10	0.6	0.6	0.2	1.2	1.5	1.1	2.1	2.7	1.9
11	0.4	0.4	0.1	1.1	1.5	1.3	2.2	2.6	1.7
12	0.5	0.7	0.4	1.1	1.4	1.2	2.6	2.8	1.4
13	0.4	0.6	0.4	1.4	1.8	1.3	2.5	2.7	1.2
14	0.6	0.8	0.6	1.3	1.5	1.3	2.4	2.6	1.8
15	0.7	0.9	0.1	1.2	1.6	1.2	2.3	2.7	1.6
				1.6	1.8	1.5	2.4	2.6	1.1
16				1.4	1.6	1.0	2.0	2.6	1.8
17				1.3	1.6	1.2	2.1	2.7	1.9
18				1.5	1.7	1.4	2.2	2.5	1.3
19				1.2	1.5	0.9	2.6	2.7	1.7

20				1.2	1.4	1.1	2.4	2.5	1.5
21				1.3	1.6	1.4	2.8	2.9	1.8
22				1.4	1.4	1.3	2.6	2.7	1.6

Table E.1 (continued)

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
23				1.5	1.5	1.6	2.1	2.3	1.5
24				1.2	1.5	1.1	1.9	2.0	1.4
25				1.6	1.6	1.5	2.1	2.2	1.7
26				1.4	1.3	1.3	2.7	2.8	1.9
27				1.3	1.6	1.2	2.2	2.3	1.4
28				1.5	1.7	1.3	2.4	2.3	1.8
29				1.4	1.6	0.9	2.5	2.6	2.1
30				1.3	1.7	1.1	2.3	2.5	1.9
31				1.1	1.7	0.9	2.4	2.4	1.7
32							2.1	2.2	1.6

APPENDIX ZH. PI INDEX AT BASELINE

Table Zh.1

	1			2			3		
	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement
1	0.1	0.3	0.2	1.2	1.2	0.6	1.5	2.3	1.1
2	0.3	0.5	0.1	1.2	1.4	0.7	1.3	2.2	0.9
3	1.0	1.0	0.5	1.1	1.3	0.5	1.7	1.9	1.3
4	0.8	0.9	0.3	1.3	1.4	0.8	1.6	1.6	1.2
5	0.9	1.0	0.3	1.1	1.2	0.6	1.4	1.4	0.8
6	0.5	0.8	0.1	1.0	1.1	0.8	1.8	1.9	1.5
7	0.4	0.6	0.2	0.8	1.1	0.7	1.9	2.1	1.4
8	0.1	0.4	0.1	0.7	0.8	0.5	1.4	1.8	1.2
9	0.3	0.6	0.1	0.9	1.1	0.8	1.0	1.6	0.8
10	0.2	0.5	0.3	0.8	0.9	0.9	2.0	2.3	0.9
11	0.4	0.7	0.3	1.1	1.2	0.7	1.5	1.6	0.7
12	0.7	0.9	0.3	0.9	1.0	0.8	1.4	1.9	1.4
13	0.5	0.7	0.1	1.3	1.4	0.7	2.1	2.4	1.3
14	0.1	0.5	0.3	1.5	0.9	0.4	1.9	2.2	1.4
15	0.6	0.8	0.2	1.4	1.5	0.5	2.3	2.5	1.2
				0.8	0.9	0.3	2.6	2.7	1.7
16				0.6	0.7	0.5	2.7	2.7	1.3
17				1.1	1.1	0.4	2.2	2.3	1.4
18				1.0	1.0	0.5	2.5	2.6	1.6
19				1.2	1.2	0.8	2.6	2.8	1.2
20				1.1	1.1	0.7	2.4	2.5	1.4

21				1.3	1.3	0.8	2.0	2.3	1.6
22				1.2	1.2	0.8	1.5	2.1	1.1

Table Zh.1 (continued)

	1			2			3		
	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement
23				1.1	1.1	0.6	2.3	2.4	0.8
24				1.3	1.4	0.6	1.9	2.2	0.7
25				1.5	1.5	0.4	1.8	1.9	0.9
26				1.2	1.5	0.2	1.5	1.7	1.1
27				0.8	0.9	0.9	1.9	2.1	1.3
28				0.9	1.0	0.6	2.2	2.3	1.6
29				1.0	1.3	0.6	1.5	1.6	0.9
30				0.8	0.9	0.9	1.6	1.7	1.5
31				0.7	0.8	0.6	1.9	2.1	1.1
32							1.2	1.4	0.9

APPENDIX 3. ПЕРВИЧНЫЕ ДАННЫЕ ПО ИНДЕКСУ PHP

Table Z.1

	1			2			3		
	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement	Prior to implant placement	3 months after implant placement	6 months after implant placement
1	1.0	1.6	0.8	1.2	1.4	0.8	2.3	2.5	1.4
2	1.1	1.4	0.6	1.3	1.8	1.3	2.6	2.8	1.8
3	0.5	1.2	0.6	0.9	1.5	1.0	1.8	2.3	1.9
4	0.7	1.6	0.7	1.1	1.3	1.0	1.9	2.4	2.1
5	1.2	1.8	0.5	1.6	1.8	1.8	2.6	2.7	1.7
6	1.1	1.2	0.6	1.2	1.6	1.1	2.5	2.5	1.5
7	1.6	1.4	0.8	1.0	1.9	1.3	1.9	2.2	1.9
8	1.3	1.6	0.8	1.5	1.8	0.8	2.1	2.2	2.2
9	1.6	1.7	0.7	1.8	1.9	0.9	2.0	2.0	2.1
10	1.5	1.6	0.8	1.1	1.5	1.0	1.8	2.1	1.9
11	1.0	1.3	1.0	0.7	1.6	1.5	1.9	2.0	1.8
12	1.1	1.4	0.9	0.9	1.3	1.2	1.8	2.1	1.7
13	1.7	1.7	0.8	1.2	1.4	1.1	2.3	2.3	1.6
14	1.5	1.6	0.7	1.1	1.7	1.3	2.0	2.2	2.2
15	1.6	1.6	1.0	0.8	2.2	0.7	2.6	2.7	1.8
				1.3	2.3	1.4	2.4	2.5	2.1
16				1.6	1.9	1.7	2.3	2.5	1.7
17				1.5	1.7	1.8	2.5	2.5	0.9
18				1.7	1.9	1.9	2.2	2.3	0.9
19				1.8	2.6	1.4	2.9	2.9	1.0
20				1.9	2.7	1.3	2.8	2.8	1.3

21				2.4	2.6	1.2	1.8	2.1	1.6
22				1.7	1.8	1.6	2.1	2.3	2.0

Table Z.1 (continued)

	1			2			3		
	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement	Prior to im-plant placement	3 months after implant placement	6 months after implant placement
23				2.2	2.3	1.1	2.8	2.9	1.9
24				2.3	2.3	1.4	2.1	2.3	2.0
25				2.2	2.1	1.8	1.8	2.1	1.9
26				1.8	1.9	1.5	2.7	2.8	1.0
27				2.3	2.4	1.8	2.9	2.9	1.5
28				2.1	2.2	1.9	2.6	2.7	1.5
29				1.9	2.0	1.9	1.9	2.2	1.3
30				1.6	1.7	2.0	2.5	2.6	1.7
31				1.9	1.6	2.1	2.6	2.8	2.1
32							2.0	2.1	2.2

APPENDIX I. SF-36 QUESTIONNAIRE
(RUSSIAN VERSION RECOMMENDED BY THE INTER-REGIONAL CENTER FOR QUALITY OF LIFE RESERCH)

Last name First name Middle name

Date

1. In general, would you say your health is (circle one number):

Excellent 1

Very good 2

Good..... 3

Fair 4

Poor..... 5

2. Compared to one year ago? (circle one number)

Much better now than one year ago..... 1

Somewhat better now than one year ago 2

About the same 3

Somewhat worse now than one year ago..... 4

Much worse now than one year ago. 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
(circle one number on each line)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
A. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
B. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
V. Lifting or carrying groceries	1	2	3
G. Climbing several flights of stairs	1	2	3
D. Climbing one flight of stairs	1	2	3
E. Bending, kneeling, or stooping	1	2	3

Zh. Walking more than a mile	1	2	3
Z. Walking several blocks	1	2	3
I.Walking one block	1	2	3
K. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
(Circle one option in each line):

	Yes	No
A. Cut down the amount of time you spent on work or other activities	1	2
B. *Accomplished less* than you would like	1	2
V. Were limited in the *kind* of work or other activities	1	2
G. Had *difficulty* performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
(Circle one option in each line):

	Yes	No
A. Cut down the amount of time you spent on work or other activities.	1	2
B. *Accomplished less* than you would like	1	2
V. Didn't do work or other activities as *carefully* as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Circle one number.)

Not at all..... 1
Slightly..... 2
Moderately 3
Quite a bit..... 4
Extremely..... 5

7. How much bodily pain have you had during the past 4 weeks? (Circle one number.)

None..... 1

Very mild 2

Mild..... 3

Moderate 4

Severe 5

Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (circle one number)

Not at all..... 1

A little bit 2

Moderately 3

Quite a bit..... 4

Extremely..... 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. (Circle one number in each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
A. Did you feel full of pep?	1	2	3	4	5	6
B. Have you been a very nervous person?	1	2	3	4	5	6
V. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
G. Have you felt calm and peaceful?	1	2	3	4	5	6
D. Did you have a lot of energy?	1	2	3	4	5	6
E. Have you felt downhearted and blue?	1	2	3	4	5	6
Zh. Did you feel worn out?	1	2	3	4	5	6
Z. Have you been a happy person?	1	2	3	4	5	6
I.Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is each of the following statements for you? (circle one number on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
A. I seem to get sick a little easier than other people.	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
V. I expect my health to get worse	1	2	3	4	5
G. My health is excellent.	1	2	3	4	5

The questionnaire domains:

1. Physical Functioning (PF)
2. Role (physical) functioning (RP)
3. Pain (P)
4. General Health (GH)
5. Vitality (VT)
6. Social Functioning (SF)
7. Role emotional (RE)
8. Mental Health (MH)

All scores are put together into 2 total measurements — physical (1-4 scales) and mental (5-8 scales) health.

Calculation of the main parameters in the SF-36 questionnaire

Domain	Questions	Minimum and maximum values	Score range
Physical functioning (PF)	3a, 3b, 3v, 3g, 3d, 3e, 3zh, 3z, 3i, 3k	10–30	20
Role (physical) functioning (RP)	4a, 4b, 4v, 4g	4–8	4
Pain (P)	7, 8	2–12	10
General health (GH)	1, 11a, 11b, 11v, 11g	5–25	20
Vitality (VT)	9a, 9d, 9zh, 9i	4–24	20
Social functioning (SF)	6, 10	2–10	8
Role emotional (RE)	5a, 5b, 5v	3–6	3
Mental health (MH)	9b, 9v, 9g, 9e, 9z	5–30	25

In points 6, 9a, 9d, 9g, 9z, 10, 11, the score is obtained by reverse count.

Calculation formula:

[(real value) – (minimum possible value)] : (possible range of values) × 100.

Requirements for presentation of results:

1) specified number of observations per parameter;
2) descriptive statistics — M ± SD, Me (LQ; UQ), % (n/N);
3) score accuracy (p-value); CI (for key survey results) and p-value;
4) report the implemented statistical methods (parametric and nonparametric) and software.

Recommended statistical packages for processing results are StatSoft Statistica v.6.0, SPSS 9.0.