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Paradigm shift from reactive treatments to predictive approach, targeted prevention and personalisation of medical services in dentistry: Multi-professional view

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Periodontal health as the key to the paradigm shift from reactive to predictive, preventive and personalised medicine

In dentistry, reactive treatments of manifested disorders still represent the golden standard as evident from alarming epidemiologic statistics globally. To this end, 100% prevalence of dental caries in the Russian population has been demonstrated followed by clinically manifested periodontal diseases. In contrast, *making a complex dental care tailored to the person to promote population health in the frame-work of predictive, preventive and personalised (3P) medical approach* is considered cost-effective and ethical approach benefitting population at large [1]. Noteworthy, the prominent risk factors and comorbidities linked to the severe disease course and poor outcomes in COVID-19-infected individuals, such as elderly, diabetes mellitus, hypertension and cardiovascular disease, are frequently associated with significantly altered oral microbiome profiles, systemic inflammatory processes, poor oral and dental health. Consequently, the issue-dedicated expert recommendations are focused on the perio/dental health to improve individual outcomes and reduced morbidity under pandemic conditions. Innovative screening programmes predictive diagnostics and adapted treatment schemes are crucial for the complex person-tailored perio/dental care to improve medical services provided to the population. 3PM concepts distinguish between primary, secondary and tertiary healthcare. Predictive approach in individualised primary care is considered most cost-effective.

How important is primary prevention of disease against the background of a fully healthy patient?

It is crucial for the preservation of existing health. It is especially important for young people, regardless of their gender, in terms of identifying future diseases with regard to genetics, lifestyle and nutrition, and occupation. Of course, we understand that here there is not only a significant difficulty in the physician's activity itself (increasing knowledge of related specialties and the ability to record and interpret laboratory results), but also the lack in many (all?) countries of regulatory bodies and standards of medical care in terms of disease prevention and prophylaxis. The age shift in detection of new diseases (strokes, myocardial infarction, cancer and others) towards a younger age now makes it necessary to introduce this approach. We will try to use specific examples to explain the above.

What should this approach to pathology prevention look like at the dental office?

There is an urgent need to monitor and prevent carious and non-carious dental hard tissue lesions and periodontal disease in the practice of dentistry. To solve this problem, we should not form any new positions, but it is the responsibility of all dentists to do it at any preventive examination or spontaneous patient's visit to the doctor. It is not necessary to identify patients with a complete absence of dental caries, it is enough to pay attention to other intact (fully clinically healthy) teeth during treatment of already existing pathologies, to identify visually undetectable foci of demineralization in enamel, for example by photo-induced fluorescence method. Policy decisions by the medical administration are also needed to initiate such work. Such an approach will eventually produce a significant economic effect, which is difficult to determine right now, but this effect will affect not only medical organizations, but also patients.

How can we prevent caries in healthy teeth in the presence of caries in other teeth?

As mentioned above, it is especially important to prevent caries in intact teeth when patients come to the dentist with one or more teeth affected by caries. This kind of activity of dentists can be called secondary prevention of caries, if we mean the condition of the whole mouth or prevention of caries in intact teeth not affected by caries, that is to carry out primary prevention of caries in individual teeth. In the presence of caries in other teeth, this approach, in our opinion, is of great importance, since patients themselves go to the dentist and he only has to pay attention not only to the teeth with caries, but also to intact teeth. This work is not time consuming and does not require much specialization, because only light-induced fluorescence is used to identify hidden to the eye foci of enamel demineralization in the form of spots when exposed to green light. For this purpose, there are also special devices developed in Voronezh (the device of local red light irradiation "ULOX" and "Stomasvet"). This type of activity prevents not only dental caries, but, as mentioned earlier, most of the non-carious dental diseases that occur from disorders of metabolic processes in the hard tissues at the preclinical level. This will help save money for patients and the budget of dental organizations. Instructions for dentists on this type of activity can be voiced in conference presentations, instructional guidelines (printed and digital).

Are there criteria for assessing the development and risk factors of caries?

These criteria were developed at N.N. Burdenko All-Russian State Medical University and tested by EGOHID system - "Global European program of dental health indicators development", which evaluates dental status and caries risk factors according to a number of criteria, including self-assessment of teeth appearance, compliance with proper brushing regime, frequency of toothache and more than 40 other components. This approach enhanced population-based monitoring and improved prevention by unifying the approach to dental caries risk assessment. This activity was carried out in 666 high school students in Voronezh, Russia (472 people) and Adana, Turkey (194 people).

What does the preventive direction look like with respect to periodontal health?

An element of prevention can be the wider implementation of already available methods of diagnosis and therapy. As an example of secondary prevention of periodontal pathologies (chronic periodontitis in particular), the use of the "Vector" apparatus system improved the therapeutic effect in the form of bone regeneration in more than 52% of cases, which contributes to the prevention of aggravation in patients who are at risk of developing this pathology.

But to avoid the existentialism of concentrating applied approaches around subjective, often casuistic experiences, a world-renowned structure such as EPMA is needed. Even better, if, after discussion at EPMA and appropriate decisions, this type of primary and secondary prevention of dental hard tissue diseases of

patients is recommended by EPMA and accepted organizationally in different countries, and in each country, at the level of medical associations and authorities.

What is the main problem that may arise in the personalized therapy of the identified pathology?

It should be based on the correction of the identified disorders of the patients' organs and organ systems that affect oral pathology. This activity requires the involvement of non-dental diagnostic and treatment laboratory and clinical systems, which can also be governed by policy and organizational decisions and recommendations. The problem is that one of the main directions of such activity should be the advanced training of doctors in related specialties, which will ultimately determine the high quality of specialists' work.

What achievements in the prevention of dental diseases can already be noted?

In Russia, in Voronezh region, in the structures of Burdenko All-Russian State Medical University and multi-profile clinic "Olympus Zdorovya" this type of activity has been used for a long time (more than 5000 patients). The results of this work have been discussed closely (statistically) for the last 5 years. For this purpose, the centre of individual prophylaxis of caries and the international league of individual prophylaxis of oral diseases headed by Prof. A.A. Kunin have been working in Burdenko All-Russian State Medical University for more than 10 years.

In addition to caries, it is of great importance for periodontal disease. At the age of 16-26 years, with the proper help (both from the dentist and other specialists) you can achieve the complete elimination of future pathology or significantly reduce its manifestations. When treating existing periodontal disease it is necessary to conduct secondary prevention after the complete elimination of the pathological process in order to avoid atrophy of the jawbone tissue and the need for costly treatments in the future (implantology, complex prosthetics, high-tech surgical interventions). Our experience in treatment, prevention and prophylaxis of periodontal pathology based on large contingent of patients (1240 people) shows the necessity of such approach. We have held training seminars, master classes not only in Russia, but also in Germany, Lithuania, Latvia, Estonia, Turkey, Azerbaijan. But the implementation of this approach is still at a low level.

Why does the introduction of the prophylactic approach meet resistance in clinical structures?

Because, as with dental hard tissue diseases, it is necessary to regulate in other countries and cities recommendations for such medical activities, the success of which, according to studies by the Burdenko Higher Medical School (over 3000 patients), is quite significant. In this case, it is EPMA not only implementing reports and publications on this topic, but also issuing methodological guidelines and recommendations, able to track their implementation through its representatives in various countries (and maybe special working groups) summarizing such activities.

How does EPMA help its institutional members achieve significant results in PPPM promotion?

N.N. Burdenko Moscow State Medical University has been an institutional member of EPMA for 10 years. This has made it possible not only to intensify scientific research and the implementation of its results in medical institutions in Voronezh and Russia, but also, with the support of EPMA, to translate the results obtained at the European level.

This approach is especially important for young patients as it will allow to reduce the number of patients suffering from caries and periodontal pathologies when they reach 40 and more years of age.

Significant effect was achieved in the treatment and prevention of dry mouth. Conducting a screening of dental students at the Burdenko All-Russian State Medical University (over 500 people), we concluded that this symptom is typical for a large number of diseases (Flammer syndrome, mycoses, diseases of the gastrointestinal tract, nervous system, etc.).

Moreover, in a certain percentage of cases (up to 20%), pathologies of various organs and systems already determine differences in diagnostic methods of investigation and in most cases claim to be an early diagnostic sign of an emerging pathology.

Importance of the diagnostic approach and risk assessment will be discussed using the example of identifying oral fungal microflora

It is known that yeast-like fungi of the genus *Candida*, along with streptococci, staphylococci and others, are natural "inhabitants" of the oral cavity. Their detection should be single (up to 3-4 blastospores in the field of view). And it does not depend on the presence or character of plaque on the tongue, which is determined by the nature of the food taken, which is not always healthy. According to our data, among 1112 young people examined (up to 35 years old), 368 (33%) had up to 8-12 elements of yeast-like fungi in each field of vision and allowed to reveal active form of catarrhal or erosive-ulcerative gastritis at FGDS when there were no complaints with the only symptom being dryness of the mouth. This symptom gave insignificant quantitative increase of fungal microflora, which depended on the presence of gastric pathology without clinical manifestations. In addition, other pathological processes were also revealed: propensity to stress, allergic pathologies, Flammer syndrome, skin diseases were diagnosed in the presence of other symptoms. Our studies have proved that dry mouth is not a permanent symptom, depending on the intake of food, but a statement of the arisen pathology of the body. DRC Group, a renowned European manufacturer of R.O.C.S. moisturizing toothpaste, studied more than 500 patients with dry mouth among young people in Voronezh. In 45% of them, when using this paste for a year, the manifestations of dry mouth were eliminated, while the rest had one or another pathology of organs or systems of the body that required therapy. But for realization of such approach it is necessary for dentists to acquire additional knowledge about general somatic pathologies. Although in Russia, dental students in the relevant departments study all types of human pathologies, apparently, they still do not focus their attention enough on non-dental pathologies. In this regard, for the active implementation of the prediction and prevention of diseases of the body through dental manifestations appropriate organizational and training actions are needed.

Undoubtedly, the majority of dentists should possess such knowledge, which allows the prevention and detection of organ pathology through the dental status.

This is actively promoted by the EPMA, which organized a dental department in 2012, which for almost 10 years has not only promoted, but also cited concrete results of this approach to public care in its publications and speeches.

Of course, the importance of preventing human pathologies in terms of economics does not require much proof, not only for the personal economic benefit in the future for the patients themselves, but also for medical organizations, since the costs of treating various pathologies can be very significant. We would like to intensify this direction with the full support of EPMA with the possibility of estimating the economic benefits of treating different pathologies in different countries, which would help to shift the paradigm of thinking towards prevention on a political, organizational and methodological level. In this case, we would be able to eliminate the conflict between treatment and prevention by achieving a comprehensive and harmonious unity between them.

Multi-professional recommendations in the frame-work of 3P medicine

Development of innovative screening programmes is essential to promote population health by application of health risks assessment, individualised patient profiling and multi-parametric analysis, further used for cost-effective targeted prevention and treatments tailored to the person. The following healthcare areas are considered to be potentially strongly benefiting from the above proposed measures:

- suboptimal health conditions,
 - stress overload and associated complications,
 - periodontal health and dentistry,
 - inflammatory disorders, healing and pain management,
 - metabolic disorders,
 - cardiovascular disease,
 - cancers,
- improved individual and population outcomes under pandemic conditions such as COVID-19.

In a long-term way, a significantly improved healthcare economy is one of benefits of the proposed paradigm shift from reactive to Predictive, Preventive and Personalised Medicine (PPPM/3PM). A tight collaboration between all stakeholders including scientific community, healthcare givers, patient organisations, policy - makers and educators is essential for the smooth implementation of 3PM concepts in daily practice [2].

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Inflammatory Cytokine Levels in tear fluids of Type 2 Diabetes-Related Dry Eye

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Keywords: diabetes, tear fluid, proteins, luminex, multiplex, biomarkers, cytokines, dry eye

Background

Tear fluid biomarkers are commonly investigated to enhance the understanding of ocular surface conditions (1). For example, biomarker studies have shown that dry eye disease (DED) is associated with increased inflammatory cytokine expression in the tear fluids of affected individuals (2,3). The effect that diabetes has on the ocular surface, however, is poorly understood. Many patients with diabetes experience corneal complications and DED (4). Moreover, it has been shown that DED symptoms are more common in people with type 2 diabetes (T2D) and are associated with reduced quality of life (QoL; 5).

Therefore, this study aimed to increase the knowledge of DED in T2D by assessing a panel of tear fluid cytokines, alongside clinical ocular surface health measures of tear quality and quantity.

Working hypothesis, materials and methods:

It was anticipated that there may be altered cytokine levels in those with T2D and DED and there may also be significant differences between the groups for the clinical measurements of tears.

A total of 123 subjects were recruited and divided into 4 groups: T2D with DED (T2D+DED, n=47); T2D only (T2D=41); subjects with dry eye only (DED, n=17) and healthy controls (n=18). Tear quality was measured via fluorescein Tear Break Up Time (fTBUT) and tear quantity was measured by the Schirmer test. Inflammatory cytokines (EGF, Fractalkine, IFN- γ , IL-10, IL-17A, IL-1RA, IL-1 β , IL-2, IL-4, IL-6, IL-8, IP-10, MCP-1, TNF- α , VEGF) were analysed in tear fluids by Multiplex magnetic bead analysis and measured by the luminex platform.

Results

For the 4 study groups, IL1RA was significantly higher in the T2D+DED than the T2D-only group ($p=0.001$). For IL-6, statistically significant differences were determined when comparing the groups. There were significantly higher IL-6 concentrations in the T2D+DED versus the DED group ($p=0.001$) and versus the T2D group ($p=0.03$), as well as compared to the healthy controls ($p=0.01$). For IL-8, there were significantly higher concentrations detected in the T2D+DED group than the DED group ($p=0.05$), and versus the T2D group ($p=0.03$), as well as the healthy controls ($p=0.02$).

For clinical measures of tears, fTBUT value was significantly higher in the T2D versus T2D+DED ($p<0.001$) and DED groups ($p=0.003$). Healthy controls had a significantly higher fTBUT value than T2D+DED ($p=0.002$) and DED groups ($p=0.006$). In the Schirmer test, healthy controls had significant higher Schirmer values than

the subjects in the DED and T2D+DED groups ($p<0.001$). In addition, Schirmer was significantly higher in T2D alone, than the T2D+DED and DED groups ($p<0.001$).

Conclusions and expected PPPM impacts

Overall, subjects with T2D and T2D-associated DED had reduced tear fluid quality and quantity. Of particular interest, differences in IL-6 and IL-8 levels for T2D-associated DED versus non-diabetic DED suggests a different inflammatory pathogenesis between these 2 groups. Thus, IL-6 and IL-8 could be used to specifically differentiate T2D-associated DED versus non-diabetic DED. Further investigations are needed in larger patient cohorts to examine this further.

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Effect of *SLC47A1* and *SLC47A2* gene polymorphisms on the glycemic response to metformin in type 2 diabetes mellitus patients

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Keywords:

metformin; multidrug and toxin extrusion proteins; single nucleotide polymorphism; solute carrier family 47 member 1 (*SLC47A1*); solute carrier family 47 member 2 (*SLC47A2*)

Background

We aimed to evaluate the influence of single nucleotide polymorphisms (SNPs) in the *SLC47A1* (922-158G > A; rs2289669) and *SLC47A2* (–130G > A; rs12943590) genes on the relative change in HbA_{1c} in type 2 diabetes mellitus (T2DM) patients of South India who are taking metformin as monotherapy. It also aims to study the effects of these SNPs on the dose requirement of metformin for glycemic control and the adverse effects of metformin

Working hypothesis, materials and methods:

Diabetes patients on metformin monotherapy were recruited based on the eligibility criteria (n = 105). DNA was extracted and genotyping was performed with a real-time PCR system using TaqMan® SNP genotyping assay method. The HbA_{1c} levels were measured using Bio-Rad D-10™ Hemoglobin Analyzer.

Results

After adjusting for multiple comparisons (Bonferroni correction) the difference found in the glycemic response between the “GG” genotype and “AG/AA” genotype groups of the *SLC47A2* gene was not significant ($p = 0.027$; which was greater than the critical value of 0.025). Patients with “GG” genotype showed a 5.5% decrease in HbA_{1c} from baseline compared to those with the “AG/AA” genotype (0.1% increase). The SNP in the *SLC47A1* gene also did not influence the glycemic response to metformin ($p = 0.079$). The median dose requirements based on the genotypes of the rs1294359 variant ($p = 0.357$) or rs2289669 variant ($p = 0.580$) were not significantly different. Similarly, there was no significant difference in the occurrence of adverse effects across the genotypes in both the *SLC47A1* ($p = 0.615$) and *SLC47A2* ($p = 0.309$) genes.

Conclusions and expected PPPM impacts

The clinical response to metformin was not associated with the SNPs in the *SLC47A1* and *SLC47A2* genes coding for the multidrug and toxin extrusion protein (MATE) transporters. Furthermore, the studied SNPs had no influence on the dose requirement or adverse effects of metformin.

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ECG as a tool for estimating biological age

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Keywords: biological age, ECG, ageing,

Background

Biomarkers of biological age (BA) are of utmost importance for P3 Medicine since they are predictive of life longevity and premature ageing and are used to monitor anti-ageing measures.

Working hypothesis, materials and methods:

Ageing leaves specific changes in ECG. ECG films can be used to match biological with chronological age. Mawi company has processed 10,000 ECG films of subjects of various ages and gender <https://mawi.band/> to design machine-learning algorithms for determining BA [1]. To validate this algorithm, 51 subjects were involved in preliminary matching of biological age with chronological age. This method was compared with other established approaches for BA determination (e.g. physician-led method with 42-item Rockwood-based frailty index as the main reference [2], DNAm PhenoAge [3]). Moreover, the leave one out method was employed to design an additional algorithm based on DNAm PhenoAge and ECG signals. ECG were recorded using Mawi Vital multisensory device. The following statistical tests were employed for revealing associations between the obtained result: 1. Bivariate correlation. 2. Mean arithmetic error (MAE) 3. Qualitative binary age estimation. Each employed method relied on a binary estimation of matching of physician and algorithm determined age.

Results

All tested methods were highly correlated with physicians determined age. ECG based method turned to be superior in comparison with other methods; 9 out of 10 cases correctly pointed to biological age using ECG. Based on MAE, the ECG method was the most accurate for biological age estimation (Tabl.1)

Tabl. 1 Comparative evaluation of biological age determination using different methods.

	Bivariate correlation.	MAE	binary estimation
ABlood	0,911	12,62	40,00%
aECGBlood	0,906	12,43	40,00%
aECG	0,902	3,62	88,57%
aECG2	0,877	4,70	77,14%
aECG3	0,885	3,90	77,14%

Conclusions and expected PPPM impacts

The ECG-based method of biological age determination is an easy and feasible approach to biological age estimation. This method paves the way for timely distinguishing subjects at high risk of accelerated ageing and fits well with the 3 P medicine paradigm

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Prognostic significance of MDM2 expression in prostate cancer

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Keywords: MDM2, expression, prostate cancer, Slovak population.

Background

MDM2 (murine double minute 2) protein is the main regulator of cell cycle through inactivation and degradation of the p53 tumor suppressor protein. It binds directly to the p53, via its E3 ubiquitin ligase, and the ubiquitinated p53 can be transferred to the cytoplasm and degraded by proteasomes (1). Moreover, MDM2 presents several p53-independent roles in transcription, cell-cycle regulation, differentiation, or DNA synthesis (2). However, the role and clinical implication of MDM2 expression in prostate cancer remains poorly understood. We therefore aimed to investigate the expression and prognostic role of MDM2 in prostate cancer.

Working hypothesis, materials and methods:

A total of 65 frozen tumor and BPH tissue samples were examined using quantitative real-time polymerase chain reaction (qRT-PCR) and western blot analysis. Clinical and pathological data of patients including tumor stage, tumor grade and PSA were also recorded. Association between MDM2 expression and clinical factors was analyzed by the student's t-test.

Results

The relative expression MDM2 mRNA was significantly higher in prostate cancer tissues than in BPH tissues ($p > 0.05$). The relative MDM2 expression was significantly related to the Gleason score ≥ 7 ($p = 0.05$) and age > 70 ($p = 0.017$). However, other clinical parameters such as PSA and TNM stage had no obvious influence on the expression of MDM2 ($p > 0.05$). Western blot analysis revealed a similar trend for MDM2 protein levels in tumor tissues.

Conclusions and expected PPPM impacts

We can conclude that higher MDM2 expression is associated with increased risk of prostate cancer, in particular in older individuals with Gleason score ≥ 7 . Considering the important role that MDM2 plays in prostate cancer, a better understanding of the regulation of MDM2 will help us to develop novel and more effective cancer therapeutic strategies to target MDM2.

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Estrogen receptor alpha promoter methylation status in prostate cancer

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Keywords: prostate cancer, estrogen receptor alpha, methylation, expression

Background

Sex steroid hormones are essential in normal prostate growth, but can also serve as initiators and promoters in prostate carcinogenesis. Loss or downregulation of estrogen receptor α (ER α) expression in prostate cancer has been frequently documented. Inverse correlation between ER α expression and histological grade or pathological stage was also found. The ER α gene CpG island methylation is one of the mechanism contributing to decreased or completely lost ER α gene expression. In normal somatic cells, CpG islands are usually unmethylated. In contrast, cancer cells often display anomalous patterns of DNA methylation and hypermethylation is a common and early alteration in many tumor types.

Working hypothesis, materials and methods:

The aim of the study was to evaluate the possible association between methylation status of the promoter of the ER α gene and the risk of prostate cancer development and progression. The case-control study was performed with bisulfite-modified tissue DNA samples from 34 prostate cancer and 33 BHP patients. Four sets of primers (ER1, ER3, ER4 and ER5), representing the most important regions of the ER α CpG island with respect to the ER α gene expression, were used for methylation-specific PCR analysis.

Results

The ER α methylation in at least one region was observed in 20 of 34 (58.8 %) prostate cancer tissues but in only 4 of 33 BHP tissues (12.1 %). The methylation in the regions ER1 and ER4 were specifically detected only in prostate cancer tissues (48.3% of tissues with methylation), but not in BHP tissues. We detected ER α methylation in at least one region in 45.5 % of prostate cancer tissues with Gleason score ≤ 7 and in 65.2 % of prostate cancer tissues with Gleason score > 7 .

Conclusions and expected PPPM impacts

This study demonstrated possible significance of ER α gene promoter methylation as a potential diagnostic and/or prognostic marker of prostate cancer.

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Prehabilitation as an integral procedure in predictive, preventive and personalized medicine and modern and effective healthcare

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Keywords: prehabilitation, pppm, 3PM, exercise & physical activity, nutritional optimisation, psychological wellbeing, enhanced recovery after surgery, visions, future healthcare

Background

According to our search in the scientific literature, one of the first use of the term “prehabilitation” can be traced back to the beginning of 1940’s of the 20th century, during the WW II [1], when it was suggested by Selective Service System of the US Army recruiting young men for the service in the army. Originally it was understood as the procedure dedicating to solve health-related problems prior to the recruitment or prior to the unwanted manifestation during a military operation. In parallel, the pre-placement examinations of the employees in the industry was introduced by W.A. Sawyer in 1942 [2]. Later on, in 1952, in the German journal, the term “preoperative” is used in relation to the preoperative breathing exercise in thoracic surgery [3].

In the beginning of the 1980’s the meaning of the “prehabilitation” changed and it is now defined as “the process of expanding patient’s functional and psychological capacity to reduce potential deleterious effects of a significant stressor, which is the surgical procedure itself” [4]. The Cambridge dictionary defines “prehabilitation” in medical context as “*activities done by someone before they have a medical operation in order to improve their physical strength and help them to recover more quickly after the operation*” [5]. According to the *BJA Education* journal, prehabilitation is “the practice of enhancing a patient’s functional capacity before surgery, with the aim of improving postoperative outcomes” [6]. The Collins dictionary defines “prehabilitation as “the preparation of patients prior to major surgical procedures to enhance general health and well-being with the outcome of decreasing morbidity and mortality” [7]. So, basically, all definitions of “prehabilitation” are currently, one way or the other linked to surgery.

Prehabilitation and PPPM

Here we want to emphasize and extend the meaning of “prehabilitation” in the context of predictive, preventive and personalized medicine as presented by EPMA [8,9] because we find it to be an excellent example of practical application of PPPM in the modern healthcare services.

Prehabilitation can use all the tools and knowledge accumulated and published so far in the predictive, preventive and personalized medicine, including the research in suboptimal health state [10] of the particular patient who is to undergo a planned therapeutic/surgical procedure, outcome of which depends on the particular health status of the patient. This status, in our opinion, should be assessed with the help of available medical technologies in order to predict potential problems and avoiding them through using adequate preventive actions, being it personalized nutritional support based on the particular analysis of the patient’s blood, particular physical exercises to increase fitness, psychological support, disease/procedure-related education of the patient, as well as using health-supporting environmental factors in all potential medical fields such as surgery, organ transplantation, oncology, obstetrics, dentistry, neurodegenerative diseases, genetically determined diseases, pandemic management, and other fields of medical care.

In the context of our previous plans for implementation of PPPM in the hospital structure [11], here we propose implementation of prehabilitation into the routine procedures of medical care in any hospital that wants to increase the quality of provided healthcare and bring predictive, preventive and personalized medicine to the patients who will, undoubtedly, benefit from such a change. We are aware that realization of this vision is not an

easy mission to be accomplished and the question of proof-of-concept as it was in 2017 [5] but we suggest international cooperation among all subjects who share the same attitude towards turning current healthcare into the future healthcare may speed up the realization. The network of EPMA institutional members provides a very good platform for such a cooperation.

Conclusion and expected impacts

The vision is long-term but at the very beginning, it is reasonable to focus on the patients at high risk for postoperative morbidity and mortality, such as older surgical patients who are frail [12, 13]. Nonetheless, in the later phases of implementation it may likely be of value, as several researchers already propose [14], to offer prehabilitation for a much wider spectrum of surgical patients, and, as we believe, also for other patients in need of specific medical procedures.

The baseline in each of multimodal approach of prehabilitation (exercise & physical activity, nutritional optimization, psychological wellbeing, education and other), is personalized intervention, given the possibility of prediction, thus preventing negative clinical outcomes.

A rapid return to full physical function after major surgery and/or other intervening medical procedures, has the potential to improve outcomes for patients, thus allowing them to return home and resume normal activities earlier. Furthermore, accelerated recovery is expected to have economic benefits and potentially more efficient use of both, the available hospital beds, as well as the use of always-limited financial resources in healthcare [15].

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Prevention and prediction of the development of postoperative sensitivity in the treatment of abfractional lesions of the teeth

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Keywords: Personalized dentistry, preventive dentistry, therapeutic dentistry, teeth abfraction, postoperative sensitivity

Relevance

The prevention of postoperative sensitivity in the treatment of ablative lesions of teeth by direct composite restoration, according to the scientific stomatological literature, is insufficiently developed.

Objective of the study

To work out the personalized algorithm of adhesive preparation at treatment of ablative lesions of teeth by method of direct composite restoration with the purpose of prevention of development of postoperative sensitivity.

Materials and methods of research

A personalized adhesive protocol was developed for use in the treatment of ablative lesions of the teeth by direct composite restoration, including, in addition to the actions provided for in the instructions for the adhesive system, dynamic dentin etching, dentin treatment with 5% glutaraldehyde solution, creation of an adaptive layer of flowable composite (LML technique) and aimed at preventing postoperative sensitivity. Filled adhesive of the 5th generation was used. The efficacy of the treatment of ablative dental lesions with direct composite restorations was evaluated. 218 direct composite restorations in 69 patients aged 30 to 49 years were evaluated; follow-up periods were 2 weeks, 6, 12, 18 and 24 months after treatment.

Results and discussion

In the study group (supplemented adhesive protocol), 88.4±2.82% of restorations corresponded fully to clinical requirements (grade A) 2 weeks after treatment, 79.9±3.53% after 12 months, 68.9±4.08% after 24 months on all studied criteria - no hypersensitivity, no marginal staining of the restoration, no tactile defects of marginal contact - which was an effective prevention of hypersensitivity of dental hard tissue. In the comparison group (adhesive preparation according to the instructions), the number of restorations meeting the criteria was significantly lower: after 2 weeks - 68.5±4.92%, after 12 months - 44.9±5.27%, after 24 months - 25.8±4.68% ($p<0.005$). Considerable difference in the obtained results was determined by the above-mentioned evaluation criteria to evaluate the initial signs of changes in enamel mineralization, which should serve as an effective prophylaxis against carious and non-carious dental lesions.

Conclusion

Absence of postoperative sensitivity, marginal staining and tactile defects of the marginal contact of restorations indicates the prevention of enamel mineralization processes that can lead to the development of carious and non-carious dental lesions. It is reasonable to use the data obtained to predict the effectiveness of treatment and prevention of dental abfraction lesions by direct composite restorations and prevention of the development of postoperative sensitivity.

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A functional approach to periodontal research is a bridge between individual prevention and personalized orthodontics

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Keywords: Ultrasonic Doppler flowmetry, Predictive orthodontics, Preventive orthodontics, Personalized orthodontics, Gingival blood flow

Many problems of functional diagnosis of periodontal and dental pulp status still remain unaddressed in the clinical practice of prevention of orthodontic treatment complications. The planning of treatment and prevention of complications is impossible without a strictly personalized approach to the assessment of periodontal status. Based on the anatomical, ontogenetic, and functional affinity of these structures, we first proposed the isolation of the pulpo-periodontal complex. Methods of ultrasonic Doppler flowmetry and digital occlusiography were used for functional analysis. The data of 63 people (57% men, 43% women) in the age group from 16 to 30 years old at different stages of orthodontic treatment were analyzed (35 people (57%) - distal occlusion, 15 people (23%) - mesial occlusion, 13 people (20%) - anomalies of the separate teeth positions). The control group consisted of 54 people; the analysis of their data did not reveal any pathological changes and were taken as normal. T-scan diagnostics was performed in each study phase after activation of orthodontic appliance, where the occurrence of transient supercontacts was observed. The study revealed an unprecedented 74.6% ($p<0.05$) decrease in volumetric and linear blood flow in all representatives of the study group, without reference to a specific nosology. At the same time, the indices return to the average values within a month. Such complex reactions allowed us to distinguish the pulpo-periodontal complex as a single functional structure. The obtained data indicate an acute need for continuous stage-by-stage monitoring of their condition. Timely detection of such non-obvious disorders will allow us to personalize the process of prevention of orthodontic complications at the level of clinical reception of each individual patient.

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The use of the method of exogenous personified prevention of caries based on the molecular composition of the dental biofilm

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Keywords: Personalized dentistry, preventive dentistry, biofilm, microstructures, caries

The study of changes occurring in the molecular and phase composition of the biofilm formed on the surface of teeth will allow a successful transition to a personalized approach in dentistry when using remineralization therapy. The purpose of our study was to study the features of the molecular composition of the dental biofilm at the stages of exogenous and endogenous personalized prophylaxis.

The study involved 72 participants (30 men and 42 women), aged 18-25 years, physically healthy, with sufficient average caries resistance of their oral cavity. In the first phase of the study, biofilm samples were taken from the participants after mechanical brushing of the teeth with a soft toothbrush for 3 minutes, and preliminary rinsing of the mouth with clean water. In the second stage of the experiment, the next day, the patients used a toothpaste with calcium glycerophosphate to brush their teeth and, according to the established procedure, biofilm samples were taken. One day later, the patients started taking tablets of mineral and vitamin complex based on calcium glycerophosphate (one tablet 3 times a day) without brushing the teeth with a toothpaste with calcium glycerophosphate. Three days after taking the first tablet, in the morning, biofilm samples were taken in the same manner as the procedure for taking them. The molecular composition of the biofilm samples was examined using Infrared Microspectroscopy beamline equipment (Australiansynchrotron, Victoria, Australia).

On the basis of the data obtained, as well as the results of calculations of the indices of ratios between the organic and mineral components and subsequent statistical analysis, we were able to assess changes occurring in the molecular composition of the dental biofilm during the stages of exogenous and endogenous prophylaxis in patients. It was shown that the presence of statistically significant differences in these coefficients indicates that patients have different mechanisms of adsorption of ions, compounds and complexes coming from the oral fluid into the dental biofilm at the stage of exo/endogenous prevention, where the endogenous method was more effective than exogenous one.

Understanding of features of remineralization of enamel of teeth states that the factor of time of presence of mineral complexes in an oral cavity at endogenous receipt on a constant basis and at exogenous receipt (brushing of teeth) on a temporary basis plays the important role. In this regard, the dentist should cooperate with the gastroenterologist in the evaluation of the gastrointestinal tract, knowing its role in the saturation of the blood and salivary gland secretion with mineral complexes, thus emphasizing the need for a multidisciplinary approach to prevention and prognosis. The great importance of population prophylaxis in the context of these findings should be noted.

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Personalized treatment and prevention of dry mouth

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Keywords: glossodynia, personalized dentistry, preventive dentistry, dry mouth, oral hygiene

It is known that dry mouth occurs in many diseases of the body and brings a significant reduction in the quality of life. In addition, dry mouth is an important symptom for the detection and prevention of not only various diseases of the oral mucosa, but also many organs and systems.

We followed up 83 patients, of whom 29 (34,9%) were diagnosed with oral mucosal candidiasis, 19 (22,9%) - second form diabetes, 24 (28,5%) - oral mucosal red squamous lichen, 11 (13,3%) - glossodynia of neurotrophic origin.

Specific treatment by doctors of the relevant profile did not eliminate the phenomena of dry mouth in the period of therapy, was not stopped by the dietary regime recommended by endocrinologists, dentists and neurologists. During the period of active therapy, in order to treat and prevent dry mouth mucosa, patients were offered brushing with ROKS moisturizing toothpaste during the treatment of the underlying disease, which continued for oral candidiasis for up to one month, diabetes and glossodynia continuously during life, for red squamous lichen during active treatment and periodically thereafter.

During examination we used general and biochemical blood and urine analyses, express cytobacterioscopy of oral mucosa, simple and dilated (with stains) stomatoscopy, which revealed the degree of epithelium keratinization disorders. Fibrogastroscopy was used to detect pathology of the digestive system. At the beginning of diagnostics, great importance was given to anamnestic data.

Complete elimination of dryness of the oral mucosa occurred in 27 (93,1%) patients treated for candidiasis, and in 12 (50%) patients treated for lichen planus erythematosus. This prophylaxis of dry mouth allowed its complete elimination during the whole period of observation (3 years).

In the rest, as well as in patients with diabetes and glossodynia, a definite decrease in dry mouth was found in brushing teeth twice a day (after breakfast and after dinner), which significantly improved the standard of living of patients.

Thus, the personalized treatment and prevention of dry mouth in patients with candidiasis, diabetes, red squamous lichen planus and glossodynia has a good effect when using ROKS moisturizing toothpaste. On the other hand, reducing the activity of dry mouth mucosa is a prevention of the psychological profile of these patients, removing the irritant effect on the CNS.

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Preventive diagnosis of fissure enamel caries using Raman microspectroscopy

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Keywords: Personalized dentistry, preventive dentistry, microspectroscopy, microstructures, caries

Diagnosis of caries and its initial forms is of key importance in preclinical prevention in the developed world. In the case of initial forms of caries, personalized monitoring and precision examination of the affected area is necessary to exclude the situation of non-invasive sealing of the lesion, the consequence of which is secondary caries and pulp inflammation. Despite the sufficient degree of research, dental fissure caries is a subject of current study, where an important task is to diagnose the hidden forms of cariesogenic areas that are not visually detectable. This approach is necessary in the context of prevention of both directly carious process and caries complications at different levels of the process development.

In this work a study of microregions of enamel fissures on teeth extracted from patients for orthodontic indications was carried out. Raman spectra were obtained using an Olympus CX-41-based RamMix M532® Raman microscope and a 532 nm excitation laser with a power of 30 mW per focussed surface and a beam diameter of 2µm.

In the course of examination of visually intact fissures pigmented areas of the order of 200x50 µm were found. Precision scanning of these areas revealed the presence of characteristic areas correlated with demineralized enamel, determined by the presence of a broad maximum in the spectrum in the region of 960 cm⁻¹. Raman screening of the region near the pigmentation boundary detected the presence of bacterial microflora, which was associated with the appearance of a maximum observed in the spectra in the 1330 cm⁻¹ region. Bacterial microflora was found to be confidently detected based on a gradual decrease in the intensity of the ~1330 cm⁻¹ band up to ~ 50 µm from the border of the pigmented area. It should be noted that pigmented areas due to their small size cannot be diagnosed visually in clinical conditions, however, their reliable appearance can be detected using spectroscopic methods of analysis.

The data obtained in our work are potentially significant for the implementation of PPPM strategy, as they can be used as reference data for the development of a new approach of preventive diagnosis of the development of initial and clinically unrecorded stages of human dental fissures, as well as preventive monitoring of fissure condition before noninvasive sealing in clinical practice.

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Prevention and prediction of the spread of COVID 19 by detecting early dental manifestations in infected patients

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Keywords: personalized dentistry, preventive dentistry, COVID-19, personalized dentistry, preventive dentistry, oral discomfort

The use of personal protective equipment during the pandemic of coronavirus infection cannot guarantee 100% protection of infection and, consequently, the spread of COVID 19. Preventing the spread of infection is only possible by predictive detection of infected individuals, which is possible during dental appointments, since preclinical signs of infection have specific manifestations in the oral cavity. Prospective clinical observations of 345 patients with a positive SARS-COV-2 test and asymptomatic course revealed a number of patterns and correlations. The presence of diabetes mellitus and glossadenia were excluded in the examined patients. At the same time the following complaints were revealed in the early stages of coronavirus infection (in the absence of obvious clinical signs): periodic or constant discomfort in the oral cavity (89%); coughing and burning of the oral mucosa (100%); tongue irritation (83%); loss of taste sensitivity and sense of smell (60%); dysgeusia - perverted taste sensation (for example, metallic taste) (54%); disosmia - altered smell (82%); dysesthesia - feeling of burning or tingling in the mouth (68%). Already at the beginning of the disease, catarrhal stomatitis develops with pronounced hyperemia, presence of aphthae, ulcers (67%); symptomatic gingivitis (100%); bleeding gums, causal and then spontaneous (92%); paresthesias, hyperesthesia, burning of the SOPR (89%). During this period, periodontal diseases often worsen and become abscessed. One of the symptoms of coronavirus infection doctors began to refer a rash on the skin, in 17% of cases the rash was localized on the skin of the face.

Thus, the detection of enanthematic or exanthematic elements of lesions, oral discomfort, during the pandemic may be a prognostic "entry filter" criterion for identifying patients infected with coronavirus infection and be considered COVID indicators (markers).

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Correlation dependence of the personalized assessment of the biopotentials of the masticatory muscles by electromyography in adolescents with high and medium caries resistance of hard dental tissues

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Keywords: Personalized dentistry, preventive dentistry, electromyography, caries resistance, preventive orthodontics

Based on many years of research by the dental departments of N.N. Burdenko Voronezh State Medical University the importance of methodological approaches to the study of masticatory muscles functions with the assessment of oral homeostasis and timely therapy and prevention of dental caries as well as its intensity in the Voronezh region is emphasized. The evaluation of the functional state of the superficial masticatory and temporal muscles by means of electromyography and mouth cavity was carried out in a prospective cohort study of 62 teenagers aged 13-16, living in the same ecological conditions and receiving similar methods of treatment and prevention of oral cavity diseases with high and medium caries-resistance of dental hard tissues. The bioelectrical activity of the masticatory muscles proper, determined in microvolts (μV), was proved to be significantly lower in patients with moderate caries-resistance than in adolescents with high caries-resistance. The total value of bioelectrical activity of masticatory muscles in children with average caries susceptibility was $757, 23 \pm 25,14 \mu V$ compared to the similar parameter in the group of examined patients with high caries susceptibility, where it was $1013,25 \pm 31,42 \mu V$, which is significantly higher than parameters of the group of children with average caries susceptibility. The difference in this parameter was about 26%. At the same time, there was an imbalance in the parameters of bioelectrical activity between the masticatory and temporal muscles proper, increased fatigability of masticatory muscles in response to statistical load in adolescents with average caries-resistance, which may lead to lower pressure gradient of tissue fluid in the dental pulp chamber, impossibility of its sufficient inflow to dentin and enamel tubules and, as a result, to the decrease of enamel resistance with the increase of its electric conductivity and creation of cariesogenic situation in the oral cavity in contrast to adolescents with high caries-resistance who have significantly higher activity parameters of masticatory muscles. The physiological mechanism for ensuring sufficiency of the hydrodynamic pressure gradient in the capillaries of the dental pulp is the chewing function. Thus, the assessment of the functional state of the masticatory muscles states the ability to create sufficient tissue pressure for the interstitial fluid of the dental pulp to escape to the enamel surface, forming a biological film that protects the enamel surface from the products of microorganisms. This conclusion may allow to complement and expand the concepts of personalized prevention of caries process within the concept of PPPM.

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Elimination of primary preclinical demineralization of enamel as a method of preventing caries of intact teeth

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Keywords: Personalized dentistry, preventive dentistry, primary demineralization, preventing caries, therapeutic dentistry

Not prevention, but prevention of caries should be performed at the earliest disruption of natural remineralization of the enamel of intact teeth.

239 patients with intact teeth were examined. Light-induced fluorescence was performed to detect enamel staining, which was confirmed by the COSRE test (clinical determination of enamel remineralization rate). In 112 (47%) respondents, enamel stains (shadows) and decreased enamel remineralization rate up to 8-9 days (normal 3-4 days) were detected. These data revealed areas of enamel requiring primary prevention of caries and non-carious dental diseases such as erasure, wedge-shaped defect, discoloritis and others.

Staining of clinically intact enamel in the area of stains with nuclear dyes penetrating the demineralization spaces disappeared slower than normal after acid action, and scanning electron microscopy and X-ray spectral analysis of this enamel zone showed an 8+0.75% decrease in Ca concentration. According to our patent, patients were offered to brush their teeth for a month with toothpaste Magnesium (ROKS), because our previous studies have shown that in such primary preclinical demineralization more actively strengthens enamel not F, but Mg, forming a denser inclusion in the enamel hydroxyapatite.

The results of our studies have shown that after a month there was a disappearance of stains enamel and normalized the rate of its remineralization in 98 (87.5%) patients, ie, was achieved prevention of dental hard tissue disease and eliminated the primary preclinical demineralization of enamel. Carried out atomic force microscopy of enamel determined the correct structure of the enamel tunnels, which were located at an angle of 90° to each other, that is to contribute to the prevention of diseases of dental hard tissues. In 14 (2,5%) patients there were detected signs of abnormal architectonics of enamel tunnels, which apparently did not allow to eliminate the primary demineralization and required additional remineralizing therapy.

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Preventive personalized technologies of cytoprotective treatment of erosive and ulcerative gastroduodenal lesions

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Keywords: preventive personalized medicine, erosive and ulcerative gastroduodenal lesions, somatic pathology, cytoprotective treatment, granular sorbents.

Abstract

The problem of prevention and treatment of erosive and ulcerative gastroduodenal lesions (EUGDL) and their complications is one of the urgent problems in medicine. In the structure of gastroduodenal bleeding, acute erosions and gastroduodenal ulcers account for 52.3-64.7%. At the same time, the most tragic situation is observed in people with decompensated somatic pathology, in whom the development of bleeding most often ends in a fatal outcome. The appointment of proton pump inhibitors is not a reliable way to prevent EUGDL and does not prevent the possibility of bleeding. Clinical alertness and identification of risk factors for the development of EUGDL allows timely initiation of preventive measures to prevent gastroduodenal bleeding [1,2,3].

The study included 114 patients who underwent treatment in the multidisciplinary hospital Voronezh city emergency hospital №1 for the destabilization of a somatic disease, in whom EUGDL were detected during treatment in the hospital. Ischemic heart disease with rhythm disruption was observed in 38(33.3%) people; progressive angina pectoris – 11(9.6%) people; hypertension – 51(44.8%) people; pneumonia and COPD – 9(7.9%) people; diabetes mellitus – 5 (4.4%) people.

Erosive and ulcerative gastroduodenal lesions by their nature were distributed: acute erosions of the stomach and/or duodenum – 44(38.6%) people, symptomatic gastroduodenal ulcers – 32(28.1%) people, multiple erosions and ulcers – 11(9.7%) people, gastric ulcer and duodenal ulcer – 19(16.7%) people, Mallory-Weiss syndrome – 4(3.5%) people, arrosed vessel of the stomach and/or duodenum – 4(3.5 %) people.

There were 62(54.4%) men, 52(45.6%) women, the average age was 62.51 ± 10.67 years. All patients were randomly divided into the main (58 people) and control (56 people) groups.

In patients of the main group, a prophylactic personalized prognostic treatment program was used, based on early diagnosis and preventive use of cytoprotective treatment of EUGDL with granular sorbents to prevent complications. All patients of the main group underwent diagnostic esophagogastroduodenoscopy (EFGDS) on days 2-3 after admission. When acute erosions were detected, the granular sorbent Aseptisorb-A, which had analgesic properties, was applied using an insufflator. On gastroduodenal ulcers produced pneumo-insufflation of the sorbent Aseptisorb-D, endowed with antibacterial properties (Patent RF 2532492).

When signs of erosive-ulcerative bleeding were detected, the algorithm changed: in patients of the main group, the method of prophylactic endoscopic hemostasis was used by applying powdered hemostatic Zhelplastan to the defect in combination with the Sephadex G-25 sorbent (Patent RF 2633925).

In the control group, the traditional method of consultations "on demand" was used, diagnostic EFGDS was performed when the first symptoms appeared, and prophylactic local treatment of EUGDL was not carried out. From antiulcer therapy, patients of both groups received proton pump inhibitors (Nexium), antacids, anti-Helicobacter pylori therapy (if indicated). In the control group in patients with bleeding, the well-known methods of endoscopic hemostasis without granular sorbents were used.

The work was supported by the Council for Grants of the President of the Russian Federation (Grant MK-1069.2020.7).

The conducted studies showed that the timely implementation of EFGDS made it possible to detect EUGDL without signs of bleeding in 41 out of 58 (70.7%) patients, and only in 17(29.3%) patients, erosions and ulcers were complicated by bleeding. In the control group, EUGDL without signs of bleeding was detected in 18 of 56 (32.1%) patients. The remaining 38 (67.9%) patients were diagnosed with EUGDL complicated by bleeding. When using personalized methods for preventing bleeding from EUGDL, it was noted that after insufflation, the sorbents swelled, formed a cytoprotective hydrogel layer on the defects, protecting them from aggressive gastric and duodenal contents. In all patients of the main group, the healing of EUGDL up to 1.0 cm in diameter occurred by epithelization in 73.2% of cases ($P=0.029$), and ulcers over 1.0 cm healed in the form of a tender scar.

The presented therapeutic program of preventive personalized prognostic measures for the prevention of gastroduodenal bleeding allowed to improve the diagnosis of uncomplicated EUGDL from 32.1% to 70.7% ($P=0.001$) and to reduce the number of hemorrhagic complications from 67.9% to 29.3% ($P=0.001$).

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New aspects of vector therapy in the secondary prevention of chronic periodontitis

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Keywords: periodontal diseases, "Vector" system, ozonized water, therapeutic and prophylactic measures.

Relevance

High prevalence of periodontal diseases among Russian population, deterioration of life quality in proportion to the activity of pathological process require improvement of prophylactic and preventive treatment measures. In this situation high-tech apparatus methods are becoming more widespread - the system "Vector" for sanitation of periodontal pockets (PC) with simultaneous antiseptic treatment with ozonized water, designed for personalized prevention and conservative therapy in periodontology.

The aim of the study was to study the impact of the modified vector-treatment technique within the framework of the secondary prevention and personalized therapy of chronic periodontitis (PC) on the tooth tissues and metabolic processes in them.

Material and methods

We included 71 patients diagnosed with chronic generalized periodontitis into the study process. All persons underwent professional tooth brushing as part of the secondary prevention, followed by training in individual oral hygiene. In the main group (36 people-51%) ultrasound treatment of teeth by "Vector" system with ozonized water was carried out at the 2nd visit. In the control group (35 people - 49%) a course of traditional pharmacotherapy was prescribed.

Clinical and laboratory diagnostics included: collection of the anamnesis, examination, stomatoscopy, index evaluation, radiological examination, bacterioscopic and cytological tests, scanning electron microscopy (SEM) and X-ray microanalysis (XRAM).

Results of the study

The application of the developed method of the secondary prevention and personalized therapy of periodontitis produced a pronounced clinical effect. Index indices were 2 times lower in comparison with the patients of the control group which testified to the liquidation of inflammation in periodontal structures and successful prevention of the process progression. These results were confirmed by the data of cyto-bacterioscopy and extended stomatoscopy throughout the year. Bone tissue regeneration up to 3 mm was proved radiologically in 52,7% of cases in the patients of the main group who received personalized treatment with the use of ultrasound and ozonized water

To confirm the clinical effectiveness of our developed method of prevention and treatment of chronic periodontitis, we performed laboratory examination of the hard tissues of 17 teeth removed as a result of orthopedic treatment. The combination of automatic SEM of enamel, dentin and cementum at magnification up to 50,000 times and PSMA enabled us to determine their composition and peculiarities of metabolic processes. In the group of standard prophylaxis and treatment, PSMA of enamel chemical composition recorded a decrease of Ca by 1.4%, Mg by 4.5% and Na by 38.3%. We explain this fact by the decrease in the intake of these elements from the oral fluid due to the inflammatory-destructive process as well as microcirculation disorders in the periodontal structures surrounding the dental hard tissues, which does not meet the goals of prevention. The representatives of the main study group registered an increase in the content of "building" elements: Ca - on 35,2%, P - on 54,4%, Mg - on 76,2%, Na - on 32,5%. Our studies

have shown great variability in the concentration of Mg, as the most active component in the metabolic processes of enamel. The amount of "destructive" elements accompanying pathological reactions in the hard tissues of the tooth and periodontium decreased: Cl by 43.5%, N by 9%, C by 22.3%. The indicators obtained with the help of PCMA allow us to conclude about the positive effect of preventive and personalized treatment measures with the use of "Vector" system with ozonized water on the increase of caries-resistance of enamel due to the normalization of periodontal tissues.

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Return youth to the periodont prediction and personalized prevention in periodontology

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Keywords: periodontal diseases, personalized dentistry, preventive dentistry, periodontology, histomorphology

The epithelial layer of the oral mucosa of the elderly and old age thins mainly due to the spiky cells. The connective tissue of the gingiva becomes denser, the amount of intercellular fluid decreases, elasticity is lost, fibers become coarser and the number of fibroblasts decreases. The epithelial layer is thinning in places with non-keratinized epithelium and, on the contrary, hyperplasia is noted in places with keratinized epithelium.

In our work, we applied a combination of regenerating preparations to the periodontal and oral mucosa tissues. We introduced hyaluronic acid gel for application to the periodontal tissues and injections of our own plasma into the traditional protocol of supporting therapy.

Results of experimental data (20 white rats, 127 cytological, 54 bacteriological studies) of injections of own plasma, state the following changes. The volume of intercellular fluid increased, the number of fibroblasts increased. The number of elastic fibers in the mucosa, and in the periodontal ligament the number of collagen fibers increased. Thickness of epithelium increased due to the layer of spiky cells and cylindrical cells.

Clinical observations (32 patients) application of hyaluronic acid gel allowed to eliminate pathogenic microbiota of periodontal pocket (according to bacteriological research). The bacteriological semination decreased by 49%. Injections of own plasma allowed to eliminate inflammation: the color, turgor of the oral mucosa was restored, there was no bleeding. Clinical objective observations were confirmed by macrohistochemical studies.

The results of the experimental and clinical data allow the following correlations to be deduced. Morphohistological criteria indicative of age-related degenerative changes moved to the regressive stage. Criteria corresponding to active reparative processes tend to grow.

Thus, the proposed clinical technique for rejuvenation of oral mucosa and periodontal tissues is effective and can be proposed as a predictive preventive direction to prevent age-related dental changes.

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Rehabilitation of patients after open curettage of periodontal pocket as a method of preventive, predictive and personalized dentistry

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Keywords: Personalized dentistry, preventive dentistry, periodontal diseases, open curettage, rehabilitation

Curettage of periodontal pockets in the presence of granulation and mineralized dental deposits is one of the mandatory stages of the protocol for the management of patients with periodontal pathology. In our opinion, this procedure should be planned from the position of the prevention of possible aggravation of the pathology severity, prevention of possible complications, and the applied medications should be selected taking into account the personalization of treatment.

Studies were carried out in two stages: experimental (20 white rabbits), which allowed to study histochemical and cytological changes, and clinical, which allowed to evaluate the effectiveness of the proposed method. We treated 127 patients, of whom 56 (44%) were men and 71 (56%) were women, with moderate to severe periodontal disease requiring open curettage.

The results of the research allowed us to draw the following conclusions. The protocol for open periodontal curettage should include placement of an osteoinducer in the pocket. This preparation not only stimulates collagen and elastin reproduction, proven by experimental studies, but also creates a highly alkaline environment that suppresses pathogenic microflora canthomation, proven by bacteriological studies. In our opinion, the patient's rehabilitation protocol after open periodontal curettage should include treatment with injections of the patient's own plasma for a guaranteed result. This procedure allows in the shortest time to eliminate inflammatory processes, stimulates the reproduction of fibroblasts, supports collagenogenesis "running" osteoinducer that allows to simulate a state close to the physiological and achieve maximum restoration of periodontal structures.

Thus, in our opinion, the improvement of the procedure of open curettage of periodontal pocket by predictive introduction into the treatment protocol osteoinductive preparation in combination with prophylactic injections of own plasma, can significantly increase the effectiveness of treatment measures and restore periodontal condition close to physiological.

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Personification of dental status of patients during diagnosis, treatment and prevention of recurrences of erosive-ulcer lichen planus

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Keywords: lichen planus, local irritants, nuclear aberrations, Kohonen network, Delphi programming

Relevance

Manifestations of lichen planus on the oral mucosa are a symptom of chronic recurrent dermatosis, characterized by an unspecified etiopathogenesis, severe, often permanent course, the possibility of malignancy of lesion elements, a variety of trigger factors, including local ones. In addition, this condition of the mucous membrane has a negative effect on the state of oral hygiene, and, consequently, on the metabolic processes of the hard tissues of the tooth. The most difficult clinical problem is the search for effective methods for the treatment of continuously recurrent severe forms of lichen planus manifestations on the mucous membrane of the mouth and the red border of the lips.

Purpose of the work

Personification of local risk factors for severe course of complicated forms of lichen planus on the mucous membrane of the mouth and the red border of the lips.

Materials and methods

85 patients with severe lichen planus on the oral mucosa and the red border of the lips were examined. All patients were examined according to a program specially developed by the authors with an algorithm of a neural network system, which allows planning a treatment regimen based on the most significant signs. A program that performs differential diagnosis of lichen planus using the Kohonen network and is implemented in the Delphi programming system. In addition, the buccal epithelial cell micronucleus test was used.

Results

Elimination of local irritating factors in the oral cavity in patients with severe manifestations of lichen planus on the oral mucosa and the red border of the lips made it possible to achieve a stable remission of the disease and prevent relapses and exacerbations. Cytological methods have proven that the frequency of occurrence of nuclear aberration in tissue cells affected by lichen planus is an absolute marker of lichen planus.

Conclusion

The personalized results obtained prove the need to eliminate the leading local irritating factors in the complex personalized treatment of patients with severe manifestations of lichen planus on the oral mucosa and the red border of the lips in order to achieve a stable remission and prevent relapses.

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Modern approach to individual prevention of recurrent caries in persons with decompensated form of cariosis

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Keywords: recurrent caries, composite material, brushite crystal, means of individual oral hygiene, decompensated caries, Rij criteria.

Relevance

The problem of recurrence of the carious process, due to the insufficient effectiveness of hygiene products, remains very relevant to this day, especially in persons with a decompensated form of caries activity. In this regard, it is of interest to study new individual oral hygiene products with a remineralizing effect, in particular, containing brushite crystals. This substance has unique adhesive properties and tropism to hydroxyapatite crystals of the enamel surface. The principal mechanism of action of the "RemarsGel" system is a chemical reaction that occurs when calcium nitrate from tube No. 1 is mixed with ammonium hydrogen phosphate from tube No. 2, as a result of which brushite crystals are formed on the surface of the teeth.

Material and research methods

The clinical study is a comparative characteristic of the effectiveness of a standard prophylaxis program (with the use of fluoride-containing personal oral hygiene products) of recurrence of a carious process in patients with a high degree of caries activity and a developed program for the use of a natural two-component complex for strengthening and remineralization of RemarsGel enamel. Efficacy was monitored using Ryge criteria immediately after refurbishment and 1, 12 and 36 months after it. Morphological studies were carried out using SEM. Research results and discussion. When statistically processing the data obtained, immediately after sanitation and 1 month after it, the differences in the Ryge criteria in groups No. 1 and No. 2 were statistically insignificant ($p = 0.488$ and $p = 0.563$, respectively). 12 months after the debridement, the Ryge restoration quality indices in group 2 are higher than in group 1, the differences are statistically significant with $p \leq 0.001$. After 36 months, the statistical significance of the difference in the quality parameters of the restoration increases to $p \leq 0.0001$. The results are confirmed by the data of scanning electron microscopy.

Conclusion

The high efficiency of brushite crystals has been proven in terms of preventing violations of the integrity of the enamel-composite joint as a leading etiological factor in the recurrence of the carious process, which makes it possible to reasonably recommend RemarsGel in the presence of a significant number of adhesive restorations in the oral cavity, made both by direct and indirect methods, especially in case of decompensated caries. process.

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Analysis of changes in periodontal vascular hemodynamics in patients with type 1 DM after conservative periodontal therapy as a method of predictive, preventive and personalised (3P) medical approach

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Key words: predictive preventive personalised medicine, diabetes mellitus, microcirculation, ultrasonic dopplerography, professional oral hygiene

Topicality

The microcirculatory bloodstream of the periodontium is an active hemodynamics zone of the body and under diabetes mellitus (DM) is subjected to pathological changes much earlier than vessels of other organs. Reduced local immune responses in conjunction with diabetic microangiopathy over time leads to periodontal tissue damage and bone resorption, which requires timely diagnosis of blood flow and its control during treatment. Ultrasound Doppler sonography (USDG) in patients with polymorbid pathology makes it possible to predict the dynamics of blood flow changes and is a new perspective direction in modern dentistry.

Objective

To assess the hemodynamics of the periodontal vessels in patients with type 1 DM and without DM before and after conservative periodontal therapy.

Materials and methods

40 patients aged 20 to 30 years ($M \pm m - 24 \pm 0.5$) were examined, 20 of them had a history of type 1 diabetes (group 1) and the remaining 20 patients had no endocrine system pathology and formed a control group (group 2). All patients underwent evaluation of hygienic and periodontal status, ultrasonic scanning and professional oral hygiene. The repeated evaluation was performed after 4 weeks.

Results

Hygienic and periodontal status of patients in Group 1 was significantly worse than that of patients in the control group, but after the performed hygienic measures the improvement of indices was more pronounced in the group of patients with type 1 DM. Assessment of periodontal blood flow indices 4 weeks after professional oral hygiene revealed an increase of microcirculation rate in periodontal tissues in patients with type 1 diabetes ($V_{lin.} - 0,464 \pm 0,027$ cm/s, $V_r - 0,028 \pm 0,002$ ml/min), while in the control group the values changed insignificantly - ($V_{lin.} - 0,687 \pm 0,015$ cm/s, $V_r - 0,036 \pm 0,004$ ml/min).

Conclusions

Application of ultrasound examination of the periodontal vessels is an informative technique for analysis of the efficiency of the periodontal therapy performed as well as performs a predictive task in revealing the blood flow disorders. Significant improvements of hygienic and periodontal status as well as positive shifts of hemodynamic parameters of periodontal vessels in patients with type 1 diabetes in comparison with the control group were revealed, that testifies to necessity of the special personalized approach in complex treatment of periodontal diseases in patients of this group.

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Comprehensive predictive assessment of lung health status in persons of young age

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Keywords: young people, personalised medicine, henome, COPD, prediction

Background

COPD is a heterogeneous disease, the variability and diversity of which depends on a combination of genetics and risk factors. At present, during the period of the deciphered human genome, an earlier assessment of the prognostic risk of the development of cochlea in young people is needed to understand the possibilities of establishing reversible lung lesions.

Working hypothesis, materials and methods:

The aim is as a part of preventive phenotyping in young people, substantiate the importance of a comparative risk-oriented complex epigenetic and genetic assessment of the lung health status for predictive assessment of the risk of developing COPD. In this cohort study, 293 young people (11-23 years old) took part, including: 142 male and 151 female, who were divided into four groups. 1st group - 132 conditionally healthy non-smokers (51 male and 81 female), 2nd - 54 conditionally healthy smokers (39 male and 15 female), 3rd - 86 non-smokers, with chronic lung diseases (52 persons – chronic tracheobronchitis; 43 persons – bronchial asthma), 4th - 21 smokers with chronic lung diseases (HRTB - 12 persons, BA - 9 persons). To assess the differences in epigenetic and genetic criteria, methods such as spirometry, gas analysis, electronic auscultation, digital acoustic analysis of respiratory work, analysis of gene polymorphisms for the alpha1-antitrypsin-SERPINA-1 complex in venous blood serum were used. We have developed a computer program, taking into account the risk factors for the prognostic development of COPD in a cohort of smoking and non-smoking young people aged 11-23 years with or without a diagnosis of chronic lung disease.

Results

Among the most reliable, informative, sensitive and specific phenotyping indicators in assessing the prognostic degree of COPD risk in adolescents: cough, sputum production, ARI frequency per year, smoking index, electronic auscultation data, FEV1%, FVC%, FEV1 / FVC%, CO , O2, AAT, SERPINA. These criteria made up the characteristics of risk phenotypes, which allows the subjects to be graded according to groups (phenotypes) of the prognostic risk of COPD - low, moderate, high or extremely high, depending on the scale of criterion values. In young people in the context of predictive preventive personalized medicine. This made it possible to draw up an algorithm for assessing risk groups and a computer program based on this algorithm, which makes it possible to determine the phenotypes of COPD risk in young people.

Conclusions and expected PPPM impacts

Starting from adolescence, it is possible to record the initial functional disorders of the respiratory status in combination with genetic polymorphisms, which confirms the need for preventive screening for the primary identification of risk groups and the formation of preventive programs in young people. The developed algorithm and computer program make it possible to determine the prognostic risk of COPD in young people

- from low to moderate, high and extremely high, in terms of the implementation of the concept of 3P (personalized, preventive, and predictive) medicine.

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Analysis of superficial temperature distribution changes after physical activity in school children for personalization of general fitness exercises

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Keywords: thermoregulation, personalized training, school children, thermography

Background

The purpose of this work was to elaborate an objective, easy to implement assessment of the influence of physical exercises in school children that may be used for personalized training.

Working hypothesis, materials and methods

In this study 60 female and male primary school pupils were exposed to physical exercises in the form of 45-minute general fitness training. The subjects were divided into three groups: Group 1 (7-year-olds), Group 2 (9-year-olds), and Group 3 (12-year-olds). Changes in superficial body temperatures were measured by means of thermovision camera before exercises, immediately after exercises, and after a 15-minutes restitution period. Temperatures were analyzed in 12 areas of the body front and back, covering trunk, upper and lower limbs.

Results

After physical exercises, a statistically significant decrease in temperature was noted in all groups, in all areas of the body. The greatest temperature change was observed in 12-year-olds, while the smallest one was measured in the youngest subjects. The statistically significant relation between the average trunk temperature of 7-year-old and 12-year-old children, was stated.

Conclusions and expected PPPM impacts

The training should be adapted to the age-dependent body capacity and thermoregulatory mechanisms. Thermovision analysis is an effective tool for assessment and stratification, critical for the personalized approach.

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Objectives of the concept for personalized treatment and prevention of alveolar process defects with the use of osteoplastic materials

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Keywords: predictive, preventive and personalised dentistry; European Association for predictive, preventive and personalised medicine (EPMA); prevention of alveolar process bone defects; bone tissue regeneration; osteoplastic materials.

Background

The literature reveals the fact that dentofacial system health disorders together with bone destructive changes occupy the priority position in the overall structure of jaw defects. One of the most urgent and socially significant problems in contemporary surgical dentistry is bone regeneration.

Bone destructive disorders of the dentofacial zone, resulting from removal odontogenic infection site, mass lesions, cysts, traumatic tooth extraction, atrophy of the alveolar ridge due to long-term absence of teeth, periodontitis, peri-implantitis, etc. cause disfunctioning of the dentofacial system by reducing alveolar crest bone strength parameters and significant worsening of the bone conditions for functional and aesthetic rehabilitation of patients, can lead to general somatic pathologies and a decrease in the quality of life of patients [1, 2].

The problem of bone regeneration of the alveolar crest of the dentofacial zone is one of the most important in the context of the study of the biological laws for functioning and properties of human bone tissue, as well as the physical, mechanical, and chemical parameters of various replacement osteoplastic materials that can be successfully used for treatment of alveolar process defects and prevention of bone tissue atrophy. Alveolar process bone defect healing depends on a number of factors, including location, shape, and size of the defect, as well as the general somatic status of the patient, which, in some cases, prevents full replacement of the bone defect with regenerate. This needs to be considered in functional and aesthetic rehabilitation of patients. Such comprehensive approach to the diagnosis of the patient's profiling status, further individualized treatment and prevention of alveolar bone atrophy correlates with the main concept of Predictive, Preventive and Personalised Medicine (PPPM) and have a high potential for clinical use [3-5].

Working hypothesis, materials and methods

Being the dental clinic of the Dentistry Institute of VSMU named after N.N. Burdenko based, composition and properties of human bone tissue of the lower jaw and osteoplastic materials were studied: Bego Oss (Biomaterials GmbH, Germany) xenogenic material based on calcium phosphates from bovine spongy bone; Maxresorb (Botiss Dental, Germany) synthetic material consisting of hydroxyapatite and beta-tricalcium

phosphate; Bioplast-dent (VladMiva, Russia) xenogenic material based on bone hydroxyapatite and xenocollagen containing sulfated glycosaminoglycans.

In the framework of experimental studies, the morphological features of bone tissue and osteoplastic materials were studied using a scanning electron microscope JSM-6510LV JEOL (Japan).

As part of the clinical studies, a comprehensive examination and surgical treatment was performed in 21 patients aged 20 to 45 years with partial tooth loss and retinated third molars, of which 13 patients underwent open sinus lifting surgery, and 8 patients had their retinated third molars removed and the defects filled with osteoplastic material. The patients were divided into 4 groups: group 1 (9 people) – using Bego Oss (Biomaterials GmbH, Germany), group 2 (6 people) – Maxresorb (Botiss Dental, Germany), group 3 (3 people) – Bioplast-dent material (VladMiva, Russia), group 4 (3 people) – control (healing by own blood clot).

Examination of patients' condition during their postoperative period: assessment of patients' pain sensations according to digital scale (Huskisson E.S., 1974); management of a protocol of postoperative observation (postoperative edema; hematoma; wound exudate discharge; body temperature; wound healing); X-ray examination of patients according to CBCT data.

Results

The study of the samples morphology revealed that osteoplastic materials of xenogenic origin have morphology similar to the tissues of the human jawbone, which determines the success of the use of this material in order to optimize osteoreparation processes in treatment and prevention of bone defects of the dentofacial zone, however, the possibility of developing an immunological response of the body and premature resorption of the material create certain restrictions on the use of this group of materials. Synthetic materials provide penetration of osteogenic cells and high bioactivity of the material, contributing to acceleration of integration of the implant with the bone tissue, but the lack of osteoinductive properties slows down reparative osteogenesis.

According to the anamnesis, the pain in the surgery site increased in 2-3 hours. On the first day, moderate pain was observed in all the study groups in 76.2% of cases. In 23.8% of cases, the pain syndrome was mild. On the 10th day, all the groups showed clinical recovery.

According to the results of the clinical study in group 1 with the use of Bego Oss (Biomaterials GmbH, Germany) material, a lower severity of edema and hematoma was identified on the first day of the postoperative period, these phenomena were stopped in average 2-3 days earlier than in group 3 with the use of Bioplast-dent (VladMiva, Russia) and in control group 4. In group 2 with Maxresorb (Botiss Dental, Germany), the edema was less pronounced, stopped 2-3 days earlier than in group 3 and control. On the 10th day, all the groups showed clinical recovery. During the postoperative period, the patients with retinated and dystopian third molars of the lower jaw in the control group had scant hemorrhagic exudate in 33% of the patients, and a minor hematoma.

The obtained results of postoperative X-ray examination indicate a uniform and hermetic filling of the maxillary sinus and the wells of the removed teeth with osteoplastic material.

Conclusions and expected PPPM impacts

Comparative characteristics of the pain syndrome did not reveal significant differences between the studied osteoplastic materials. When using Bego Oss (Biomaterials GmbH, Germany) and Maxresorb (Botiss Dental, Germany), clinical recovery was achieved on day 7 in 100% of cases, in contrast to the Bioplast-dent (VladMiva, Russia) material, with the use of which complete clinical recovery occurred on day 10. When

healing with a natural clot, scanty hemorrhagic exudate was observed in 33% of the patients, and a minor hematoma was observed in the first week of postoperative follow-up observation. The use of Bego Oss (Biomaterials GmbH, Germany) and Maxresorb (Botiss Dental, Germany) osteoplastic materials in the surgical replacement of alveolar process defects contributes to complete replacement of the bone defect and favorable course of the postoperative period. The use of Bioplast-dent (VladMiva, Russia) contributes to full replacement of the bone defect, but a longer postoperative period.

Thus, the use of osteoplastic materials for bone-destructive changes in the jaw alveolar process contributes to full replacement of the bone defect, which eliminates secondary deformation and contributes to prevention of jaw bones atrophy, which fits into the paradigm of predictive, preventive and personalised medicine (PPPM).

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Flammer syndrome and pregnancy from the standpoint of the connective tissue status of mothers

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Keywords: Flammer Syndrome, hereditary connective tissue disorders, pregnant, newborn children

Background

The phenotype of the Flammer Syndrome (FS) is usually associated with ocular symptoms of the type of normal pressure glaucoma in combination with manifestations of vascular dysregulation [1]. In this regard, the influence of this syndrome, including vascular disorders, on the condition of pregnant and newborn children may be of particular interest [2]. Since a significant part of the diagnostic signs of FS has something in common with the symptoms of nonspecific hereditary connective tissue disorders (HCTD) [3], it seems relevant to study the status of pregnant women from these positions. Such common features include the following - body weight lack, dyscirculatory complex, low stress resistance, etc. Aim: to evaluate some manifestations of CT dysfunction in pregnant women and indicators of the trophological status of newborns, taking into account the presence of FS signs in their mothers.

Working hypothesis, material and methods

To test the working hypothesis about the possible pathogenetic community of FS and HCTD 60 pregnant women (average age 27.2 ± 2.5) were under observation. The main group consisted of pregnant women with FS diagnosed using a specialized questionnaire (O. Golubnitschaja, J. Flammer, 2018) [4] ($n=26$); the control group included women of comparable age ($n=34$), without this syndrome. The term of delivery and height-weight indicators of both pregnant and newborn babies were evaluated (Quetelet index I). Also, the most diagnostically significant phenotypic signs of CT insufficiency were evaluated in women – thumb symptom, wrist symptom and other stigmas of dysembriogenesis [3]. The women were examined for the presence in the past and/or present of focal chronic infection (FCI) such as pyelonephritis, tonsillitis, sinusitis, etc. The data were processed using the MSExcel (2010) statistical software package.

Results

The trophological status of newborns, reflecting the state of nutrition in the intrauterine period, was markedly different in the group with the presence of FS compared to the control - hypotrophy was detected significantly more often - 35.2% and 20.4% in the two groups ($p=0,031$), normotrophy - less often (51.3% and 57.1%, $p=0,581$) and hypertrophy – less often (13.5% and 22.5%, $p=0,059$). Newborns from mothers with signs of FS were characterized by lower indicators of gestational age - 38.7 ± 0.67 and 39.9 ± 0.48 weeks ($p=0,063$). Some features of the status of pregnant carriers of FS are also noteworthy. For example, occurrence of low-weight cases among them, that is, weighing less than 2500g, was equal to 25.0% and 6.25% in these groups. At the beginning of pregnancy, the body mass index of women with FS was

20.9±0.17kg/m², and in the control group - 23.2±0.22kg/m² (p=0.046). The presence of history of FCI, mainly in the form of chronic tonsillitis, was detected in 38.5% and 14.7% of women from the main and control groups (P=0.018). The presence of such markers of CT dysfunction as joint hypermobility in the form of a thumb and/or wrist symptoms was registered in 34.6% and 11.7% of women in the compared groups. Signs of the type of curved little finger, arachnodactyly, changes in the auricles, etc. were also more often observed in the main group.

Conclusion and expected PPPM impacts

The more frequent occurrence of phenotypic signs of HCTD in pregnant women with FS may indicate the commonality of these conditions from the standpoint of the systemic involvement of various organs in the pathological process due to the ubiquitous presence of CT in all body systems. This approach also seems promising from the point of view of possible correction of disorders detected in FS, since the frequently occurring presence of magnesium deficiency in HCTD [5,6]. The positive effect of magnesium replacement therapy on various functional disorders have already been proven. Therefore, the presented approach to the study of the FS problem in relation to HCTD seems promising for optimizing early prediction and subsequent personalized prevention of trophic disorders in children born from women with FS.

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Visceral fat measurement is crucial for stratification of low weight individuals towards metabolic abnormalities and disease predisposition

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Keywords: visceral fat, lean, underweight, ultrasonography, metabolic syndrome, predictive preventive personalised medicine (PPPM / 3PM)

Background

Health risks associated with potentially masked individual underweight have been recently presented by multi-professional group of PPPM experts [1].

Working hypothesis

Visceral fat (VF) ultrasound (US) patterns might be a valuable biomarker to stratify low BMI individuals with abnormal metabolism diagnosed with or predisposed to associated pathologies.

Methodology and study design

30 subjects with BMI below 19 were investigated (age 22-56 years; 18 females), waist circumference (WC) was under 90 cm.

Including criteria: 30 patients diagnosed with metabolic and immunity-associated pathologies such as early hypertension (3 cases), DM type 2 (4 cases), increased levels of cholesterol (3 cases) and gout / hyperuricemia (3 patients); rheumatic diseases (sclerodermia - 2 patients, lupus - 2 patients, RA - 4 patients); autoimmune conditions (thyroiditis) - 4 patients; asthma - 5 patients.

Exclusion criteria: Patients diagnosed with cancer and cachexia

Control group set-up: 30 healthy subjects with low BMI and 30 healthy subjects with normal BMI (19-25).

Methodology: Extensive protocol of abdominal US using convex 2-7 MHz probes evaluating fat accumulations measuring visceral fat and subcutaneous (SF) fat thickness (cm) and areas (cm²) on US [2]. All subjects underwent general clinical, lab tests; point of care ultrasound imaging was done where needed (muscles, colon, etc.).

Results

The subcutaneous fat thickness in lean individuals was 12 ± 5 mm versus 16 ± 7 mm in controls. Visceral fat thickness was 5 ± 2 in healthy lean individuals, 20 ± 10 in lean individuals with diagnosed pathologies and 12 ± 5 mm in controls with normal BMI ($p < 0.05$ compared to the control group), poorly correlated with waist circumference and BMI in both groups. Visceral fat thickness was increased over **25 mm** (figure 1) in lean individuals with all rheumatic diseases, metabolic diseases (early life hypertension, DM type 2, increased levels of cholesterol) also with gout / hyperuricemia. Compared to the control group, the patient group demonstrated increased visceral fat patterns (19-23 mm) in lean cohort with asthma. Lean patient group with diagnosed pathologies demonstrated relevant ultrasound patterns of comorbid conditions, including signs of liver, kidney disease, colitis, duodenogastral reflux, GERD. Microsplenia (spleen size under

90x30 mm) was detected in all patients with rheumatic diseases, autoimmune conditions (thyroiditis), in individuals after / during steroid treatment. Small amounts of fluid in the pelvic / abdominal cavity were found in 13 lean patients; sarcopenia (decreased thickness and pennation angles of gastrocnemius muscles on ultrasound) was diagnosed in 8 lean patients.

Conclusions and expert recommendations in the frame-work of PPPM

- Ultrasound patterns of fat redistribution with increasing visceral fat thickness were demonstrated in low weight individuals as correlating with metabolic abnormalities, several pathologies and potentially disease predisposition.
- Above demonstrated diagnostic approach creates a robust platform for targeted preventive measures to mitigate potentially associated disease development in low weight individuals such as abnormal metabolism and blood pressure, gout, systemic inflammation, thyroidal diseases, asthma etc. [1].
- Individualised patient profiling is strongly recommended based on involved visceral fat thickness patterns for treatments tailored to the person [1-4].

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Figure 1. Case report; visceral fat patterns increased in lean individual with rheumatoid arthritis. Female patient 24 year of age, BMI=19; Ultrasound sagittal scan in epigastrium demonstrates fat thickness of 4 mm, visceral fat thickness increased over 25 mm.

The first-level gut microbiome analysis in severe alcoholic hepatitis within the framework of predictive, preventive, and personalized medicine

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Keywords: gut microbiome, pathobiome, alcohol-associated liver disease-ALD, severe alcoholic hepatitis-SAH, cirrhosis dysbiosis ratio -CDR, prediction, personalization, alpha diversity, predictive preventive and personalized medicine (PPPM/3PM)

Background

Slovakia ranks the first in the world in the prevalence of decompensated cirrhosis. Alcohol-associated liver disease (ALD) is the most frequent etiology of cirrhosis. Treatment options for the most serious subtype of ALD, alcoholic hepatitis (AH), are limited. In fact, for the phenotype of AH with the highest short-term mortality, i.e. severe AH (SAH), the only approved treatment are timely administered corticosteroids (possibly combined with N-acetyl-cysteine). Not surprisingly, prognosis of AH has not changed since 70's of the last century [1].

Gut microbiome (MB) is one of the most important components in the pathophysiology of AH. A handful of recent studies have addressed MB in AH as either diagnostic tool, or a therapeutic target [2]. The first approach was based on the hypothesis that, dysbiotic MB (pathobiome) could serve as the prognostic marker capable of predicting severity of AH, response to therapy, and survival. In terms of therapy, it was proposed that, manipulating AH pathobiome could fill a therapeutic gap and improve prognosis in the most severe phenotypes of SAH [3]. Broader changes found in the composition of MB in patients with ALD cirrhosis - such as cirrhosis dysbiosis ratio (CDR) – are, as of yet, difficult to decipher as being of help in a daily clinical practice and having exploited their predictive and preventive potential [4].

Working hypothesis, materials and methods

We hypothesized that, CDR, which has been shown to associate with the evolutionary stages of chronic liver disease, may be associated with the subtypes of acute decompensation of advanced chronic liver disease triggered by SAH (such as ACLF and its grades) and mortality. We have also analyzed alpha diversity of MB in patients with AH and controls.

Our study enrolled 36 patients with SAH and 22 healthy controls. Fecal samples were collected from patients with SAH at time of diagnosis at the Department of Internal Medicine and HEGITO (Hepatology, Gastroenterology and Liver Transplantation), F.D. Roosevelt University Hospital. Collection of lyophilized fecal samples of healthy controls were obtained from Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava. After DNA isolation using QIAamp PowerFecal Pro DNA Kit (Qiagen), microbiome profiling was performed using 16S ribosomal RNA amplicon sequencing. The libraries were prepared using the PCR products according to the MiSeq System guidelines (Illumina). Obtained data were analysed with QIIME 2. CDR (cirrhosis dysbiosis ratio) was calculated according to Bajaj et al. [5].

Results

Obtained results have shown differences in the microbiome of healthy controls when compared to the patients group. The fecal microbiomes of patients had lower alpha diversity and higher beta diversity than the microbiome of healthy controls in gut bacteria. Preliminary data from our study suggest that the alpha diversity does not significantly correlate with the severity of AH and with the prognosis in terms of mortality. Significant differences in CDR were found between controls ($2,7 \pm 1,1$) and patients with AH (mean $\pm$ SD; $6,9 \pm 4,5$). However, similar to alpha diversity, no correlations of CDR with the presence or grade of ACLF as well as with ACLF mortality were observed.

Conclusion and Expected PPPM impacts

Gut microbiome, as portrayed by the means of summary indices such as alpha diversity and CDR, clearly distinguishes patients with SAH from healthy controls. However, these rather rough reflections of pathobiome do not allow for more personalized predictions of prognosis inside the SAH - such as evolution into acute-on-chronic liver failure (ACLF), subclassification/grading of ACLF, and mortality [6].

Gut pathobiome is involved in the evolution of AH and is studied as a determinant of therapeutic effects but its complex role is not yet fully understood [7]. Our primary analysis confirms that both CDR and alpha diversity significantly associate with SAH. However, for the more personalized prediction of prognosis within the group of patients with syndrome of SAH, individual taxa have to be scrutinized one by one.

Confirmatory results provided by our first-line analysis will continue to impact in-depth study of SAH pathophysiology [8]. However, it has become clear after this analysis that the main impact of mapping pathobiome will dwell in discrimination of specific taxa associated with prognosis inside the SAH in terms of ACLF evolution, response to first- and second-line therapy, as well as mortality [9]. Undoubtedly, it may further unlock the potential for application of PPPM in this particular pathology and bring new possibilities for targeted prevention through using natural substances, positively influencing gut microflora as already reported for other pathologies [10].

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