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Identification of genetic polymorphisms associated with complicated postoperative course and unsatisfactory outcomes of reconstructive interventions on the facial skull bones using bone autografts

Abstract

Introduction
Enhancing the effectiveness of reconstructive and restorative operations in patients with the facial skull bone defects and the prevention of complications in the postoperative period is a pressing issue in modern maxillofacial surgery. One of the promising directions in addressing this problem is the application of a personalized approach to choosing the treatment strategy in patients, including that one based on the study of genetic predisposition to metabolic disorders and reparative regeneration of bone tissue. A number of genes associated with the main mechanisms regulating remodelling and reparative regeneration of bone have polymorphisms, which have been proven to increase the risk and unfavorable progression of osteoporosis. However, their potential impact on bone regeneration and remodelling of bone grafts in the replacement of jaw defects and pre-implantation preparation has not been studied.

Objective
To identify genetic polymorphisms that most significantly affect the processes of bone tissue regeneration and remodelling of free bone autografts, as well as those associated with an increased risk of complications in patients following the replacement of jaw defects and pre-implantation preparation (augmentation of the alveolar processes).

Materials and methods
The study included 40 patients who underwent replacement of jaw defects and augmentation of alveolar processes using free bone autografts obtained from local and distant donor zones. In all patients, 16 genes and their polymorphisms that affect bone tissue metabolism and increase the risk of osteoporosis were analyzed using PCR. The effectiveness of surgical interventions, the frequency and nature of postoperative complications were studied in the immediate and late postoperative period using clinical methods and CBCT. The effect of genetic polymorphisms on the risk of complications and unfavorable outcomes of surgical interventions was studied by univariate and multivariate logistic regression models, calculating odds ratios with 95% CI. A significance level of $p<0.05$ was considered statistically significant.

Results
Among 40 patients, 14 experienced various complications related to the development of inflammatory processes, disruptions in reparative regeneration, and remodelling of the graft in the recipient area. An increase ($p<0.05$) in the risk of complications was found for patients with polymorphisms of the RANKL CT genes [rs9594738] and RANKL CT [rs9594759], with odds ratios (OR) of 6.1 (95% CI 1.1-34.0) and 6.1 (95% CI 1.1-35.0) respectively, as well as an increased risk ($p<0.02$) for patients with the ESR1: -397 T>C gene, OR=13.5 (95% CI 1.5-124).

Conclusions
Genetic polymorphisms associated with an increased risk of osteoporosis and metabolic disorders of bone tissue likely influence the course of the postoperative period in patients who underwent reconstructive surgeries and pre-implantation preparation on the upper and lower jaw. The greatest effect on the risk of complications, including the loss of bone grafts, was observed with polymorphisms RANKL CT [rs9594738], RANKL CT [rs9594759], ESR1: -397 T>C, associated with the RANK-RANKL-OPG signalling pathway. The widespread application of techniques for detecting these polymorphisms in clinical practice for diagnostic and prognostic purposes requires further study and validation of these candidate genes in larger cohorts of patients from different ethnic groups, as well as the use of methods for multifactorial assessment of various genetic and epigenetic factors.

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Keywords

Bone grafting, gene polymorphisms, complications, wound healing, pre-implantation preparation, bone tissue, reconstructive surgery.

INTRODUCTION

The processes of bone regeneration and remodelling have been actively studied over the past decades, including for the purpose of developing new treatment approaches in patients with bone fractures, for replacing bone defects, and for osteointegration of implants. Significant achievements in this direction have been associated with the introduction of new therapeutic strategies, such as guided tissue regeneration, tissue engineering, the use of stem cells, CAD/CAM technologies, and the improvement of fixation elements. Modern maxillofacial surgery and surgical dentistry possess a wide range of manipulations aimed at replacing bone defects, creating additional bone volume in areas of its existing deficit, and optimizing the physical-mechanical properties of bones in zones of interest (1). Despite this, the results of reparative regeneration and remodelling of bone transplants in patients with defects and deformations of the facial skull bones and/or bone deficiency in dental defects often turn out to be unpredictable and vary greatly among different patients. Along with certain achievements, contemporary literature also reports complications that occur in the early and late postoperative period, qualitatively changing the course of biological processes and leading to clinical failures (2). These include infection and rejection of bone transplants, their excessive resorption, and inadequate fusion/integration with the bone tissue of the recipient area.

The authors point out the higher frequency of complications and unsatisfactory clinical outcomes in patients belonging to the "risk group", which is determined by the confluence of unfavorable factors related to the general condition of the patient, local conditions at the site of intervention, and, last but not least, genetic predisposition. The accumulation of clinical evidence supporting the likely impact of a number of genetic and epigenetic factors on the course of biological processes of reparative regeneration and remodelling of bone underscores the need for a personalized approach to choosing a treatment strategy in patients requiring reconstructive and bone-plastic operations on the facial skull bones and in pre-implantation preparation. Effective prevention of complications, according to the authors, implies researching the causes and risk factors to find optimal ways of affecting certain links in the pathogenesis in patients with an increased risk of an unfavorable postoperative course. Deepening the understanding of the mechanisms of complication development and the regulation of bone metabolism will also allow for the selection of a treatment strategy based on clear objective criteria and reduce the impact of subjective factors in decision-making, prognosis, and implementation of the treatment plan (3).

It is known that bone tissue is a complex dynamic system that interacts with the surrounding environment to effectively distribute stresses and deformations (4,5). This is based on the process of permanent adaptive remodelling of bone – changes in its structure and properties depending on varying load conditions (6-8). The signals that initiate this process have not yet been precisely identified. To date, it has been proven that key mechanisms regulating the structural-functional state of bone include the RANK-RANKL-OPG pathway, associated with the secretion of RANKL molecules and its inhibitor – osteoprotegerin by osteoblasts. RANKL is an activator of RANK–surface-bound receptor of osteoclasts, which in turn activates the nuclear factor kappa-beta (NFkβ) and macrophage colony-stimulating factor (M-CSF). These lead to the activation of differentiation and increased activity of bone cells. Other important molecular mechanisms include the Wnt signalling pathway, receptors for estrogens and vitamin D, etc. These mechanisms are genetically determined and associated with the expression of corresponding genes. (9,10). The effect of allelic variations of genes associated with regulatory mechanisms of bone tissue metabolism has been studied in a series of works (11,12). It has been established that there are certain genetic polymorphisms that affect the risks of osteoporosis, resorptive fractures, and delayed reparative regeneration. These polymorphisms have not been extensively studied in modern maxillofacial surgery, and their diagnostic and prognostic significance in reconstructive jaw surgery and pre-implantation preparation is not evident (13).

The aim of this study was to identify genetic polymorphisms that most significantly affect the process of bone tissue regeneration and the remodelling of free bone autografts, as well as those associated with an increased risk of complications in patients after jaw defect replacement and pre-implantation preparation (augmentation of alveolar processes).

MATERIALS AND METHODS

This prospective study examined the immediate and long-term outcomes of reconstructive operations on the upper and lower jaws, including augmentations of the alveolar process during preparating patients for the placement of dental implants. The study involved 40 patients (22 women and 18 men), aged between 18 and 62 years (average age 41.7±9.1). All patients underwent surgery at the Department of Surgical Dentistry of the Bogomolets National Medical University Dental Medical Center and the Department of Maxillofacial Surgery of the Kyiv Regional Clinical Hospital during the period from 2020 to 2023.

The study included patients with jaw defects (including

The genetic polymorphisms studied in patients during the research

Genetic Polymorphism	Function
COL1A1:-1997 C>A	collagen type I alpha 1 chain – encodes the α1 subunit of type I collagen, which forms fibrils of connective tissue. Polymorphism of this gene leads to a disturbance in the ratio of α1 and α2 chains and changes in the molecular structure of the protein.
COL1A1: 1546 G>T	
CYP19A1 A>G	Aromatase plays a key role in the biosynthesis of estrogens. It stimulates the proliferation and activity of osteoblasts and inhibits their apoptosis.
CYP19A1 C>T	
ESR1: -397 C>T	They encode the alpha receptor of the estrogen hormone, which participates in the development of the musculoskeletal system.
ESR1: -351 G>A	
IL6 -174 G>C	Encodes cytokine (IL-6), which is involved in inflammatory reactions; stimulates the maturation of B lymphocytes, induces osteoclasts.
LRP5 1999 G>A	Low-density lipoprotein receptor-related protein 5 – a co-receptor of the Wnt/beta-catenin signalling pathway; stimulates the proliferation of osteoblasts.
LRP5 3989 C>T	
RANKL C>T [rs9594738]	Receptor activator of nuclear factor kappa-B ligand or – a ligand for TNFRSF11B receptors, a key factor in the differentiation and activation of osteoclasts.
RANKL C>T [rs9594759]	
TNFRSF11B 245 A>C	Tumor Necrosis Factor Receptor Superfamily Member 11b or osteoprotegerin - a cytokine receptor, which, when bound to RANKL, inhibits the differentiation of osteoclasts.
TNFRSF11B 245 A>G [rs4355801]	
TNFRSF11B 163 T>C	
VDR 283 A>G	D3 receptor- encodes a receptor that binds vitamin D3; participates in calcium metabolism.
VDR: 2 A>G (Lys2Arg) [FokI]	

Tab. 1 Stress perceived between different age groups during pregnancy

pronounced atrophy of the alveolar process) that were replaced with autologous bone grafts from regional (chin or external oblique line of the lower jaw) or distant (iliac crest) donor sites. Exclusion criteria were as follows: patients under 18 years of age, the presence of concomitant somatic pathology in decompensation, oncological and mental illnesses, HIV infection, pregnancy and lactation, non-compliance with medical recommendations, or refusal to participate in the study.

Positive outcomes of the reconstructive operation were considered to be the absence of complications in the early and late postoperative periods, and normal course of reparative regeneration and remodelling of the graft. Negative outcomes were considered to be the development of complications: infection of the operation area and the development of purulent-inflammatory processes in the bone and surrounding soft tissues, suture dehiscence, exposure of fixation elements (screws, plates, meshes, patient-specific implants), loss of the graft associated with its rejection, sequestration, or excessive (more than 90%) resorption. In cases where several complications occurred in one patient, only the most severe was considered.

As potential predictors/risk factors of complications, polymorphisms of genes that are potentially associated with the risk of osteoporosis and bone metabolism disorders, according to literature data, were studied (Table 1).

All patients underwent a comprehensive clinical and radiological examination using CBCT (Cone Beam Computed Tomography) on a PlanmecaProMax 3D tomograph before undergoing surgical interventions. The control of the early (up to 1 month) and late (up to 1 year) postoperative periods was based on control examinations and control tomographies, which were performed at intervals of up to 1 month, 3 and/or 6 months, and 12 months after surgery.

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Tab. 2 Genetic polymorphisms identified in the patients of the studied series

Genetic Polymorphism	Homozygote for the Mutant Allele %	Hetero-zygote %	The Impact of Genetic Polymorphisms on the Risk of Complications	
			Value 2	P
COL1A1:-1997 C>A	0	40	0.07	p>0.05
COL1A1: 1546 G>T	0	35	0.39	p>0.05
CYP19A1 A>G	17.5	65	1.6	p>0.05
CYP19A1 C>T	_0	12.5	0.06	p>0.05
ESR1: -397 C>T	27.5	52.5	14.6	p<0.001
ESR1: -351 G>A	17.5	52.5	0.1	p>0.05
IL6 -174 G>C	22.5	50	0.3	p>0.05
LRP5 1999 G>A	2.5	22.5	1.3	p>0.05
LRP5 3989 C>T	12.5	35	0.18	p>0.05
RANKL C>T [rs9594738]	26	74	4.06	p<0.05
RANKL C>T [rs9594759]	33	67	3.2	p<0.05
TNFRSF11B 245 A>C	0	10	0.4	p>0.05
TNFRSF11B 245 A>G	42	58	0.01	p>0.05
TNFRSF11B 163 T>C	8	92	1.0	p>0.05
VDR 283 A>G	41	59	0.02	p>0.05
VDR: 2 A>G (Lys2Arg) [FokI]	43	57	0.06	p>0.05

163 T>C; VDR 283 A>G; VDR 2 A>G

Amplification was by real-time PCR on an Applied Biosystems™ 7500 Real-Time PCR System (Life Technologies Corporation, USA) with reagents from NPF "Litech". Genomic DNA samples were isolated from stabilized blood using the Genomic DNA Mini Kit (Invitrogen, USA). These studies were conducted in the laboratory of the Research Institute of Experimental and Clinical Medicine at the Bogomolets National Medical University.

To determine the nature of the sample distribution, the Kolmogorov-Smirnov test was used. Statistical analysis of the obtained data involved calculating mean values, standard deviation, and standard error of the mean (for quantities that followed a normal distribution). For qualitative characteristics, the frequency of their occurrence was determined in percentages. The significance of discrepancies relative to the main resulting parameters was assessed using the Pearson's chi-square ($\chi 2$) test.

Subsequently, univariate and multivariate logistic regression models were constructed to determine factor characteristics (genes and their polymorphisms) and their impact on the resulting parameters (complications in the early and late postoperative stages). Threshold/critical values for the risk of complications were determined using ROC curve analysis and the Youden index. This involved evaluating the area under the ROC curve (AUC) and 95% CI. Odds ratios (OR) with 95% CI were calculated to assess the impact of risk factors. A significance level of $p<0.05$ was considered statistically significant. The analysis was conducted using the statistical package EZR v.1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) (14).

The clinical research was organized due to the principles of bioethics and patient rights were ensured in accordance with the Helsinki Declaration (2008) and the Basic Legislation of Ukraine on Healthcare (1992). The study materials were reviewed by the Bioethics Committee of the Bogomolets National Medical University (Protocol № 139 dated 26.11.2020).

RESULTS

Among the studied patients, genetic polymorphisms associated with an increased risk of osteoporosis were quite common (Table 2).

Analysis of treatment results revealed that various forms of complications occurred in 14 (32.5%) patients. In patients who received bone grafts from regional

Value	Model coefficient, b m	Significance, p	OR (95%CI)	AUC (95% CI)
RANKL C>T [rs9594738] Homozygote CC	Reference p<0.05			
RANKL C>T [rs9594738] CT, TT	1.79±0.9	<0.05	6.1 (1.1-34.0)	0.7(0.53-0.84)
RANKL C>T [rs9594759] Homozygote CC	Reference p<0.05			
RANKL C>T [rs9594759] CT, TT	1.8±0.9	<0.05	6.1(1.1-35.0)	0.7(0.54-0.85)
ESR1: -397 T>C, Homozygote CC	Reference p<0.05			
ESR1:-397 CT, TT	2.6±1.2	<0.02	13.5(1.5-124)	0.81(0.66-0.95)

Tab. 3 Univariate logistic regression models for genes likely associated with the risk of postoperative complications.

areas (chin, external oblique lines of the lower jaw), the frequency of complications was 30.7% (4 out of 13 patients), and for iliac crest grafts, it was 33% (10 out of 27 patients). The structure of complications was dominated by infectious, purulent-inflammatory processes. Complete loss of the bone graft, due to infection, sequestration, or excessive resorption, was noted in 6 patients (15%), exposure of fixation elements with wound edge dehiscence occurred in 2 cases (5%), and in addition, infection of the surgical wound with suppuration of bone and soft tissue, not accompanied by loss of grafts, was present in 6 cases (17.5%). In accordance with the research objective, the genes and their polymorphisms (factor characteristic) that most significantly affect the course of bone tissue regeneration processes and are associated with disturbances in regenerative processes (resulting characteristic) were identified in patients after reconstructive interventions in the maxillofacial area. In univariate logistic regression models, the authors evaluated16 candidate genes that could influence complications. To identify a set of independent factor characteristics associated with the risk of complications, we selected independent risk factors.

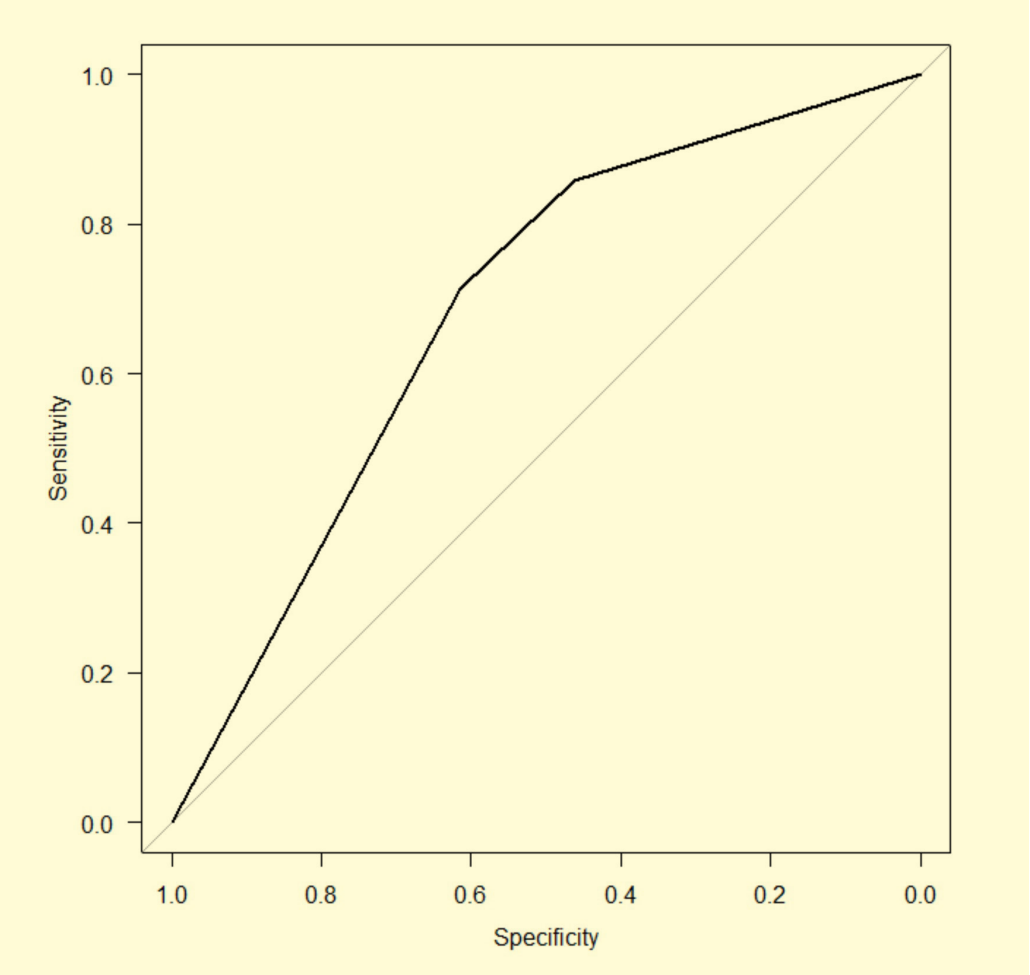

Fig. 1 The operating values curve for the univariate model predicting complications for the RANKL C>T gene [rs9594738]. AUC =0.7 (95% CI 0.53-0.84).

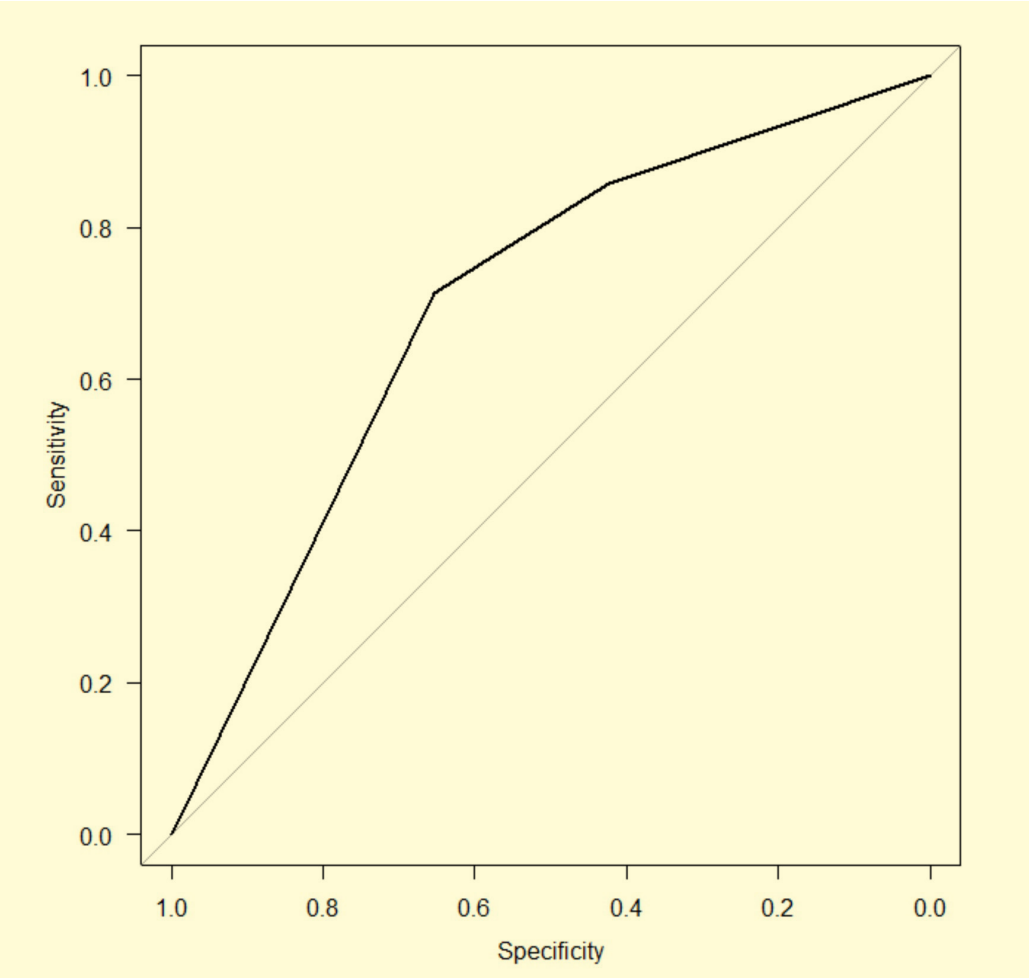

Fig. 2 The operating values curve for the univariate model predicting complications for the RANKL C>T gene [rs9594759]. AUC =0.7 (95% CI 0.54-0.85).

Among them are the factors with a significance level of <0.05 (Table 3).

The factor models based on the identified characteristics proved to be adequate, with the AUC indicating a strong association with the risk of complications (Fig. 1-3).

We found an increased risk ($p<0.05$) of complications for patients with polymorphisms in the RANKL CT [rs9594738] and RANKL CT genes [rs9594759], with an odds ratio (OR) of 6.1 (95% CI 1.1-34.0) and OR=6.1 (95% CI 1.1-35.0), respectively, compared to patients without polymorphisms in these genes. Additionally, there was an increased risk ($p<0.02$) for patients with the ESR1: -397 [T.TT] genotype, with an OR=13.5 (95% CI 1.5-124), compared to patients with ESR1: -397 TC, CC gene polymorphisms.

The multifactorial logistic regression model, formed from the aforementioned factor characteristics (genes and their polymorphisms), did not reveal an increased risk of complications in patients in the postoperative period when combining several unfavorable genotypes

DISCUSSION

Undoubtedly, the course of the postoperative period in patients undergoing facial bone surgeries, including using the bone grafts for replacing existing bone defects and creating additional volume during pre-implantation preparation, is significantly affected by genetic and epigenetic factors. The action of these factors in various combinations through complex mechanisms of regulation of reparative regeneration and bone remodelling leads to significant variability in the results of surgical interventions, which do not always satisfy patients and surgeons.

While the role of factors related to the general condition of patients, local conditions at the site of intervention, and the specifics of surgical techniques have been thoroughly studied in the research, the role of genetic factors remains largely unexplored. Currently, there is information regarding the impact of genetic polymorphisms on the development and course of infectious processes, wound healing, scar formation, and bone tissue metabolism. The latter has mainly been studied in the context of potential impact on the development of osteoporosis and has been linked to regulatory mechanisms that ensure the functioning of bone tissue. In this context, a number of genes responsible for osteogenesis, the metabolism of bone tissue in physiological and pathological states, and their specific polymorphisms capable of disrupting this process at the cellular level in the "inhibitor-receptor"

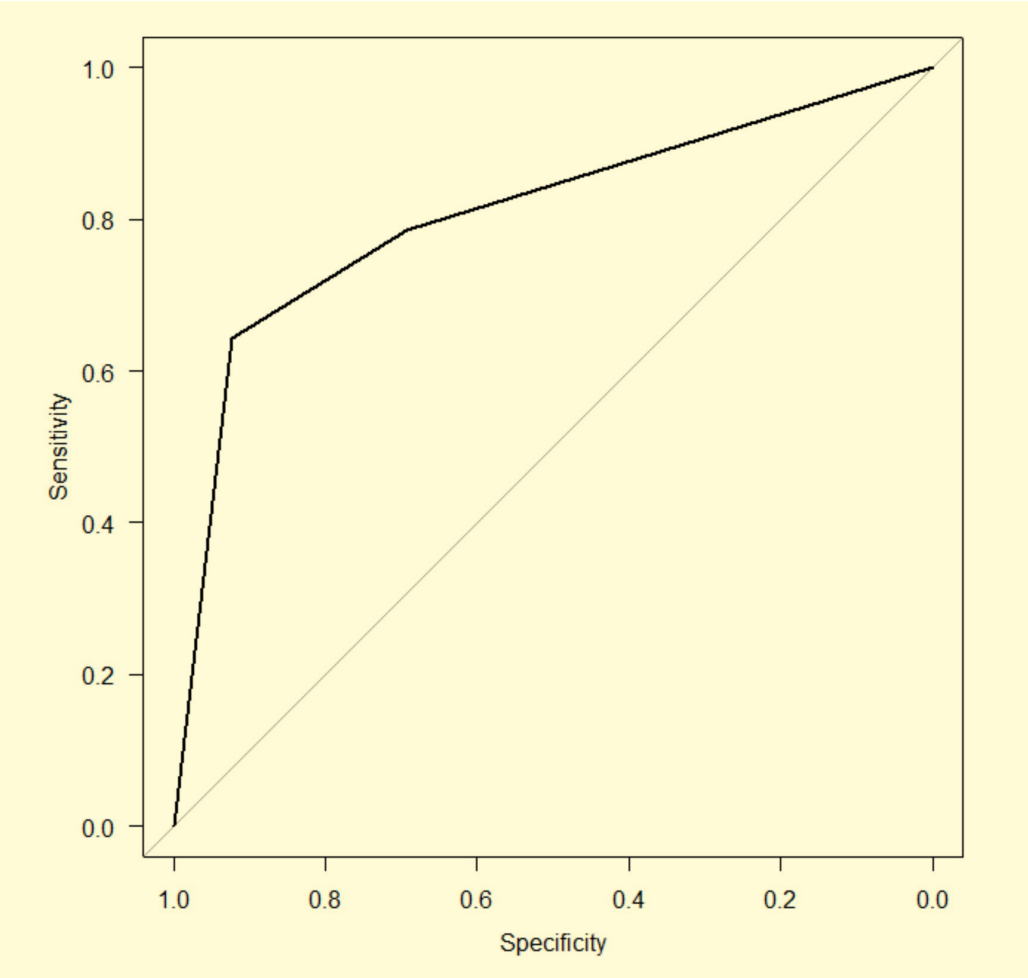

Fig. 3 The operating values curve for the univariate model predicting complications for the ESR 1[C>T] gene. AUC =0.81 (95% CI 0.66-0.95).

system have been identified.

These include genes responsible for the synthesis of collagen, estrogen receptors, aromatase, proteins that provide the Wnt/beta-catenin signalling pathway, certain interleukins, receptors for vitamin D3, RANKL, TNF, etc. The authors associate disturbances in the mechanisms of regulation associated with these proteins with the development of severe osteoporosis, craniosynostosis, and other musculoskeletal pathologies, including those of the craniofacial region (15). However, the impact of genetic polymorphisms on complications during bone tissue remodelling following surgery for defect replacement or targeted tissue regeneration for subsequent dental implant placement stays almost unexplored.

In the research we studied the effect of polymorphisms in 16 different genes associated with an increased susceptibility to osteoporosis on the risk of complications in patients after jaw reconstruction by various types of bone grafts ed. Here, the highest risk of complications was associated with polymorphisms in genes responsible for the synthesis of RANKL (Receptor activator of nuclear factor kappa-B ligand or TNF RSF11B ligand), which is a key factor in the differentiation and activation of osteoclasts through the RANKL-RANK-OPG cytokine system. RANKL is a type II transmembrane glycoprotein belonging to the tumor necrosis factor (TNF) family (16,17). It is produced by cells of the osteoblast lineage, T lymphocytes, B lymphocytes, and megakaryocytes and, apart from its effect on osteoclasts, plays a significant role in T-cell immune response (18,19). The expression of this glycoprotein is regulated by many factors: glucocorticoids, vitamin D3, IL-1, TNF-α, TGF-β, Wnt ligand signalling pathway, and LPS (20,21).

Lukasz Czupkallo pointed out that the expression of RANKL is suppressed by 17β-estradiol, IL-13, TGF-β1, but vitamin D3, IL-1β, IL-6, IL-7, IL-11, IL-17, TNF, PTH, IFN-γ, prostaglandin E2 (PGE2), facilitate its expression in the presence of the active macrophage colony-stimulating factor (M-CSF) (22). The interaction of RANKL, its receptor RANK, and antagonist OPG, through a complex cascade of reactions, normally determines the balance of bone formation and resorption processes that continue throughout the life of the organism (23-25).

Another gene whose polymorphisms likely influenced the risk of complications in the patients was ESR1, which encodes the alpha receptor for the hormone estrogen. The estrogens act through two types of receptors: ERα and ERβ, but their distribution depends on the type of bone tissue (ERα is predominantly found in cortical bone, while ERβ is in trabecular bone). Estrogen receptors

are expressed in bone marrow stromal cells, osteoblast precursors, T and B cells, among others (24). Estrogen receptors are closely related to the aforementioned RANK-RANKL-OPG signalling pathway. Their activation is associated with the suppression of TNF gene expression, as well as a decrease in osteoclast sensitivity to RANKL. This results in reduced osteoclastic activity affected by estrogens (26,27). Estrogens, acting through the receptor system, also reduce apoptosis of osteoblasts and increase their functional activity (28,29).

The mechanisms mediated by RANKL link the bone and immune systems of the body, which are regulated by related groups of biologically active molecules. This is why, in our study, where disturbances in the process of reparative regeneration and remodelling of bone were closely associated/caused by the development of infectious purulent-inflammatory processes, the impact of corresponding genetic polymorphisms was found to be the highest. Concurrently, the development of the infectious process depended not only on the characteristics of the reparative regeneration of bone and its structural-functional state but also on the condition of the soft tissues, defensive mechanisms, including immune responses, the state of hemodynamics, etc. This, to some extent, explains the lack of a significant impact of polymorphisms in other genes responsible for bone metabolism on the frequency of complications with the given number of observations.

Szewczyk J. and colleagues identified a statistically significant impact of the IL-1B-511 gene polymorphism on the course of reparative regeneration processes and the formation of bone mineral density in patients with alveolar process defects (30). Other authors, such as Lin YH (2007), Gayathri R (2011), Cattabriga M (2001), reached similar results, studying bone tissue resorption around dental implants, in periodontal patients (31-33). In our study, we did not investigate polymorphisms of the IL-1 genes; however, polymorphisms of other pro-inflammatory cytokine genes (for example, IL6), given the number of observations, did not show a significant impact on the frequency of complications in the patients.

Overall, our research confirmed the role of genetic factors in the processes of reparative regeneration and bone remodelling in the early and late postoperative periods in patients who underwent reconstructive interventions on facial bones. We identified gene polymorphisms, predominantly associated with the RANK-RANKL-OPG signalling pathway, which potentially have the greatest diagnostic and prognostic value in this category of patients. The presence of polymorphisms in genes RANKL CT [rs9594738], RANKL CT [rs9594759], and ESR1: -397 [T.TT] was significantly associated with a higher frequency of complications, including complete loss of the graft. At the same time, it should be noted that the course of the postoperative period in patients with bone defects is influenced by a large number of internal and external factors, which significantly affect the final outcome and probably have no less significance than genetic predisposition (34). The development of complications, which in our series were predominantly of an infectious, purulent-inflammatory nature, depended on the condition of the soft tissues, local hemodynamics, and immunity, no less than on genetically determined features of the structure and functionstate of bone tissue. Therefore, the question of the possible diagnostic application of the genes-candidates we identified requires further study on larger cohorts of patients from different ethnic groups, as well as the use of methods for multifactorial assessment of various genetic and epigenetic factors..

CONCLUSIONS

Genetic polymorphisms associated with an increased risk of osteoporosis and metabolic disorders of bone tissue significantly influence the course of the postoperative period in patients after reconstructive surgeries and pre-implantation preparation of the upper and lower jaw. The greatest effect on the risk of complications, including the loss of bone grafts, was observed with polymorphisms and genes RANKL CT [rs9594738] ($\chi 2$= 4.06), RANKL CT [rs9594759] ($\chi 2$= 3.2), ESR1: -397 T>C ($\chi 2$= 14.6), ($p<0.05$), associated with the RANK-RANKL-OPG signalling pathway. The univariate logistic regression models we created allow for the prediction of the risk of surgical failures in this category of patients with a sufficient level of sensitivity and specificity. However, the widespread application of techniques for detecting these polymorphisms in clinical practice for diagnostic and prognostic purposes requires further study and validation on larger cohorts of patients from different ethnic groups, as well as the use of methods for multifactorial assessment of various genetic and epigenetic factors.

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