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The beautiful thing about learning is nobody can take it away from you—B. B. King

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THE ROLE OF SOCIAL NETWORKS IN HUMAN LIFE

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ABSTRACT

The number of users of social networks is growing day by day. This increases the likelihood that brands on social media will reach more people every day. For this reason, it has become very important for brands to communicate on social media platforms such as product sales and service promotion.

In this part of our article, we will tell you about the most used social media platforms. Social networks are websites set up for a specific purpose where people interact with each other using symbolic gestures and facial expressions, as in their social lives. The series of articles about "Social Networks", one of the essentials of popular culture, which we started a while ago, continues with "3F Phenomenon".

Keywords: Social network, Social media, Internet

РЕЗЮМЕ

Количество пользователей социальных сетей растет день ото дня. Это увеличивает вероятность того, что бренды в социальных сетях с каждым днем будут охватывать все больше людей. По этой причине для брендов стало очень важно общаться в социальных сетях, таких как продажа продуктов и продвижение услуг.

В этой части нашей статьи мы расскажем вам о наиболее часто используемых платформах социальных сетей.

Социальные сети - это веб-сайты, созданные для определенной цели, где люди взаимодействуют друг с другом с помощью символических жестов и мимики, как в своей социальной жизни. Цикл статей о «Социальных сетях», одной из основ популярной культуры, которую мы начали некоторое время назад, продолжается «3F Phenomenon».

Ключевые слова: Социальная сеть, Социальные сети, Интернет

Introduction: We will give brief information about the most popular social networks in the world. Today, the biggest examples of social networks are websites such as Facebook, Twitter, Linked IN.

The number of Facebook users is about 2.4 billion. Men make up 56% of Facebook's user base, while women make up 44%. The average number of active users on Facebook is usually between 25 and 34 years old.

If you look at Instagram statistics, the number of active users seems to have reached about 1 billion. Approximately 50.9% of relevant users are women and 49.1% are men. Most Instagram users are between the ages of 18-24 and 25-34.

Twitter; The number of Twitter users is about 339 million. If you look at the statistics of Twitter users, it is clear that 38% of users are women and about 62% are men.

Main text: We have prepared and collected the details of the most popular social networks in the world, in short, for you. As mentioned earlier, each social network is a separate research topic in itself. With this in mind, we started a series of articles on "Social Networks". A different channel is added to this series of articles every week. Thus, we deliver the world's most popular social networks closely and with academic discipline.

The huge database of the Internet is enriched with new news every second. As the Internet expands, it is possible to communicate virtually with people around the world, correspond, participate in various online forums, read electronic versions of books, magazines and newspapers, shop, listen to the radio, watch television, and keep up to date with daily events. Information is available. All of this gives people the widest possible use of the Internet to gain knowledge.

One of the most popular projects on the Internet today is social networks. Therefore, in many advanced countries, teachers of computer science, foreign languages, geography and other fields have begun to use Internet resources for educational purposes. If a few years ago, social network servers were considered a place for young people to have fun and spend time, and they were seen as very harmful projects that negatively affect the education of young people, and the Internet as a source of poor quality abstracts and inaccurate information. Thanks to the updated virtual electronic libraries, virtual encyclopedias and social networks, the Internet has gained a positive character and is widely used in education.

In the digital realm, a social network that allows people to socialize and communicate with each other helps people identify themselves online. So, each social network has different features. For example; there is a character limit on Twitter. For this reason, it is not suitable for people who like to talk at length. LinkedIn is a professional business network, and Instagram is a photo sharing site. In addition, while it is possible to have fun and improve you on some social networks, spending time on others can be just a waste of time.

Result: There are many such social networks today. Although these networks differ in many respects, in general, they all allow users to share. Thus, content, images or videos shared by a person can be easily spread around the world. Social networks are designed to cover all internet and mobile devices. Such platforms have unique content and slogans for users. The retention rate of such records is quite high. Social networks are generally formed by users.

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POST-COVID 19 ENCEPHALITIS IN PATIENT WITH DE NOVO MUTATION IN THE SCN1A GENE, A CASE REPORT

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ABSTRACT

Seizures are defined as a transient occurrence of signs and symptoms due to an abnormal, excessive or synchronous neuronal activity in the brain, characterized by abrupt and involuntary skeletal muscle activity. The presence of cephalgic syndrome, infectious-toxic encephalopathy, hypo- and anosmia and ageusia are pathognomonic conditions in COVID-19 infected patients.

Post-Covid 19 encephalitis develops to encephalopathy in children with epilepsy. Based on the clinical appearance and the parameters that showed past Covid-19 infection, a diagnosis of post-COVID19 encephalopathy was confirmed. To confirm the diagnosis, clinical examinations, MRI of the brain, electroencephalography, lumbar puncture, laboratory tests (including CBC, CRP, basic metabolic panel, liver panel, hemostasis with D-dimer) are necessary. Based on the brain changes registered on the EEG record, the physical findings and the presence of SARS CoV 2 IgG antibodies, it was concluded that a child with an initial diagnosis of epilepsy, developed encephalopathy after asymptomatic COVID 19 infection.

Keywords: Post-COVID19 complications, encephalitis, Dravet syndrome, epilepsy, de novo mutation, children

Introduction: Although the predominant clinical presentation of SARS-Cov-2 infection is respiratory disease, neurological manifestations are being recognised increasingly.

SARS-CoV-2 infects cells through angiotensin-converting enzyme 2 (ACE2), an ubiquitous receptor that interacts with the viral surface S glycoprotein. Recent reports show that the virus affects the central nervous system (CNS) through symptoms and complications that include dizziness, altered consciousness, encephalitis and even stroke. These can immerge as indirect immune effects due to increased cytokine production or via direct viral entry into the brain tissue.

Many viruses, including Corona virus, have nervous tissue tropism and can cause severe neurological damage. SARS-CoV-2 is not an exception as it has demonstrated neurotropic properties and an ability to cause neurological disease. However, the neuropathogenic mechanisms of SARS-CoV-2 are not fully explained. This necessitates an evaluation of the possible contributions of neurological tissue damage to the morbidity and mortality caused by COVID-19.

Although there are limited numbers of studies describing neurological complications specifically, still neurological problems as this one appear to be pretty rare. However, children with severe and critical illness, especially those with multisystem inflammatory disease, appeared to have a higher prevalence of neurological symptoms.

Compared to adults, neurological complications in children have been reported only in few cases and fortunately, the illness appears to be less severe in children.

Encephalitis is serious condition of neurologic dysfunction due to inflammation of the brain parenchyme. A wide variety of infectious and non-infectious etiologies are associated with

encephalitis, though the cause in more than half of cases remains unexplained, despite extensive testing. Given the heterogeneous and wide differential diagnosis, epidemiological, clinical, laboratory and radiographical investigations are necessary to guide the diagnostic evaluation and treatment. The majority of the pathogens reported to cause encephalitis are presented by viruses. Another major challenge for patients with encephalitis is to determine the relevance of an infectious agent identified outside the CNS; these agents may play a role in the neurologic manifestations of illness, but not necessarily by directly invading the CNS. In addition, it is important to distinguish infectious encephalitis and postinfectious or postimmunization encephalitis or encephalomyelitis (e.g., acute disseminated encephalomyelitis [ADEM]), which may be mediated by an immunologic response to an antecedent antigenic stimulus from an infecting microorganism or immunization.

Dravet syndrome is a severe epilepsy that occurs in childhood, most prominently characterized by fever-induced seizures. The disease progresses to other types of seizures (myoclonic, partial) and is simultaneously associated with progressive cognitive and behavioral deficits. The typical presentation is characterized by hemiclonic or generalized clonic seizures triggered by fever during the first year of life, followed by myoclonic, absence, focal and generalized tonic-clonic seizures. Non-convulsive status epilepticus and epileptic encephalopathy are common. Development is normal in the first year of life, but most individuals eventually suffer from intellectual impairment. Dravet syndrome is associated with mutations in the sodium channel alpha1 subunit gene (SCN1A) in 70-80% of the affected individuals. SCN1A mutation results in inhibition of the GABAergic inhibitory inter neurons, leading to excessive neuronal excitation. The "interneuron hypothesis" is the current most accepted pathophysiological mechanism of Dravet syndrome. The mortality rate is increased significantly in Dravet syndrome. Ataxia, a characteristic crouched gait and Parkinson's symptoms may develop in some patients. It is likely that Dravet syndrome is underdiagnosed in adults with treatment-resistant epilepsy. Early diagnosis is important to avoid anti-seizure medications that exacerbate seizures.

The incidence of Dravet syndrome is estimated at 1 per 22,000-40,000 based on studies in the United Kingdom and Denmark and it affects males twice as often as females. It typically causes an epileptic encephalopathy. Seizure onset is typically in the first year of life, with prolonged febrile and afebrile hemiclonic or generalized clonic seizures in previously healthy children. *Status epilepticus* occurs commonly in Dravet syndrome, both the convulsive and non-convulsive types.

The observation of a positive family history of febrile seizures and epilepsy in individuals with Dravet syndrome and *de novo* mutations in *SCN1A* suggest that the mode of inheritance is polygenic and that other modifier genes such as *SCN9A* contribute to the phenotype.⁵

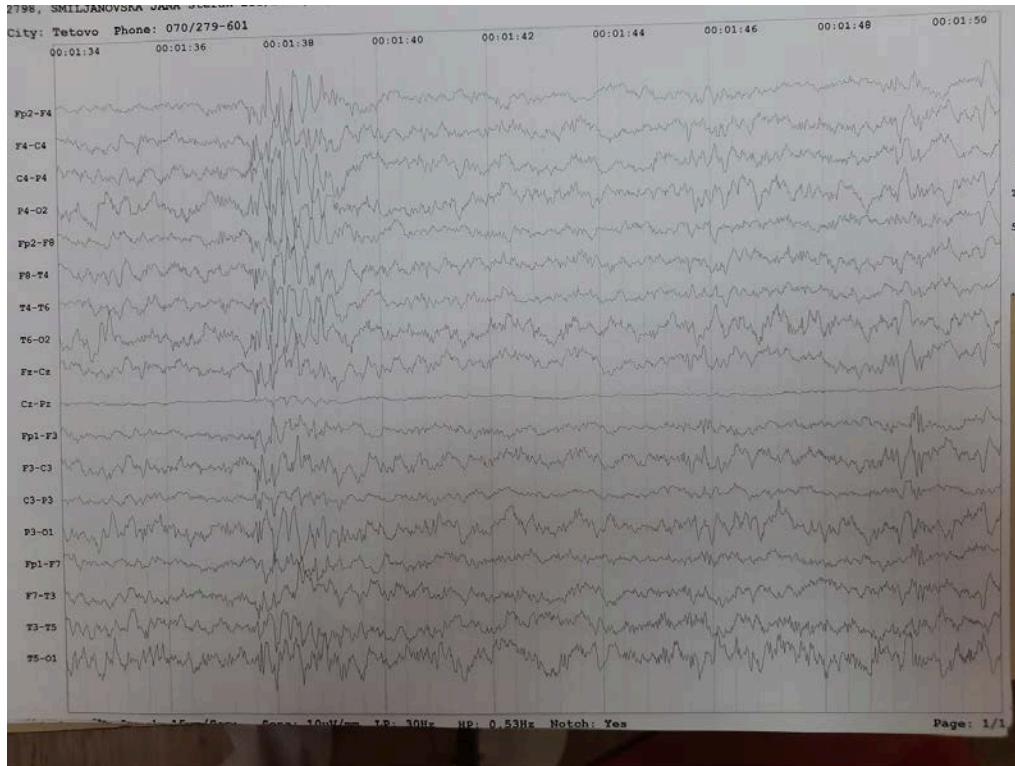
Dravet syndrome typically presents in the first year of life with prolonged, febrile and afebrile, generalized clonic or hemiclonic epileptic seizures in children with no pre-existing developmental problems. Other seizure types including myoclonic, focal and atypical absence seizures appear between the ages of 1 and 4 years.

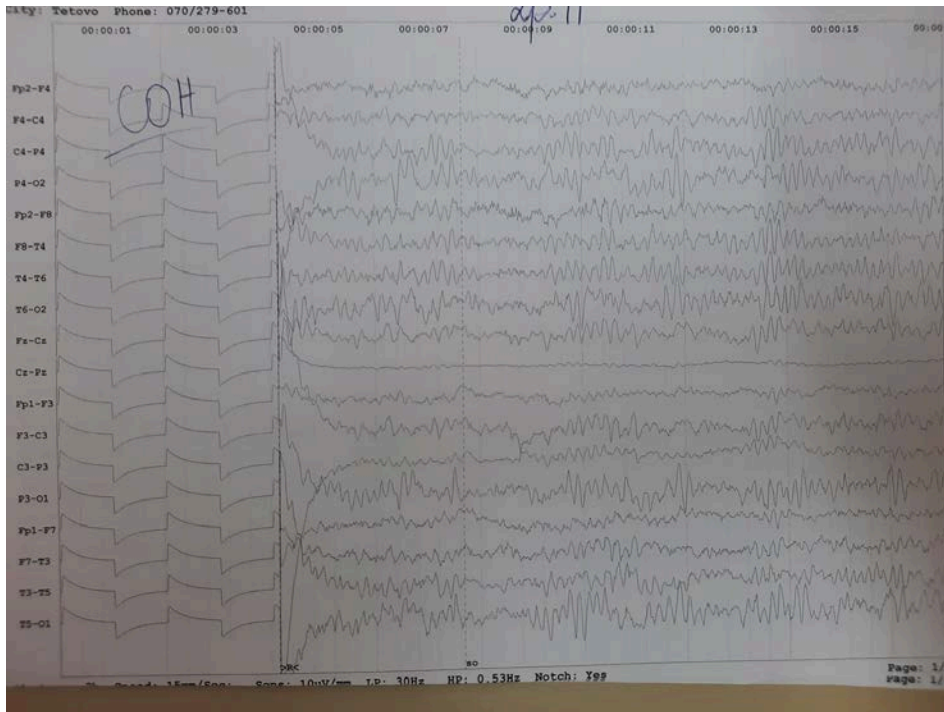
The epilepsy is usually refractory to standard anti-epileptic medication and starting from the second year of life affected children develop an epileptic encephalopathy resulting in cognitive, behaviour and motor impairment. Seizure types within Dravet syndrome, such as status epilepticus, may be life threatening and sudden unexpected death in epilepsy can occur.

The majority of children (70–80%) have a mutation in the voltage-gated sodium channel type I alpha subunit gene, *SCN1A*, and recent evidence suggests that the nature of a mutation may affect the phenotype.

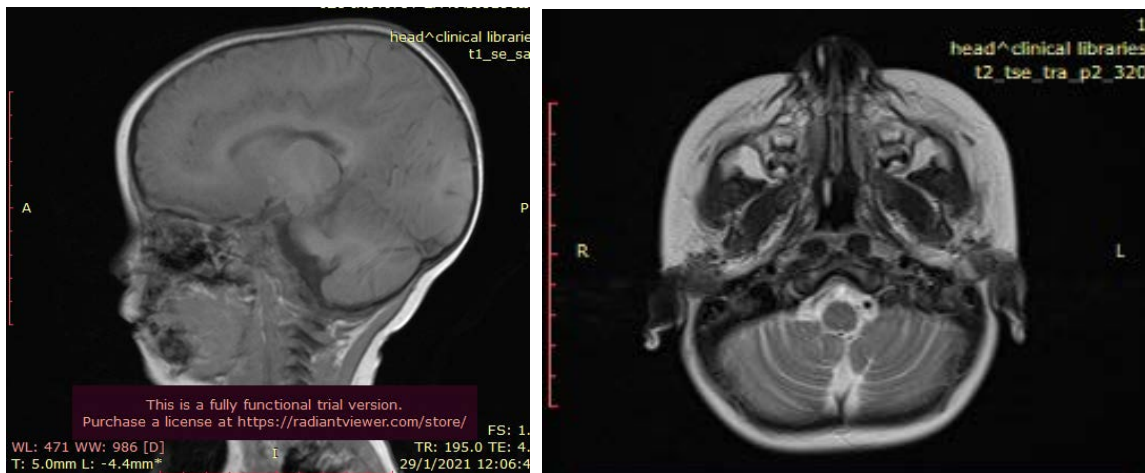
The first systematic UK population-based evaluation showed the incidence of *SCN1A* mutation-positive Dravet syndrome at 1:40 900. This figure, however, might be an underestimate, as we have recently seen an increase in genetically proven cases, including cases of germinal and somatic mosaicism, and a widening of the spectrum. The estimated mortality of 6% at 5 years of age highlights that children with Dravet syndrome face a substantial risk of early epilepsy-related death compared with children with idiopathic epilepsy.

Case report: We present a 16-month-old female child who is regularly followed at the neurology department from 6 months of age with Dg: Epilepsy. The child was treated with Levetiracetam and Valproic acid, but despite the therapy seizures still persisted. At the last visit, the EEG registered fast alpha rhythm, with bihemispheric complex of spike wave complexes (as shown below).





MRI of the brain before the admission: revealed normal finding (Picture 1).



Picture 1

Otherwise, she is first-pregnancy child, born in term, with orderly perinatal and postnatal course, with a negative family history.

Initially the patient was admitted in the intensive care unit due to convulsive epilepsy status. At the admission she was unconscious, pale, with occasional apnea and tachycardia. Due to inability to purchase the attack, the child was sedated and placed on mechanical ventilation with endotracheal intubation. After a 47 days-stay at the intensive care unit, the patient was stabilized and transferred at the neurology department.

On the admission at the neurology department, she was soporous, visual contact was not established and right divergent strabism was noted. Additionally, there was hypotonia of body axis, spasticity of all four limbs, live tendon reflexes and positive bilateral Babinski, with contractures in ankle joints.

The laboratory biochemical analyses, inflammatory markers, degradation products and gas analyzes showed no deviations of the regular values. (Table 1)

Table 1: Serum laboratory analyses

Blood	Value	Reference value
White blood cells (WBC)	10,32	3.50 – 10.00 x 10 ⁹ /l
Red blood cells (RBC)	5,72	3.50 – 5.20 x 10 ¹² /l
Hemoglobin (Hb)	161	11.2 – 16.5 g/l
Platelets (PLT)	181	50 – 400 x 10 ⁹ /l
CRP	0.8	0.0 – 5.0 mg/L
Glucose	4.92	4.10 – 5.90 mmol/L
Urea	1.8	2.6 – 6.4 mmol/L
Creatinine	34	0 – 104 umol/L
Sodium	138	136 – 145 mmol/L
Potassium	5,1	3.5 – 5.1mmol/L
Calcium	2,61	2.10 – 2.55mmol/L
Magnesium	0.78	0.70 – 1.00mmol/L
Total proteins	72	64 – 83g/L
Albumins	43	40 – 49 g/L
AST	207	15 – 59 U/L
ALT	100	9 – 72U/L
GGT	167	0 – 36U/L
LDH	1454	0 – 500U/L
CK	91	29 – 200 U/L
CK-MB	239,54	0.00 – 24.00U/L
Serum ammonia	34.37	18.20 – 72.20 umol/L

The lumbar puncture with the obtained finding of a clear LCS without elements, from the chemical analysis obtained in the proteins = 3.36g / L, Lactate <1.5 mmol / l, Glycaemia = 3.89 mmol / l, out of the CSF there was not isolated pathogen.

Table 2: Laboratory values in CSF

CSF	Value	Reference value
Appearance	Clear	Clear
Glucose	3.89	2.7 – 4.1 mmol/L
Protein	3.36	0.15 – 0.45 g/L
Lactate	< 1.5	1.1 – 2.4 mmol/L
Meningitis/encephalitis panel	Negative	



Due to the finding of elevated liver enzymes and hepatomegaly, a gastroenterohepatologist was consulted. The recommended virological markers for hepatitis were within reference range. However, a hepatoprotective was included in the therapy. (Table 3)

Table 3: Liver enzymes and virological markers

		IgM	IgG	Value
Anti-HBc	Negative			
Anti-HBs	Negative			
AntiHCV	Negative			
HAV		Negative	Negative	
HBc		Negative		
HBsAg	Negative			
EBV		Negative	Positive	
Toxoplasma gondi		Negative	Negative	
CMV		Negative	Positive	
Rubeolla		Negative	Positive	
Herpes I and II			9.82	< 1.0

In the hemostasis elevated D-dimers were found, hemoconcentration and reactive polyglobulia due to which the therapy with LMWH enoxaparine was converted to fraxiparine, recommended by hematologist. (Table 4)

Table 4: Hemostasis

D dimer	35712...1030..8081...10108...17009...1405 ngr/MI	0-500 ng/mL
Prothrombin time (PT)	11.4...12.8...10.8...11.7...11.4...12	9,8(13)14,2 s
Activated partial thromboplastin time (aPTT)	21.1...31.9...26.5...28.9...31.4...27.9	27,9(33)37,7 s
Thrombin time	20.3...18.2...17.1...15.4...21.6...18.1	16,1(22)24,1 s
Anti Xa	0.5...0.6...1.1...0.04	
Fibrinogen	3.2	(2.3 (3.1) 3.5 g/L

The findings of the COVID-19 specific IgG showed an elevated range of 54.59 AU/ml (Table 5)

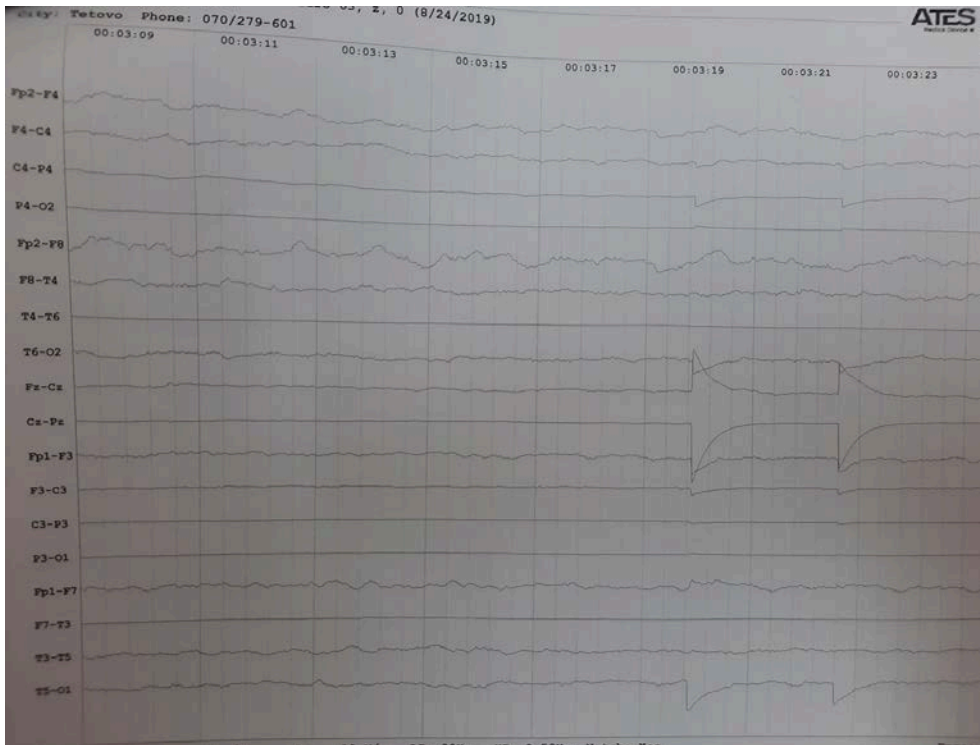
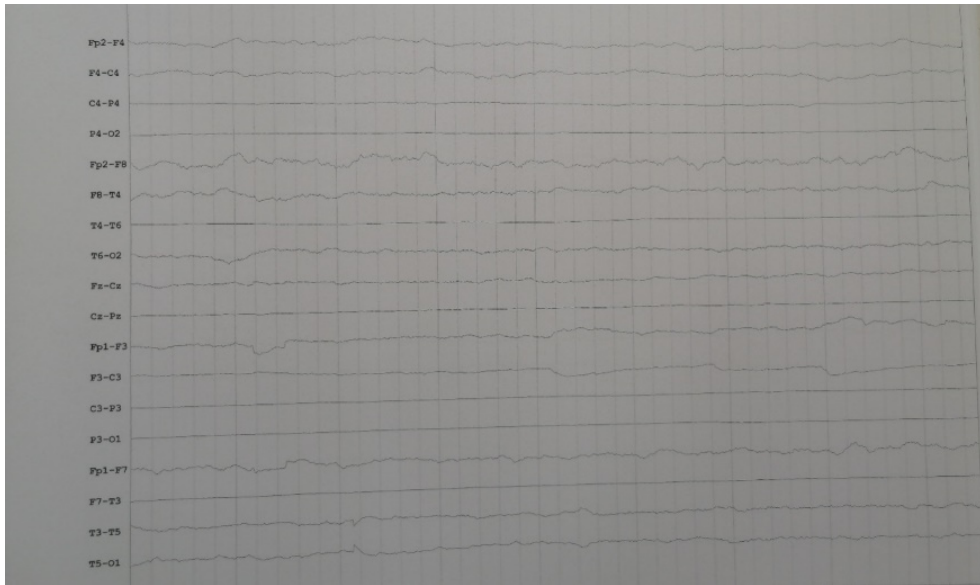
	Value	Reference values
COVID-19 RBD (Receptor Binding Domain) IgG	54.59	< 1.00 AU/mL

We considered examination by a nephrologist, obtained by ultrasonography on UGT, and due to hypertension, we administered antihypertensive per os for several days, after which the values of arterial tension become normal.

During the stay, the patient was initially placed on continuous oxygen support, feeding was conducted at first by a nasogastric tube, then self-feeding, the vital parameters were continuously

monitored, with need of aspiration of airway secretions and drainage, as well as regular implementation of physical therapy.

Two-times electroencephalography (EEG) during sleep showed no registered brain activity (Picture 2)

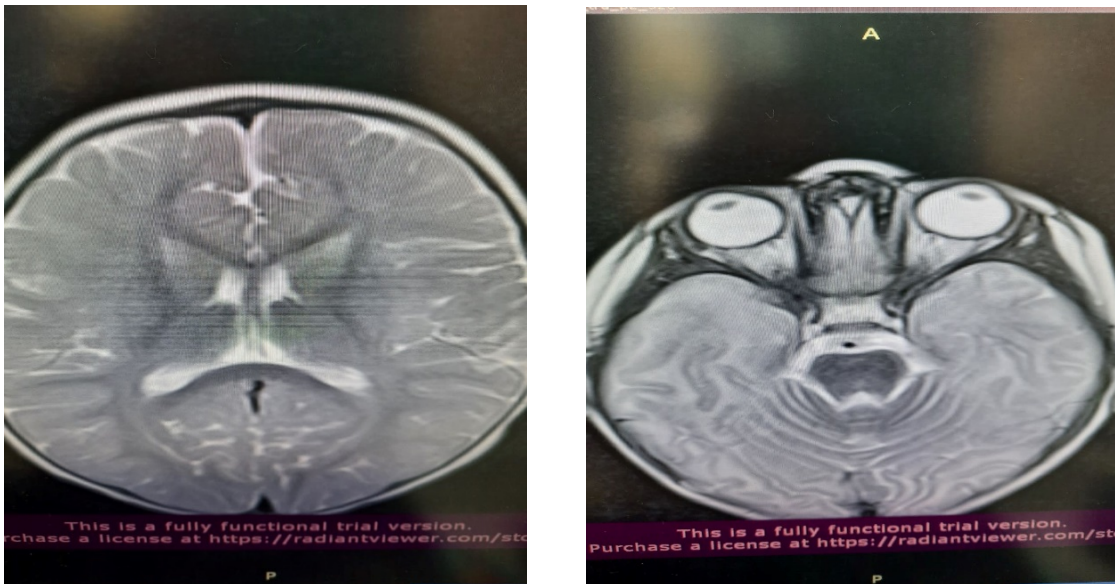


Picture 2

Parenteral double antibiotic therapy with carbapenem and aminoglycoside was administered, as well as the regular double oral antiepileptic therapy.

During the stay for the whole time there was not changing in the condition in terms of neurological status.

The patient was released from the neurology department with subcutaneous antiaggregation therapy, double antiepileptic therapy (Valproic acid and Levetiracetam), hepatoprotective therapy, vitamin therapy and recommendation for physical therapy and regular follow-up visits. The second brain MRI (after Covid-19 infection) as well as the first one, showed no abnormal findings (picture 3).



Picture 3

Discussion: The affected child had no history of specific COVID-19 symptoms. The only proof of past infection was the elevated COVID-19 specific IgG (IgG 54,59 AU/ml).

The results of the performed genetic testing with targeted sequencing of 4,800 clinically significant genes, using the TruSight One kit, Illumina, and bioinformatics of genes associated with the patient's condition, showed the presence of a pathogenic change in the CSN1A gene (c.111DG> A p.Trp370er), in heterozygous form. Pathogenic changes in the SCN1A gene are associated with Developmental and epileptic encephalopathy, (non-Dravet), Dravet syndrome, Generalized epilepsy with febrile seizures type 2, FF febrile seizures familial, Migraine, familial hemiplegic type 3 with autoimmune type 3.

The SCN1A gene is located on chromosome 2 and encodes a protein that represents an alpha subunit of the sodium membrane channel called NAV1.1. These channels are primarily located in the brain, where they control the flow of sodium ions into the cells. These channels are involved in transmitting signals between two nerve cells.

The variant c.111DG> a p.Trp370er in exon 9 of the SCN1A gene is a nonsense variant which at the protein level of position 370 causes the replacement of the amino acid tryptophan with a stop codon leading to premature cessation of normal protein synthesis. Variant c.111DG> A has not

been previously described in the literature. Examination of the parents did not show the presence of variant c.111DG> A, indicating that the change was de novo mutation.

In a UK cross-sectional online survey by Balestrini et al., the impact of Covid-19 in Dravet syndrome was investigated. In 50% of people with Dravet Syndrome who developed possible or probable COVID-19 symptoms, seizure worsening was reported, in terms of increased seizure frequency or duration or both. Medical attention was required in 9/22 (41%), all of whom were children. In this cohort of patients with Dravet Syndrome it was observed an infection rate, determined by compatible symptoms of 19%, with no deaths and benign outcome in most cases despite the underlying complex epilepsy, although children often required medical attention. Early adoption of preventative measures, including testing of symptomatic individuals, regular surveillance for people living in residential care facilities, and shielding of individuals with comorbidities increasing the risk of severe outcome, may limit the impact of COVID-19.

Although there is no cure for Dravet syndrome, most treatments aim to reduce seizures. Valproic acid and clobazam are used as first-line medications. Topiramate and ketogenic diet include the second-line treatment. Levetiracetam, Ethosuximide, Cannabidiol and vagal nerve stimulation (VNS) are used as third-line seizure treatment. On the other hand, medications that should not be given include Carbamazepine, Oxcarbazepine, Lamotrigine, Vigabatrin (sodium channel blockers), as these can worsen seizures in Dravet syndrome.

Conclusion: Most children with COVID-19 have mild symptoms or have no symptoms at all. However, some children can get severely ill from COVID-19. They might require hospitalization, intensive care, or a ventilator to help them breathe. In rare cases, they might die. There are also rare cases among the child populations with post covid complications, especially with the development of encephalitis as a consequence of a previous asymptomatic infection. These “post-covid-encephalitis” patients additionally need specific rehabilitation with neurologic stimulation (neurorehabilitation). According to a study conducted by Laura Bach in 2014 in patients with autoimmune encephalitis, positive outcomes were achieved for all patients using a variety of interventions which included behavioural management, family psycho-education and an integrated holistic multi-disciplinary team community approach. Majority of the patients with post infectious encephalopathy has markedly differing cognitive profiles suggesting that in the context of long term rehabilitation outcome, cognition may have less valence than emotional and behavioural factors. However, this kind of rehabilitation should be conducted in specialized centers equipped with staff that is educated for this kind of therapy specifically.

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ISSUES OF IMPLEMENTATION OF SYSTEM OF CONTROL IN SUSTAINABLE FINANCIAL AND ECONOMIC MANAGEMENT OF INDUSTRIAL ENTERPRISES

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ABSTRACT

In recent years, pondium problems in many countries around the world have created a financial crisis, negatively affecting the macroeconomic performance of many countries, which has led to a decline in gross domestic product (GDP) as well as greater problems in economic development. The globalization of economic processes in the world has increased the uncertainty of the external environment in the national economy of both individual and national economies as a whole, creating the need to develop scientifically based methods and approaches to effective management of industries.

Today, the formation of an effective management system of the economic system must be based on the principles of sustainable development. Management should be carried out in order to achieve the level of financial sustainability of the enterprise, on the one hand, and on the other hand, in accordance with the strategic objectives of the actual situation of the business entity. This is because the existence of objective uncertainty in the external environment of the enterprise and the subjectivity of decisions make it necessary to develop a control system for the stability of the enterprise, which should allow the formation of optimal management decisions aimed at increasing financial and economic stability. Thus, the stability of an economic system based on scientific methods of modeling and optimization in a dynamic environment, based on preventive measures and the principles of adaptive management.

Keywords: sustainable, system, management, enterprise, model, function, purpose, uncertainty.

Introduction: The globalization of economic processes, firstly, the expansion of economic ties, increasing competition and production, secondly, improving the performance of enterprises caused by short and long economic waves caused by the crisis, thirdly, the information revolution that provides information capital and scientific and technological progress; and a change in the economic paradigms that influence the transformation of the "controlling" category [1,2,4].

However, most researchers agree that controlling is a new concept of business management based on the latest methods and technologies of enterprise management, its essence, functions and tasks are in the genesis of the category of "controlling" [10, 11].

The German economist Dietger Hahn, who laid the foundation for this concept, wrote that controlling "can be interpreted as the provision of information based on the results of enterprise management" and that controlling should be considered as planning and control.

The above conditions, on the one hand, make it necessary to create a new type of enterprise sustainability control, which will include the existing types of control over the processes taking

place in the enterprise, as well as the resources of the enterprise. On the other hand, based on the principles of preventive management, it is possible to reduce the degree of negative impact of the external environment of the enterprise on the level of sustainability of the enterprise.

Management of an industrial enterprise in terms of financial and economic stability based on the application of a control system: Control over the financial and economic stability of an industrial enterprise operating in a dynamic environment implies close interconnection of all its subsystems, which operates not only ensures the formation of adequate goals that take into account the characteristics of This fact once again proves the need to develop a comprehensive approach to the management of industrial enterprises based on the application of controlling technologies.

Therefore, control should act as a means of increasing the level of financial and economic stability of the business entity, taking into account the dynamics of the processes taking place in the mini-economic system.

Graphically, the essence of the application of a sustainability control system in an industrial enterprise can be presented in the form (1).

It is clear from Figure 1 that at the entrance to the system there is a fluctuation of the target, which goes beyond the boundaries of sustainable development of the enterprise, and at the output, the target falls into the field of fixed values. The target of this economic system can be financial indicators. For example, the company's profit or cash flow, relative indicators such as sales revenue or market share, and quality indicators such as product quality. Any of the examples we provide can be targeted. The only thing to remember is that when setting a goal in the form of a quality indicator, it is necessary to formalize it.

If we have to analyze the functions of controlling, then based on the analysis of the scientific views of modern scientists, it is necessary to note the following:

- coordinating function;
- methodical function;
- information and analytical function;
- innovative function.

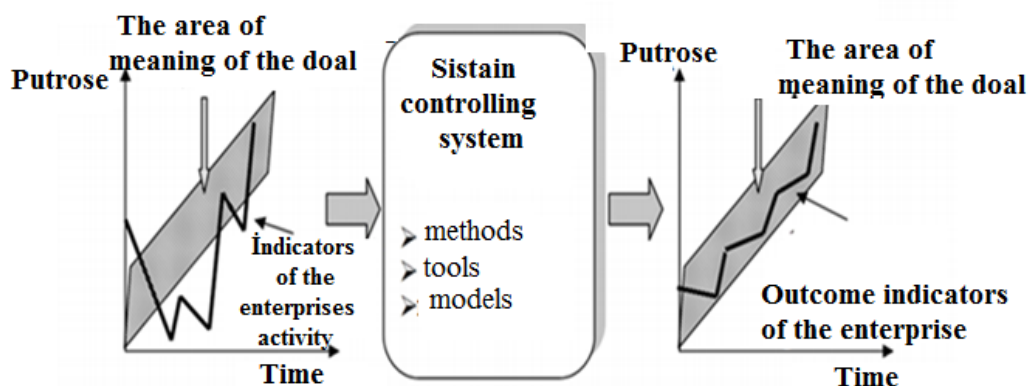


Figure 1: Boundary of enterprise activity

Source: Created by graphic authors.

The coordinating function of control is, in a sense, in the coordinated establishment of a planning and control system. The methodological function of control involves the search for sources of funding and the formation of financing strategies, taking into account the overall strategic goals of the enterprise. Formation of tactical and strategic financial plans taking into account the strategic goals of the enterprise's activity and development, as well as information from previous reports, current financial and economic analysis to identify deviations from the planned level, factor analysis and sensitivity to fluctuations in economic system input parameters.

If we talk about the information-analytical function of control, then the following tasks should be solved:

- comparison of planned and actual prices;
- assessment of the probability of achieving tactical and strategic goals; -
- determination of possible deviations of financial-economic and technical-economic indicators;
- analysis of deviations of actual results from planned prices;
- Factor analysis of deviations, development of a set of measures aimed at reducing the negative impact of identified factors.

The function of innovative control is especially relevant in the context of intensification of scientific and technological progress, instability of the external environment, which leads to additional risks. Because the commercial viability of innovative processes depends on the effectiveness of the management system. At the same time, the function of innovative control is mainly aimed at equalizing technical, temporary and economic risks.

It should be noted that everything is very clear with these functions. Thus, during the reign of the systemic paradigm, not only the definition of "controlling" but also its functions change. In the context of the transition to the concept of "sustainable control", the goal setting function plays an important role when the enterprise is considered as an economic system. Many German authors, such as P.R. Preisler explains that goal setting refers to controlling functions, that "goal setting" - in other words, it is "management" and therefore this function should be performed by managerial relationship managers [5,6,7]. On the other hand, there are often supervisors who help managers more clearly formulate adequate strategic and tactical goals for the operation and development of the enterprise and move them to specific quantitative plans, not only in terms of quality. Only as a result of effective cooperation between the head of the enterprise and the supervisor can a progressive control system be implemented. Defining a goal should become one of the key functions of an industrial enterprise's sustainability control system. It should consist of productive joint work of managers and supervisors aimed at forming an adequate strategic goal for the operation and development of the business entity in an unstable, changing environment based on proactive or adaptive management [4, 9]. These ideas can be found in the works of the classical theory of management S.D. Falco. SDFalko views control as a "navigation system". Its idea is also found in the definition of the "controlling" category developed by the International Monitoring Group (IGC, Switzerland). The following requirements must be taken into account:

- simulation models;
- regulation of the production process;
- external influences;
- target regulation;
- determination of purpose;
- internal environment of the enterprise;
- control subsystem of the enterprise;

-Experience gained in previous management periods.

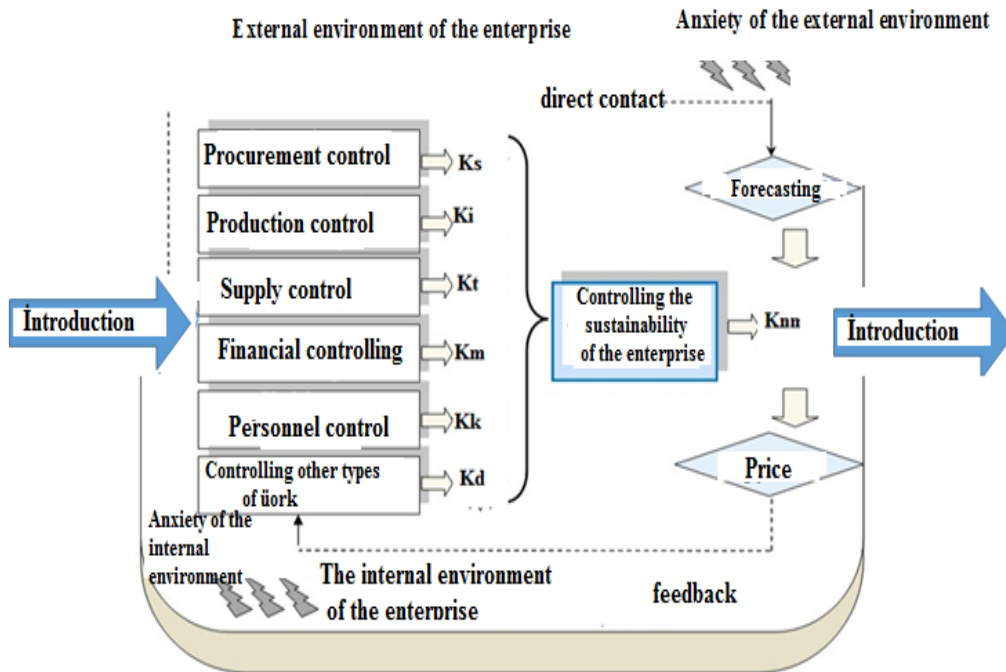
The next step should be to identify possible scenarios for the development of the enterprise, depending on the impact of certain concerns on the mini-economic system. In addition, simulation models must be built for selected scenarios. Based on the selected scenarios for the development of the enterprise, optimization economic and mathematical models should be formed that will determine the optimal scenario of the development of the business entity corresponding to a given level of financial and economic stability. In the process of solving the problem of optimization, it is necessary to identify periods of development of the economic system that are "dangerous" in terms of possible loss of stability, as well as to analyze the sensitivity of the level of the economic situation [7, 12]. In the long run, this will increase the level of financial and economic stability as close as possible to the strategic development goal, which was formed at the stage of targeting the economic system and adjusted in the process of applying governance.

Controlling the sustainability of an industrial enterprise is not possible without close interaction of the enterprise's subsystems (managed), as well as the subsystem that performs management functions. For example, goal setting in the system must be reciprocal. In addition, it should be noted that only with close interaction of all subsystems of the industrial enterprise it is possible to form adequate goals that take into account not only the interests of stakeholders, but also the characteristics of the business entity.

Development of integrated indicators for determining the level of financial and economic sustainability of an industrial enterprise: On the one hand, the management of an industrial enterprise needs a system that monitors the effectiveness of the sustainability control system so that it can be used for future forecasting; . This system must be built taking into account the basic principles and limitations of the integrated indicator of the sustainability of an industrial enterprise, as well as the results of the analysis and the modern portrait we have obtained. To solve this problem, the industrial entity's production, sales, personnel, information, etc. The sustainability of subsystems should be identified in the management system to address the goal. Thus, the solution of the problem can be determined on the basis of determining the integrated indicators of the subsystems of material and economic sustainability of the industrial enterprise. Then the connections of the subsystems can be given graphically as follows (Figure 2).

Figure 2: Graphical interpretation of the financial and economic sustainability control system of an industrial enterprise

Source: Created by graphic authors.



Referring to Figure 2, the functional dependence of the integrated indicator of financial and economic stability of the enterprise can be summarized as follows:

$$f(x) = f(x_1, x_2, x_3, \dots, x_n), \quad (1)$$

where x is the financial and economic sustainability of the enterprise; $x_1, x_2, x_3, \dots, x_n$ - stability of each subsystem, respectively; n is the number of analyzes of the enterprise subsystems.

In order to establish a controlling system to determine the level of operation of each subsystem of the industrial enterprise, it is proposed to apply a tactical stability factor:

$$k_{tst,i}(t) = \frac{N_i(t)}{N_{t,goal,i}(t)}, \quad (2)$$

where $k_{tst,i}(t)$ - coefficient of tactical sustainability of the i -subsystems of the enterprise to achieve a relatively set goal; $N_i(t)$ - Key Performance Indicator of the actual i -subsystems of the enterprise; $N_{t,goal,i}(t)$ - the main indicator of the tactical stability of the i -subsystem of the enterprise in t -moment.

It should be noted that in order to assess the tactical coefficient of the objective of each subsystem of the enterprise entity, the stability of the industrial enterprise should be calculated in the variants of the external and internal environment (Figure 2) arising from the established nature of the control system. In this regard, formula (2) will be presented in the form of an expression (3) so that it is possible to determine the sustainability of the target relative to the lower limit. Then (3) can be expressed as follows:



$$k_{t,st,min}(t) = \frac{N_i(t)}{N_{t,goal,min}(t)}, \quad (3)$$

where $k_{t,st,min}(t)$ – is the indicator of integral stability of the enterprise subsystem in. To determine the sustainability of the enterprise relative to the upper boundary:

$$k_{t,st,max}(t) = \frac{N_i(t)}{N_{t,goal,max}(t)}, \quad (4)$$

where $k_{t,st,max}(t)$ – is an indicator of the integral stability of the enterprise subsystem in relation to the upper limit of the tactical target in the period t.

Assuming that the main indicator of the tactical stability of the i-th subsystem of the enterprise is taken as an increase in cash flows or an increase in profit, then the integral stability coefficient can be interpreted as follows, taking into account the operation of the enterprise's subsystems over time t:

- adjustment $k_{t,st,i}(t) < 1$ In the short term, the industrial enterprise operates unstable, requires urgent management decisions based on controlling technologies;
- indicator $k_{t,st,i}(t) = 1$ In the short term, the industrial enterprise operates continuously, the results obtained correspond to the goals set by the management ring at the stage of goal setting;
- $k_{t,st,i}(t) > 1$ industrial enterprise is operating stably.

Suggested indicator: -first, it is considered in connection with the purpose system of the enterprise expressed in the stage of goal setting.

- Second, it allows us to consider the dynamics of the industrial enterprise.

- Third, the proposed indicator is universal. Because the main indicators of the sustainability of the i-subsystem of the enterprise may be different, which depends on the specific goals of each business entity identified at the stage of goal setting.

Evaluating the effectiveness of the application of the control system in the development of an industrial enterprise: First, let's consider the principles of assessing the impact of the application of a control system on the sustainability of the enterprise, taking into account the stochasticity and dynamism of the operating environment. In this case, we use the indicator of financial and economic sustainability of the business entity as the main criterion for assessing the efficiency of the enterprise.

It is possible to calculate the level of financial and economic sustainability of an industrial enterprise with the application of the control system by the formula:

$$\Delta V_{ks(t)} = V_{e^*(t)} - V_{v(t)}, \quad (5)$$

where $\Delta V_{ks(t)}$ – is the probability of financial and economic sustainability of the industrial enterprise with the application of the control system for period t; $V_{e^*(t)}$ – the probability of financial and economic sustainability of the industrial enterprise before the application of the control system for period t; probability of financial and economic sustainability of the industrial enterprise after application of $V_{v(t)}$ – control system t.

In formula (5), we can write it mathematically as follows:

$$\Delta V_{ks(t)} = V_{e(t)} - V_{v(t)} = \left[F \left(\frac{SF_{d,max}^{**}(t) - SF_{d,t}^*}{\sigma_{SF}} \right) - F \left(\left[F \left(\frac{SF_{d,min}^{**}(t) - SF_{d,t}^*}{\sigma_{SF}} \right) \right] \right) \right] \times \left[F \left(\frac{k_{d,max}^{**}(t) - k_{d,t}^*}{\sigma_{SF}} \right) - F \left(\frac{k_{d,min}^{**}(t) - k_{d,t}^*}{\sigma_{SF}} \right) \right], \quad (6)$$

where F is the Laplace function.

From the logic of the formula (6) it can be concluded that the controlling system in an industrial enterprise works effectively if the value of the probability of increasing financial and economic stability is positive in the case of $\Delta V_{ks}(t) > 1$ and can be given as follows.

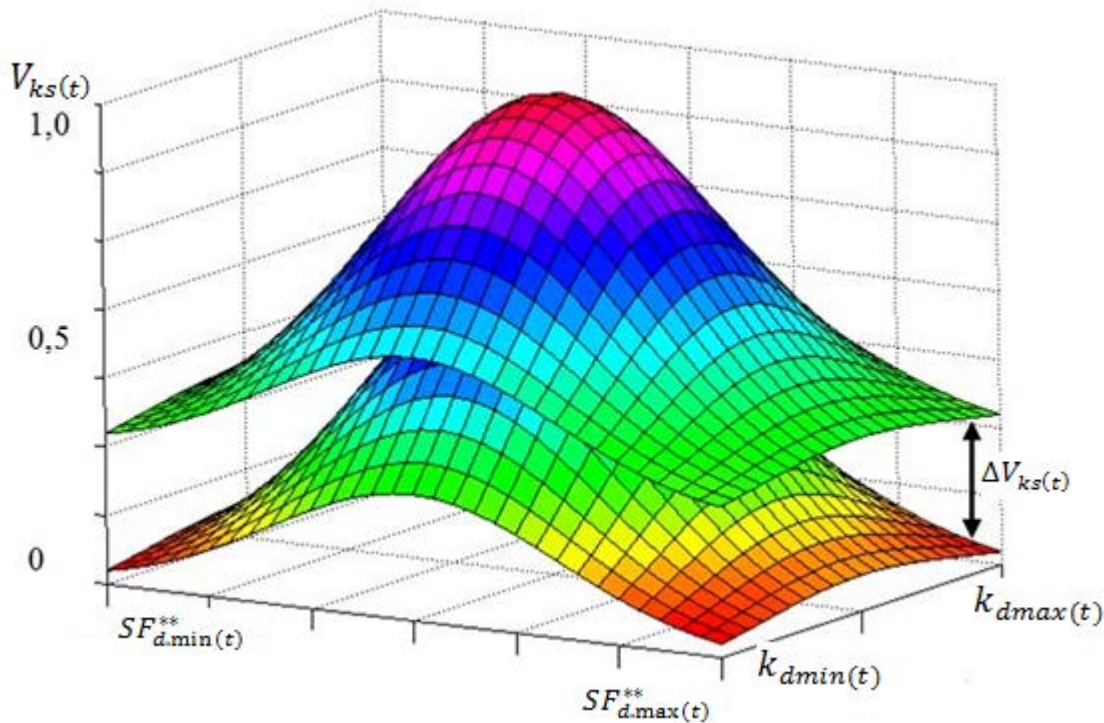


Figure 3. Graph of the level of financial and economic sustainability of the enterprise

Source: Created by graphic authors.

The meaning of Figure 3 is that based on a graphical interpretation of the integrated indicator of financial and economic sustainability of an industrial enterprise, the overall operation of the enterprise's sustainability control system can be described in the context of time. Because, the proposed methodological approach:

- first, takes into account the stochasticity of the business environment;
- secondly, considers stability in a dynamic aspect;
- thirdly, it can be used to predict the outcome in the future.

The result: 1. The dynamism of the geopolitical space and the complexity of its socio-economic structure, the globalization of economic processes in society have led to an increase in uncertainty

in the external environment of both individual and national economies as a whole. created the need to develop methods.

2. The uncertainty of the external environment of the enterprise has a direct impact on its financial as well as economic stability, which is based on the need to identify inconsistencies between the external environment and its financial and economic indicators, as well as increasing the efficiency of the business entity through control systems. conditioned the need for analysis.

3. It is proposed to use integrated indicators for assessing the level of sustainability of an industrial enterprise within the control system, taking into account the fundamentally relevant restrictive principles.

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ANALYSIS OF THE POPULATION SERVICES BY THE PRIVATE ENTERPRISES

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ABSTRACT

The individuals who make up a society need a variety of goods and services to survive and the society itself to fulfill their responsibilities. In this sense, needs are defined as deficiencies arising from people's own existence or relationships. Man tries to overcome these shortcomings. He is happy when his efforts are rewarded, and he is unhappy when his needs are not met. Meeting human needs is the basis of all economic activities. Man's needs are unlimited and definite.

Although repeated at intervals, nature offers man limited means of satisfaction. Man cannot meet these unlimited needs on his own without any effort. The main driving force that motivates people to work alone or together is their needs. To meet these needs, people form teams for activities called "work" and engage in activities.

Keywords: private enterprises, services, driving force.

РЕЗЮМЕ

Люди, составляющие общество, нуждаются в разнообразных товарах и услугах, чтобы выжить и выполнять свои обязанности. В этом смысле потребности определяются как недостатки, возникающие в результате собственного существования или взаимоотношений людей. Человек пытается преодолеть эти недостатки. Он счастлив, когда его усилия вознаграждаются, и он несчастен, когда его потребности не удовлетворяются. Удовлетворение человеческих потребностей - основа всей экономической деятельности. Потребности человека безграничны и определены.

Несмотря на то, что природа повторяется через определенные промежутки времени, она предлагает человеку ограниченные средства удовлетворения. Человек не может удовлетворить эти неограниченные потребности самостоятельно без каких-либо усилий. Основная движущая сила, которая мотивирует людей работать в одиночку или вместе, - это их потребности. Чтобы удовлетворить эти потребности, люди объединяются в группы для выполнения действий, называемых «работа», и участвуют в них.

Ключевые слова: частные предприятия, услуги, движущая сила.

Introduction: These activities are aimed at meeting the needs, and the process of meeting them with purposeful activities works the same for all people. However, the type and severity of needs, activities, and goals vary from person to person. Some needs are a priority for some. For example; For some people, meeting the needs of their physiology is a priority, while for others, the need for shelter is a priority.

Various goods and services in one region, within the borders of one country or in the world. The sum of individual requirements arising for this purpose is called aggregate demand. so far all the goods and services put forward to meet it are defined as the aggregate offer.

It is the task of the economy to ensure a balance between aggregate demand and aggregate supply and to make every effort to provide goods and services to meet and eliminate all existing needs. The economy consists of all the efforts that provide goods and services to meet existing needs. However, the economic and social structure does not seem to be sufficient. Because there are goods and services that can meet individual requirements to a large extent, but aggregate demand can not exceed the total goods at a given time and can not be provided with services. Human needs are unlimited, and natural resources are limited. None of these needs can be obtained from nature alone without effort. Therefore, measures should be taken to help meet their needs for access to economic goods and services.

Main text: The quality of goods and services produced to meet human needs is called utility. It is the basis of goods and services produced on a profit basis. It is a capital production; “Creation, storage, transportation and use of useful goods and services, sale, etc. It can be defined as a process that covers all activities. The result of the production process is called the product.

It can be said that the production function is a process of transformation in general. In this process, inputs such as raw materials, semi-factories, materials, capital, human resources, and labor goods and services become output. Production will “meet human needs with revenues from physical and human resources. If the factors of production are called, it is defined as the process of transformation of results. Various factors must be taken into account. In order for people and the society in which they live to survive, they need a variety of goods and services to perform their duties properly.

These needs are very complex and create deficiencies in humans. People are deprived of this and engage in various economic activities based on social relations and organizations. These economic efforts are organized and made as a result of human needs.

Production takes place when demand is met. Production is carried out by combining a number of resources called factors. The combination of these resources creates a demand-oriented supply of goods and services. This process continues in an interactive way and forms the basis of the so-called business units. "The production of economic goods and services by harmoniously combining the factors of production in order to meet the needs of the people and to make a profit. Economic units operating in the market or in the market are called enterprises.

Although the will is a force, desire is a learned driving force. For example; we need shelter but we would like to have a luxurious house.

Conclusion: Before the Industrial Revolution, enterprises were mainly human labor, animal power, economic units that produce and sell agricultural products using natural energy such as water and wind energy. With the invention of the steam engine and its use in industry, like many things, the concept of business has changed. The first revolution in production methods and techniques showed itself. Primary production methods were replaced by more scientific and advanced methods. Along with labor-intensive enterprises, capital-intensive enterprises also appeared. So there was a lot of production for the market. In addition to focusing on scientific methods, management thinkers such as Taylor, Fayol, and Weber and their management approaches made business science. Later, the Business Sciences further developed and reached its present form with today's modern approaches.

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WAYS TO PROTECT BANK ASSETS IN CRISIS IN AZERBAIJAN

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ABSTRACT

The article is about the current structure and features of Azerbaijani banking. The article follows the global financial crisis that began in 2008. Restructuring of Azerbaijan's banking sector has been investigated. The Central Bank prevents the crisis in order to ensure financial stability. The important reforms that have been analyzed and are effective in solving global financial problems and the implementation of a policy aimed at modernization in the banking sector have been recommended.

Systemic risk is an important issue for banks in the banking sector. The section refers to the threat of bankruptcy and liquidity problems, in other words, the possibility of a systemic banking crisis. Systemic banking crises have led to significant real economic and financial costs. Although the real consequences of the banking crisis are that economic costs are usually measured in terms of production losses, the cost of transferring government funding to financially troubled banks is related to costs.

Keywords: banking system, banking crisis, systemic banking, real economy

РЕЗЮМЕ

Статья посвящена нынешней структуре и особенностям азербайджанского банкинга исследования не проводились. Статья посвящена мировому финансовому кризису, начавшемуся в 2008 году. Проведено расследование реструктуризации банковского сектора Азербайджана. Банковские факты ЦБ по предотвращению кризиса в целях обеспечения финансовой стабильности. Были рекомендованы важные реформы, которые были проанализированы и эффективны в решении глобальных финансовых проблем, а также в реализации политики, направленной на модернизацию банковского сектора.

Системный риск - важная проблема для банков в банковском секторе. В разделе говорится об угрозе банкротства и проблемах с ликвидностью, иными словами, о возможности системного банковского кризиса. Системные банковские кризисы привели к серьезным реальным экономическим и финансовым условиям, что привело к расходам. Хотя реальные последствия банковского кризиса заключаются в том, что экономические затраты обычно измеряются производственными потерями, стоимость передачи государственного финансирования финансово проблемным банкам связана с затратами.

Ключевые слова: банковская система, банковский кризис, системная банковская деятельность, реальный сектор экономики.

Introduction: Bank failure can create systemic risk that can have significant negative externalities on both other banks and the real economy. Other banks' banking failures have negative effects on interbank operations, from the contagious effects of urgent asset sales and bank attacks, while negative effects on the real economy, falling asset prices, rising financial

intermediation costs, declining credit and money supply, and so on. occurs depending on factors. These negatives, which increase as the bank grows in size, are a systemic problem of a small number of bank failures that can lead to a banking crisis.

While recovering from the contagious effects of bank attacks, the negative effects on the real economy, falling asset prices, rising financial intermediation costs, declining credit and money supply, and so on. occurs depending on factors. These negatives, which increase as the bank grows in size, are a systemic problem of a small number of bank failures that can lead to a banking crisis. It is used to compensate banks for economic and social losses. The global financial system is in a risky volatility in the second half of the year.

Main text: The crisis that began in the United States in 2008 spread to Europe and from there to Europe, and has spread to the rest of the world, including the former Soviet Union. As in the past, the period of rapid development of the world economy is over. Abundance of income on financial assets supported by low interest rates

and the process of overestimating assets to increase profits,

lack of financial assets, non-liquid markets, the value of financial assets and real estate listed on the stock market.

We can show Azerbaijan as a country that has provided a positive adaptation to the unstable period of world financial markets. Its economy has shown sufficient determination in the financial and banking sectors, which have suffered the least from the crisis.

In 2009, the Central Bank of Azerbaijan implemented anti-crisis monetary policy, maintained macroeconomic and financial stability, eliminated liquidity gaps in the economy, and stabilized business flows between banks and businesses. The Central Bank has ensured financial stability by keeping the exchange rate stable and supporting the Azerbaijani banking sector with liquidity.

The main advantages of monetary policy are: integration into world markets through the reduction, stability of the national currency, the gradual removal of restrictions on the rise and fall of prices for goods and services. The exchange rate of the manat is set by lending authorities to reduce inflation and solve problems. Measures were taken to raise money for the oil fund, and as a result, certain successes were achieved. Undoubtedly, the importance of this policy for its development cannot be overlooked.

The financial system in Azerbaijan consists of government policies and regulations regarding borrowing and lending and asset transfer. The system consists of banks, insurance companies, other financial institutions, the pension system, financial markets and payment systems.

The development of Azerbaijan's financial system and the entire market infrastructure depends on the activities of commercial banks, insurance companies and other financial institutions.

The main purpose of the Central Bank's activity is to ensure price stability in the country within its mandate. In addition, the stability and development of banking and payment systems are among the central bank's goals. Bank failure can create systemic risk that can have significant negative externalities on both other banks and the real economy. While the banking failures of other banks outweigh the negative effects of interbank transactions, the sale of urgent assets and the contagious effects of bank attacks, negative effects on the real economy, falling asset prices, increased financial intermediation costs, reduced credit and money supply, etc. occurs depending on factors.

Conclusion: The negatives, which increase as the bank grows, can lead to a systemic problem of a small number of bank failures. This is because of the bubbles in the assets; The causes, processes, financial and economic impacts, policy recommendations for prevention and its relationship to financial crises have a large place in the economic literature. The risks to which banks are exposed are generally; It is classified as "credit risk", "market risk", "liquidity risk", "operational risk" and "political risk". The provision of financial instruments, such as loans or securities, may result from the borrower's inability to receive on time. The concept of credit risk is used to describe the probability of loss.

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THE USE ADIPOSE-DERIVED STEM CELLS (ADSCS) IN DISEASES OF THE SKIN AND IT'S MORPHO-PYSIOLOGICAL ASPECTS

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Introduction: The Adipose-derived stem cells ADSCs are heterogeneous, no specific marker for them has been identified, and the location of stem cells in adipose tissue is difficult to determine. However, most of them occur in the perivascular regions. The morphology of ADSCs resemble fibroblasts, consisting of a large endoplasmic reticulum and nuclei. ADSCs do not have a specific marker and the expression of antigens is similar to bone marrow MSCs: CD10, CD13, CD29, CD34, CD44, CD54, CD71, CD49b, CD90, CD105, CD117, and STRO-1. However, they do not express the hematopoietic markers, such as CD14, CD16, CD31, CD45, CD56, CD61, CD62E, CD104, CD106, CD144, the endothelial cell markers CD31, CD144, and von Willebrand factor. Moreover, they are privileged cells with reduced immunogenicity; therefore, there is no expression of HLA-DR [1]. ADSCs may also be a precursor of chondrocytes, osteocytes, muscle cells, neurons, and fibroblasts as well as keratinocytes under proper conditions. However, their most important function is the stimulation of surrounding cells to differentiate into specialized cells under the influence of certain growth factors [2]. It has been shown that the ADSCs are even necessary for the activation of epidermal stem cells in the skin. Their exogenous administration mobilizes other stem cells, including the stem cells of the epidermis from the “bulge” region of the hair follicle. This action is based on the production of growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF- β), hepatocyte growth factor (HGF), transforming growth factor (TGF- β), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), stromal factor 1-alpha, and cytokines, such as IL-6, 8, 11, 12, and TGF- α . This paracrine secretion of cytokines explains their high concentrations in obese patients [3]. ADSCs also inhibit the production of proinflammatory cytokines, enhance the production of anti-inflammatory IL-10, and stimulate the regulatory T cells. They also stimulate angiogenesis by differentiation in endothelial cells. ADSCs can protect against apoptosis, which offers great opportunities for their use in regenerative medicine [4]. Expression of the receptor for PDGF and CD10 is constant, regardless of the number of passages. Traktuev et al. showed that cells with the CD34+/CD31 phenotype have the ability to stabilize the endothelial network in vitro and stabilize neovascularization in vivo. In addition, perivascular ADSCs (CD146+) also function as a niche for hematopoietic stem cells in vitro [5].

Methodology: Out of the particular interest is platelet-derived growth factor-D (PDGF-D), which is secreted by the ADSCs. It is a mitogen for mesenchymal cells, which induces the transformation of cells and also accelerates tumor growth, but its role is not quite understood. Kim et al. showed that PDGF-D and PDGF receptor β are expressed in ADSCs, but PDGF-B is not. PDGF-D can increase the proliferation and migration of ADSCs for the generation of mitochondrial reactive oxygen species (MTRose) and by controlling mRNA expression of various growth factors (VEGF, FGF-1, FGF5, EGF, leukemia inhibitory factor, inhibin, and IL-11) [6]. ADSCs from this niche have ultrastructural features similar to primitive MSCs (large nucleus,

immature cytoplasmic organelles). Although Rubio et al. reported that human ADSCs can undergo malignant transformation during long passages of more than four months, five years later, the authors were not able to reproduce the phenomenon of transformation, most likely due to contamination artifacts [7]. The ADSCs have an antioxidant effect. They can capture free radicals and heat shock protein in ischemia status. Research has revealed that during the aging processes and in diabetes, the function of ADSCs is impaired.

Vitamins can affect the proliferation of ADSCs. The addition of folic acid and vitamin B12 slightly increases their activity in cell culture, while vitamin C significantly stimulates ADSCs in a dose-dependent manner. Vitamin C increases the expression of the mRNA of HGF, VEGF, bFGF, and KGF. There are some differences in the physiological and biological features of ADSCs derived from different anatomical sites. Siciliano et al. compared the characteristics of stem cells from mediastinal fat and skin. Subcutaneous ADSCs demonstrated greater proliferation and differentiation capacity, an increased IL-6 secretion, and a smaller VEGF-C than ADSCs isolated from the mediastinum. ADSCs from the mediastinum showed a higher proangiogenic potential. On the other hand, ADSCs from the visceral fat have a reduced susceptibility to apoptosis, and ADSCs from the pericardium, omentum, and groin have a different phenotype. Excessive weight has an influence on the differentiation potential and immunogenicity of ADSCs. The study by Perez et al. demonstrated that stem cells derived from murine and human nonobese sources had increased sensitivity to insulin and can inhibit lipolysis during differentiation into mature adipocytes. In contrast, cells isolated from obese patients showed an impaired uptake of glucose, insulin resistance, and less antilipolytic effect of insulin. Moreover, they released a greater amount of proinflammatory cytokines (mainly TNF- α) and showed disturbances in the production of adiponectin [8].

Interestingly, the preferred factor for proliferation, migration, and differentiation of the ADSCs is hypoxia (an oxygen concentration of 1–5%). Hypoxia induces the expression of HIF-1 α (hypoxia-inducible factor 1- α) and increases the production of growth factors, particularly VEGF, bFGF, and HGF which are involved in neovascularization. This phenomenon is observed in obesity. Local hypoxia in the adipose tissue induces the formation of free radicals (ROS) and leads to the secretion of growth factors which stimulate the formation of new blood vessels [9].

Pachon-Pena et al. have also found that obese-derived hADSCs demonstrate increased proliferation and migration capacity, but decreased lipid droplet accumulation, which is correlated with a higher expression of human leukocyte antigen- (HLA-) II, a cluster of CD106 differentiation, and a lower expression of CD29. Of interest, adipogenic differentiation modified CD106, CD49b, and HLA-ABC surface protein expression, which was dependent on the donor's BMI. Moreover, low oxygen tension increased proliferation and migration of lean but not obese hASCs, which was correlated with an altered CD36 and CD49b immunophenotypic profile [29]. Moreover, in obesity, ADSCs indicate changes in their transcriptomic profile (set of mRNA molecules present in a particular point of a cell) with a loss of plasticity, simultaneously showing an increasing similarity to the adipocyte phenotype [10].

Conclusions: Nowadays, ADSCs are used in aesthetic dermatology for skin rejuvenation, to correct wrinkles, to correct facial lipoatrophy, and even to improve erections. They are described in the treatment of perianal fistulas in Crohn's disease, bone grafts, and type 1 diabetes. However, the therapeutic use of ADSCs is still experimental.

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TREATMENT OF NON-HEALING SKIN WOUNDS WITH USAGE OF ADIPOSE-DERIVED STEM CELLS

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ABSTRACT

The promising results derived from the use of adipose-derived stem cells (ADSCs) in many diseases are a subject of observation in preclinical studies. ADSCs seem to be the ideal cell population for the use in regenerative medicine due to their easy isolation, nonimmunogenic properties, multipotential nature, possibilities for differentiation into various cell lines, and potential for angiogenesis. This article reviews the current data on the use of ADSCs in the treatment of non-healing of chronic wounds.

Introduction: Brown and white adipose tissue is a source of mesenchymal stem cells, specifically adipose-derived stem cells (ADSCs). It is an inexpensive, unlimited reservoir of stem cells. From 300 ml of adipose tissue, $2-3 \times 10^8$ ADSCs can be obtained. This is between 100 and 1000 times more than the mesenchymal stem cells from the bone marrow. In addition, they can be easily obtained with no ethical dilemmas pertaining to their use [1,2].

Methodology: Skin damage leads to debilitating effects forming wounds. A wound is defined as a disruption of the normal anatomic structure and functional integrity of the skin. Chronic or nonhealing wounds are wounds that do not progress through the normal wound healing process, resulting in an open laceration of varying degrees of severity [3]. Impaired healing is often associated with ischemia, diabetes mellitus, tumor, venous and pressure ulcers, and severe infections, and it can be the cause of reduced quality of life, disability, and even death. Therefore, wound healing remains a major challenge, and there is a need to develop treatments for improved therapy. Among the various strategies, the most promising seems to be the use of stem cells. This process remains a challenge to date and causes debilitating effects with tremendous suffering. Recent advances in tissue engineering approaches in the area of cell therapy have provided promising treatment options to meet the challenges of impaired skin wound healing [4]. The healing of the wound is a complex process, covering four mutually overlapping phases: hemostasis, inflammation, proliferation, and remodeling [5]. For the proper process to proceed, all steps must occur in the correct order and time. In many chronic wounds, the elongation inflammatory phase leads to the damage of normal tissues, the production of an excessive amount of proinflammatory cytokines, and the prolonged presence of neutrophils, which causes the degradation of the extracellular matrix (ECM) due to an increase in the secretion of matrix metalloproteinases (MMPs) [6]. The restoring the integrity of the skin involves several cell types, extracellular matrix components, and cytokines [7]. It is believed that what is physiologically responsible for the renewal of epidermal stem cells is located only in the basal layer of the epidermis. However, after damage to the skin, stem cells “bulge” in the region of the hair follicle and take additional responsibility for skin regeneration, particularly in the initial stage [8]. Cell cultures enriched with stem and progenitor cells can be administered to patients via various

methods: a direct application on the wound (e.g., as a suspension), injectable (arteriography), intravenous administration, or application of the culture on the appropriate biological scaffold. The most populous cells are the autologous progenitor cells of the epidermis. Current research is focused on bone marrow and adipose-derived stem cells being used in wound healing [9]. ADSCs are involved in the process of healing indirectly by secreting a number of growth factors (IGF, TGF- β 1, VEGF, HGF, and FGF2) with a paracrine action that activates keratinocytes and fibroblasts of the skin by stimulating the processes of neovascularization through the generation of anti-inflammatory cytokines, as well as having antioxidant and antiapoptotic effects. ADSCs release wound healing factors and can stimulate recruitment, migration, and proliferation of endogenous cells in the wound environment. The studies suggest that ASCs can affect other cell types specifically in skin tissue via the paracrine method. They may also be directly transformed into fibroblasts and keratinocytes. The first attempts at healing chronic wounds were performed using ADSCs from lipoaspirate, even without culturing in vitro. This technique is commonly used in aesthetic medicine, avoiding the manipulation that might influence their biological functioning. The simplest method is the application of a component of the adipose tissue-derived multicellular stromal vascular fraction (SVF), after enzymatic digestion and centrifugation of lipoaspirate. SVF is a heterogeneous population of MNCs that include ADSCs of the mesenchymal phenotypes (analogous to MSCs), endothelial progenitor cells (EPCs), hemopoietic progenitors, monocytes, leukocytes, and pericytes. Pericytes are the most important for angiogenesis, and they stabilize nascent blood vessels [10]. Researchers nowadays are focused on the three-dimensional (3D) culture systems of ADSCs to build multicellular constructs with an extracellular matrix (ECM) and to demonstrate better therapeutic efficacy. The study by Cerqueira et al. used human ADSCs with an extracellular matrix (ECM) as a natural tissue glue that was applied to three layers to form a 3D structure (these are known as “technique sheets”). The next step in the current research is looking for additional materials that may resemble a physiological niche for stem cells to enhance cell retention. Conditioned media for ADSCs have been reported to enhance angiogenesis, enhance epithelialization, and affect recruitment or proliferation of macrophages and endothelial progenitor cells during the healing process.

Conclusion: Based of various studies, the best wound healing is achieved by using ADSCs with platelet-rich plasma (PRP). On the other hand, higher concentrations of PRP in vitro culture can slow down the rate of regeneration due to proteolytic enzymes (PRP-collagenase, elastase, and cathepsin) which inhibit cell growth. The best results have been achieved after using a maximum 10% PRP. Healing of chronic cutaneous wounds and ulcers is troublesome and may require the use of skin substitutes. Adipose-derived stem cells have immense potential as an autologous cell source for treating wounds and regenerating skin,

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TREATMENT OF VITILIGO AND ALOPECIA WITH USAGE OF ADIPOSE-DERIVED STEM CELLS

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There are promising research outcomes of the use of adipose-derived stem cells (ADSCs) in many diseases are a subject of observation in preclinical studies. ADSCs seem to be the ideal cell population for the use in regenerative medicine due to their easy isolation, nonimmunogenic properties, multipotential nature, possibilities for differentiation into various cell lines, and potential for angiogenesis. This article reviews the current data on the use of ADSCs in the treatment of vitiligo and various types of hair loss.

Introduction: Bone marrow adipose tissue is a source of mesenchymal stem cells, specifically adipose-derived stem cells (ADSCs). It is an inexpensive, unlimited reservoir of stem cells. From 300 ml of adipose tissue, $2-3 \times 10^8$ ADSCs can be obtained. This is between 100 and 1000 times more than the mesenchymal stem cells from the bone marrow [1–3]. ADSCs are heterogeneous, no specific marker for them has been identified, and the location of stem cells in adipose tissue is difficult to determine. However, most of them occur in the perivascular regions. The morphology of ADSCs resemble fibroblasts, consisting of a large endoplasmic reticulum and nuclei [4-5].

Methodology: The Skin Depigmentation-Vitiligo is a disorder caused by the loss of melanocytes. Repigmentation of vitiligo depends on available melanocytes from three possible sources: from the hair follicle unit which is the main provider of pigment cells, from the border of vitiligo lesions, and from unaffected melanocytes within depigmented areas. Melanocytes rarely undergo mitosis without growth factors; therefore, mitogenic factors are used in transplantation treatments [6].

ADSCs can be a source of growth factors for melanocytes cultured in the presence of keratinocytes. Lim et al. showed efficacy in mice and Sprague-Dawley rats after administration of human melanocytes alone or enriched with human ADSCs. Better results have been shown with a coadministration of melanocytes and ADSCs, which were grown separately and then mixed in a ratio of 1 : 1, 1 : 2, or 1 : 3, as compared to the administration of pure melanocytes alone [7].

Although the interaction between ADSCs and melanocytes are well known, in the study of Kim et al., an increase in the secretion of HGF by ADSCs after prior exposure to bFGF or EGF was demonstrated. They showed that the proliferation and migration of melanocytes were significantly stimulated by coculturing the ADSCs in comparison with monoculture melanocytes. This may be related to the presence of bFGF and melanocyte growth factor (MGF) produced by ADSCs. The ratio of melanocytes with positive expression of TRP-2, E-cadherin, and N-cadherin were significantly increased in the cocultures with ADSCs compared to keratinocyte and melanocyte monocultures. Melanocytes with a positive expression of TRP-2 (tautomerase dopachrome) are considered to be melanocyte precursors, but TRP-1 positive is considered to be diverse and mature. This is an important result, because the greater the number of immature melanocytes, the better clinical outcomes. In addition, cadherin-calcium-dependent cell adhesion receptors take part in cell-cell interactions. E-cadherin determines the adhesion between keratinocytes and

melanocytes, and N-cadherin facilitates the contact between fibroblasts and melanocytes. They also play a role in the differentiation of melanocytes. These studies have confirmed that cultures with ADSCs increase the proliferation and migration of melanocytes, while reducing their differentiation.

Skin depigmentation-Alopecia Multipotent stem cells can regenerate hair follicles and sebaceous glands in the skin. The stem cells can be used to regenerate hair growth in a number of therapeutic methods:(i)the reversal of pathological mechanisms that contributes to hair loss (androgenetic alopecia);(ii)complete regeneration of hair follicles with “bulge”;(iii)neogenesis of hair follicles with a stem cell culture.

Hair follicles are surrounded by subcutaneous fat cells and skin, which make up the interfollicular dermal macroenvironment, important in maintaining normal cell growth in the region bulges and hair follicles. ADSCs are necessary for the activation of epidermal stem cells. Their action is based primarily on the secretion of growth factors, such as VEGF which regulates hair growth and the size of the hair follicle by stimulating angiogenesis, HGF which is engaged in the length of the phases of the hair cycle, PDGF which induces and maintains the anagen phase, and IGF-1 which controls the cycle of hair growth and hair cell differentiation. ADSCs stimulate angiogenesis and enhance blood supply to the hair papilla cells. They also have immunomodulatory and immunosuppressive effects through direct interactions between the cells and secrete prostaglandin E2 (PGE2), leukemia inhibitory factor (LIF), and kynurenine. Huang et al. studied the effect of ADSCs on papilla cells of the hair. During the cell culture, the hair retained its own markers. After adding ADSCs (isolated from rats), characteristics common to coculture were observed. There were mixed papilla and medulla cells with ADSCs. The core and the inner shell of the outer coat also contained ADSCs. The best results were achieved in the second cocultures [8]. It was also shown that subcutaneous adipose tissue played an important role in the extension of the anagen phase. There was a proliferation of progenitor cells, which were adipocytes in the transition from the telogen phase to the anagen phase of the hair follicle. The layer thickness of subcutaneous adipocytes during active hair growth (anagen) increased significantly compared to their amount in the resting phase (telogen). ADSCs stimulated hair follicle cells via peroxisome proliferator-activated receptor, which has been detected in three isoforms (PPAR α , PPAR γ , and PPAR δ). In contrast, mature adipocytes have a negative effect on the proliferation of hair follicles, as well as the proliferation of fibroblasts surrounding the follicle in the cocultures. Changing the properties of the adipocyte cell lines may cause skin and hair disorders. Lipid metabolism may lead to defects in the structure of the skin and its functions. Overexpression of human apolipoprotein C1 (APOC1) with hyperlipidemia in transgenic mice results in abnormal hair growth correlated with the expression of the human APOC1 gene in the skin. Musina et al. assessed the influence of hypoxia as a stimulating factor for ADSCs to secrete growth factors. Subcutaneous injection induces the anagen phase in mice, as well as increases the proliferation of human follicular cells, keratinocytes, and hair papillae. Under the influence of hypoxia, there is an increased secretion of insulin-like growth factor binding protein- (IGFBP-) 1 and 2, M-CSF, M-CSF receptor, PDGF- β , VEGF, and decreased EGF secretion. Unfortunately, the studies proved that the two-dimensional (2D) culture of the papilla cells lose their ability to form the hair (trichogenicity) and require a spheroidal form (3D) in culture [9,10].

Conclusions: ADSCs appear as the ideal cell population for the use in regenerative medicine:they are unlimited in supply and easily obtainable from adipose tissue; they are autologous, nonimmunogenic cells;they have a multipotential nature and easily differentiable into various cell

lines; they have a significant potential of angiogenesis; they can be easily cultured and have high affinity for 3D scaffolds.

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Stomatology & Dentistry
Innovations in Medicine
Biophysics and Biochemistry
Radiology and Microbiology
Molecular Biology and Genetics
Botany and Virology
Microbiology and Hydrobiology
Physiology of Plants, Animals and Humans
Ecology, Immunology and Biotechnology
Virology and Immunology
History of Biology
Entomology

COMPUTING AND APPLIED SCIENCES

History of Science and Technics
Information, Computing and Automation
Innovative Technologies
Mathematics & Applied Mathematics

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Economy and Management of a National Economy
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Accounting, Analysis and Auditing
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Demography, Labor Economics
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Branches of Law
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Proceedings of Energy Economic Research Center. ENECO
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DOI PREFIX: 10.36962/ETM
ETM Equipment, Technologies, Materials
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