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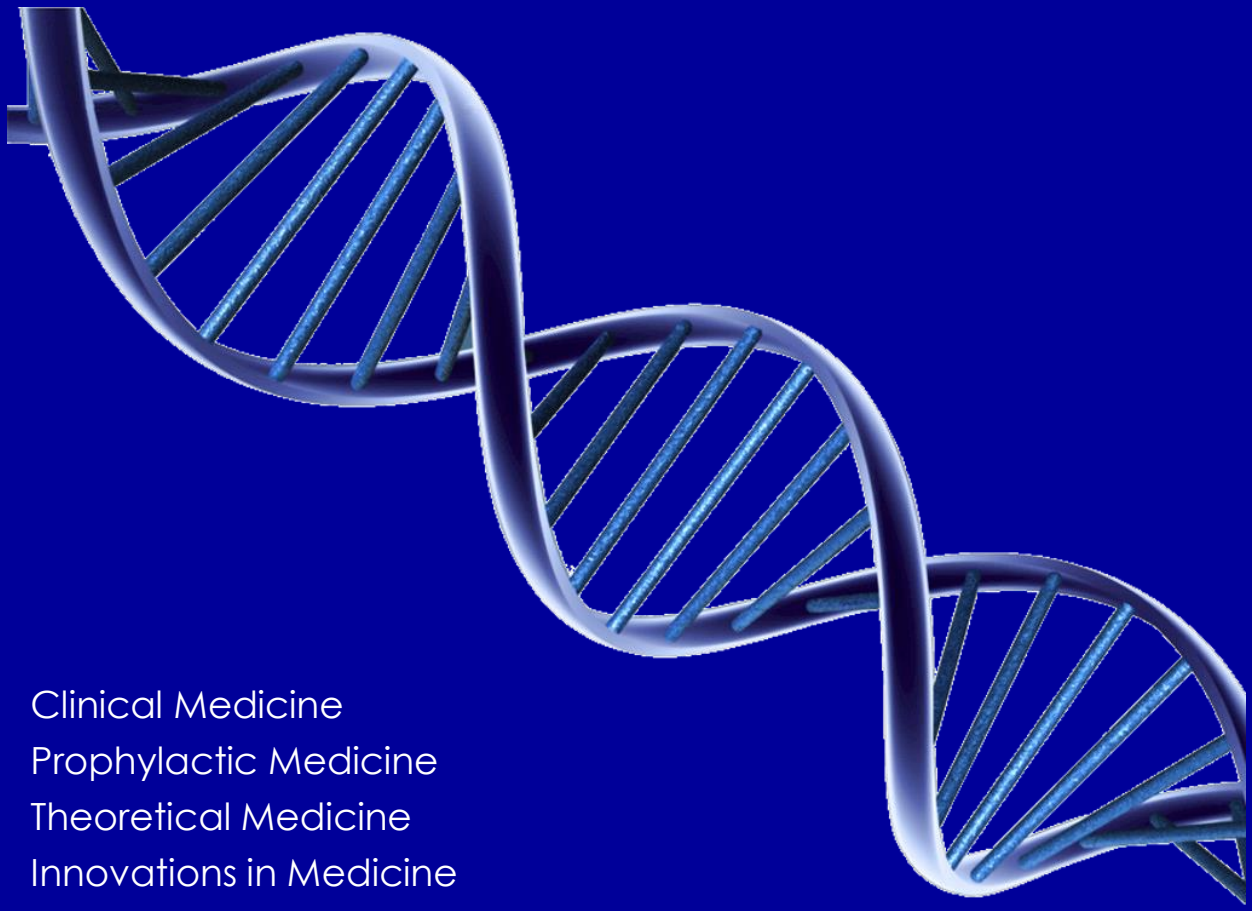

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ADALİMUMAB: USAGE İN A CASE WİTH PSORİASİS AND DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

There are different biological treatments for psoriasis and one of these treatments is adalimumab. Here we want to present a case with psoriasis and Duchenne muscular dystrophy treated with adalimumab. A 23-year-old male patient with psoriasis and Duchenne muscular dystrophy applied to our dermatology clinic. At the sixth week control of the patient we achieved PASI 90 response. Duchenne muscular dystrophy is a rare disease and its coexistence with psoriasis is a very rare status. No similar case report was found in the literature. We wanted to present both this rare status and psoriasis progression under adalimumab treatment.
Keywords: psoriasis, adalimumab, Duchenne muscular dystrophy

Introduction: Psoriasis is a sharply demarcated, chronic, inflammatory skin disease, characterized by erythematous plaques. Most important factors in the pathogenesis of psoriasis are genetic and environmental factors and ethnicity. There are different biological treatments for psoriasis and one of these treatments is adalimumab (1,2). Here we want to present a case with psoriasis and Duchenne muscular dystrophy treated with adalimumab.
Case report: A 23-year-old male patient with psoriasis and Duchenne muscular dystrophy applied to our dermatology clinic. He didn't have any other diseases. He had psoriasis for 12 years and didn't smoke or drink alcohol. We determined his psoriasis area and severity index (PASI) as 10.2 (figure 1,2). Earlier he used methotrexate but developed resistance to this treatment. We started adalimumab for our patient after receiving the opinions of the physiotherapy and rehabilitation clinic of our hospital. At the sixth week control of the patient we achieved PASI 90 response (figure 3,4). The clinical follow-up of our patient continues in our outpatient clinic. We didn't experience any drug-related side effects so far.

Discussion: Although the prevalence of psoriasis is different in each country, it can ocur at any age. There can be some comorbidities in the patients with psoriasis; hypertension, kardiovascular diseases, diabetes mellitus, dyslipidemia. In the treatment, earlier PASI75 response but nowadays PASI 90 and even PASI 100 responses are targeted. Biologics are very important and quite effective agents in the treatment of psoriasis. One of these biologics is adalimumab (1,2).

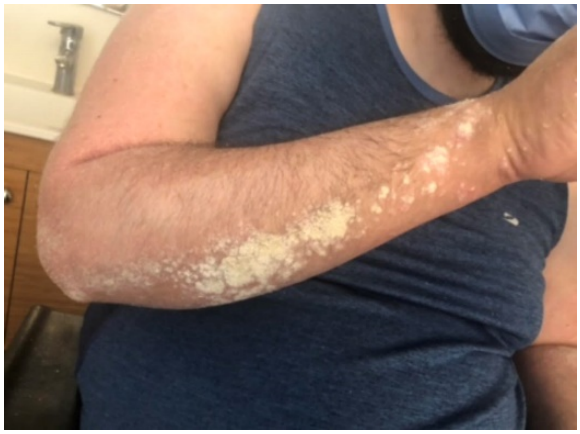

Figure 1. Squamous plaques on the arm

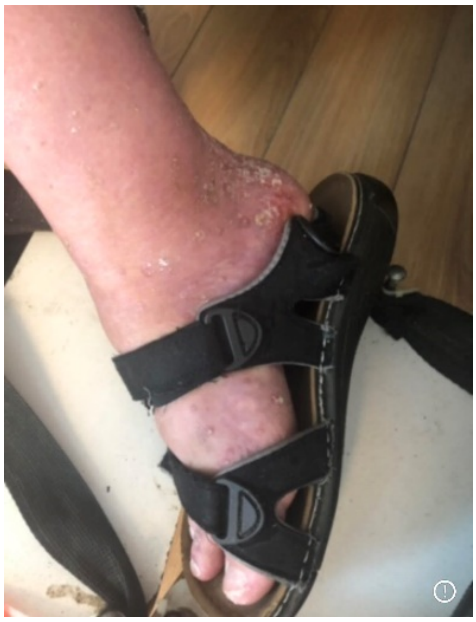

Figure 2. Squamous and erythematous plaques and papules on the foot

Adalimumab, tumor necrosis factor α (TNF-α) inhibitör, is a recombinant, fully human monoclonal antibody. Adalimumab binds to TNF-α with high affinity and specificity and thus prevents the interaction between TNF-α and p55 and p75 subunits of TNF-α reseptor. Adalimumab exits in the preferred molecules for the treatment of cases with moderate or severe plaque psoriasis. It has also approved for use in other diseases; rheumatoid arthritis, juvenile idiopathic arthritis, ankilosing spondylitis, psoriatic arthritis, Chron's disease. Rarely, It can cause severe adverse effects; tuberculosis, lupus like syndrome, demyelinating diseases, congestive heart failure, pancytopenia, rising of transaminases, palmoplantar pustulosis, lichenoid reactions, bullous eruptions, alopecia, hepatotoxicity, malignancies. It has been found that it doesn't increase mortality (3,4). In the follow-up of our case, any adverse reactions have been observed.

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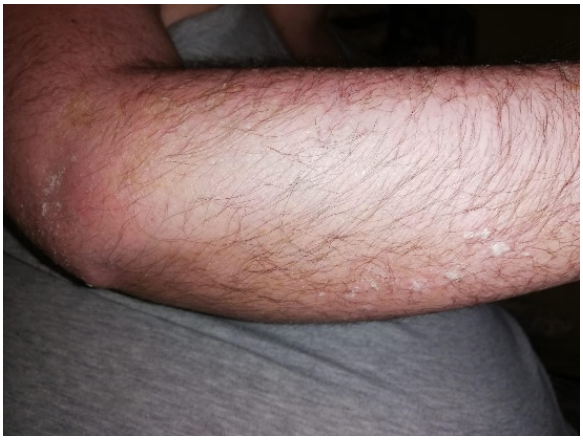

Figure 3. PASI 90 response on the arm

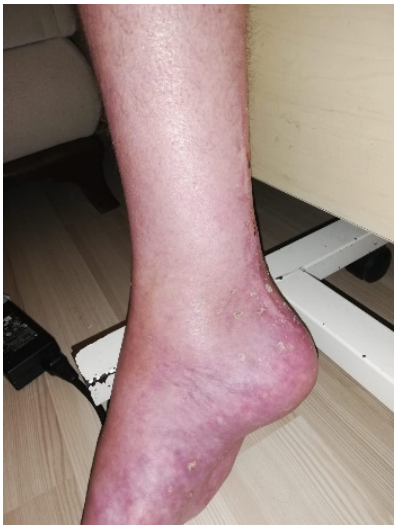

Figure 4. PASI 90 response on the foot

Duchenne muscular dystrophy progressing with progressive degeneration and atrophy in the muscles is the most common, inherited illness in all muscle diseases. Especially, it occurs in male cases (5). Our patient is male, too and his PASI 90 response is going on. He completed his third month under adalimumab treatment.

Duchenne muscular dystrophy is a rare disease and its coexistence with psoriasis is a very rare status. No similar case report was found in the literature. We wanted to present both this rare status and psoriasis progression under adalimumab treatment.

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MANIFESTATIONS OF SARS-COV-2-INDUCED COVID-19 ON THE SKIN AND ORAL MUCOSA

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ABSTRACT

Over the past centuries, it is difficult to find diseases similar in resonance to the corona-virus infection COVID-19 caused by SARS-CoV-2. From the day of manifestation of the infection, it has become the dominant nosology, and its etiological agent has dramatically changed, in its favor, the species spectrum of anthropogenic pathological microorganisms. The review is devoted to the skin manifestations of new coronovirus infection (SARS-CoV-2), information about which is constantly updated. However, this information has not been systematized yet. The purpose of this review is to analyze the dermatological manifestations of a new coronavirus infection. On average, 12.5—20.4% of patients with confirmed COVID-19 have developed skin manifestations. The question of whether the skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself remains open at the moment. The possible mechanisms of development of skin lesions and the role of diseases of complement system and blood hypercoagulation in the pathogenesis of the disease are discussed in the article. The review also provides descriptive and clinical examples of skin manifestations in COVID-19. Since COVID-19 tends to be asymptomatic within 14 days, skin manifestations can be an indicator of infection, which leads to the timely diagnosis. In addition, doctors' awareness about skin symptoms associated with COVID-19 infection plays a big role in preventing misdiagnosis of the disease.
Keywords: COVID-19, SARS-CoV-2, Skin, Oral Mucosa.

Over the past centuries, it is difficult to find diseases similar in resonance to the corona-virus infection COVID-19 caused by SARS-CoV-2. From the day of manifestation of the infection, it has become the dominant nosology, and its etiological agent has dramatically changed, in its favor, the species spectrum of anthropogenic pathological microorganisms. The first information about the new disease was registered in December 2019 in China. Since January 2020, the disease has spread to other countries of the world. Since February 2020, residents of South Korea, Iran, Italy, Spain and the United States have been infected with COVID-19, and later almost the whole world. On March 11, 2020, World Health Organization declared a pandemic caused by COVID-19. The high level of contagiousness and asymptomatic transmission of the infection led to its rapid spread around the world and a pandemic [1]. SARSCoV-2 is a single-stranded RNA virus and belongs to the coronavirus family. The virus enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor located on the surface cells [2]. The lungs are a major target organ for

COVID-19, with patients experiencing symptoms ranging from mild flu-like symptoms to fulminant pneumonia and potentially fatal respiratory distress syndrome [3]. A number of cases have been recorded during the pandemic COVID-19 who reported skin manifestations of the infection**.** The purpose of this article is to systematize the literature on various skin manifestations in COVID-19. According to literary sources, during the pandemic period, a number of cases of COVID-19 with skin manifestations were recorded: Similar information was first reported from Italy - Gianotti [4] described Exanthema, Purple maculopapular vesicular, Papular- erythematous, and Diffuse maculopapular eruption resembling Grover's disease; Recalcati [5] reported an erythematous and vesicular rash, as well as urticaria; Present, Case [6] described a maculopapular pruritic rash resembling Grover's disease, Diffuse maculopapular rash, macular hemorrhagic rash, and Papular-vesicular pruritic rash; Marzano [7] described a papulo-vesicular exanthema similar to the chicken pox rash, and Mazzotta [8] described erythematous rounded lesions; Erythematous rash was described by the French dermatologist Mahé [9], and disseminated erythematous rash and urticaria were described by Henry [10]; Spanish investigators Estébanez [11] reports erythematous pruritic papules (yellow) and Fernandez [12] reports urticaria; In Thailand, researchers described petechiae (Joob [13]), in Iran - an erythematous rash (Kamali and Aghdam [14]), and in Qatar - cranial ischemic lesions, which are red-violet papules (Alramthan [15]), in Belgium - infiltrated plaques on an erythematous background (Kolivras [16]), in Russia - papulo-necrotic angiitis, hemorrhagic angiitis, acroangiitis (acrodermatitis), papulo-vesicular rashes, disseminated maculopapular rash and purpurous rash (toxidermia) (Aleksey, Khryanin [17]), in the homeland of infection in China, acroischemia with digital cyanosis, blistering or dry gangrene, and urticaria (Zhang [18]), and in the United States, transient non-pruritic unilateral livedo reticularis, unilateral asymptomatic livedo reticularis (Manalo [19]) and diffuse to maculopapular non-pruritic rash similar to dermatological symptoms in measles (Najarian, Hunt [20]). In the course of treatment of a patient with COVID-19, we described several skin symptoms, but only one differed from the literature symptoms: an erosive element against the background of erythema on the genitals in a 64-year-old man, developing associated hyperthermia on the 4th day after diagnosis. The pathological element was eliminated from the skin 8 days after the patient's hospitalization; 14 days passed until the complete regeneration of the skin against the background of local treatment with combined topical preparations. (Photo 1)

Among the literary sources, there are only a few reports about the manifestation of COVID-19 on the oral mucosa. On the part of scientists, special attention is paid to the violation of taste in the form of hypogeusia, dysgeusia or ageusia during the disease. Apparently, oral manifestations dominate in the main post- COVID-19 period in the form of hyperemia, dry atrophy, hemorrhage, erosion, ulcers of the mucous membrane, pseudomembranous-erythematous form of candidiasis, aphthous rash in the oral cavity, dryness and peeling of the upper and lower lips [21, 22].

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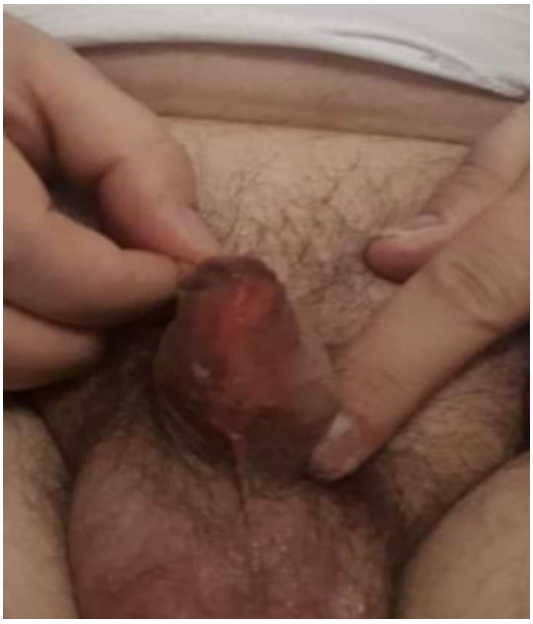

Picture 1. Erosive element on the genitals with COVID-19

As you know, a rash is not uncommon among infectious pathologies, the most common and characteristic symptoms of such viral infections as measles, rubella and Dengue fever are skin rashes (exanthema). With coronavirus infection caused by COVID-19, the formation of exanthema may be associated with an inflammatory response of tissues to the effects of toxins and metabolites of the pathogen during the implementation of the main mechanisms of inflammation; However, while skin manifestations associated with COVID-19 have been increasingly reported recently, the pathological mechanisms of skin lesions in patients with COVID-19 remain poorly understood. Skin manifestations of COVID-19 can be divided into two main groups depending on the pathophysiological mechanism of their development: clinical signs similar to viral exanthems (immune response to viral nucleotides) and skin rashes secondary to systemic consequences caused by COVID-19 (especially vasculitis and thrombotic vasculopathy). [23].
To assess the possible impact of SARS-CoV-2 on human skin, one must take into account the fact that SARS-CoV-2 is a single-stranded RNA virus consisting of 16 non-structural proteins (NSP 1-16) that play a role in the replication of coronoviruses. For example, NSP3 has the ability to block the host's innate immune response and stimulate cytokine expression, NSP5 can inhibit interferon (IFN) signaling, and NSP16 avoids MAD5 (melanoma differentiation-associated gene 5) recognition by suppressing hostile immunity [24]. Some studies have shown a direct effect of viral infection on T cells by detecting SARS-like particles and SARS-CoV-2 RNA in T lymphocytes. It has been shown that in some patients an overactive immune response can cause a "cytokine storm" (an increase in the level of pro-inflammatory cytokines, in particular, IL-6); these cytokines can reach the skin and stimulate dermal dendritic cells, macrophages, mast cells, lymphocytes, neutrophils, and promote rashes such as erythema, urticaria, vesicles, and others. [25]. Intervention in the host by SARS-CoV-2 results in infection of functional receptor-target cells expressing type II (ACE2) angiotensin-converting enzyme (ACE), such as type 2 alveolar cells or other unknown target cells. ACE2 is also present in the skin in the basal layer of the

epidermis, in the endothelial cells of dermal blood vessels, and in the tissue of the eccrine appendages. Some researchers have suggested a direct pathogenic effect of the virus on the epidermis through ACE2, leading to acantholysis and dyskeratosis. COVID-19-endothelitis through ACE2 may explain the systemic impairment of microcirculatory function in various vascular beds and its clinical consequences in patients with COVID-19. It has been shown, in particular, that virus-induced endothelial damage may be a key mechanism in the pathogenesis of "frostbite" in COVID-19, and possibly also in the development of microangiopathy. [26, 27].
Considering the data of the analyzed literary sources, it can be concluded that in case of COVID-19, lesions of the skin and mucous membranes of the oral cavity can be the first or only signs of the disease. The question of whether skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself remains open at the moment. The probable mechanisms of development of skin lesions and the role of diseases of the complement system and the state of blood hypercoagulability in the pathogenesis of their development are discussed. In this regard, much remains to be explored, from this point of view, this scientific work can be considered as a step in the process of studying COVID-19 caused by SARS-CoV-2.

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MODERN SCIENTIFIC RESEARCH DEVELOPMENT ISSUES OF HIGHER PHARMACY EDUCATION, SCIENCE, INNOVATION AND PERSPECTIVES TOWARDS ON UNIVERSAL PHARMACIST' PROFESSION GLOBALLY

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ABSTRACT

The main objective of the study was to analyze the modern scientific research development issues of higher pharmacy education, science, innovation and perspectives towards on universal pharmacist' profession globally. The study was a quantitative investigation and analysis of the characteristics of pharmaceutical vocational inquires and challenges in the direction on pharmacists' profession, role, problems, perspectives and innovations in pharmaceutics and medicine in Georgia by using questionnaires. Were conducted a survey study. The in-depth interview method of the respondents was used in the study. The 7 types of approved questionnaires were used (Respondents were randomly selected): Questionnaire for chief pharmacists: 410 chief pharmacists participated in the study. Questionnaire for patients: 1506 patients (customers of drug-stores) participated in the study. Questionnaire for the employed pharmacy faculty-student: 222 employed pharmacy faculty students participated in the study. Questionnaire for health-care specialists: 307 public health specialists participated in the study. Questionnaire for pharmacist specialist, 810 pharmacist specialists participated in the study. Were used methods of systematic, sociological (surveying, questioning), comparative, mathematical-statistical, graphical analysis. The data were processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p< 0.05$ as significant for all analyses. According to the study results, the level of basic training of pharmacists should be in compliance with the contemporary requirements. The pharmacist should have deep knowledge in pharmacology, in pharmacotherapy, in toxicology, in pharmaceutical care, in clinical pharmacy, in pharmacokinetics, in pharmacodynamics, in basic of medicine and in other

pre-clinical and clinical directions. Such knowledge can be obtained only in the higher pharmaceutical education institutions. Therefore, pharmacist working in pharmacy must have only higher pharmaceutical education. It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best feedback regulation and revision in the healthcare specialists' team work. Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide. To achieve that it is necessary to raise awareness of specialists on the essence of pharmacists' profession and functions among the medical personnel and general public.
Keywords: scientific, pharmacist, pharmacy, profession, medicine, pharmaceutics, education.

Introduction: In the pharmacy field, an increase of negative trends, such as poor mechanisms of interaction between professional education and the pharmaceutical market, a slow adaptation of graduates to the market reality is being observed [1-5]. A difference between the increasing demands of the patients' and the level of specialists' knowledge, as well as adaptation to market reality can affect the process of professional development of pharmacists and the quality of pharmaceutical care in general [6-11]. The mentioned trends, as well as the pharmacists' professionals' increasing role and responsibility in the health care system, make the necessity to analyze the current practical experience and evaluate the theoretical background of the specialists' development, as well as identify new contributing factors for their development as professional pharmacist practitioners [12-19].An integral part of the state system of measures to implement the rights of citizens for protecting their health, via using the quality pharmaceutical care services [20-26]. The provision of pharmaceutical care maintenance is significantly dependent on the pharmacist personnel qualifications. In this concern, the professional qualification of drug experts is under the state control and is one of the state regulations objects in regard to the drug-medicine relationship aiming to maintain the competence of expert specialists throughout their careers with the varying requirements for professional quality [27-32]. In developed countries and in many developing countries in the pharmacy field there are also state regulations like as in family medicine [33-38]. A pharmacist, as a family doctor, should have the higher, post-graduate and consistent education in pharmacy, and also needs to hold the pharmacist license and periodic accreditation by the board of pharmacy [39-43]. In the western countries, pharmacists are the specialists with the higher pharmaceutical education who have graduated from the state-recognized and accredited colleges and universities, and only such qualification specialists are allowed to work in the pharmacy [44-46]. A pharmacy opening permission is issued only the pharmacists who holding higher pharmaceutical education with the pharmacist diploma [47-51]. The literature analysis showed that a study of individual aspects of the pharmacists' professional development is directed to elaborating of the necessary requirements to ensure effective pharmaceutical care, postgraduate education, finding strategies for the better management of pharmacist personnel, pharmacists' job satisfaction and issues of their psycho-social adaptation to the emerging market conditions [52-58]. However, weighable studies aimed at understanding the perspectives of the pharmacist in the career aspect and the ways to provide high-quality pharmaceutical care have not been carried out yet [56-69].

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Objective: main objective of the study was to analyze the modern scientific research development issues of higher pharmacy education, science, innovation and perspectives towards on universal pharmacist' profession in medicine and pharmaceutics in Georgia.

Material and methods: Research objectives are materials of sociological research: the study was quantitative investigation by using survey (questionnaire). Research objectives are materials of sociological research: the study was quantitative investigation by using survey (questionnaire). The in-depth interview method of the respondents was used in the study. The 7 types of approved questionnaires were used (Respondents were randomly selected): Questionnaire for chief pharmacists: 410 chief pharmacists participated in the study. Questionnaire for patients: 1506 patients (customers of drug-stores) participated in the study. Questionnaire for the employed pharmacy faculty-student: 222 employed pharmacy faculty students participated in the study. Questionnaire for health-care specialists: 307 public health-care specialists participated in the study. Questionnaire for pharmacist specialist, 810 pharmacist specialists participated in the study.; Totally 3888 respondents were interviewed in Georgia. We used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program. Results and discussion: The survey was conducted through the questionnaires.1506 patients were interviewed in Georgia. Questions and answers are given in the tables. On each question are attached diagrams or table. Questionnaire and diagrams are numbered. The data was processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. Study of The data was processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p < 0.05$ as significant for all analyses. The study's ethical items. In order to provide the study's ethical character each participant of it was informed about the study's goal and suggested of willingness of the work to be done. So, the respondents' written or oral compliance was got on that issue. All the studies were carried out by the selected organizations administrations' previous compliance. Were used Informed consent form for each respondent to participate in an anonymous survey. During the whole period of research, the participants incognita was also provided. For the international rules' and criteria' conformity this human subject comprising given study was discussed and confirmed on the Bioethics Committee sessions of the YSMU. In order to meet the objectives, set in the research we also used the results obtained through analysis of available official information, studies and opinions about pharmacists, as well as the methods of quantitative studies. The research implementation required the following sub studies: The modern scientific research development issues of higher pharmacy education, science, innovation and perspectives towards on universal pharmacist' profession in medicine and pharmaceutics in Georgia.

Results and discussion: On the basis of performed study results the following have been found: Mostly essential pharmaceutical activity issues for the respondents' pharmacists' majority were: new drugs, generic drugs, chemical and brand names of them; psychology of communication (relationships) with customers; issues of pharmacotherapy of certain diseases, pharmacology, pharmacodynamics, pharmacokinetics and pharmaceutical care (See tabl.1). It is apparent, that in the

higher pharmaceutical education universities programs should be emphasized on the following subjects: pharmacotherapy, pharmacology, pharmaceutical care, clinical pharmacy and drugs toxicity.

Table 1. Mostly essential pharmaceutical activity issues for the respondents' pharmacists.

The most essential (relevant) for respondents issues of pharmaceutical activity	Count	Percent (%)
1. New drugs, generic drugs, chemical and brand names of drugs	518	64.0
2. Psychology of communication (relationships) with customers	478	59.0
3. Issues of pharmacotherapy of certain diseases	541	66.8
4. The safety, effectiveness and quality of the drugs	558	68.9
5. Pharmacology, pharmacodynamics and pharmacokinetics issues	572	70.6
6. The normative legal regulation of pharmaceutical activity	364	44.9
7. Drug technology issues	241	29.8
8. Pharmacognosy	110	13.6
9. Pharmaceutical organization and economics and pharmaceutical business	154	19.0
10. Pharmaceutical management and marketing	281	34.7
11. Pharmachemistry	90	11.1
12. Toxicology	96	11.9
13. Clinical pharmacy	267	33.0
14. Pharmaceutical care	487	60.1
15. Pharmaceutical analysis	77	9.5
16. Toxicological chemistry	50	6.2
17. Pharmaceutical technologies	86	10.6
18. Nutrition	95	11.7
19. Pharmaceutical cosmetics and perfume	178	22.0
20. Social pharmacy and Public Health	146	18.0
21. Computer technology and pharmaceutical information	140	17.3
22. Phytotherapy	132	16.3
23. Routes of drug administration	183	22.6
24. Drug forms and drug design	158	19.5
25. Drugs' toxic effects	196	24.2
26. Rules of drug administration	237	29.3
27. Cost-effectiveness and cost-benefits of drugs	124	15.3
28. Terms and conditions of storage of drug (conditions and shelf-life)	259	32.0

The most impacting factors influencing on the young pharmacists' work satisfaction were found and evaluated during the research. These factors included the correspondence of qualification to work, correspondence of the work nature to capabilities of personality, existence of perspective for professional promotion, possibility to qualifications enhancement, existence of high degree of responsibility for the result of work, information about affairs of the company and of the staff activity, working conditions, existence of the labor contract of working regimen and salary, existence of benefits' scheme for employees, support and assistance of the chief, direct relations with manager(s),relations with colleagues, possibility for the career enhancement (See tabl.2).

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Table 2. The report of impacting factors - influenced on respondents' work satisfaction.

Report on the question about estimation of the impacting factors, which have an influence on the work satisfaction (estimate each factor under the 5- point scale system).	Mean	Median	Std. Deviation
1 Correspondence of the got qualification to work	4.65	5.00	0.603
2 Correspondence of the work nature to capabilities of personality	4.42	5.00	0.721
3 Existence of perspective for professional promotion	4.21	4.00	0.907
4 Possibility to qualifications enhancement	4.13	4.00	0.895
5 Existence of high degree of responsibility for the result of work	3.87	4.00	1.141
6 Information about affairs of the company and the colleagues' activity	4.09	4.00	0.946
7 Working conditions	3.67	4.00	1.127
8 Existence of the labor contract	3.66	4.00	1.102
9 Working regimen (schedule)	3.25	3.00	1.140
10 Salary	2.65	3.00	1.053
11 Existence of benefits' scetch for employees	2.25	2.00	1.145
12 Support and assistance of the chief (manager)	3.41	4.00	1.223
13 Direct relations with the chief	3.44	4.00	1.185
14 Relations with colleagues	4.04	4.00	0.937
15 Possibility to career enhancement	3.89	4.00	0.962

Coupling the data of respondents' answers' analysis of the questions "Indicate your sex" (Q1) and „Are you satisfied with the time duration of your job? " (Q26) it became apparent that variables are gender dependent (P=0.048), there is a statistically significant differences between two groups, that means that the male pharmacists were less satisfied with the time duration of work, rather than the female pharmacists (See tabl.3).

Table 3. Respondent pharmacists' satisfaction with the time duration of job

Satisfaction with time duration of work of the respondent pharmacists according gender			
Respondent pharmacists' satisfaction with the time duration of job			
Are you satisfied with the time duration of your job?	Q1 Indicate your sex		Total
	1 Female	2 Male	
1. Yes	22.38%	14.70%	22.10%
2. Partially	34.10%	36.70%	34.20%
3. No	43.51%	48.60%	43.70%
Total	100.0%	100.0%	100.0%

Coupling the data of respondent's answers' analysis of the questions "Indicate your sex" (Q1) and „Are you satisfied with your income? " (Q27) it became apparent that variables are gender dependent (P=0.019), there is a statistically significant differences between two groups, what means that the male pharmacists were less satisfied with income, rather than the female pharmacists (See tabl.4).

Table 4. Satisfaction of the respondent pharmacists with income according gender

Crosstab			
Satisfaction of the respondent pharmacists with income according gender			
Are you satisfied with your income?	Q1 Indicate your sex		Total
	1 Female	2 Male	
1. Yes	10.59%	0.00%	10.20%
2 .Partially	25.48%	23.30%	25.40%
3. No	63.82%	76.70%	64.30%
Total	100.0%	100.0%	100.0%

Analysis the data of respondents answers on the question „Do you think that the Government should make the certification of pharmacists? "(Q) revealed the following in different categories: the majority of chief pharmacists, of consumers of medications, of the employed students, of the healthcare specialists and pharmacists considered, that Government should make certification of pharmacists (P<0.000) There are statistically significant points between variables. (See Fig 1).

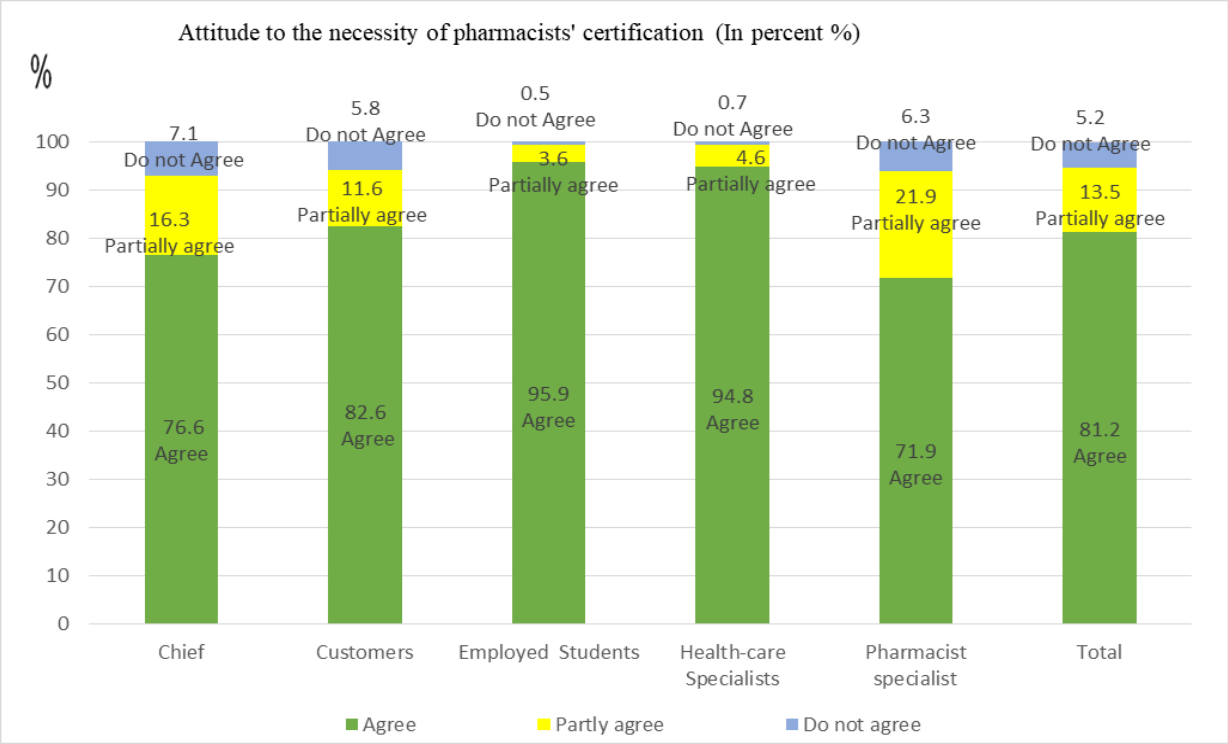

Fig. 1. Attitude to the necessity of pharmacists certification

For the majority of respondents' patients' mostly asked the pharmacists about the rules of drugs intake and prices of drugs. For the less than half part of the respondents mostly asked about the drugs' adverse effects and quality. For about the one third of them mostly asked about help in selection of analogue of drugs, indication/contraindication of drugs, the terms and conditions of

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their storage (conditions and shelf-life), the drugs dosage, rules of drug administration and selection of OTC drugs (See tabl.5).

Table 5. The respondents' mostly asked questions to pharmacists.

The questions mostly asked to pharmacists (several answers were possible)	Count	Percent (%)
1. About rules of intake of medications	950	63.1
2. About adverse effects of medications	625	41.5
3. About prices of medications	925	61.4
4. About help in selection of analogue of medication	449	29.8
5. About quality of medications	640	42.5
6. About availability of medications in a pharmacy	399	26.5
7. About indication/contraindication of medications	471	31.3
8. About terms and conditions of storage of drugs (conditions and shelf-life)	464	30.8
9. About medications dosage	505	33.5
10. About routes of drug administration	292	19.4
11. About drug forms	289	19.2
12. About drug design	130	8.6
13. About drugs toxic effects (toxicity)	297	19.7
14. About principles of pharmacotherapy	55	3.7
15. About rules of drug administration	386	25.6
16. About drugs generic, chemical and brand names	156	10.4
17. About selection of OTC drugs	409	27.2
18. Some specific information about drugs	380	25.2
19. Effectiveness of drug	312	20.7
20. About drugs action and their interactions	284	18.9
21. About drugs safety	321	21.3
22. About cost-effectiveness of drugs	51	3.4

The study of the professional adaptation of pharmacists indicated that inadequate professional knowledge, improper performance of the acquired professional skills were the main reasons for imperfect pharmaceutical care supply. The majority of the pharmaceutical organizations' heads and also the young specialists considered the coexistence of a mentor (experienced professional pharmacist) as the main factor of professional improvement for pharmacists' professional adaptation. The pharmacists' personnel must show stirring involvement in sharing their cognition, understanding, science, skill and contributing partnership and cooperation within the colleagues and other health care professionals in pharmacy direction.

It is quite significant, that pharmaceutical companies regularly perform study of pharmacists' work satisfaction. The pharmaceutical companies should determine combination of factors that effect on the pharmacists' work satisfaction. Pharmaceutical companies should create favorable working conditions for pharmacists to enable the maximal realization of the pharmacists' professional capabilities, skills and habits. A balance between the workload and pharmacists'

personal life should be more harmonized, convenient, resourceful and more poised. This will increase the quality of pharmaceutical care in pharmacies.

It should be noted, that pharmacist's satisfaction with income is a very sensitive factor that has a significant impact on the quality of pharmaceutical services performed in pharmacy, so the pharmacists' salary should be revised and increased.

It should be noted that in developed countries and in many developing countries pharmaceutical specialty is regulated profession alike the family medicine. In western countries pharmacist as a family doctor need higher pharmaceutical education, diploma and continuous pharmaceutical education, pharmaceutical license and periodic accreditation. Only pharmacists with higher pharmaceutical education have the right to work as pharmacists' position in the pharmacies. On the pharmacists' certification programs should be only involved pharmacists who have graduated pharmaceutical faculties from state recognized and accredited universities.

The majority of higher pharmaceutical education pharmacists' specialists were female; among them the largest majorities were working on the pharmacist position at pharmacies. The Government and pharmaceutical companies should create promotional conditions for males to make pharmacist profession attractive for men. It is very important for career advancement and satisfaction to provide a balance between the workload and man personal life for the satisfaction by income, for pharmacists' professional satisfaction, for pharmacist job satisfaction, and also for the career promotion perspectives.

The Government should take care of the profession of pharmacist authority. The pharmacist's profession in the health care system should increase the authority and social importance by the state support. Pharmacist's profession should become of more power and authority; a pharmacist should have a much higher status in the healthcare system. Therefore, the role of a pharmacist is significantly increased in the healthcare system and is directly related to his professional education level. Therefore, pharmacist should have appropriate higher pharmaceutical education. All the mentioned is achieved then, when the pharmacist profession will move into the health-regulated professions list.

The level of basic training of pharmacists should be in compliance with the contemporary requirements. The pharmacist should have deep knowledge in pharmacology, in pharmacotherapy, in toxicology, in pharmaceutical care, in clinical pharmacy, in pharmacokinetics, in pharmacodynamics, in basic of medicine and in other pre-clinical and clinical directions. Such knowledge can be obtained only in the higher pharmaceutical education institutions. Therefore, pharmacist working in pharmacy must have only higher pharmaceutical education.

To increase the pharmacist's professional qualification, professionalism, professional knowledge and competency the higher pharmaceutical education universities programs should more emphasize the mentioned subjects. It is too important, that a pharmacist should realize and understand that qualification upgrading study courses, professional trainings and professional workshops are of great necessity for further professional advancement. Thus, the Government should develop continuous pharmaceutical education programs accessible to all pharmacists. The qualification upgrading study courses, professional education or training courses should be available for all pharmacists. Pharmacist's education process should not be stopped. Developing a continuous pharmaceutical education system will enhance the professionalism of the pharmaceutical personnel. Experiential education should encourage perfection of critical opinion and the problem resolving processes along with the medicine discovery.

Opinion that certification of pharmacists should be mandatory was more common among health care specialists than among chiefs (Chi-square = 45.2, p<0.001) and among pharmacists (Chi-square = 68.9, p<0.001), but the there was no statistically significant difference between chiefs and pharmacists. It was more common also among customers /patients than in pharmacists (Chi-square = 44.2, p<0.001). The necessity of pharmacists' certification was stated more often by employed students than by pharmacists (Chi-square = 57.3, p<0.001).

Pharmacy faculty students should take part in the patient care practice in hospitals, society proceeding settings and in other practical experiences. Students should have the possibility to apply the clinical and pharmaceutical information taught in classes when studying in medical facilities by working under the supervision of volunteer mentors (the healthcare specialists or professionals). The research activity of the pharmaceutical faculty students in all fields of pharmaceutical practice should be encouraged.

Quality reliance refers to the necessity to improve higher pharmaceutical education to guarantee a useful, sustainable and steady activity and appropriate skills and competencies of the tomorrow's labor resources. The pharmacy degree programs should be proposed at the higher pharmaceutical institution level and entire experimental constituent element in the clinical facilities.

It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best feedback regulation and revision in the healthcare specialists' team work. Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide. To achieve that it is necessary to raise awareness of specialists on the essence of pharmacists' profession and functions among the medical personnel and general public.

On the basis of the theoretical and logical analysis the structure and composition of the factors have been developed, considering the objective (external), subjective (internal) and universal factors, which influence on the professional formation of the pharmacist. These factors comprised the content of work, position, correspondence of qualification and nature of work to capabilities, aspirations and inclinations of the pharmacist, the existence of perspective for professional promotion. The existence of perspectives for career promotion, the possibility to enhance qualifications, a high degree of responsibility for the work results, regimen, labor salary and the system of benefits scheme for employees, support and assistance of a manager, direct relations with manager and colleagues serve the essential base for the pharmacists' successful work. The unity of criteria for pharmacist professional formation, for the common professional formation (characteristic to all stages) and the specific professional formation (characteristic to the separate stage) had been developed.

Conclusion: The level of basic training of pharmacists should be in compliance with the contemporary requirements. The pharmacist should have deep knowledge in pharmacology, pharmacotherapy, toxicology, pharmaceutical care, clinical pharmacy, pharmacokinetics, pharmacodynamics, basic of medicine and other pre-clinical and clinical directions. Such knowledge can be obtained only in the higher pharmaceutical education institutions. Therefore, pharmacist working in pharmacy must have only higher pharmaceutical education. It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best feedback regulation and revision in the healthcare specialists' team work.

Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide. To achieve that it is necessary to raise awareness of specialists on the essence of pharmacists' profession and functions among the medical personnel and general public.

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MORPHOLOGICAL RESEARCH USAGE OF BIOPLAST - DENT IN EXPERIMENT

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Introduction: One of the urgent problems of modern dentistry is the search for the most effective means and methods of bone grafting [1, 2, 3]. These funds should optimize and at the same time stimulate the processes of reparative osteogenesis [4,5,6,7]. Osteoplastic materials are used in the surgical treatment of dental diseases accompanied by bone tissue destruction: chronic periodontitis, jaw bone cysts, etc [8,9,10,11,12,13].

Summary: The work represents experimental and morphological studies of regeneration of damaged areas of maxillo-facial bones. Time course of healing of induced defects in the low jaw bone filled with bioplast - dent and was studied in experimental rabbits. On days 7, 14, 21 and 28 four rabbits from each group were killed and the defect investigated by X-ray and histological methods. We stained the micropreparations ith hematoxilineeosine. Bioplast - dent granulate exerted the best effect on bone repair. In experiments with bioplast - dent, bone regenerate replaced up to one half of the area of defect by day 28.

Aim of the research: the aim of the study was to conduct a comparative analysis of the dynamics and nature of the bone reparative process in standard experimentally reproduced bone defects filled with osteoplastic material - bioplast - dent.

Material and methods: The experiments were carried out on chinchilla rabbits weighing up to 2 kg (n=32). In animals under general Calipsol anesthesia, a standard defect with a diameter of 4-5 mm was created on the lower jaw bones. At the end of the operation, the wounds were sutured with silk thread. In control animals (n=16), bone defects were left to heal under a blood clot, and in animals of the main group (n=16), bioplast-dent granules were injected into the bone defect. The animals were decapitated under anesthesia on the 7th, 14th, 21st and 28th days after the bone wound was applied. There were 4 rabbits per observation point in each group. The bone fragments were fixed in formalin, decalcified in Trilon-B, and embedded in paraffin. Sections were stained with hematoxylin and eosin.

Results and discussion: In the group of observations with bioplast - dent granulate, on the 7th day from the start of the experiment, the animals in the area of experimental exposure had extensive bone defects filled with tightly lying mineral granules, represented by a part of oxyphilic particles of accumulations of small dark crystals in the central sections of defects between bioplast - dent particles . Thin strands of a weakly oxyphilic homogeneous protein substance were located in these areas. Cellular elements were completely absent. The bone wall had a space free from granulate, filled with cellular-fibrous connective tissue, with a loose

structure, high cellularity and a low level of collagenization. In the centripetal direction, there was a tendency for cellular elements to grow into bioplast-dent deposits. The strands from young fibroblasts penetrated to the periphery into the deposits of the mineral between its granules (Fig. 1).

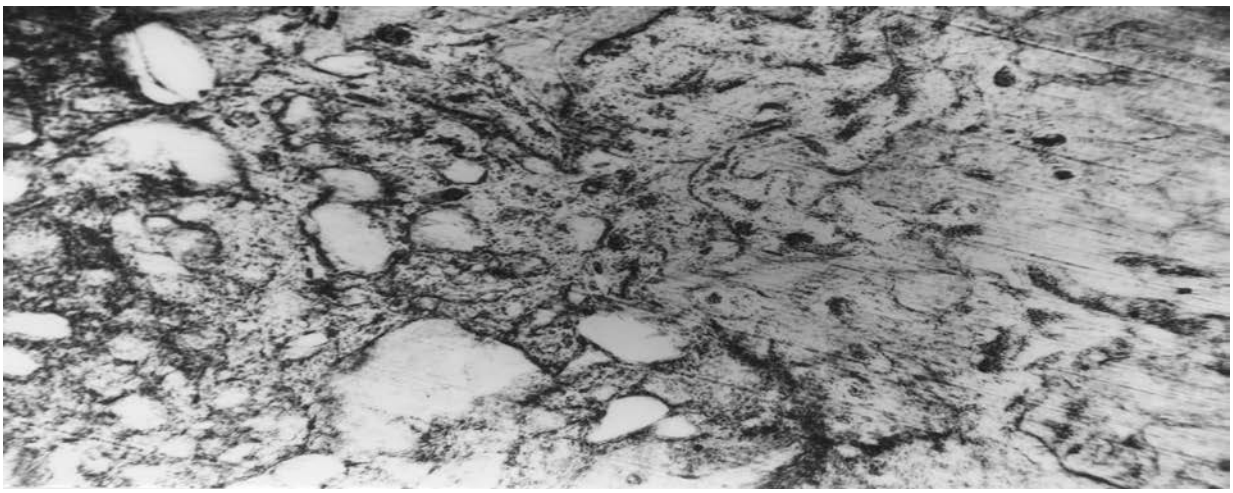

Fig 1. Extensive bone defect, oxyphilic particles Bioplast-Dent (7th day of the experiment).

On the 14th day from the beginning of the experiment, the bone edge of the defects was characterized by the loss of osteocytes and signs of pronounced phenomena of structural restructuring: numerous and randomly oriented gluing lines, variegation of the pattern of the bone substance, irregularity of osteons, etc. At the same time, areas were noted where a layering of a new bone substance occurred on the maternal bone, in the form of individual trabeculae or strips of osteoid.

On the 21st day of the experiments, active development of the soft tissue regenerate was found in the bone defect. Between the bioplast - dent granules there were layers of cellular fibrous tissue, which covered the deposits of bioplast - dent and forming, around them, thin cellular, with an admixture of delicate fibers, rims. Quite often, giant multinucleated cells were located here. In the granules themselves, in some places, the remains of bioplast - dent crystals were found. Often strands of fibroblasts have grown into them.

Closer to the bone wall of the defects, the soft tissue regenerate was represented by coarse fibrous connective tissue. The bone edge itself was dense and compacted. There were areas where newly formed bone structures were deposited on the maternal bone, in some places closely adjacent to bioplast-dent deposits, with a tendency to replace them.

On the 28th day from the beginning of the experiments, the bone regenerate half-filled the bone defect. Powerful trabecular systems captured bioplast - dent granules, as a result of which they turned out to be walled up in the newly formed bone substance. Closer to the central sections of the bone regenerate, osteon systems appeared in the maternal bone, the bone substance matured and became indistinguishable from the old bone (Fig. 2).

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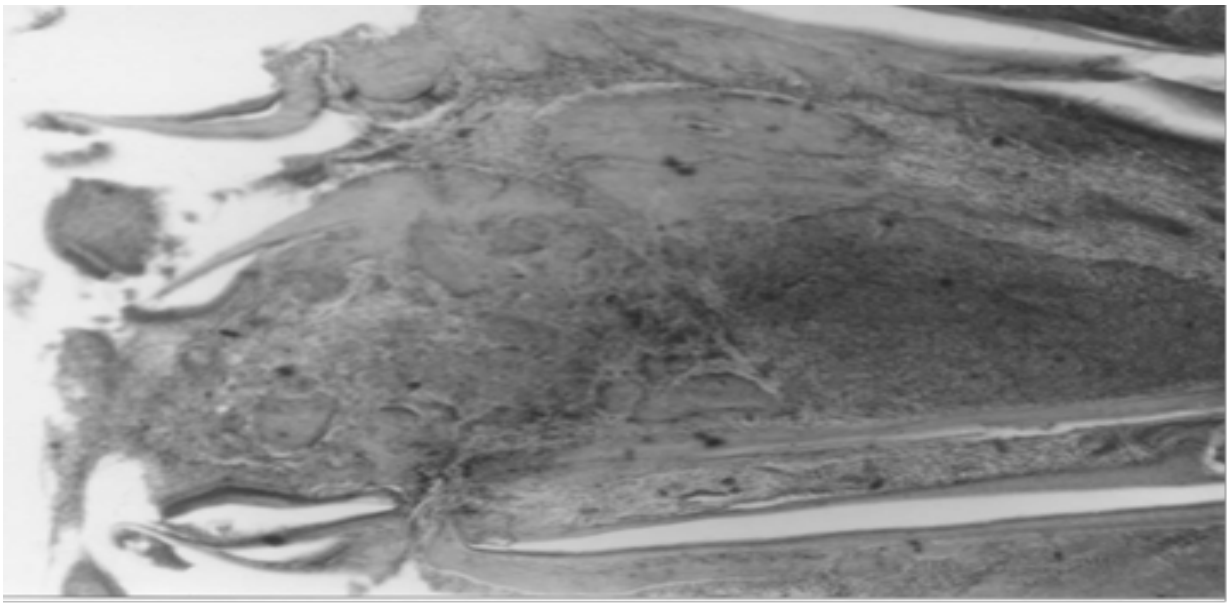

Figure 2. Bone defect replaced by regenerate (28th day of the experiment).

Thus, according to our observations, the bone tissue of the animals of the main group was characterized by the most pronounced intensity of reparative osteogenesis, while inflammatory infiltrates were still noted in the control group at the end of the experiment, and osteoblast reproduction was just beginning. Bioplast - dent granules, being germinated tissue elements of the regenerate, provide the closest contact between cells penetrating into the pores and bioplast - dent crystals, as a result of which optimal conditions are created for its interaction with the tissue environment and stimulation of reparative osteogenesis. The action of bone growth factors, carried out through increased proliferation, differentiation and synthetic function of bone cells. The presence of a phage in an osteoplastic preparation determines its anti-inflammatory properties and, thus, accelerates reparative osteogenesis. Thus, the bioplast-dent osteoplastic material can be recommended for large-scale use in dental practice.

Conclusion: Bioplast - dent granules, being germinated tissue elements of the regenerate, provide the closest contact between cells penetrating into the pores and bioplast - dent crystals, as a result of which optimal conditions are created for its interaction with the tissue environment and stimulation of reparative osteogenesis. The action of bone growth factors, carried out through increased proliferation, differentiation and synthetic function of bone cells. The presence of a phage in an osteoplastic preparation determines its anti-inflammatory properties and, thus, accelerates reparative osteogenesis. Thus, the bioplast-dent osteoplastic material can be recommended for large-scale use in dental practice.
Keywords: Osteogenesis stimulation, reparative regeneration, morphological, X-ray.

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ФАКТОРЫ РИСКА РАЗВИТИЯ ОСТЕОПОРОЗА ПРИ САХАРНОМ ДИАБЕТЕМ 2 ТИПА В ПОСТМЕНОПАУЗАЛЬНОМ ПЕРИОДЕ

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РЕЗЮМЕ

Проблема оптимизации диагностики и профилактики костной патологии при сахарном диабете требует большего внимания. Вероятность неудовлетворительного ремоделирования костной ткани требует адекватного мониторинга риска развития остеопороза при сахарном диабете, ранней диагностики патологических изменений и поиска оптимального лечения. Оценка минеральной плотности костной ткани и мааркеров костного ремоделирования у женщин в постменопаузе позволит проводить своевременное выявление остеопороза, патогенетически верную стратегию лечения и профилактики переломов, таких как переломы бедренной кости.
Ключевые слова: остеопороз, сахарный диабет 2 типа, постменопауза.

Женщины болеющие сахарный диабет 2 типа (СД2) подвержены значительно более высокому риску переломов, который, даже при нормальной или повышенной минеральной плотности костной ткани (МПК) [1]. Выявлено, что в общей популяции среди женщин уровень встречаемости остеопороза составляет более 30% в менопаузальном периоде и 43,3% среди женщин в постменопаузе, в то время, как среди лиц с сахарным диабетом 2 типа достигает 75% [2]. Усугубляющим фактором риска при этом становится период перехода пациенток с СД в постменопаузальный возраст. СД, и без того предрасполагающий к остеопоротическим процессам, отягощается постменопаузальным остеопорозом. Коморбидное обострение данных процессов, обладающих разным механизмом действия на костную структуру, усугубляет изменении костных характеристик [3]. При этом для СД наиболее характерно нарушение структуры кортикальной кости, преимущественно шейки бедра и периферического скелета, а при постменопаузальным остеопорозе повреждается главным образом трабекулярная ткань с преимущественным поражением позвонков [4,5]. Однако, патогенетические механизмы данного влияния остаются мало изученными.

Недостаточная компенсация СД, высокий уровень гликированного гемоглобина, также способствуют потере минерального компонента костной ткани [6-8]. Данные факты необходимо принимать во внимание при оценке состояния минеральной плотности костной ткани и показателей ее метаболизма у женщин в постменопаузе при СД 2 типа. Сложно переоценить актуальность своевременной диагностики костных изменений у данной категории больных на стадии остеопении.Систематизация данных о характере изменений костной структуры у больных в постменопаузе в зависимости от степени компенсации сахарного диабета поможет определить основные принципы гуморальных механизмов, обеспечив адекватные клинические рекомендации.

Целью данного исследования была оценка особенностей изменения МПК в поясничном отделе позвоночника и проксимальном отделе бедренной кости у пациенток с СД 2 типа, отягощённым постменопаузальным остеопорозом.

Материалы и методы: В одномоментное исследование были включены 96 женщины в возрасте 47-59 лет (средний возраст – 51.5±2.4) с сахарным диабетом 2 типа. Средняя продолжительность заболевания была 4.1±2.2 лет. Контрольную группу составили 32 женщины (средний возраст – 52.6±2.3) без сахарного диабета в анамнезе.

Все женщины обследовались по общепринятой схеме: выяснение анамнеза, гинекологическое обследование, антропометрические измерения с вычислением индекса массы тела ИМТ = М $_{ТЕЛА}$(кг)/рост^2(м^2). Менопаузальный статус обследуемых женщин оценивали с помощью индекса Куппермана, степень компенсации СД определяли по уровню гликозилированного гемоглобина — HbAIc. Однократно определяли липидный профиль и глюкозу крови. Параметры фосфорно-кальциевого обмена оценивались по концентрации ионизированного кальция и неорганического фосфора в сыворотке крови. О состоянии формирования костной ткани судили по активности общей щелочной фосфатазы и содержанию N-концевого пептида проколлагена-1 типа (P1NP) в сыворотке крови. Об уровне резорбции костной ткани судили по содержанию бета -С -концевого телопептида (beta-CTX) в крови.

Состояние костной массы определяли путем измерения минеральной плотности костной ткани методом двухэнергетической рентгеновской абсорбциометрии (DXA) в поясничном отделе позвоночника (L_I-L_{IV}), шейке бедренной кости (Neck). Диагностика остеопороза осуществлялась согласно критериям ВОЗ - по Т-критерию, в стандартных отклонениях (SD) от нормативных показателей пиковой костной массы здоровых женщин. Величина SD до-1 расценивалась как норма, от -1 до -2,5 SD - как остеопения, выше -2,5 SD - как остеопороз.

Обработку полученных данных проводили с использованием методов вариационно-математической статистики программы «Биостат» с соблюдением общих рекомендаций для медицинских и биологических исследований. Значение $p < 0,05$ считалось статистически значимым.

Результаты и обсуждение: У пациенток с СД 2 типа в сравнении с контрольной группой в 1,5 раза чаще выявлялось снижение минеральной плотности костной ткани. Не определялось прямой зависимости наличия и выраженности изменения плотности костной ткани от длительности сахарного диабета. Однако частота выявления пациентокс остеопенией прямо зависела от степени компенсации диабета.Было выявлено, что лишний вес при сахарном диабете имеет прямую корреляцию с МПК, а инсулинорезистентность - обратную. Отрицательная корреляционная зависимость определяласьмежду HbAlc и минеральной плотностью кости шейки бедра.

У женщин с СД 2 типа в постменопаузе отмечалось нарушение структуры как трабекулярной, так и кортикальной костной ткани, что проявлялось структурными изменениями поясничного отдела позвоночника и проксимального отдела бедренной костина измеренных методом DXA [2, 8]. Изучение маркеров костного метаболизма у больных СД 2 типа показало, что по мере снижения минеральной плотности костной ткани, концентрация креатинина по отношению к концентрации beta-CTx увеличивается в 72% случаев, что с учетом динамики денситометрических показателей свидетельствует о преобладании резорбции костной ткани над процессами костного формирования. Особенностями динамики маркеров костного метаболизма при СД 2 типа является отсутствие прямой зависимости изменений маркера beta-CTx, активности щелочной

фосфатазы, PINP от выраженности потерь МПК; у женщин изменение активности щелочной фосфатазы и повышение уровня beta-CTx выявляется раньше изменений абсорбциометрических показателей.

При сравнении показателей фосфорно-кальциевого обмена и плотности костной ткани достаточно высокая степень корреляции выявлена только между показателями минеральной плотности костной ткани и ионизированного кальция ($r = -0,321$; $p = 0,03$), а также между МПК зоны L_I-L_{IV} и маркером beta-CTx ($r = -0,436$; $p = 0,006$), что свидетельствует об усиленной резорбции костной ткани. При этом, начиная с состояния субкомпенсации диабета, существенно и достоверно нарастает резорбция костной ткани (увеличение уровня beta-CTx) у 76% больных и снижается минеральная плотность кости.

Таким образом, можно сделать заключение, что неудовлетворительно контролируемый гликемический профиль является независимым фактором риска остеопороза. У женщин, с СД в сравнении с пациентками группы контроля, уже через 5 лет постменопаузы, отмечена в 2 раза более высокая степень снижения МПК, что свидетельствует о выраженном нарушении костного ремоделирования на фоне СД в постменопаузе. Необходимо отметить, что при хорошем гликемическом контроле существенно уменьшается риск возникновения этих изменений. Эти данные свидетельствуют о том, что женщины с сахарным диабетом нуждаются в более интенсивном контроле состояния костной ткани, чем здоровые женщины. При СД 2 типа остеопенический синдром зависит от длительности заболевания и степени его компенсации.

Заключение: Наши данные подтверждают способность маркера beta-CTx выявлять различия в риске остеопоротических переломов у женщин в постменопаузе с СД2 по сравнению с контрольной группой без диабета. Активность общей щелочной фосфатазы не отражает сущность метаболических изменений костной ткани при сахарном диабете. Необходимо отметить, что у пациенток страдающих СД 2 типа остеопенический синдром зависит не столько от возраста, как от длительности заболевания, степени компенсации гликемического профиля. Также, чем выше уровень HbA1c, у женщин больных диабетом, тем ниже плотность кости поясничного отдела позвоночника. Оценка состояния минеральной плотности костной ткани и показателей ее метаболизма у женщин с диабетом в постменопаузе позволит своевременно выявлять изменения костного ремоделирования и способствовать предупреждению переломов, в том числе такой тяжелой травмы, как перелом шейки бедренной кости.

Ключевые слова: остеопороз, сахарный диабет 2 типа, постменопауза

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RISK FACTORS FOR THE DEVELOPMENT OF OSTEOPOROSIS IN TYPE 2 DIABETES MELLITUS IN POST-MENOPAUSAL PERIOD

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ABSTRACT

Women with type 2 diabetes mellitus (T2DM) are at a significantly higher risk of fractures, even with normal or elevated bone mineral density (BMD). It was found that in the general population among women, the incidence of osteoporosis is more than 30% in the menopausal period and 43.3% among postmenopausal women, while among people with type 2 diabetes it reaches 75%. An aggravating risk factor in this case is the period of transition of patients with diabetes to postmenopausal age. DM, already predisposing to osteoporotic processes, is aggravated by postmenopausal osteoporosis. Comorbid exacerbation of these processes, which have different mechanisms of action on the bone structure, exacerbates changes in bone characteristics. At the same time, for DM, the most characteristic is a violation of the structure of the cortical bone, mainly the femoral neck and peripheral skeleton, and in postmenopausal osteoporosis, mainly trabecular tissue is damaged, with a predominant lesion of the vertebrae. However, the pathogenetic mechanisms of this influence remain poorly understood.

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Objective: to evaluate the features of changes in BMD in the lumbar spine and proximal femur in patients with type 2 DM aggravated by postmenopausal osteoporosis.

Methods: A total of 96 postmenopausal women with T2DM and 32 control women without diabetes were assessed for bone mineral density (BMD, using dual energy X-ray absorptiometry), biochemical bone markers β-isomerized C-terminal telopeptides (β-CTx) and total procollagen type 1 amino-terminal propeptide (P1NP) and glucose metabolism.

Results: In patients with type 2 diabetes When comparing the indicators of phosphorus-calcium metabolism and bone density, a fairly high degree of correlation was found only between the indicators of bone mineral density and ionized calcium ($r = -0.321$; $p = 0.03$), as well as between the BMD of the L_I-L_{IV} zone and beta-CTx marker ($r = -0.436$; $p = 0.006$), which indicates increased bone resorption. At the same time, starting from the state of diabetes subcompensation, bone tissue resorption significantly and significantly increased bone resorption (increased levels of beta-CTx) in 76% of patients and reduced bone mineral density.

Conclusion: Our data support the ability of the beta-CTx marker to detect differences in the risk of osteoporotic fractures in postmenopausal women with T2DM compared with non-diabetic controls. The activity of total alkaline phosphatase does not reflect the essence of metabolic changes in bone tissue in diabetes mellitus. It should be noted that in patients suffering from type 2 diabetes, osteopenic syndrome depends not so much on age as on the duration of the disease, the degree of compensation of the glycemic profile. Also, the higher the HbA1c level in women with diabetes, the lower the bone density of the lumbar spine. Assessment of the state of bone mineral density and indicators of its metabolism in postmenopausal women with diabetes will allow timely detection of changes in bone remodeling and contribute to the prevention of fractures, including such a severe injury as a fracture of the femoral neck.
Keywords: osteoporosis, diabetes mellitus type 2, post menopause.

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THE SCIENTIFICS DISCUSSION OF WORLDWIDE CHALLENGES OF COVID-19 PANDEMIC AND GENERAL DRUG THERAPY APPROACHES TO COMBAT THE COVID-19 DISEASES

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ABSTRACT

A new type of coronavirus (COVID-19) SARS-CoV-2 originated in Wuhan, China and has caused a global pandemic. COVID-19 is a newly emerging infectious disease caused by SARS-CoV-2 and is known as SARS. By July 1, 2020, more than 10 million people worldwide will be infected with SARS-CoV-2. Typical manifestations of COVID-19 are fever, sore throat, fatigue, cough, and shortness of breath combined with recent exposure. Most COVID-19 patients have mild to moderate illness; however, 5 to 10% have a serious and even life-threatening illness. The death rate is around 2-3%. Therefore, there was an urgent need for a specific and effective antiviral treatment. Supportive measures such as oxygenated ventilation and fluid handling remain the standard of care today. Several clinical studies are ongoing to determine the most effective drug or combination for this disease and it is highly recommended that patients be included in ongoing studies. The safety and effectiveness of antiviral drugs could only be demonstrated in randomized clinical trials. Several active ingredients such as chloroquine, hydroxychloroquine, favipiravir, monoclonal antibodies, antisense RNA, corticosteroids, convalescent plasma and vaccines were currently being evaluated. A variety of therapeutic interventions were aimed at determining the most effective regimen. The purpose of this article is to describe the treatment strategies that have been used for patients with COVID-19 and to review all available literature.

Introduction: According to WHO, effective pharmacotherapy options for COVID-19 have been summarized, and nonsteroidal use has been declared controversial, anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). In accordance with the recommendations, a combination of drugs against COVID 19 was used. Some of the more promising drugs include chloroquine phosphate and hydroxychloroquine,

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which are both antimalarial drugs, remdesivir, lopinavir-ritonavir with or without a combination, according to a preliminary WHO study. interferon, which is an anti-HIV drug and plasma pharmacotherapy for convalescents. However, some antiviral drugs (Rideliver, favipiravir) and antimalarial drugs (chloroquine, hydroxychloroquine) have emerged as potential drugs. Pharmacotherapy evidence of efficacy and continuous research have been developed in the article. In addition, data were obtained regarding the inflammatory pathogenesis of this virus, leading to a cytokine storm in susceptible individuals. Thus, cytokine anti-inflammatory drugs such as anakinra and tocilizumab are undergoing numerous trials and some of the results are encouraging. Likewise, the use of anti-inflammatory cytokines such as IL-37 and IL-38 is believed to be beneficial and under investigation. Several clinical trials are currently underway that test the efficacy of single and combination pharmacotherapy using the drugs advertised in this review, and new drugs are being monitored, developed, and improved.

Background: SARS-CoV-2 virus entered into the target cells by binding with the hACE2 receptors. Spike glycoprotein promotes the entry of the virus into host target cells [1-2]. Literature reported a significant mutation in receptor binding sites and membrane proteins of the previous SARS-CoV to turned as SARS-CoV-2 virus, responsible for most dreadful pandemic COVID-19 [14]. These modifications may be the probable reason for the extreme transmission and pathogenicity of the virus. A hasty spread of COVID-19 throughout the world is highly threatening, but still, scientists do not have a proper therapeutic measure to fight with it. Scientists are endeavoring across the world to find effective therapy to combat COVID 19 [3-4]. Several drugs such as remdesivir, hydroxychloroquine, chloroquine, ribavirin, ritonavir, lopinavir, favipiravir, interferons, bevacizumab, azithromycin, etc. are currently under clinical trials [19-22]. Vaccine development from various pharmaceutical companies and research institutes is under progress, and more than ten vaccine candidates are in the various phases of clinical trials. This review work highlighted the origin, emergence, structural features, pathogenesis, and clinical features of COVID-19. We have also discussed the in-line treatment strategies, preventive measures, and vaccines to combat the emergence of COVID-19 [5-6].

Aim of the Research was to study the worldwide challenges of the COVID-19 pandemic and general therapy approaches towards fighting the COVID-19 diseases.

Methods: The main question of this article was to research and analyses the worldwide challenges of the COVID-19 pandemic and general therapy approaches towards fighting the covid-19 diseases. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Routers and Google Scholar mostly, using search terms bases, including the words to research and analyses the worldwide challenges of the COVID-19 pandemic and general therapy approaches towards fighting the COVID-19 diseases. In addition to the desired subject understanding. Then, each article was discussed and an abstract of the total information gathered during the process was provided, aiming at easy understanding of the public. To establish these outcomes, over two hundred articles were investigated. We brought together all published data to comprehensively examine the effects in a systematic review, to define the roll out of the study of the research and analyses of the worldwide challenges of the COVID-19 pandemic and general therapy approaches towards fighting the COVID-19 diseases.

Discussion: The global SARS-CoV2 pandemic, in the absence of effective preventive and therapeutic measures, has resulted in significant morbidity and mortality from this disease. Some clinical trials of traditional antiviral therapies have been conducted around the world, but the results remain controversial. In general, choosing the appropriate treatment for COVID-19 patients will depend on a number of factors, including the stage of the disease and its symptoms. Because of the differences in individual genetics of drug metabolism, as well as the variety of immune responses to the coronavirus, prescribing drugs in different patient populations can also be challenging [7-9]. Therefore, it was advisable to consider individualized medicine in the future to choose the best treatment along with an effective dose with minimal side effects. Various studies are currently ongoing to evaluate vaccines against SARS-CoV2. However, due to genetic changes in the viral nucleic acid in different hosts, these specific vaccines cannot have a definite preventive effect. Several therapies, conducted in various clinical trials from January 2020 to date, can help find more effective treatments for SARS-CoV2 with minimal side effects. In addition, structural and molecular studies of viral proteins and various drug candidates can play an important role in the search for a specific target for therapeutic agents. Because of the conflicting benefits of antiviral agents for COVID-19, drug efficacy has been assessed primarily as combination therapy [10-12]. In the current context, it appears that combination therapy with antiviral drugs, including viral RNA polymerase inhibitors (e.g. remdesivir), viral protease inhibitors (e.g. such as IVIg), and the use of adjunct therapies (such as melatonin and vitamin D) can be recommended to effectively control COVID-19. It is therefore necessary to aim for the development of a specific drug / treatment and / or vaccine, reduce morbidity and mortality from SARS-CoV2 infections and create the scientific capacity to rapidly diagnose and treat new viruses in the future [13-15].

Entry process in the body: Many cell types represent ACE2 and cross-membrane serum protease 2, two cytokines, which are important for viral penetration, including nasal and breathable epithelial cells (pneumococcal), resident immune cells. Lungs, endoblasts and neurons. Intestinal cells, heart attack cells, liver cells and kidney cells. However, the mRNA present in these cell types is not sufficient. Further research is needed to analyze the protein expression of these input factors and to demonstrate true virus penetration and active replication of all these cell types [16-18]. Interestingly, ACE2 has recently been shown to be an interferon stimulating gene (ISG), which means that interferon occurrence in the microenvironment at the virus replication point can further increase the spread of the virus [19-20]. Molecular details of the entry process with nail proteins and host receptors/core receptors have been investigated. The poly-base part of the fur is located at the intersection of subdomains 1 and 2 of the protein, which may explain the large number of cell types that can be infected with the virus, as well as various organic manifestations that can occur, including thrombosis complications caused by infection of endothelial cells by a virus. This study will identify the middle antibodies or small molecules that can target this stage of the life cycle [21-22].

Mechanisms of Coronavirus-induced toxicity: The virus can be cytotoxic in the early days of infection. In biopsy or autopsy studies of infected COVID-19 patients, the pulmonary disease showed diffuse cell lesions with showcase membrane formation, filtration of mononuclear cell/macrophage airways and diffuse thickening of the cell wall. [23-24]. The lungs of patients with COVID-19 also have severe endothelial damage associated with the presence of intracellular viruses and cell membrane damage. [9] Virus particles were observed in epithelial cells with electron microscopy, suggesting that these lesions may be partly due to cytotoxicity [25-27].

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Overview of SARS-CoV-2 virology: The pathogen of COVID-19 is the new coronavirus, officially called SARS-SV-2. It was named after SARS-COVID for genomics. [28-29] Coronaviruses are large-format RNA viruses (+mRNA) with a positive value from the Coronavirus family. The coronary virus can affect a wide range of vertebrates, including bats, birds, psoriasis, snakes, mice and humans. Due to the sequence similarity exists in bats of the transmits of coronary virus, SARS-CoV-2 is currently believed to be of zoonotic origin and has acquired a secondary ability to be transmitted from person to person. [159-162] In particular, detection of 1) mutations in the binding receptor area, (2) the position of the division of multi-beta receptor at the intersection of sub bands 1 and 2 protein and the O-glycosylation site where the virus can effectively interact with the high convergence (via nail protein) of real cell receptors (angiotensin 2 [ACE-2] to bypass the immune response, perhaps by hiding O-glycylation [30-33].

Vaccines: Further studies with re infected patients provide information about protective correlations that are important for the development of the vaccine. In the past two decades, three coronaviruses have spread around the world, creating epidemics that have resulted in serious health problems without vaccination [34-38]. Based on vaccine development, we can consider the use of recombinant sub-American vaccines, DNA vaccines, and mRNA vaccines as different methods. Lower US vaccines are considered extremely safe because they should stimulate the immune system without spreading infectious viruses. The development of such vaccines requires further knowledge of synthetic organisms of SARS-CoV-2 proteins and/or N. glycoprotein SRAS-CoV-2 is a mediator that binds to the host cell and is necessary for the transmission of the virus. This is the main purpose of the vaccine for many SARS-CoV-2 candidates [39-40]. DNA vaccines are based on direct injections of plasmids that encode the desired viral antigens and cause different immune responses. mRNA vaccines include mRNA vaccines that encode antigens that are transferred to the host's mobile device during vaccination. mRNA vaccines have advantages over traditional vaccines, including poor genomics, increased immune response, and faster development and production of multidimensional antigens [41-43]. A preliminary report on the SRAS-CoV-2-Mrarm vaccine has been published. Vaccine 1273 patient Candidate mRNA is a modified nucleoside vaccine mRNA that is encapsulated by Nano lipid particles and encodes improved glycoprotein SARS-CoV-2 that is structurally stabilized before synthesis [44-45]. A Phase I open-label dose update was performed in 45 healthy adults who received two vaccines for 1273 patients every 28 days. After the second vaccination, all survey participants showed activity that neutralized the serum. Before the second vaccination, the neutralizing activity of the pseudo virus was low, confirming the need for a two-dose vaccination schedule. Finally, immune responses to SARS-CoV-2 are caused by the 1273 patients vaccine in all participants without limitation. In order to bind and neutralize antibodies to SRAS-Covid-19, it is necessary to determine the value of the head and its ability to prevent infection [46-48]. Cellular and amusing immune responses have been linked to vaccine protection against infection or reintegration following infection with SARS-CoV-2 in rhesus monkey models. Since natural history studies show that SARS-COVID cannot cause long-term reactions to antibodies, a long-term prediction would be appropriate. A safety assessment is also needed to respond to concerns about the possible worsening of vaccination-related respiratory diseases. It is estimated that a dose of 100 micrograms in 3 doses results in a strong neutralization of CD4 T lymphocytes and their response to Th1 along with a more positive response profile than the highest dose [49-50].

Viral treatments for COVID-19 include: monoclonal antibodies, new drugs, or antiviral drugs in development. To address the pandemic immediately, the only option is to reuse antiviral drugs for reasons of time, after evaluating their safety and effectiveness. Remdesivir was considered the highest priority among therapeutic agents based on a wide range of antiviral drugs. Among the repurposed drugs, the study of the antiretroviral drug (HIV protease inhibitors), lopinavir / ritonavir, alone or in combination with interferon beta, was considered a second option suitable for rapid use in clinical trials [51-53]. However, immunotherapy such as convalescent serum or other agents is also contemplated as a treatment option.

Viral therapy research should include the identification of multiple therapeutic candidates for clinical evaluation, along with the development of in vitro and in vivo studies. To maximize treatment efficacy, combination therapy should be designed for additive or synergistic effects or to reduce the risk of drug resistance [54-56]. The lack of information on the clinical course, epidemiological and therapeutic studies, as none of them have been developed for COVID-19, is an important milestone.To achieve rapid success in COVID-19 research and development (R&D), it is urgent to identify animal models that can mimic the characteristics of human diseases for in vivo preclinical studies. Therapies (antiviral drugs) and clinical trials of prophylactic drugs need to be developed to protect populations at risk. Reduce mortality and improve the clinical outcome of the disease; The research agenda should include preventive research, combination therapy, evaluation and safety research of repurposed agents to advance the fight against the COVID-19 epidemic [57-58].

Compared to other +RNA viruses, coronaviruses have large genome and a complex genome expression strategy. Many of the coronavirus proteins expressed in the infected cell contribute to the coronavirus-host interplay. For example, by interacting with the host cell to create an optimal environment for coronavirus replication, by altering host gene expression or by counteracting the host's antiviral defences [59-60]. Like other coronaviruses, SARS-COV-2 human-to-human transmission via respiratory droplets, contaminated hands or surfaces has been described, with incubation period of 2-14 days (the median incubation period is approximately 4–5 days before symptom onset). Faecal–oral transmission route is possible but yet unproven [52-55]. COVID-19 is similar to the severe acute respiratory syndrome coronavirus virus (SARS-CoV) in its epidemiology, pathogenicity and clinical results, though COVID-19 has better genome sequence identity with SARS-CoV (79%) compared to Middle East Respiratory Syndrome coronavirus (MERS-CoV). Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle. SARS-CoV-2 infection causes clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus [61-62].

The clinical manifestations of COVID-19 vary with mild upper respiratory tract infection, lower respiratory tract infection involving non-life-threatening pneumonia, and life-threatening pneumonia with acute respiratory distress syndrome [200-203]. By the time of hospital admission, COVID-19 patients show the following symptoms: a fever and dry cough; more rarely - patients also experience shortness of breathing, muscular pain, headache/dizziness, diarrhoea, nausea/vomiting [63-64].

Together with investigations in SARS-CoV-2 virology of SARS-CoV-2, main pathogenetic mechanisms and immunological responses underlying the clinical manifestations of COVID-19 is essential for determination of immunoregulation and rational therapies against SARS-CoV-2 [70-71]. The virus main entrance way is through mucosal tissues: nose, mouth, upper respiratory tract, and less frequently conjunctival mucosa [65]. The pathogenesis of SARS-CoV-2 infection

induces an aggressive inflammatory response strongly damaging the airways. Therefore, disease severity in patients is determined not only by the viral infection but also by the host response. Severity of the disease also correlates with increasing age [66-67]. To better understand the host–pathogen biology of COVID-19 will offer important clarifications into management of the disease, including identification of new therapies [68-69].

Colchicine-is used safely in a wide variety of cardiovascular diseases. Its potential mechanisms of action include the non-selective inhibition of the NLRP3 inflammasome, which is considered to be the main pathophysiological component of the clinical course of patients with COVID-19. The Covid-19 study aims to investigate whether colchicine could positively influence the clinical course of COVID-19 [52]. This will be a prospective, clustered, randomized, open, controlled study [70-71].

Ribavirin-An analog of nucleosides, ribavirin (Virasol), is a broad-spectrum antiviral agent used to treat hepatitis C, respiratory syncytial virus, and some viral hemorrhagic fevers (e.g. Lassa) [24, 25]. Several mechanisms by which ribavirin exerts its antiviral effects have been identified, including lethal mutagenesis, chain termination as specific or non-specific, and inhibition of nucleotide biosynthesis for RNA target viruses [72]. The desired specific mechanism of action of ribavirin has not yet been fully clarified [73]. In addition, it is a broad-spectrum drug and cannot specifically fight coronaviruses [11]. The proposed mechanism of action of ribavirin on SARS-CoV2 is the inhibition of viral RNA synthesis and mRNA capping [74]. The antiviral activity of ribavirin against animal CoVs and SARS-CoV1 has been proven, although the effectiveness with interferon against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is controversial. While several studies have shown the effectiveness of ribavirin and interferon alone [75,76] the combination of these drugs has not shown positive results in critically ill patients with MERS [77,78]. The effectiveness of ribavirin has been assessed primarily as a combination therapy. Successful responses to ribavirin monotherapy and/or combination therapy have been reported in several case studies [79–80]. A multi-center, prospective, open-label, randomized phase II study was conducted in COVID-19 patients in Hong Kong. In the control group, patients received lopinavir 400 mg and ritonavir 100 mg every 12 hours for 14 days, and the combination group received lopinavir 400 mg and ritonavir 100 mg every 12 hours, ribavirin 400 mg every 12 hours, and three doses of 8 million, international units of interferon β-1b for 14 days. This combination therapy was well tolerated and shortened the time to a negative nasopharyngeal swab and hospital stay in patients with mild to moderate COVID-19 [38]. In addition, an open, prospective, randomized and controlled clinical trial is being conducted at a single center to assess the efficacy and safety of various antiviral therapies (ribavirin + interferon α-1b, lopinavir/ritonavir + IFN α-1b and ribavirin + lopinavir/ritonavir + IFN α-1b) in 108 COVID-19 patients. The results of this study may be useful to provide clear evidence for the use of these therapies in the treatment of patients with mild to moderate COVID-19 [81,82]
It is also worth noting that ribavirin had several known side effects such as hemolytic anemia, hypocalcemia, and hypomagnesemia [83]. It is also contraindicated in autoimmune hepatitis, hemoglobin disorders, kidney failure, pregnant women or men with pregnant partners, and people who are hypersensitive to it [84]. Due to the inconsistent benefits of ribavirin for COVID-19 and its serious safety concerns, as well as the very poor quality of the evidence, current evidence does not warrant its use to treat COVID-19. Combination therapy appears to offer the best chance of

clinical effectiveness. Therefore, extensive randomized controlled clinical trials are needed to confirm its effectiveness in terms of mortality, virological and clinical outcomes of COVID-19. The effects of ribavirin in combination with other therapies are being investigated in clinical studies [85-86].

Bevacizumab-is a recombinant humanized monoclonal antibody against Vascular Endothelial Growth Factor (VEGF), was first approved by United States Food and Drug Administration (USFDA) on 26th February 2004 for the first-line treatment for metastatic colorectal cancer. Subsequently, the FDA approved this product along with chemotherapy to treat many cancers like lung cancer, renal cancer, cervical cancer, ovarian cancer, etc. In addition, recent studies suggest that higher levels of blood VEGF in COVID-19 patients compared with normal and also pulmonary edema, dyspnea, acute respiratory distress and acute lung injury are the most detrimental symptoms of COVID-19. Numerous studies reported that VEGF was a critical factor in pulmonary edema, acute respiratory distress and acute lung injury [87-88].

Tocilizumab was approved by the USFDA for the treatment of severe cytokine release syndrome (CRS) in addition to idiopathic arthritis, rheumatoid arthritis and giant cell arteritis [129]. Several clinical studies have shown that tocilizumab improves some clinical symptoms in COVID-19 patients [131]. A prospective, opened, multicentre, open-label peer-to-peer pilot study on the off-label use of tocilizumab in patients with severe COVID-19 showed improved breathing and laboratory performance. The effectiveness of tocilizumab in SARS-CoV2 was investigated in patients with severe or critical COVID-19 who received the drug in addition to conventional therapy. Fever and other symptoms improve significantly after a few days [89-90]. One study looked at the effect of low-dose tocilizumab on mortality in 85 patients with COVID-19-associated pneumonia and respiratory failure. Patients in the tocilizumab group showed significantly better survival rates than patients in the control group. An important limitation of this study is the lack of a randomized, double-blind approach [91]. In addition, a study from an academic medical center in the United States reported that most of the patients who received tocilizumab had no significant clinical improvements in temperature or oxygen demand. These data suggest that tocilizumab should be used with caution in patients with severe COVID-19 [92]
Side effects of long-term treatment with tocilizumab are severe infections (such as pneumonia, urinary tract infections, cellulitis, etc.), gastrointestinal perforation, infusion reactions (such as high blood pressure, headache and skin reactions), anaphylaxis, thrombocytopenia, increased liver enzymes and increased lipid profile [93]. Side effects of tocilizumab have also been reported in patients with COVID-19 [121-126]. The safety and efficacy of subcutaneous administration of tocilizumab have been reported in a number of cases in patients with COVID-19 pneumonia. No significant side effects were observed except for a slight increase in liver enzymes two days after ingestion, followed by immediate normalization. In fact, x-ray findings and clinical symptoms have improved [94]. Tocilizumab was recommended for the treatment of COVID-19 in the Novel Coronavirus Pneumonia Diagnosis and Treatment Protocol published by the Chinese government [95]. In addition, 32 studies are currently ongoing to evaluate the effectiveness of tocilizumab in COVID-19 (Table 2). Further controlled clinical studies are needed to clarify the true clinical effect of this IL-6 blocking therapy on COVID-19 infection and to determine the optimal patient selection and timing for tocilizumab use during the disease process. In addition to demonstrating its effectiveness and the above side effects, it has several limitations, such as being an expensive

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drug that can only be administered intravenously. Therefore, future research needs to be more focused, including comparing different dosages and routes of administration [96-97].

Siltuximab (CNTO 328) is a monoclonal antibody conjugate of interleukin-6 (IL-6) and therefore neutralizes IL-6 bioactivity. It also promotes tumor cell death and is approved for the treatment of certain viral diseases such as HIV, human herpesvirus-8 (HHV-8), multicentric Castleman's disease (CDM), multiple myeloma (MM), myelodysplastic syndrome (MDS), prostate cancer, ovarian cancer, lung cancer and reduced anorexia and cancer-associated cachexia. [98-99]

Sarilumab -(Kevzara®) is an IL-6 receptor antagonist and has been FDA approved for the treatment of moderately to severely active rheumatoid arthritis in adults who are inadequate or cannot tolerate one or more disease-modifying anti-inflammatory drugs [100]. It has the potential to treat COVID-19 as IL-6 plays an important role in cytokine storms [101]. It binds to soluble and membrane-bound IL-6 receptors. Since the IL-6 measurement is not available in most cases, the (CRP) levels can be useful for monitoring treatment response of therapy [102]

IL-6 pathway inhibitors — Tocilizumab is an interleukin (IL)-6 receptor inhibitor used for rheumatic diseases and cytokine release syndrome. Elevated IL-6 levels have been described in patients with severe COVID-19, and case reports have described good outcomes with tocilizumab [111], but systematic evaluation of the clinical impact of tocilizumab on COVID-19 has not yet been published. Treatment guidelines from China's National Health Commission include the IL-6 inhibitor tocilizumab for patients with severe COVID-19 and elevated IL-6 levels. Tocilizumab, as well as sarilumab and siltuximab, which also target the IL-6 pathway, are being evaluated in clinical trials [103-104].

About other indicated agents against COVID -19:

Atazanavir (ATV) with a protease inhibition mechanism is approved for the treatment of HIV or AIDS [119]. As mentioned in previous sections, the pathogenicity of CoV requires non-structural proteins such as protease, an enzyme that is critical for the conversion of polyproteins to CoV. Hence, atazanavir prevents the formation of a mature viral particle and suppresses SARS-CoV2 infection. In a study based on molecular docking analysis of SARS-CoV2 helicase inhibitors, Borgio and colleagues showed that atazanavir can interfere with SARS-CoV-2 helicase activity [105]. A recent study by Beck and his colleagues based on the target transformer molecule interaction (MT-DTI) also showed that atazanavir was the best compound tested to inhibit SARS-CoV2-like proteinase activity. Order atazanavir> remdesivir> efavirus> ritonavir> dolutegravir [106-107].

Baricitinib is an anti-inflammatory drug used to treat refractory rheumatoid arthritis [152]. The most important anti-inflammatory mechanism of baricitinib in rheumatoid arthritis is the inhibition of Janus kinase (JAK) enzymes [35-37]. With SARS-CoV2, however, baricitinib prevents the virus from entering cells through various mechanisms. It inhibits AP2-associated protein kinase 1 (AAK1): an enzyme that promotes viral endocytosis [89-91]. Baricitinib also inhibits viral endocytosis by interacting with cyclin-associated kinase G (GAK). It is also suggested that baricitinib reduces inflammation by inhibiting JAK1 / 2 enzymes [15-19]. Consequently, baricitinib may have beneficial clinical effects in COVID-19 patients and be an

alternative treatment option for COVID-19, especially in patients with coexisting rheumatoid arthritis. However, inhibition of JAK-STAT kinase by baricitinib disrupts the antiviral activity of congenital interferons [17-18]. Also, baricitinib may cause some symptoms of upper respiratory tract infections, nausea and thrombosis in rheumatoid arthritis patients receiving this medicine. Therefore, the efficacy and safety of baricitinib in COVID-19 infected patients are still unclear. At the time of writing, several clinical and observational studies have been recorded on the efficacy and safety of baricitinib for the treatment of COVID-19. One of these has been completed and the main outcome of this pilot study was the safety assessment of baricitinib. It did not increase the risk of infections, cardiovascular and hematological side effects after 2 weeks of treatment [37-39].

Levamisole, levisomer and tetramisole, belong to the class of medical membranes and are the first representative of a new class of drugs that increase cell resistance, a synthetic compound with low molecular weight. The immunosuppressive and immunostimulatory effects of levamisole have been demonstrated on the basis of dosage and timing of clinical use [40-43]. According to previous studies, the in vitro combination of levamisole and ascorbic acid can reverse the proliferation of depressed accessory / stimulating ganglion cells. Levamisol lymphocyte spread often occurs when standard lymphocytes are treated with measles virus in vitro. Therefore, levamisole may also be considered for the treatment of COVID-19 [44-45].

Darunavir: As an HIV protease inhibitor, darunavir (DRV) can prevent the formation of mature infectious virus particles by selectively inhibiting the cleavage of the Gag-Pol polyprotein in cells infected with the virus. In February 2020, Chinese researchers announced the suppressive effects of DRV on SARS-CoV-2 infection. Cell experiments have shown that virus replication is significantly inhibited by DRV at a concentration of 300 μM. Darunavir in combination with cobicistat (DRV / c) has been shown to significantly inhibit SARS-CoV2 replication. This combination therapy has been approved by the US Food and Drug Administration (FDA) for the treatment of AIDS patients. To improve the pharmacokinetics and pharmacodynamics of darunavir, cobicistat, like ritonavir, may act as an LPV / r booster and inhibit cytochrome P450 (CYP3A) [46]. In addition to in-vitro and clinical studies, several in-silico studies have also confirmed the effectiveness of the antiviral activity of DRV against SARS-CoV2. DRV's potential therapeutic effect against SARS-CoV2 may be primarily due to its inhibitory effects on papain-like viral protease (PLVP) and basic protease. Darunavir has been shown to have high ligand affinity and is a potential candidate that may interfere with communication between the SARS-CoV2 receptor binding domain and ACE2. Therefore, it is currently proposed that DRVs be reassigned for the treatment of SARS-CoV2 infection due to their potential impairment in cell recognition, attachment, and invasion [47-48].

Lopinavir-ritonavir – This combined protease inhibitor, which has primarily been used for HIV infection, has in vitro activity against the SARS-CoV and appears to have some activity against MERS-CoV in animal studies However, lopinavir-ritonavir appears to have minimal to no role in the treatment of SARS-CoV-2 infection outside of a clinical trial. The WHO has launched a multinational trial to further evaluate remdesivir, hydroxychloroquine/chloroquine, and lopinavir-ritonavir with and without interferon beta [49-50].

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Results from a randomized trial do not demonstrate a clear benefit of lopinavir-ritonavir. In a randomized trial of 199 patients with severe COVID-19, the addition of lopinavir-ritonavir (400/100 mg) twice daily for 14 days to standard care did not decrease the time to clinical improvement compared with standard care alone [86]. There was a trend towards decreased mortality with lopinavir-ritonavir (19 versus 25 percent), and the numerical difference in mortality was greater among those who were randomized -within 12 days of symptom onset, but neither difference was statistically significant [57-59].

Oseltamivir (Tamiflu) is an antiviral neuraminidase inhibitor used to treat and prevent influenza A and B. Oseltamivir exhibits its antiviral activity by inhibiting viral neuraminidase activity and viral replication. Oseltamivir suppressed viral replication at least in some cases. Coronaviruses do not use neuraminidase to replicate viruses; Therefore, oseltamivir is unlikely to have therapeutic value. It was removed from the SARS-CoV2 treatment protocol. The only study that looked at the effects of oseltamivir on coronaviruses found that even at high concentrations of the drug, it was ineffective in preventing SARS-CoV1 [60-62].

Arbidol –is a low molecular weight indole-based molecule, has a broad spectrum of antiviral activity against numerous DNA and RNA viruses. It has been shown that Arbidol can inhibit the penetration of influenza A and B viruses as well as hepatitis C viruses into host cells, thereby blocking virus fusion [63-64]. Arbidol is approved in Russia and China for the prevention and treatment of infections of the upper respiratory tract caused by influenza A and B viruses [148]. Other studies have also shown that arbidol hydrochloride can inhibit the fusion of the virus membrane with host cells and block virus replication [11]. In recent years, the effectiveness of arbidol against SARS-CoV1 and MERS-CoV has been proven in many studies [11]. Due to the lack of significant side effects, arbidol is patented for the treatment of SARS-CoV1 [65]. Since the antiviral effect of arbidol against SARS-CoV1 has been confirmed in cell experiments [66], it was proposed to use it as the drug of choice for the treatment of SARS-CoV2 [17]. An in vitro study showed that arbidol can effectively inhibit the replication of SARS-CoV2 [71]. The recommended dosage regimen of arbidol for adults with SARS-CoV2 was 0.2 g at any time twice daily and was not taken for more than 10 days [14]. So far, the dosage regimen of arbidol in children with SARS-CoV2 has not been recommended [76]. It has been shown that arbidol in a concentration of 10–30 μmol / L can have an effective inhibitory function against SARS-CoV2 infection and can also reduce the pathological effects of the virus in host cells [102]. Molecular modeling studies have shown that some SARS-CoV2 proteins such as spike, E-channel, Nsp7-Nsp8 complex, Nsp14 and Nsp15 can interact with arbidol [11,15].There are some side effects of arbidol therapy, such as nausea, diarrhea, dizziness, and increased serum aminotransferase levels. In addition, arbidol should be used with caution in patients with impaired liver function due to its metabolism in the liver. Arbidol can also compete with drugs with a high binding rate to plasma proteins and increase the concentration of combination drugs due to 89.2–91.6% of the binding rate to proteins [76].

Chloroquine and hydroxychloroquine have received a lot of attention due to their inhibition of enzymes or viral processes, particularly in Iran, the United Kingdom, and France. However, the FDA has withdrawn the emergency use permit due to serious side effects and other potential side effects. The potential benefits of chloroquine and hydroxychloroquine no longer outweigh the

potential risks with permitted use [7]. hydroxychloroquine is better than chloroquine and has reported positive results in some pre-clinical in vitro data and protocols. Both antimalarial drugs can do more harm than good due to the many side effects and should not be prescribed for more than 7 days. In rare cases, cardiac arrest, retinal damage, and eye toxicity are major concerns, especially since people with heart disease are at higher risk for difficulties [87-89].

Conclusion: Thus, treatment approaches that are currently being studied include antiviral and anti-inflammatory cytokines, anti-infective and life-sustaining therapy, monoclonal antibodies, and passive immunotherapy, especially in patients with severe illness. However, while a therapeutic strategy against the disease is important, the most important way to prevent the spread of the virus is to develop a widely available effective and safe vaccine. In the future, it will be wise to choose a personalized medication to choose the best treatment along with an effective dose with minimal side effects. Various studies are currently underway to evaluate vaccines against SARS-CoV2. However, due to genetic changes in viral nucleic acid in different hosts, these specific vaccines may not have a clear preventive effect.

Keywords: Worldwide, therapy, treatment, COVID-19 diseases, pandemic.

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MORPHOLOGICAL RESEARCH USAGE OF BIOPLAST - DENT IN EXPERIMENT

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Introduction: One of the urgent problems of modern dentistry is the search for the most effective means and methods of bone grafting [1, 2, 3]. These funds should optimize and at the same time stimulate the processes of reparative osteogenesis [4,5,6,7]. Osteoplastic materials are used in the surgical treatment of dental diseases accompanied by bone tissue destruction: chronic periodontitis, periodontitis, jaw bone cysts, etc [8,9,10,11,12,13].

Summary: The work represents experimental and morphological studies of regeneration of damaged areas of maxillo-facial bones. Time course of healing of induced defects in the low jaw bone filled with bioplast - dent and was studied in experimental rabbits. On days 7, 14, 21 and 28 four rabbits from each group were killed and the defect investigated by X-ray and histological methods. We stained the micropreparations ith hematoxilineeosine. Bioplast - dent granulate exerted the best effect on bone repair. In experiments with bioplast - dent, bone regenerate replaced up to one half of the area of defect by day 28.

Aim of the research: the aim of the study was to conduct a comparative analysis of the dynamics and nature of the bone reparative process in standard experimentally reproduced bone defects filled with osteoplastic material - bioplast - dent.

Material and methods: The experiments were carried out on chinchilla rabbits weighing up to 2 kg (n=32). In animals under general Calipsol anesthesia, a standard defect with a diameter of 4-5 mm was created on the lower jaw bones. At the end of the operation, the wounds were sutured with silk thread. In control animals (n=16), bone defects were left to heal under a blood clot, and in animals of the main group (n=16), bioplast-dent granules were injected into the bone defect. The animals were decapitated under anesthesia on the 7th, 14th, 21st and 28th days after the bone wound was applied. There were 4 rabbits per observation point in each group. The bone fragments were fixed in formalin, decalcified in Trilon-B, and embedded in paraffin. Sections were stained with hematoxylin and eosin.

Results and discussion: In the group of observations with bioplast - dent granulate, on the 7th day from the start of the experiment, the animals in the area of experimental exposure had extensive bone defects filled with tightly lying mineral granules, represented by a part of oxyphilic particles of accumulations of small dark crystals in the central sections of defects between bioplast - dent particles . Thin strands of a weakly oxyphilic homogeneous protein substance were located in these areas. Cellular elements were completely absent. The bone wall had a space free from granulate, filled with cellular-fibrous connective tissue, with a loose

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structure, high cellularity and a low level of collagenization. In the centripetal direction, there was a tendency for cellular elements to grow into bioplast-dent deposits. The strands from young fibroblasts penetrated to the periphery into the deposits of the mineral between its granules (Fig. 1).

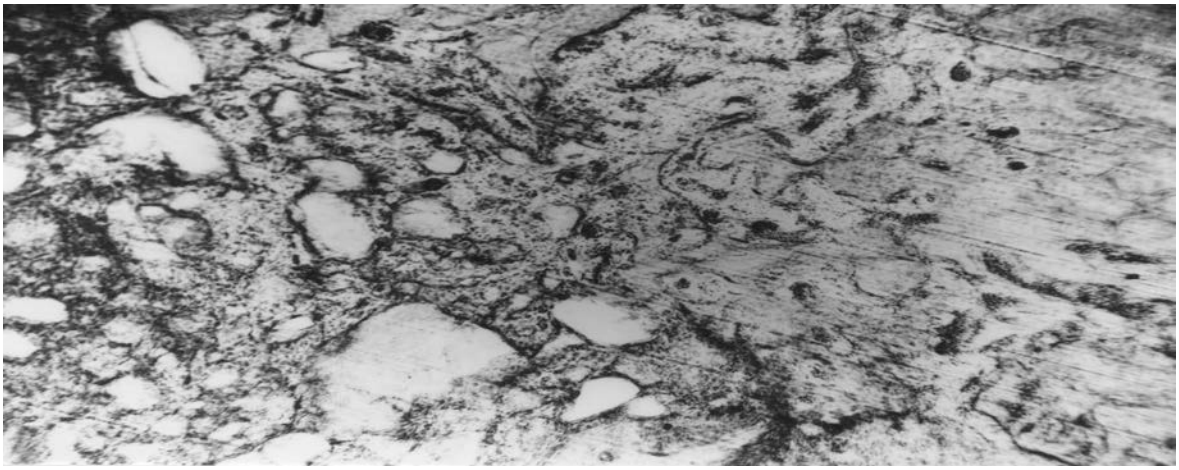

Figure 1. Extensive bone defect, oxyphilic particles Bioplast-Dent (7th day of the experiment).

On the 14th day from the beginning of the experiment, the bone edge of the defects was characterized by the loss of osteocytes and signs of pronounced phenomena of structural restructuring: numerous and randomly oriented gluing lines, variegation of the pattern of the bone substance, irregularity of osteons, etc. At the same time, areas were noted where a layering of a new bone substance occurred on the maternal bone, in the form of individual trabeculae or strips of osteoid.

On the 21st day of the experiments, active development of the soft tissue regenerate was found in the bone defect. Between the bioplast - dent granules there were layers of cellular fibrous tissue, which covered the deposits of bioplast - dent and forming, around them, thin cellular, with an admixture of delicate fibers, rims. Quite often, giant multinucleated cells were located here. In the granules themselves, in some places, the remains of bioplast - dent crystals were found. Often strands of fibroblasts have grown into them.

Closer to the bone wall of the defects, the soft tissue regenerate was represented by coarse fibrous connective tissue. The bone edge itself was dense and compacted. There were areas where newly formed bone structures were deposited on the maternal bone, in some places closely adjacent to bioplast-dent deposits, with a tendency to replace them.

On the 28th day from the beginning of the experiments, the bone regenerate half-filled the bone defect. Powerful trabecular systems captured bioplast - dent granules, as a result of which they turned out to be walled up in the newly formed bone substance. Closer to the central sections of the bone regenerate, osteon systems appeared in the maternal bone, the bone substance matured and became indistinguishable from the old bone (Fig. 2).

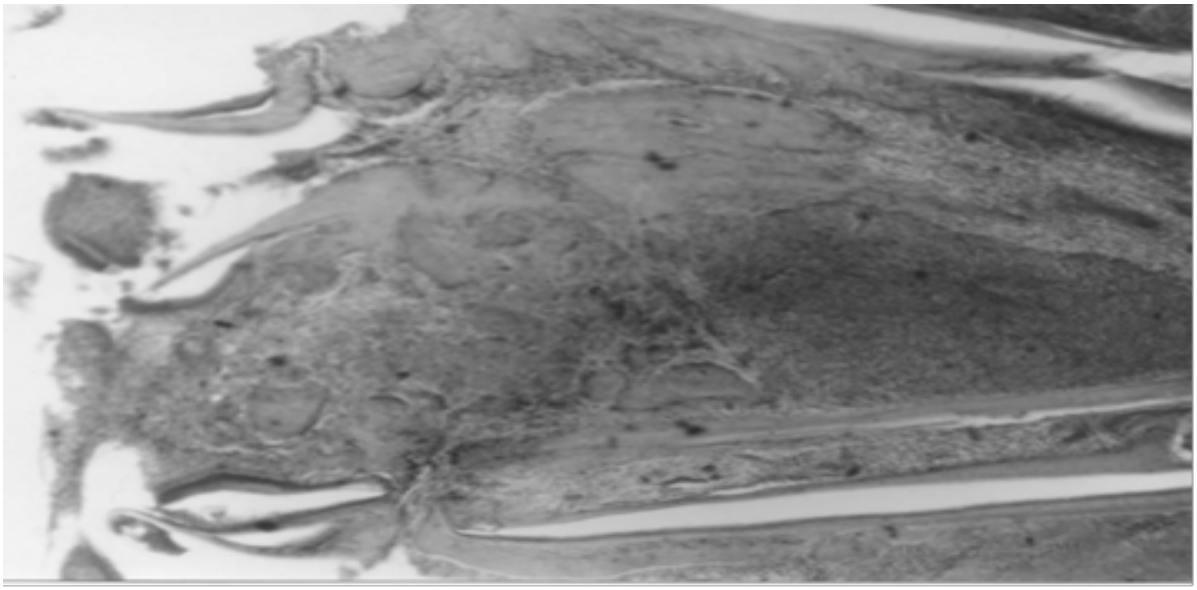

Figure 2. Bone defect replaced by regenerate (28th day of the experiment).

Thus, according to our observations, the bone tissue of the animals of the main group was characterized by the most pronounced intensity of reparative osteogenesis, while inflammatory infiltrates were still noted in the control group at the end of the experiment, and osteoblast reproduction was just beginning. Bioplast - dent granules, being germinated tissue elements of the regenerate, provide the closest contact between cells penetrating into the pores and bioplast - dent crystals, as a result of which optimal conditions are created for its interaction with the tissue environment and stimulation of reparative osteogenesis. The action of bone growth factors, carried out through increased proliferation, differentiation and synthetic function of bone cells. The presence of a phage in an osteoplastic preparation determines its anti-inflammatory properties and, thus, accelerates reparative osteogenesis. Thus, the bioplast-dent osteoplastic material can be recommended for large-scale use in dental practice.

Conclusion: Bioplast - dent granules, being germinated tissue elements of the regenerate, provide the closest contact between cells penetrating into the pores and bioplast - dent crystals, as a result of which optimal conditions are created for its interaction with the tissue environment and stimulation of reparative osteogenesis. The action of bone growth factors, carried out through increased proliferation, differentiation and synthetic function of bone cells. The presence of a phage in an osteoplastic preparation determines its anti-inflammatory properties and, thus, accelerates reparative osteogenesis. Thus, the bioplast-dent osteoplastic material can be recommended for large-scale use in dental practice.
Keywords: Osteogenesis stimulation, reparative regeneration, morphological, X-ray.

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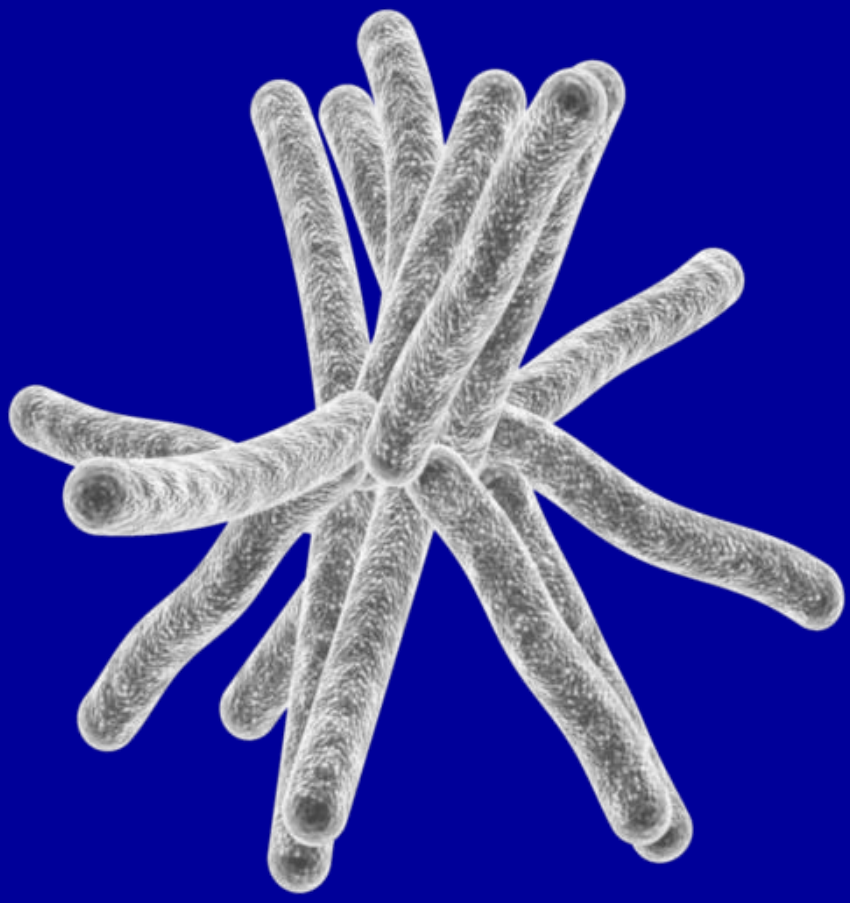

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