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ASSISTED REPRODUCTIVE TECHNOLOGIES IN CENTERS FOR BIOMEDICAL ASSISTED FERTILIZATION WITHIN AND OUTSIDE THE NETWORK PLANS IN THE REPUBLIC OF SERBIA AND THEIR FINANCING

Biljana Đorđević

FAKULTET ORGANIZACIONIH NAUKA, UNIVERZITET U BEOGRADU

ABSTRACT: INTRODUCTION: Assisted reproduction technologies (ART) are technologies that are used today, in the treatment of infertility, on human germ cells (oocytes and sperm) and embryos. Currently in the Republic of Serbia, there are various procedures of assisted reproduction technologies that are used to treat infertility in patients depending on medical indications. The availability of assisted reproduction technologies has been evolving over the years, and their application differs in biomedically assisted fertilization centers that are in the Network Plan (state institutions) and outside the Network Plan (private institutions). The aim of this article is to analyze available ART methods in Fertility centers within and outside the Network plan regulated by the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization (Official Gazette of the Republic of Serbia", No. 72/2009), their financing and availability to patients in the Republic of Serbia. **METHOD**:This article is assembled upon seeking documents using the Internet and based on analyzed literature available on the Internet. **RESULTS:** The results were gathered by analyzing official ART centers' websites and analyzing available external secondary data from the National health insurance fund and the Institute for public health "Dr Milan Jovanovic Batut". Fertility clinics in the Republic of Serbia have access to all the important technologies for ART. ART technologies funded by National health insurance fund include in vitro fertilitation, intracytoplasmic sperm injection and frozen embryo transfer. Patients whose medical indications require for some other technology may approach Fertility Centers outside the Network plan on their own budget. **CONCLUSION:** Based on the available and updated data we can conclude that Fertility centers in the Republic of Serbia have access to all the important technologies for ART. Fertility centers within the Network plan can implement only the technologies financed and invoiced by the Fund.

KEY WORDS: infertility, biomedical assisted fertilization centers/Srbija, Assisted reproduction technologies , Fertilization in vitro, frozen embryo transfer, preimplantation genetic diagnosis.

INTRODUCTION

Assisted reproduction technologies are technologies that are applied today, in the treatment of infertility, on human germ cells and embryos. Currently in the Republic of Serbia, there are various procedures of assisted reproduction technologies that are used to treat infertility in patients depending on medical indications. The availability of assisted reproduction technologies has evolved over the years, and their application differs in biomedically assisted fertilization centers that are in the Network Plan (state institutions) and outside the Network Plan (private institutions). Assisted reproductive technology (ART) is a group of state-of-the-art therapeutic procedures for the treatment of infertility [1].

Assisted reproductive technologies

ART refers to all technologies used to manipulate gametes outside of the human body. Those most commonly used are in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). They do not include technologies such as intrauterine insemination (IUI) that manipulates only male gametes [2]. Innovative technologies that increase the success rate have also been developed. Some of them are in vitro maturation (IVM), preimplantation genetic diagnosis (PGD), sperm and oocyte donation (SD, OD) [3], frozen embryo transfer (FET) procedure and assisted hatching (AH).

Medical indications for different assisted reproductive technologies

In vitro fertilization (IVF) is an assisted reproductive technology that may be applied only to patients whose spermogramme shows normospermia. Cultivated sample is then laid among the egg cells and fertilization occurs alone. Medical indications for IVF require for the male patient's sample to show normospermia [4], and

indications for the female patient require blocked Fallopian tubes, ovulation problems, endometriosis [5] and genetic diseases that result in miscarriage [2].

Intracytoplasmic sperm injection –ICSI is a technology of micromanipulation where one sperm is injected in the egg cell cytoplasm, thus fertilizing it. Medical indications for ICSI are mostly connected to male infertility, as well as patients who haven't achieved fertilization through IVF [5]. Male infertility comprises oligospermia, asthenospermia, teratospermia, obstructive and non-obstructive azoospermia, when sperms are collected surgically (PESA – percutaneous epididymal sperm aspiration, TESA / TESE – testicular sperm aspiration / extraction). In the case of the presence of antispermatozoal antibodies in both partners, the ICSI method is performed, and after thawing frozen seed samples, the microfertilization method is also applied [2].

Frozen embryo transfer (FET) is an embryo transfer obtained in one of the previous procedures by the classical IVF or ICSI method, followed by frozen vitrification processes. In the FET process, the embryos are thawed and returned to the previously prepared substance. Advantages of FET procedure lie in the fact that the excess embryos from IVF procedures is frozen and then transferred in successive cycles, which enables high cumulative rate of in vitro fertilization [6].

In vitro maturation – IVM is a cycle in which egg cells are gathered from antral follicles of unstimulated or mildly stimulated ovaries. Immature ova are gathered, and the last phase of their maturation is done under laboratory conditions. Medical indications for IVM cycles include patients with polycystic ovary syndromes (PCOS) so as to decrease the risk of ovarian hyperstimulation [7]. In patients with estrogen-dependent cancers (oncology patients), stimulated cycles with standard ovulation stimulation protocols are avoided because they stimulate follicle growth and stimulate estrogen production, so eggs are collected from antral follicles of unstimulated ovaries.

Preimplantation genetic diagnosis – PGD is a micromanipulation technology done by biopsying several embryo cells 5-6 days old, followed by analyzing genetic material of biopsied cells. Medical indication for PGD includes patients with high risk of passing down hereditary diseases to child, patients with repeated miscarriages and patients above 38 years of age with risk of aneuploidy.

Assisted haching – AH is a micromanipulation technology by which zona pellucidia on embryo is pierced so as to facilitate its release, which increases implantation, as well as pregnancy rates. Medical indications include multiple failed in vitro procedures, as well as multiple failed transfers of frozen embryos.

Frozen oocyte replacement – FORs [8] are cycles which use frozen ova (Oocyte cryopreservation – OoC) [9].

Oocyte donation (OD) represents inseminating ova of the female donor with sperms taken from a male partner. The child's genetics comes from the male partner. Medical indications for oocyte donation include premature ovarian failure (POF), poor quality of ova and oncologically treated patients.

Sperm donation (SD) represents inseminatinf ova from a female partner with sperms coming from a donor. Medical indications for sperm donation are azoospermia, or other sperm abnormalities.

ART financing

Public financing among countries is available for an entire series of reproductive technologies, including IVM, PGD, AH, OD, SD. Seven countries (Denmark, France, Slovenia, Sweden and the UK (England, Scotland, Wales) fullyor partially finance IVM trhough national health programs. Twenty-two countries (Australia, Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Finland, France, Greece, Hungary, Israel, Italy, Latvia, New Zealand, Norway, Russia, Spain, Sweden, the UK (England, Scotland, Wales) fully or partially finance PGD through their national health programs. There is no documented evidence that the AH expenses are paid through public financing, and there is no documented evidence that the expenses sperm or ovum donation for in vitro are paid through national financing program [3].

ART financed by the National health insurance fund is done in Fertility centers from the Network plan and there are no other options for technologies that cannot be invoiced through National health insurance fund's forms [10]. Technologies such as IVF and ICSI were funded until 2017, and ever since then the National health insurance fund has financed new technologies, such as FER procedure, as well [11,12]. Fertility centers outside the Network plan offer some other mentioned ART

technologies apart from IVF and ICSI that are financed by patients themselves.

According to Article 23 of the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization, ("Official Gazette of the Republic of Serbia", No. 40/2017 and 113/2017, etc.), a Fertility Center must keep medical records sent to the biomedicine Board. Those records delivered to the Board for biomedicine include data on all ART technologies. Those forms are delivered to the Board for biomedicine, stating which technologies have been used in ART procedures and this is recorded in the state register.

The aim of this article is to analyze available ART methods in Fertility Centers within and outside the Network plan regulated by the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization (Official Gazette of the Republic of Serbia", No. 72/2009), their financing and availability to patients in the Republic of Serbia.

MATERIAL AND METHODS

This article is assembled upon seeking documents using the Internet and based on analyzed literature available on the Internet. The results were gathered by analyzing official ART centers' websites and analyzing available external secondary data from the National health insurance fund and the Institute for public health "Dr Milan Jovanovic Batut".

RESULTS

Fetility Centers with whom the National health insurance fund has concluded the contract on providing infertility treatments are:

- Fertility Centers within the Network plan:

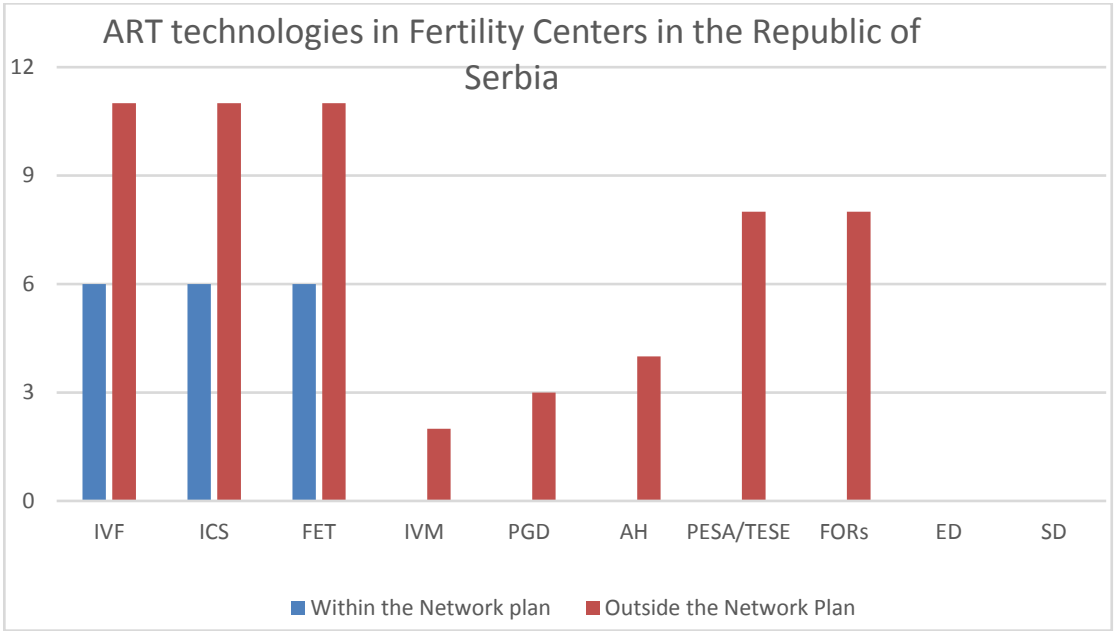
1. Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, Belgrade
2. Gynecology and Obstetrics Clinic, Clinical Centre of Vojvodina, Novi Sad
3. Obstetrics and Gynecology Clinic, Clinical Centre of Nis, Nis
4. Obstetrics and Gynecology Clinic "Narodni Front", Belgrade
5. Gynecology and Obstetrics Center, General Hospital of Valjevo, Valjevo
6. Clinic of Gynecology and Obstetrics, Clinical Center of Kragujevac, Kragujevac

- Fertility Centers outside the Network plan:

1. Special Gynecological Hospital for Treatment of Infertility "Nikolov", Kragujevac
2. Special Hospital for Infertility Treatment "Spebo Medical", Leskovac
3. Speical Hospital for Gynecology "Perinatal", Novi Sad
4. "Ferona" IVF Clinic, Novi Sad
5. Special Hospital for Gynecology "GINS", Novi Sad
6. Special Gynecological Hospital "Genesis", Novi Sad
7. Special Gynecological Hospital "Teofanović", Belgrade
8. Special Gynecological Hospital "Beograd", Belgrade
9. Special Gynecology Hospital with Maternity Ward "Jevremova", Belgrade
10. General Hospital "Analife", Belgrade
11. Special Hospital for Infertility Treatment "Intermedicus Bis", Belgrade

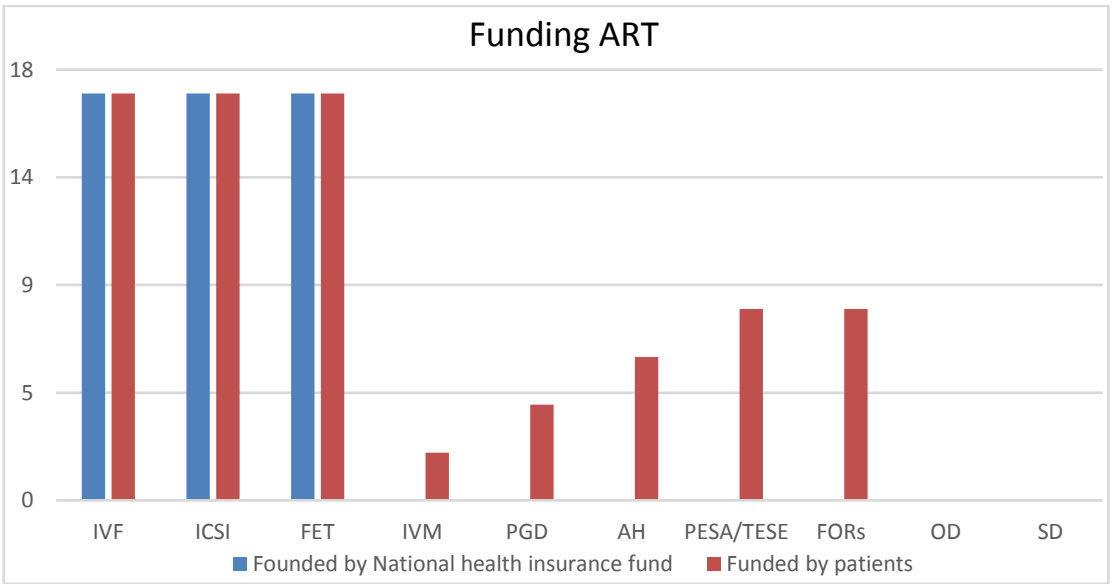
Fertility Centers in the Republic of Serbia have access to all the important technologies for ART. ART technologies available in Fertility Centers within and outside the Network plan are displayed on Chart 1.

Chart 1. ART technologies available in Fertility Centers within and outside the Network plan in the Republic of Serbia



ART technologies funded by National health insurance fund include in vitro fertilitation, intracytoplasmic sperm injection and frozen embryo transfer. Patients whose medical indications require for some other technology may approach Fertility Centers outside the Network plan on their own budget (Chart 2).

Chart 2. ART technologies funded by National health insurance fund and funded by patients



DISCUSSION

Additional challenges for couples in our country are weakness of the so-called National System for the implementation of ART procedures. Such problems are relatively numerous. They concern the assembling necessary diagnostic analyses and documentation for eligibility and criteria needed

for the onset of the procedure. Frequent inadequate equipment of institutions and expertise of staff that provide services during the BMPO procedure, lack of application of the most modern methods and procedures of reproductive medical science, as well as the existence of a relatively long waiting period for the procedure itself. The time dimension is extremely important here, taking into account that the patient's age is extremely important for the success of fertilization [13].

Earliest found data in the Republic of Serbia date from 2004, where eight private clinics are mentioned and their internal documentation could not be obtained. In Serbia, ART was only done on Clinic for Gynecology and Obstetrics of the Clinical Centre of Serbia. Summary annual reports show that the number of treatments varied and it probable depends on the (under)development of technology, but also on the social and economic factors. These data show that the number of ART in public institutions, compared to the number of started cycles in Serbia for the year of 2000, amounted to 178 started cycles; 296 started cycles for the year of 2001; 174 started cycles for the year 2002; and 149 started cycles for the year of 2003. A very expensive ART procedure in Serbia was financed by couples themselves [1].

National health insurance fund has financed infertility treatments by Biomedical Assisted Fertilization procedures since 2006, according to indications prescribed by Natinonal Expert Commission of the Ministry of Health of the Republic of Serbia. Between 2009 and 2013, The Ministry of Health has passed the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization (Official Gazette of the Republic of Serbia", No. 72/2009), as well as a series of bylaws that regulate this area. As the existing capacities of medical institutions within the Network plan are not enough to meet the needs of all insured individuals, National health insurance fund has concluded contracts for administering mentioned services with private medical institutions on several occasions [14].

In the year of 2013, there were 634 second phases of assisted IVF fertilizations done in Serbia, accompanied by 1,105 ICSI procedures [15]. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia in 2013, the right to infertility treatment financed by the Fund (based on invoiced services of National health insurance fund) was granted to 2055 patients, 1659 of which in Fertility Centers within the Network plan (925 IVF and 734 ICSI) and 396 in private BAF Centers outside the Network plan mreže (25 IVF and 371 ICSI). Frozen embryo transfer was not financed by the Fund, so patients financed the procedure themselves in Fertility Centers outside the Network plan, of which there are no accurate data.

The total of 933 second phases of assisted fertilizations by IVF method were done in 106, followed by 1,474 ICSI methods and 140 frozen embryo transfers [11]. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia in 2016, the right to infertility treatment financed by the Fund (based on invoiced services of National health insurance fund) was granted to 2407 patients, 1,529 of which in Fertility Centers within the Network plan (854 IVF and 675 ICSI) and 878 (79 IVF and 799 ICSI) in private Fertility Centers outside the Network plan. Frozen embryo transfer also came to be funded, so there were 140 invoices from patients, 5 of which in Fertility Centers within the Network plan and 135 in private ART centers.

There were 712 second phases of assisted fertilizations by IVF method done in 2017, followed by 2,396 by ICSI method and 445 frozen embryo transfers [12]. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia in 2017, the right to infertility treatment financed by the Fund (based on invoiced services of National health insurance fund) was granted to 4064 patients, 956 of which in Fertility Centers within the Network plan (634 IVF and 322 ICSI) and 3,108 (712 IVF and 2,396 ICSI) in private Fertility Centers outside the Network plan. Frozen embryo transfer also came to be funded, so there were 445 patients, 5 of which in Fertility Centers within the Network plan and 440 in private Fertility Centers.

CONCLUSION

Based on the available and updated data we can conclude that Fertility Centers in the Republic of Serbia have access to all the important technologies for ART. Fertility centers within the Network plan can implement only the technologies financed and invoiced by the Fund.

Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia, it is evident that the number of invoiced ICSI cycles is significantly larger in Fertility Centers outside the Network plan, which shows that patients with graver medical indications are referred to private clinics. Thus for example patients with medical indications for azoospermia do not have possibility of treatment in Fertility centers within the Network plan, only in Fertility centers outside the Network plan that are financed by patients themselves. Moreover, the higher number of available ART technologies may be one of the reasons for the significant growth of services provided in private medical institutions.

P.S. A question arises as to why the lawfully granted oocyte and sperm donation services are not available neither in Fertility Centers within, nor outside the Network plan. If Fertility Centers within the Network plan are not equipped, why aren't these services available in Fertility Centers outside the Network plan?

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Vol. 46 (2021) No. 1 TIMOK MEDICAL GAZETTE Review article

GASTROENTEROCARDIOLOGY–OR WHAT DO THE GUT AND THE HEART HAVE IN COMMON?

Zoran Joksimović (1), Dušan Bastać (2), Snežana Pavlović (3)

(1) INTERNISTIČKA ORDINACIJA „JOKSIMOVIĆ" BOR; (2) INTERNISTIČKA ORDINACIJA „DR BASTAĆ" ZAJEČAR; (3) SPECIJALISTIČKA ORDINACIJA ZA INTERNU MEDICINU „DR PAVLOVIĆ KARDIOLOGIJA" BEOGRAD

Summary: The gut microbiota of our organism is a community of bacteria, archaea, fungi, viruses and parasites that make up a unique ecosystem in the digestive tract, which consists of about 1014 microorganisms. The diversity of this community between individuals occurs because of the differences in the host genome and the impact of environmental factors, including hygiene, diet, lifestyle and the use of different drugs. Significant evidence suggests that changes in the microbiota could play a role in cardiovascular diseases. The results of research papers for the last two decades have confirmed that altered gut microbiota composition (dysbiosis) contributes to the development of various diseases, including cardiovascular diseases, type 2 diabetes, chronic kidney disease, nonalcoholic fatty liver disease, chronic inflammatory bowel disease and even certain types of cancer. There is growing evidence that in the future, apart from current predisposing factors for cardiovascular and metabolic diseases, including genetic, environmental and lifestyle factors, one should count on new risk factors such as nutritional disproportion and gut dysbiosis. Thus, we look upon the relationship between the gastrointestinal tract and cardiovascular system, i.e. the "gut-heart axis" in a new way.

Key words: intestinal microbiota, nutritional disproportion, dysbiosis, cardiovascular diseases, metabolic disorders

Introduction

The study of the human gut microbiota and its role in various diseases has advanced significantly in the last decade. The human microbiota consists of all microorganisms that live in a symbiosis with the human body, while the microbiome represents the sum of all genes of the microbiota.

The human microbiome contains up to 100 times more genes than the human genome.Microorganisms can be found in various parts of the human body,but the most numerous is the microbiota of the digestive organs. The microbiota is variable among healthy people but it is also unique for an individual – no two microbiomes are the same in humans, just as there are no the same fingerprints. Although there are no two people with the same composition of the microbiota, however, there are larger similarities in the composition of microbiota among the members of the same races, ethnic groups and blood relatives.Gut microbiota is a collection of approximately 1014microorganisms. The number of bacteria in every human being is larger than the number of people who have ever lived on earth.It is a community ten times more numerous than all the cells of our organism. It consists of bacteria (about 1000 different species), archaea, fungi, viruses and parasites that make up a unique ecosystem. The microbiota plays a very important role in human health. It is of utmost importance for maintaining the homeostatic functions of the gastrointestinal tract, as it participates in digestion processes of the host, metabolism and regulation of the gut immune system. [1,2]. After birth, the digestive tract of the newborn is not inhabited by microorganisms. In the first hours of life, it is colonized by maternal microorganisms, initially coliform bacteria and streptococci, later lactobacilli and enterococci, and the number of microorganisms in the gut tract begins to increase, gradually forming a dynamic balance of the gut microbiota. Of course, the growth of these bacteria also depends on the method of birth - natural or by caesarean section [3]. In adulthood, most of the gut microbiota consists of five groups of microbes, namely: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia. The number of Gram-

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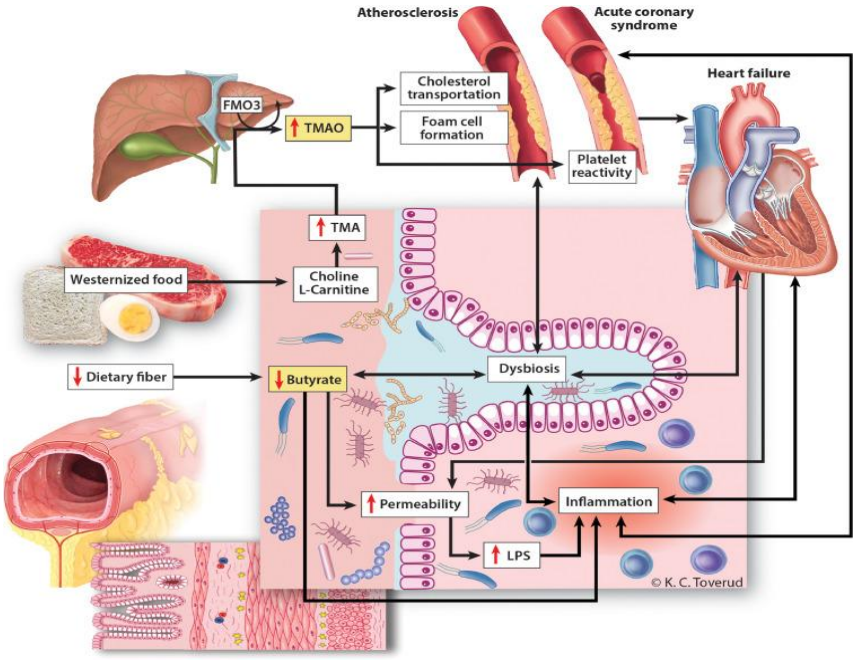
positiveFirmicutesand Gram-negative Bacteroidetesthat make up the most species in a healthy adult gut> 90% (4-5) is approximately proportional.The ratio between Firmicutes and Bacteroidetes remains relatively constant in a healthy individual although it is not the same in all individuals. The differences occur because of the difference in the host genomes, environmental factors as hygiene, diet, lifestyle and use of antibiotics [4]. Due to the acidic environment and intense peristalsis, fewer microorganisms (10–1000 / ml),most of which are Gram-positive bacteria, are present in the stomach and duodenum. Enterococci and Lactobacilli are present in the duodenum, and the number of bacteria in this area is usually 104 / ml. The colon, which is predominantly inhabited by gram-negative and anaerobic bacteria, is the richest in the number and variety of species (1012/ ml) [5].

It hasn't been fully clarified what a healthy microbiota actually is, but it has been shown that in the case of disturbed balance - dysbiosis, a disease can develop. When eating habits, environmental factors, gut infection, some drugs or other factors lead to changes in the type and amount of gut microorganisms, there occursgut dysbiosis, which causes inflammatory and metabolic disorders. Homeostasis of the gut microbiota is crucial for maintaining health in human beings, while dysbiosis contributes to the development of various diseases, including cardiovascular, chronic kidney disease, type 2 diabetes, nonalcoholic fatty liver, and even some types of cancer [1,6,7]. Gut dysbiosis may explain why some individuals are more prone to developing certain diseases. Changes in the composition of the microbiota have recently been identified as an important factor in the dysfunction of the "gut-heart axis", which contributes to the development of atherosclerosis and hypertension - two main risk factors for the development of cardiovascular diseases [1,7,8].

Picture 1. Influence of Intestinal Dysbiosis on Cardiovascular Diseases (taken from https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30024-4/fulltext for scientific purposes and not used for commercial purposes)



The gut microbiota can be considered an endocrine organ, and each microbe has the ability to produce hundreds of different known and unknown metabolites that act beyond the gut itself. As most of the bacteria that inhabit the digestive organs cannot be colonized in the laboratory at the moment, for the purpose of determining the composition of the microbiotanext-generation sequencing method and bioinformatics analysis of extracted microbial deoxyribonucleic acid (DNA) are used.In recent years, the impact of the

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composition of microbiota on various chronic and autoimmune diseases has been studied, especially in animal trials [3,8]. These trials demonstrate the importance of the microbiota in relation to health and immunity and offer new, as yet undiscovered possibilities for the use of this knowledge in the treatment of some other diseases, such as metabolic syndrome, insulin resistance, chronic inflammatory bowel disease, cancer [1,6,9].

Gut dysbiosis andatherosclerosis

Atherosclerosis is the main risk factor for cardiovascular diseases. This process is characterized by the accumulation of cholesterol and macrophages (inflammatory cells) in the vascular walls, which contributes to the formation of atherosclerotic plaques.Recent studies have shown that gut dysbiosis can contribute to the development of atherosclerosis by modulating inflammatory processes and by forming certain microbial metabolites (10-15). Integrity of the gut mucosa is the first barrier that protects the host from the intrusion of pathogens, the passage of intestinal contents and bacterial components into the blood vessels. Reduced concentrations of proteins that ensure close cell contacts and their impermeability, including zonula occludens-1 (ZO-1) also known as Tight junction protein-1 (TJP1), claudin 1, and occludin, allow increased permeability of the gut wall by disrupting the balance between mucosal cell death and regeneration of the mucosal cells [1,13,14]. If the mucous barrier is damaged, the penetration of microbes and their products into the blood vessels triggers an immune response, tissue and systemic inflammation. Impairment of the gut barrier integrity caused by gut dysbiosis, therefore, acts as a risk factor that triggers a chronic inflammation that underlies various diseases, including atherosclerosis. The main molecules-products of bacteria that are the drivers of the immune and inflammatory response are ''Pathogen-associated molecular pattern''- PAMP. PAMPs activate the innate immune response, protecting the host from infection. A wide range of different types of molecules can serve as PAMP, including glycans and glycoconjugates. Bacterial lipopolysaccharides (LPS), endotoxins found on cell membranes of Gram-negative bacteria, are considered a prototype class of PAMP.The relationship between plasma LPS levels and cardiovascular risk was first studied in 1999 by Niebauer et al. [15]. The results of the study confirmed that the level of endotoxemia was the highest in patients with the most severe cardiovascular disease. Cani et al. confirmed in their study that gut dysbiosis prevented the formation of "close contact proteins", which resulted in increased permeability of gut mucosa, and thus the passage of LPS into the blood [16]. LPS, which are produced in increased amounts in intestinal dysbiosis, can play an important role in modulating "toll-like receptors (TLRs)" which recognize bacterial products and regulate the host's immune system. TLRs are a class of proteins that play a key role in the innate immune system. They are single-pass transmembrane receptors commonly found on sentinel cells (first-line defense cells) such as macrophages and dendritic cells, which recognize structurally conserved molecules derived from microbes. Once microbes break through physical barriers such as the skin or lining of the gut tract, they are recognized by TLRs that activate immune cell responses.Clinical studies have shown that an increase in TLR is associated with anti-inflammatory activity and promotes the development of atherosclerosis in humans. The results of these studies in recent years thus confirm the role and importance of gut microbiota and dysbiosis as risk factors in the development of atherosclerosis [8,9,10,17].

In the metabolism of gut bacteria, various metabolites that participate in the development of atherosclerosis are formed. Among the most important are various amines, methylamines, polyamines, short-chain fatty acids, trimethylamine and secondary bile acids. In particular, short-chain fatty acids (SCFA) are a group of intestinal microbial metabolites that are important for metabolic diseases. Studies have shown that the intestinal microbiota is involved in the formation of trimethylamine N-oxide (TMAO) [8,14]. Trimethylamine (TMA) is a by-product of bacterial metabolism that is absorbed into the bloodstream and converted to TMAO in the liver by specific liver enzymes, flavin-containing monooxygenases. Different bacterial compositions naturally have different abilities to form TMAO. Studies in mice have confirmed that TMAO accelerates the development of atherosclerosis by stimulating cholesterol influx, inhibiting cholesterol excretion, inhibiting secondary bile acid metabolism, and / or by excessive platelet activation [3,8,10]. According to researchers,

apart from the role of a biological marker for atherosclerosis and cardiovascular diseases, TMAO could also represent a possible therapeutic goal in the future. Interestingly, inhibitors of TMAO production have been developed that target various microbial TMA lyases. These drugs reduce TMAO levels and reverse atherosclerosis in animal models. TMA lyase has become the current potential therapeutic target of TMAO modulation [18].

Gut microbiota and hypertension

Apart from dyslipidemia and atherosclerosis, hypertension is another major risk factor for CVD that is genetically sensitive and influenced by environmental factors [19]. As early as 1982, it was shown that antibiotic treatment could cause higher blood pressure [15]. On the other hand, a number of studies showed that antibiotic use had a beneficial effect on blood pressure. These data, as well as the observed relationship between dysbiosis and cerebrovascular events, indirectly suggested a relationship between the gut microbiota and hypertension as assessed in recent studies. [20,21]. Furthermore, in spontaneously hypertensive rats, a significant decrease in the number and diversity of microbes in the gut and a decrease in the number of cecal "good bacteria" from the species Bacteroidetes was documented, which was accompanied by a proportional increase in the number of "bad bacteria" from the species Firmicutes.The studies have also shown that transplantation of cecal microbiological content from hypertensive animal donors can reproduce hypertension in previously normotensive animals [22]. In a study on mice, it was shown that dysbiosis of the gut microbiota can cause angiotensin-II-induced vascular dysfunction and hypertension. As another study found, the absence of gut microbiota protects mice from angiotensin II-induced arterial hypertension, vascular dysfunction, and end-organ damage caused by hypertension [23,24].

Thus, it is obvious that the gut microbiota is involved in the development or worsening of hypertension. Although the exact underlying mechanisms and the relationship between the gut microbiota and hypertension have not been established, existing evidence from animal trials and clinical studies highlights the role of short-chain fatty acids - SCFA and oxidized low-density lipoprotein (ox-LDL) in the development of hypertension. Short-chain fatty acids, such as acetate, proprionate, and butyrate, are formed mainly from soluble dietary fiber polysaccharides [23]. The groups of microbes in the gut that metabolize polysaccharides to different types of SCFA are specific. The main acetate-producing bacteria are Streptococcus, Prevotella, Bifidobacterium, Clostridiums, and A. Muciniphila [25]. Propionates are produced by Bacteroides, Salmonella, Dialister, Veillonella, Roseburia, Coprococcus, Blautia, and others. [26]. Butyrates areproduced by Lachnospiraceae, Ruminococcaci Acid amino coccaceae [27]. Fiber and acetate supplementation led to an increase in the number of Bacteroides acidifaciens and was associated with improved gut dysbiosis, hypertension, and heart failure in hypertensive mice [28]. Too many butyrate-producing bacteria have been associated with elevated systolic and diastolic blood pressure in pregnant women [29]. G protein-coupled receptors (GPCRs) are receptors on the cell surface that detect SCFA molecules outside the cell and activate cellular responses. The three GPCRs regulated by SCFA are: GPR41, GPR43, and GPR109A [30]. SCFAs stimulate GPCR-regulated pathways to affect the renin-angiotensin system to modulate blood pressure. Olfactory receptor 78 (Olfr78) is another type of GPCR expressed in the kidney that detects SCFA [31]. Both Olfr78 and GPR41 are expressed in smooth muscle cells ofsmall-diameter blood vessels. In another study, stimulation of GPR41 resulted in a reduction in the hypotensive response [32]. SCFA, propionate induces vasodilation and produces an acute hypotensive response in mice by modulating the activity of Olfr78 and GPR41 [33]. All these findings reveal that the gut microbiota plays an important role in modulating blood pressure via SCFA and suggests that hypertension is associated with dysbiosis.

Apart from altered regulation of various receptors via SCFA, gut dysbiosis also contributes to hypertension by Oxidized LDL-mediated vasoconstriction [34]. Microbial dysbiosis promotes the expression of pro-inflammatory cytokines and induces oxidative stress that stimulates LDL oxidation [35]. Higher levels of oxidized LDL (Ox-LDL) reduce NO production, reduce the degree of vasodilation and stimulate the production of vasoconstrictor substances, including endothelin-1, which plays

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a crucial role in maintaining vascular tone and cardiovascular homeostasis. Disturbed balance leads to hypertension. However, the causal relationship between gut dysbiosis and hypertension is complex and has not been fully assessed. The exact role of the gut microbiota in mediating hypertension, the pathways and mechanisms involved require further detailed research.

Gut microbiota and heart failure

There is growing evidence of a connection between the gut microbiota and the pathogenesis of heart failure. In the English literature, the term "gut hypothesis of heart failure" [36-39] is used to define this connection. This hypothesis explains that decreased cardiac output (DCO) and increased systemic arrest can cause gut ischemia and / or edema of the gut wall, leading to increased bacterial penetration into blood vessels, thus increasing the concentration of endotoxins in the circulation. This can trigger inflammation in patients with heart failure. Exogenous factors such as diet, exposure to bacterial infections, or medication may reduce the diversity of the gut flora. Endogenous factors such as acute humoral imbalance, chronic gut congestion or ischemia-hypoxia, acid-base imbalance, impaired gastrointestinal motility, and nutritional deficiency can potentially alter the gut flora [40]. With the development of heart failure, the characteristics of the bacterial community change. Studies have shown that the number of gut flora in patients with chronic heart failure decreased, and the number of pathogenic bacteria increased significantly with the progression of the disease, including Campilobacter, Shigella, Salmonella, Yersinia enterocolitica and Candida species [41,42,43]. 16SrRNA analysis in patients with heart failure has reported a reduction in SCFA-producing bacteria, such as Eubacterium rectale and Dorea longicatena [43]. Another study showed that the composition of the gut microbiota in chronic heart failure is characterized by a decrease in the number of bacteria with the potential to produce butyrate [44]. Butyrate exerts local anti-inflammatory effects in the gut mucosa and stimulates regulatory T cells [45]. It has been observed that the number of microbiological genes for LPS biosynthesis and TMAO production is increased, while the abundance of genes for butacetate acetoacetate coenzyme A transferase (key enzyme for butyrate production) is reduced in chronic heart failure [41]. It was also observed that patients with heart failure and peripheral edema had higher plasma endotoxin and inflammatory cytokine levels compared with patients without edema. After short-term diuretic therapy, serum endotoxin but not cytokine concentrations [46] decreased. In another study, the researchers confirmed that patients with heart failure and reduced gut blood flow had higher serum concentrations of immunoglobulin A - anti-lipopolysaccharide. Compared with the control group, patients had a different composition of the microbiota, the number of beneficial bacteria decreased, and the number of pathogens increased [24]. The onset and development of heart failure may be associated with a decrease in SCFA-producing bacteria and an increase in TMAO-producing bacteria, which may become a new target for the treatment of heart failure. Recently, in studies in mice,the effects of trimethylamine-lyaseenzyme inhibitors have been shown to have an effect similar to that of anti-atherothrombotic agents. [47.48].

Gut microbiota and myocardial infarction

Atherosclerotic plaques contain bacterial DNA. However, the types of bacteria found in atherosclerotic plaques are also present in the gut of the same individuals [18,19,36]. A study from South Korea shows that the presence of bacteria (microbial rRNA) was detected in the coronary thrombus during the acute phase of STEMI. The microbiological signature in the coronary thrombus showed a correlation with oral and intestinal microbiome [20]. From this it can be concluded that gut microbial communities can be a source of bacteria in plaque, which can affect plaque stability and the development of cardiovascular diseases. A recent study in rats reported a connection between the gut microbiota and the extent of myocardial infarction [38,39].

The study looked into Dahl Salt-Sensitive Rats-rats fed with foods high in salt - 8% NaCl) that drank drinking water with antibiotic vancomycin, which reduced the level ofcirculating leptin by 38%, causing a smaller myocardial infarction (area reduction of 27%) and improved restoration of postischemic myocardial contractility compared to control animals that did not receive the antibiotic.

Vancomycin changed the abundance of gut bacteria and fungi measured by the amount of 16S and 18S rRNA [39].

In rodent-based studies the use of Lactobacillus plantarumas a probiotic resulted in the reduction of circulating leptinby 41%, myocardial infraction by 29% and better recovery of myocardial contractile function by 23%. However, if rodents received leptin at a dose of 0.12 μg / kg i.v. the protective effect of probiotics on the heart was reversed. This study is the first to confirm a direct link between changes in the gut microbiota and myocardial infarction. This shows that the addition of probiotics can reduce the degree of myocardial infarction [46]. Another animal study using Lactobacillus rhamnosus showed a beneficial effect on cardiac function after an artificially induced myocardial infarction [49].

Gut microbiota and metabolic diseases

Many studies show a link between the composition of the gut microbiota and metabolic disorders in the body [50,51,52]. The role of the gut microbiota in the development of obesity has been proven by studies conducted on dehydrated mice (germfree-GF-mice) compared with conventionally bred mice (CONV-R). Sterile, germ-free mice are bred in isolators that completely block exposure to microorganisms, with the intention of protecting them from detected bacteria, viruses, and eukaryotic microbes.CONV-R mice have a 40% higher body fat content than GF-mice, which is a phenomenon independent of food intake. However, after colonization of GF-mice by gut flora coming from CONV-R mice, a significant increase in body weight and ~ 60% increase in body fat was observed, together with increased synthesis of liver triglycerides in faecal transplant recipients (GF mice), independent of food intake and total energy consumption [53]. It appears to be the mechanism by which gut microbes contribute to increased energy absorption by the formation of short-chain fatty acids (SCFA), which is the result of hydrolysis and fermentation of dietary polysaccharides. SCFAs, such as propionate, butyrate, and acetate, perform complex metabolic actions that affect host appetite, gut transittime, and fat absorption and deposition [52].SCFAs also increase the internal absorption of monosaccharides by stimulating the expression of the sodium-glucose transporter 1. SCFAs also contribute to the modulation of host appetite and food intake in interaction with G-linked proteins expressed by enteroendocrine cells and promote the release of glucagon-like peptide-1 that affects satiety. Apart from that, SCFAs affect lipid metabolism by increasing lipogenesis and inhibiting fatty acid oxidation [53]. Studies have shown specific changes in the composition of the gut microbiota in genetically obese mice compared to genetically lean mice, showing a 50% decrease in abundance of Bacteroidetes and a proportional increase in Firmicutes. These specific changes appear to contribute to increased SCFA production and fat accumulation in obese mice and in GF mice colonized by obese microbiota (54]. There are other possible mechanisms. A high-fat diet has been shown to increase the proportion of Gram-negative species in the gut microbiota, which contributes to the increased absorption of gut fragments of bacteria, such as lipopolysaccharides (LPS) in the gut. Increased circulating LPS levels lead to "metabolic endotoxemia" which manifests as weight gain, fasting hyperglycemia, and hyperinsulinemia [55]. There is growing evidence to suggest that a high-fat diet promotes changes in the composition of the gut microbiota, but the later development of the obesity phenotype is associated with metabolic endotoxemia [56].In recent years, researchers have also studied the links between dysbiosis and obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease (NASH) [50,51]. Initial studies in animals and humans supported a correlation between obesity and the abundance of the Firmicutes group of bacteria compared to the Bacteroidetes group; type 2 diabetes, however, is associated with a reduced abundance of butyrate-forming bacteria and an increased abundance of Lactobacillus spp [1,3,8,10]. The gut microbiota is involved in the development of dyslipidemias via secondary bile acids [52,53]. In the research of NASH, it was determined that some bacteria (Clostridium coccoides, Lactobacillus reuteri, Parabacteroides) affect fat metabolism, integrity of the gut wall and the process of fibrosis, thus affecting dyslipidemia [52].

Application in practice

Examples of clinical benefit of long-term microbiota change are: dietary measures, pre and probiotic therapy, antibiotic therapy, intake

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of targeted enzyme inhibitors, fecal microbial transplantation, etc. [57,58]. Studies have shown that even a five-day change in diet leads to a short-term rearrangement of the number and types of gut microbes [4]. An example of this is the dietary approach aimed at stopping hypertension (DASH diet - Dietary Approaches to Stop Hypertension), which consists of meals with fruits, vegetables, whole grains, etc. [59]. Patients in the study who were on this diet showed an improvement in quality of life and better elasticity of arterial blood vessels after three months of adherence to the measures [60]. Besides, it has been described that individuals who do not follow a prescribed diet and have a "Western diet" high in fat and red meat have elevated levels of TMAO in their urine compared to patients who follow a prescribed DASH regimen [61,62]. Reduced dietary fiber intake is associated with reduced bacterial production of short-chain fatty acid butyrate, which has immuno-modulatory effects in the gut mucosa and also serves as a major energy substrate for colonocytes. Decreased levels of butyrate in the gut could induce local inflammation, worsen dysbiosis and contribute to impaired gut barrier function, resulting in "leakage" of bacterial toxins such as LPS, which further induces local and systemic inflammation. A high-fiber diet can improve the growth of acetate-producing bacteria, reduce high blood pressure, and prevent heart fibrosis and hypertrophy [63].

Probiotics and prebiotics

Probiotics are living microorganisms which, when given in appropriate amounts, bring health benefits to the host [64]. Probiotics in clinical use contain bacterial and fungal microorganisms, including the genera Lactobacillus and Bifidobacterium and the fungus Saccharomyces boulardii [65]. The results of animal models suggest that certain strains of lactobacilli could have cardioprotective effects. Rats treated with a supplement containing Lactobacillus plantarum 299v prior to coronary artery ligation reduced infarct size and improved left ventricular function [66]. Another study showed similar cardioprotective results in a rat model of myocardial ischemia after supplementation with Lactobacillus rhamnosus GR-1 [67]. A pilot study in humans reported not only reduced systemic inflammation, but also improved ejection fraction after intervention with probiotic yeast Saccharomyces Boulardii in patients with chronic heart failure [68]. Given the potential clinical impact of microbiota modulation, as well as high morbidity and mortality from heart failure, microbiota modulation is not completely risk-free [69]. Careful clinical monitoring and pre-defined safety measures which should follow the same standards as in other clinical trials are recommended, [70] because recent genomic and epidemiological evidence of probiotic-related bacteremia or transfer of bacteria from probiotic capsules into the blood of patients in intensive care units has been reported [71]. Prebiotics are substrates that microorganisms of the host selectively use and provide potential health benefits. Dietary fiber and oligosaccharides are most commonly used as prebiotics [72]. Most modern studies that deal with microbiota processing in patients with cardiovascular disease report microbial depletion with SCFA-forming capacity such as butyrate. Prebiotics that promote microbiological fermentation of dietary fiber in SCFA may, therefore, be of potential benefit in improving metabolic regulation [73]. Some prebiotics, such as inulin, have the potential to counteract the harmful effects of antibiotics by promoting the diversity and functional capacity of the gut microbiota [74]. A randomized study with inulin food supplement or inulin-proprionate ester showed a decrease in markers of systemic inflammation with increased generation of SCFA proprionate in the colon [75]. Therefore, targeting the production of microbial SCFAs with inulin supplements or other prebiotics is an attractive strategy for future cardiovascular disease testing, although current scientific evidence does not provide validated recommendations for the use of probiotics or prebiotics as adjunctive therapy in patients with heart failure or coronary heart disease.

Antibiotics

The use of antibiotics affects the composition, diversity and function of the normal flora [76]. Antibiotics have been used successfully in animal models to reduce the degree of damage to heart cells after myocardial infarction [77,78]. Previous studies in patients with heart failure focused on gut decontamination with broad-spectrum antibiotics to reduce biotome translocation and bacterial inflammation. Although this approach succeeded in reducing markers of systemic

inflammation, a clinical effect was not demonstrated [79,80].

A recent study showed that a broad-spectrum oral antibiotic cocktail significantly increased postinfarction rupture and death in a mouse model of coronary artery ligation [81], which could suggest that an intact microbial community is needed for proper myocardial recovery at the time of myocardial injury. This study is in contrast to a previous animal experimental model that showed that oral vancomycin reduced infarct size and improved postinfarction cardiac function in rats [82], and to a study reporting that a combination of streptomycin, neomycin, polymyxin B, and bacitracin reduced infarct size along with changes in metabolites associated with the microbiota [83].

Regardless of the differences, these animal studies strongly indicate the role of gut microbiota composition in acute myocardial infarction, but the direction of microbiota changes and potential metabolic or inflammatory pathways are not yet well known. Modifying cardiovascular diseases with antibiotic therapy is not a new idea.

Between 1995 and 2005 > 19.000 patients were included in a study to treat pneumonia in patients with coronary heart disease. The study in these patients showed no clinical benefit from antibiotic therapy in relation to coronary ischemia [84]. Apart from the apparent risk of antimicrobial resistance, other safety concerns have recently emerged with potential significance for future testing. A recent ten-year follow-up showed increased cardiovascular death in patients with stable coronary heart disease treated with clarithromycin [85], leading to a 2018 FDA warning on the use of clarithromycin in patients with coronary heart disease. The FDA advises caution before prescribing clarithromycin antibiotic to patients with heart disease because of a potential increased risk of heart problems or death that may occur years later. (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-additional-data-supports-potential-increased-long). In December 2018, the FDA issued a warning on the use of fluoroquinolones indicating the possibility of aortic rupture and aortic dissection in high-risk patients, such as elderly patients with hypertension or peripheral atherosclerotic vascular disease (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-additional-data-supports-potential-increased-long). Another study reported increased risk of cardiovascular events in older women with increased cumulative antibiotic exposure in adulthood [86]. The explanation for this increased risk is not fully known in all patients, but it could include QT prolongation, arrhythmias or pro-inflammatory activities mediated by gut microbiota translocation, or other effects mediated by the gut microbiota. Considering these safety concerns and the lack of a completely clear clinical effect antibiotics have on the microbiota, caution should be exercised in future studies targeting the use of antibiotics in cardiovascular patients.

Targeted enzyme inhibitors

Apart from the above-mentioned use of TMA lyase [18], mention should be made of the results of a study in which mice used choline analogs that inhibit the action of enzymes in TMA metabolism, thereby reducing plasma TMAO concentrations. The use of choline analogues could, therefore, provide a new approach to reducing the risk of thrombosis [69]. Another interesting active ingredient that acts as a protective factor for the gut mucosa is Urolitin A (UroA) and its synthetic analogue UAS03, which improve close cell contact and gastrointestinal barrier function [87].

In recent years, fecal microbial transplantation (FMT) has been among the most mentioned interventions used to treat intestinal dysbiosis. The introduction of "good bacteria" taken from healthy subjects into the gastrointestinal tract of patients suffering from gut dysbiosis and its consequences is a new and effective therapeutic strategy. In a clinical study examining people with metabolic syndrome, there was a significantly improved insulin sensitivity after 6 weeks of FMT in which the donors were healthy people of normal weight. At the same time, FMT increased the amount of butyrate-producingbacteria [88]. Although the acceptance of the therapeutic use of FMT is increasingly present, due to the perception of this method as a "natural" treatment and relatively cheap application, the risk-benefit ratio particularly in CVS diseases remains insufficiently clearly defined because the published experience with FMT is limited and the legal norm of this therapy has not yet been precisely regulated. Furthermore, there is a fear of the infectious potential of the therapy, which led researchers to investigate the use of "synthetic stool" products with a defined

population of bacteria to alleviate such problems, and the use of "frozen donor material" such as the concept of a stem cell bank is being considered [89].

Concluding remarks

New knowledge and technologies are significantly changing medical doctrine, enabling a new, different view of the body, organs and health, as well as the causal factors of diseases. Research in the recent past, and sometimes surprising findings, have confirmed that the gut microbiota can affect the health of the host and trigger the disease by means of various pathophysiological mechanisms. Gut microbiota and dysbiosis are areas of research which,in the future,willlikely change the established methods of prevention and treatmentof diseases.

Although we can change the composition of the microbiota with prebiotics, probiotics, antibiotics, diet and "targeted enzyme inhibitors", for the time being we cannot predict and provide a detailed assessment of all the effectsof these interventions in the prevention of various diseases. With all the data obtained in biomedicine in recent decades, it seems unusual that it took so long before scientists and cardiologists began to systematically deal with the impact of 2 kg of microorganisms that colonize us and live with us "for better or worse". Although only some of the mechanisms that link the gut microbiota and certain cardiovascular diseases are presented, we must be aware of the possibilities of this research area in the development of potential drugs in the future. The newly clarified connections between dysbiosis and the pathogenesis of cardiovascular diseases offer new possibilities for early and targeted action.

P.S. Perhaps the new research will lead to a new subspecialization in internal medicine, which, as prof. Miodrag Krstićanecdotallymentionedin his lecture at the Congress of Internal Medicine in 2019, will be calledgastroenterocardiology.

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Vol. 46 (2021) No. 1 TIMOK MEDICAL GAZETTE Review article

LEADERSHIP, APPRECIATIVE MANAGEMENT AND EMPOWERMENT IN PHYSIOTHERAPY PRACTICE

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Summary: Within national health systems, there is an inadequacy in terms of human resource management due to the specificity of operational activities of health workers, patient relations and the fulfillment of organizations' requirements.The paper views distributive or shared leadership and appreciation management as a new management concept that has a focus on employees, and which especially appreciates and emphasizes professionalism, cooperation, interaction skills and employee support and proposes the application of this concept in health systems, especially in physiotherapy practice.

Key words: leadership, physiotherapeutic practice, health systems, appreciation management

INTRODUCTION

According to the World Health Organization (WHO), countries around the world face challenges in capacity building in terms of human factors, within health systems [1]. In today's healthcare work environment, it is difficult for a healthcare professional of any specialty, to harmonize the care of patients or clients, their needs, together with a large number of factors related to the organization of work in rehabilitation institutions, where they are often exposed to stressful events and experiences. Challenges associated with physiotherapy practice include patients in extremely demanding psychophysical conditions but also frequent interpersonal conflicts due to the multidisciplinary nature of the rehabilitation process in which besides physiotherapists and patients participate. health professionals with whom they need to cooperate in order to achieve the ultimate goal, which is the effective treatment of the patient or client [2,3]. Therefore, leadership, administration, management and professionalism as skills, need to be integrated as an integral part of the theory and practice of physiotherapy. These four elements symbolize business functions [4]. Accordingly, the functions of leadership, administration, management and professionalism, are not independent of each other and are also related to the elements of the client-patient model and thus integrated into the physiotherapeutic practice [5].

LEADERSHIP

Today, leadership is increasingly recognized as a key component of organizational success. It is increasingly in the spotlight precisely because it is considered a key variable of organizational behavior. The clinical and general environment, which includes health care institutions, represents a specific challenge for leadership that arises from a combination of environmental and organizational factors [6]. These factors include: diverse regulatory influences, limited financial resources, multiple hierarchical systems, divisions between administrator and clinician roles, and different employee populations [6].

Recognizing the complex challenges and diversity of roles of leaders working in a health context have led to the development of the concept of clinical leadership. The term clinical leadership originated from the practice of nursing in which nurses found themselves in managerial roles, but has evolved to include everyone with a clinical background today [7]. Clinical leadership is most focused on providing effective health care "on the front lines" through evidence-based practices to improve patients' health outcomes [8]. Clinical managers are defined as “front-line” health workers who have retained a certain clinical role, but also have a significant stake in strategic direction,

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operational resource management and collaborative work activities where health professionals work together but retain their autonomy [9]. Storey and Holtie pointed out clinical leadership functions that include: maintaining levels of employee engagement, providing technical expertise in providing action plans that are feasible and useful from a patient perspective [10].

Leadership development is a current topic in health care among all health professions. Each discipline observes it from a different aspect and has a different view on how and why the development of leadership qualities should be included in the fund of basic knowledge, skills and behaviors both within educational curricula and in health practice.

Leaders are people who have the ability to lead others to achieve desired goals and increase productivity, create sustainable change and inspire others to pursue professional development [11-13]. One of the general definitions of leadership is that it is a process of influencing others to understand and agree on what needs to be done and how to do it, and the process of encouraging and directing individual and collective efforts to achieve common goals [14]. Leadership in health care includes influencing the activities of others that are aimed at achieving certain goals, dictating and harmonizing the speed and direction of change, as well as encouraging innovative practices [15]. Development in the field of leadership in terms of acquiring knowledge and skills, is the personal choice of the individual. People who have a desire to develop leadership skills may be those who believe they have good basic leadership characteristics, have had experience in leadership positions, or are in some way encouraged to seek leadership positions. The process of leadership development is a journey that involves a personal understanding of transformational leadership and the growth of leadership practice [16]. Research in the field of leadership has identified certain characteristics that are needed to cope with the challenges of leadership in complex systems, in a time of rapid change and expansion of knowledge in the health sector [17]. Three characteristics of leadership are mentioned that are consistently related to effective leadership in various fields of health care, namely: emotional intelligence, vision and business acuity [18]. Stanley identified seven clinical characteristics of leadership including clinical expertise, direct involvement in clinical activities, communication and interpersonal skills, modeling and motivating, implementing and improving high standards of health care, empowering others, and guiding oneself in recognized values [19]. Research in health care in general, to a significant extent, studies leadership as a means of achieving quality and efficiency in the provision of health care [20,6]. In their study, Desveaux and Verrier examined the attitudes of physiotherapists about leadership characteristics in physiotherapy practice and found that three key characteristics were identified, namely communication skills, professionalism and credibility [21]. The importance of leadership in the profession of physiotherapist has been recognized by professional organizations of physiotherapists [22]. wrote about the importance of leadership versus leaders, emphasizing the importance of the very concept of leadership that transcends and applies not only to the formal roles of leaders but to all members of the profession. In the development of key competencies, it is recognized that physiotherapists in public health institutions, as well as those in private practice, significantly need leadership skills and knowledge in order to conduct their professional practice. Interestingly, back in 2015, the Australian Association of Physiotherapists, in its report on the future of the physiotherapy profession, discussed the need for strong leadership to compete for resources, encourage innovation in theory and practice, and successfully promote the profession.

One of the concepts of leadership that is mentioned in the context of wider health care as well as in physiotherapeutic practice, is distributive or, as it is also recognized in the literature, shared leadership. As a concept, distributive leadership is not quite clearly defined. Gronn characterized distributive leadership as coordinated action, achieved through spontaneous collaboration, intuitive workplace relationships that develop over time, or institutionalized practice [24,25]. Distributive leadership shifts the focus from the characteristics and behaviors of the individual leader to a systemic perspective, where "leadership" is conceived as a collective social process that arises through the interactions of multiple participants [26]. Distributive leadership is closely related to teamwork [27]. In

particular, teamwork in teams, where knowledge and ideas can be shared among team members, thereby influencing each other, is often considered important for improving and maintaining service quality [28,29]. Given that leadership in health activities, especially in the rehabilitation institutional environment, requires the establishing and maintenance of relationships through interrelated health and clinical areas and managerial roles, it can be seen as divided and distributed through the system [30]. It is shared or distributed: within the organization of institutions "from board to department, through various disciplines within teams and through social protection organizations, local government, the volunteer sector and a large number of other agencies [30]. It differs from traditional forms in that responsibilities are distributed, and some see it as a path to clinical-managerial distribution in complex health care [31]. It is necessary to understand the practice of leadership and organizational interventions, and not a simple and traditional leader-follower relationship [31]. It also requires multi-level staffing. There is a strong evidence base that staff engagement benefits both individuals and organizations, supporting wider acceptance of distributed leadership [32]. According to the Kings Fund, a think tank established by the British Parliament, distributive leadership has become the mainstay of health policy in the UK, and it is argued that it will be necessary for "the leadership of the 21st century health system to be shared. distributive and adaptive" [33]. At the core of shared leadership is Self-Leadership. Leaders must be effective self-leaders, which means that they must understand themselves, their influence on others and develop the ability to self-control, self-regulate and manage themselves. A leader must learn to lead himself before he acquires the ability to lead others in a team or organization.

Self-leadership and shared leadership are connected by their character because self-leaders willingly and enthusiastically accept common leadership roles and responsibilities in order to function complex organizational systems [35]. This certainly can be applied to work in interdisciplinary and multidisciplinary teams in rehabilitation, which is a very common work environment of physiotherapists.

APPRECIATIVE MANAGEMENT AND EMPOWERMENT

In considering leadership theory and its development, it is important to consider both the complementary and contradictory process with which it is so often associated, and that is management. A certain balance is needed in defining the differences between leadership and management but also recognizing certain overlaps between these categories [36]. An individual can be a manager without showing leadership or he can be a leader without being in a managerial role [16].

Management deals with the complexity of a system, planning, allocating resources, organizing and staffing, and controlling and solving problems, thus ensuring order and consistency [37]. Leadership deals with coping with change, setting the direction, guiding and motivating people [37]. When it comes to health facilities, it is often difficult to distinguish between leadership and management because many roles require managers to lead and leaders are expected to manage [38]. Healthcare professionals must constantly adapt to the rapid pace of change in the modern healthcare environment while still providing high quality healthcare services according to ethical principles [39]. Appreciative management is an energetic and efficient approach in encouraging organizational change, originally developed and applied in the business world in order to improve organizational culture, efficiency and profit [40]. When it comes to the health care system, it is a new management concept with a focus on employees [41]. According to the existing literature, it is a way of management where professionalism, cooperation, interaction skills and employee support are especially valued and emphasized [42]. Appreciation management also involves management support for the professional development of their employees [43]. Respectful leadership as part of appreciation management consists of trust, transfer of responsibility, taking into account people's needs, maintaining professional distance, respect, responding to mistakes collegially and with empathy, encouraging autonomy, promoting equality, encouraging development, openness to advice, acceptance criticism, stimulating potential, seeking participation, personal interest, reliability, attention, supportive and friendly interaction [44]. The features of appreciation management

can be found in studies concerning professional activity and development in physiotherapeutic practice. According to the results of a Finnish study that examined aspects of positive-appreciation management in the work environment of physiotherapists in the public and private sectors, it was found that the most developed dimension is equality and that aspects of leadership and autonomy are more recognized in managers whose basic education is in physiotherapy [45]. A study dealing with the professional development of physiotherapists in the private sector in Australia, showed that physiotherapists who have recently graduated show a need for professional development. However, they also experienced conflicts with their superiors, because the promised support in their professional development was lacking [46]. It is an undeniable fact that in the field of physiotherapy there is a need to strengthen leadership and applied management. According to Tebbitt, "Empowerment means creating and maintaining a work environment with qualities (values) that facilitate the choice of employees to invest in their own activities and behaviors that result in positive contributions to the organization's mission." He also believes that empowering employees is a crucial factor for an organization to achieve its mission, vision and strategic direction, especially in terms of organizational change. Empowering work environments are those in which employees have access to information, in which the support and resources needed to do the job are available, as well as those that provide opportunities for the growth and development of knowledge and skills [48]. Furthermore, he states that there are three structural organizational sources of power: access to information lines, support, and resources. In order for individuals to be empowered, they need to have access to the knowledge and information necessary to do their jobs. This refers to information directly related to their work, but also information about the work of the organization as a whole. Support stems from feedback and instructions received from superiors, equal in status and subordinates. Access to resources for employees means that there is the possibility of obtaining the materials, money and recognition needed to meet job requirements [49].

Empowerment means that leaders actively encourage and stimulate employees towards self-leadership [50]. Strengthening work organization, by definition, is the activity of empowering employees by providing their autonomy, discretion, control, decision width or strength. Examples of empowering leaders' behavior include encouraging participatory decision-making, leading by example, sharing information, training, and showing concern for employees [51]. In response to this behavior, employees can be expected to feel more empowered and with a strong sense of contribution, control, competence, connection, and meaningfulness [51]. Access to resources, information and support lead to increased organizational commitment, reduced level of professional burnout, increased sense of autonomy in work, increased perception of participation in management, increased job satisfaction. According to numerous studies, physiotherapists are the primary candidates for burnout at work due to close contact with patients or clients in the work environment [52]. A characteristic of a good team is the ubiquitous sense of support, security and self-confidence, where members can rely on each other in difficulties and take creative risks, confident in the support of their associates. . Helping colleagues maintain a professional reputation is one of the valued qualities of good teammates. It is these rules of interpersonal relationships in the workplace that develop the key performance of the work team and the development of self-confidence in physiotherapists [52]. All this results in: achievements and success, cooperation in the organization, patient / client satisfaction [53].

CONCLUSION

Leadership, administration, management and professionalism are part of every form of physiotherapy practice. They are the basis for organizing the work of every health activity and represent the basis for the growth and development of health services it provides. It is important that managers in physiotherapy recognize the characteristics of appreciation-positive management, so they can implement them to become part of their practices and part of their own leadership style. Leaders in physiotherapy practice should be encouraged to educate themselves in the field of management and participate in the education of others. Leadership, self-leadership, shared leadership and positive-appreciation management with

empowerment are interrelated aspects of management and functioning in teamwork and are therefore extremely important for physiotherapy practice. It is considered that one of the preconditions for successful management of the work process is the treatment of colleagues in a positive and consistent way, and the key feature of good teamwork is the ubiquitous sense of support, security and trust, where members can rely on each other in difficulties and take creative risks. , confident in the support of their associates. Mentioned interpersonal relationships develop key characteristics of a successful work team and develop self-confidence among physiotherapists

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HISTORY OF IMPLANTOLOGY FROM THE ASPECT OF OSSEOINTEGRATION AND MUCOINTEGRATION

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Summary: The tendency to replace lost teeth by implanting foreign material is as old as civilization itself. The accelerated development of implantology as a science started only in the middle of the last century. The essence of implantology is the process of osseointegration. The greatest merits for this phenomenon belong to prof. Per Ingvar Brenemark, who accidentally discovered the possibility of complete incorporation of a titanium implant into the surrounding bone. With the discovery of osseointegration and defining the conditions that enable it, the period of implantology development begins with the improvement of endosseous implantation into an efficient method of prosthetic rehabilitation, predictable outcome and extended lifespan of implants and dental restoration in function. Implantology initially aimed to improve the function and quality of life of partial and complete edentulism patients, and since the 1990s it has become prosthetically guided not only by functional but also by aesthetic principles. With the beginning of the 21st century, implantology is aimed at improving the appearance and stability of soft tissues, thus beginning the era of mucointegration.

Key words: history of implantology, osseointegration, mucointegration

INTRODUCTION

Although implantology as a science has flourished in recent decades, it should be remembered that the history of implantology stretches back to ancient times. Based on archaeological research, we find that 4,000 years ago, the Chinese used spikes of bamboo trees and implanted them in the jaw bone as a substitute for lost teeth. The ancient Egyptians, the Etruscans, and later the Phoenicians used noble metals, processed ox bones or ivory and implanted them in bone tissue. These innovative nations used gold wires to stabilize disassed teeth [1,2].

Hippocrates (5th century BC) wrote about the possibility of hardening artificial teeth using gold or silk thread to replicate the teeth removed, advising the practitioner not to "discard the teeth or teeth removed from the injured mandibula, but to return them to place, tying them to the remaining teeth with golden threads" [3]. The same recommendation was made by Aulus Cornelius Celsus (1st century BC) which in the journal "De Medicina" mentioned the possibility of replacing the missing tooth with a dental implant, taken from the kadaver, in those who lost a tooth for different reasons; however, he did not report whether such treatment was successful. However , it must be noted that the main purpose of these replacements was cosmetic , while the function of mastication was not much considered [3].

It is known that Mayans in the 7th century used various materials for aesthetic purposes, such as tirkes, quartz, serpentine, etc. and inserted carefully prepared spaces on the vestibular surfaces of mostly front teeth. Particularly interesting is the findings of Wilson Popenoe and his wife Dorothy during a survey of the Mayan civilization in Honduras, where they found a fragment of mandibula containing three replica teeth made of shellfish in alveolas. In studying this unusual find, expedition members initially assumed that the inserted elements were cosmetic treatments post-mortem, possibly as part of a complicated funeral ritual or religious practice [4].

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Picture 1. The find of a 7th-century mandle of the Mayan civilization was found in Honduras. (Taken from http://www.implantmn.com/about-dental-implants/history-and-types-of-dental-implants/ for scientific purposes and not used for commercial purposes)

Radiographs of mandible in 1970. showed the formation of a bone around the implants that resembles what is seen around modern implants. This appears to have been the first authentic aloplastic material implanted in human tissue during life. Recent and exhaustive histological research on the behaviour of shell fragments in direct contact with bone tissue in experiments with animals has confirmed the principle of oseointegration between the two tissues [3,6,7].

Until the mid-19th century numerous attempts at replantation and dental transplantation were recorded, where the works of Pare, Dupont, Fauchard and others were not much advanced in the development of implantology. In the 19th and early 20th centuries, the founders of the Baltimore School, further Maggiolo, Bonville, Gram, Paine and others used various materials, platinum, lead, silver, gold, iridium, ceramics, and used cylinder-shaped implants, hollow screws, full screws, cylindrical nets, spirals, needles, etc.

Although these cases cannot be considered entirely successful, it must be noted that during this century, from Maggiolo to Paine, researchers have progressively tried, at least on a conceptual level, to use more and more inert materials, and this is in accordance with the development of the concept of implanting aloplastic implants with retentional morphology [6,7].

In 1938, Sweden's Gustav Dahl installed a subperiostal mandibular implant with four metal columns above the gums that were later anchored to the braces.It is important to note that after this attempt, the Swedish Dental Society asked him to immediately refrain from conducting the treatment, and the punishment was expelled from society at the very moment when the procedure appeared destined for success [8,9].

In Boston in 1939. the Strock brothers began testing of vitalium implants, chromium alloys, molibden and cobalt that they had already tested on dogs. The design of subperiosteal implants was further explored and developed by Lew, Baush and Berman in 1950. [8,9]. At a conference in Milan on 27 february 1947. Italy's Manlio Formiggini proposed a hollow spiral bolt made of stainless steel wire or tantal. The Designer called the method "direct endoalveolar implantation" and marked a definitive transition to an era of endoseal implants. Formigjni then presented several clinical cases and brought with him two patients who chewed without problems with fixed dentures [9]. The dental world has experienced a justifiable period of cautious skepticism towards endoseal implants and hopes instead to make the latest subperiosteal implant technique possible. As a result, failures (due to technical errors by formigni's first students) were taken into account more than success when it came to official verdicts [3,8,9].

OSSEOINTEGRATION

Osseointegration as a concept is introduced by Per-Ingvar Branemark (1969), professor at the Institute of Applied Biotechnology, University of Gothenburg. He defined it as "a direct structural and functional connection between the living bone and the surface of the implant". He came to this phenomenon by accident. He observed microcirculation of the bone and the healing of the wounds through the titanium tube that he incorporated into the rabbit fibula. When he tried to remove the chamber after the experiment, he noticed that it had grown with bone tissue and could not be easily removed.

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That's when he discovered bone growth on the surface of the titanium chamber and good integration of bone implants. The phenomenon was called oseointegration [11,12,13,14]. Oseointegration is derived from the Greek word for bone "osteon", and Latin "integrare", which means to create a whole [11]. It was assumed that bone anchoring on the principle of feeling could work in humans, and the first toothless patients were treated in 1965. [11,12,13,14].

At the time, the osseointegration was not an accepted phenomenon. Although experiments on animals conducted in Branemark's laboratory made it clear that it was possible to anchor the bone on the condition that basic guidelines were observed, the scientific community was not convinced of the osseointegration because hystological evidence was absent. It wasn't until mid-1970, A. Schroeder, using a newly developed technique of cutting non-decalized bones and implants without separating anchored parts, showed that it was osseointegration. It was the first evidence of a direct conection of implants and bone. The original Branemark implant was created as a cylindrical; later, the conical shapes appeared [13,14,15]. Implant designs were breakthrought in the 1960s, and the basic spiral design was modified by Dr Leonard Linkow in 1963. the implant of the shape of the blade with the ability to place in maxillo and mandibul, which is now known as endooseal implantation [8,14].

In 1978, The Harvard Consensus Conference was held to establish a consensus on the use of implants at Harvard University, and the standard for a successful implant was whether the implant remained implanted and functional for five years. This standard may seem extremely short, but it illustrates what the expectations of implant treatment were at the time [8,16].

During the 1980s, Professor Zarb of the University of Toronto played a central role in holding the Toronto Conference on Oseointegration in Clinical Dentistry, where Branemark presented the results of his research over 30 years and clinical practice for nearly 20 years. With this conference as a turning point, the Branemark regime has expanded across North America. The typical Branemark regime during this period consisted of implanting four to six implants in the lower jaw and recommended a surgical two-stage technique that became widespread worldwide [8,16].

In the mid-1980s, a common implant used by many dentists was a root-shaped implant. The main factors that determined which implant system was selected relative to the other, included design, surface roughness, prosthetic considerations, simplicity of insertion into the bone, costs and success over a certain period of time [17].

After numerous clinical studies, the merits of Dr. Brennemark, Schroeder, Strauman, and especially Dr. Zarb in the 1980s expanded the indication area for the implantation of dental implants from the purely toothless and toothless jaws of patients. The results of successful oseointegration climb to more than 90 per cent, so implantology is also experiencing a commercial boom and is accepted as a valid therapeutic discipline [15,18,19].

This age is characterized by the emergence of new and modification of old designs as well as the emergence of new surgical techniques. The basis of this new philosophy consisted of oseointegration and a number of preconditions that need to be met in order for it to be achieved. Albrektsson et al. (1981) published educations about a number of factors to be taken for successful oseointegration. Oseointegration is a direct link between bone and implants, without inserted layers. However, it does not occur to 100 per cent - the development of bone and implant connections. Therefore, the definition of oseointegration is based on stability, not histological criteria, which reads "the process of achieving clinically asymptomatic rigid fixation of aloplastic material in the bone, during the functional load" [13,17]. Some scientists believe that only a biomechanical factor determines whether a fibrous capsule or bone will be created around the implant [13,18]. Contrary to this understanding, there is well-documented evidence of how the bone's response is quantitatively different depending on the type of biomaterials and the roughness of its surface. [13,20]. The surface of the dental implant is the only part that is in contact with the biological environment, and the uniqueness of the surface directs the response and affects the mechanical strength of the contact of the implants / tissue [20,21]. One of the main reasons for modifying the surfaces of dental implants is the reduction of oseointegration time. This may include mechanical treatments (for example processing and sanding), chemical treatments (acid-

etching), electrochemical treatments (anodyne oxidation), vacuum treatments, thermal and laser treatments. The surface layer on the implant is needed to increase the functional surface of the bone-implant touch so that stress is transmitted effectively. In addition, surface coating accelerates bone aposition. The latest innovations in dental implants include the use of fluoride, hydroxy-apathy, antibiotics, growth factors and laminna [20,21].

In the 1990s, the concept of prosthetics guided by surgery was replaced by the concept of prosthetic quided surgery and the focus of interest in oral implantology shifted from functional and aesthetic aspects. More or less, the imediate loading is replaced by delayed. Also, procedures of bone augmentation are being introduced to compensate for lost bone and put the implants in the correct position. So-called tissue engineering opens up completely new horizons in planning, but also in the performance of implant procedures [22].

Computer-designed production methods as well as computerized three-dimensional models are used to predict stress distribution characteristics in the implants around the bone. In recent clinical studies Blaschke and al. reported that dental implants made of zirconium are an adequate alternative to titanium dental implants. In addition to excellent aesthetic results, the authors conclude that zirconium implants enable a degree of oseointegration and soft tissue reaction that is better than titanium dental implants [23,24].

MUCOINTEGRATION

As it is known, the improvement of dental implants was done to enable optimal levels of osseointegration. However, there is another factor that is very important, the health of soft tissue. It is well known that for the health of the teeth, periodontal tissue is not only important because it stabilizes the teeth, it is a barrier between the oral cavity and the teeth. The role of soft tissue is quite similar when it comes to implants: contact between dense soft tissue and the surface of the abutment can act as a barrier to protecting and preserving the fundamental crestal bone. The anatomical characteristics of soft tissue and adjacent implants differ from soft tissue around natural dentation. Perpendicular collagen fibres known as Sharpey fibers bind natural teeth to cement, while collagen fibers tend to adher for the surface of the abutment in parallel or circular beads, which is a weaker combination. That's why the scientific community in recent years has been focused on improving the health of periimplant soft tissue, the health of the papilla around the implants, changing implant platforms, surfaces of abutments in order to better functionally adapt soft tissue. Mucogingival surgery (Pedicle grafts, gingival graft, free connective-tissue graft, etc.) can improve the appearance of periimplant contours [25,26,27].

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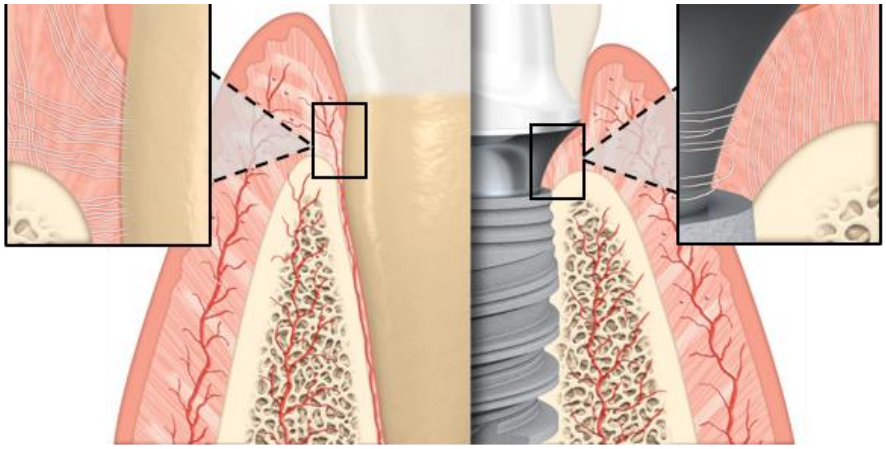
Figure 2. A comparison of the characteristics of periodonte and periimplant soft tissue. Sharpey collagen fibers are attached to the cement of the root of the teeth in the perpendicular bead, while the perimplant fibers are oriented circumferentially or parallel to the surface of the abutment. (Taken from www.nobelbiocare.com/blog/science/why-abutment-surface-matters-for-soft-tissue-health/ for scientific purposes and not used for commercial purposes)



For long-term success, it is necessary to achieve soft tissue stability around implants. The introduction of "prosthetic-guided soft healing" in implant therapy aims to condition tissue before definitive prosthetic compensation, form an optimal emergence profile of the crown for achieving a gingive aesthetic and complication prevention. In this concept, temporary crowns or individualized abutments provide support to periimplantant tissues and papillas, existing or reconstructed during the implantation phase, ensuring positive gingive architecture without loss of volume and vestibular recession due to the collapse of soft tissues [22].

The surface of the implant is an important factor for long-term survival, but the role of the abutment surface has been least examined and has been the subject of today's researchers in recent years. As has been shown in numerous studies, smooth surface abutments do not facilitate mechanical cleaning, but they accumulate little plaque compared to those with rougher surfaces. Two factors are important for soft tissue connection: nanotography and surface chemistry [24,28,29,30,31,32]. Nanotopography of the abutment surface becomes increasingly important in explaining the connection between soft tissue. Surface's nanostructure is believed to play an important role in the interaction between cells and implants at the cellular and protein levels. [33] There are numerous methods for changing the nanotography of the abutment surface. One of them prefers the method of anodization, a process that involves immersing the abutment into electrolytic fluid using voltage. These changes in nanotography that lead to binding and proliferation of fibroblasts is an important step towards binding soft tissue [34,35]. The anode process is also important for surface chemistry and energy. Research shows that anodized surfaces have a lot of hydroxyl groups that correlates strongly and increases hydrophilicity or affinity surface for water, or blood [34,36]. It has also been shown that hydrophilic surface of abutment and priorities can help with adhesia, in support of soft tissue connection , which is functional and biological seal and barrier and prevention of microbial colonization [34,35,36,37,38].

There is a clear need for the abutment surface to remain clean and intact before use, in order to achieve a protective layer through use. Atmospheric elements can be upgraded to the surface of the abutment even though it is in sterile packaging. These deposits tend to have adverse effects on surface energy that are correlated with hydrophilicity and the representation of hydroxyl groups [39,40].

When one of the world's leading implant companies, Nobel Biocare, presented the newest surface of the Xeal abutment and together with Ti-ultra implant surface marked the beginning of an era of mucointegration. A

smooth, non-porous, nanostructural, anodized surface has surface chemistry and topography that is designed to achieve soft tissue connection. Through Xeal and T-ultra Nobel biocare, it applies the anodization process to the entire implant system, from the abatment to the implant apex. That same year, they promoted the "on 1" concept, which involves an interstructure,on- 1 base, which is placed on an implant in the surgical implant phase and remains in that position during prosthetic restoration, which minimizes soft tissue trauma. The platform is therefore transferred from bone level to soft tissue level. Although this surface of abutment is on the market in 2019, it is already the subject of a two-year clinical study that showed a statistically significant increase in the height of keratinized soft tissue compared to machined abutments [29,41,42]. In addition to functional benefit, its golden hue (the result of the anodyne process) is useful in supporting natural appearance in the transmucosal zone, which can be particularly relevant in cases where thin mucous or mucosal recession is present. To ensure the condition of intactness, abutments are delivered with a protective layer that dissolves after contact with the liquid, i.e. blood. This dry packaging technology stores the surfaces of the abutment hydrophilic and surface chemistry and protects it from contamination with hydrocarbon [43].

DEVELOPMENT OF IMPLANT THOUGHT IN SERBIA

With the discovery of osseointegration begins the accelerated development of implantology in the world and in our country. This is the period when the first attempts to implantation in Serbia are made. Back in 1963 Dr. Tavcar, Dr. Škokljev and Dr. Spaić at the VMA made the first attempts to implantation two subperiostal implants in the toothless lower jaw, but after three years they were extracted. After the implant failure, skepticism reigned until 1977. The year that Dr. Skundric, Dr. Spaić and Dr. Skokljev implanted "pre-prepared wedges of a special alloy" in the form of tripods, which in the form of tripods are attached to the bone of alveolar continuation in the area of the canine and the first molar mutual. At the tips of the pegs are temporary crowns of palopont filled with silica. Encouraged by the success of the implant procedure, various implants of foreign authors, especially leafy, needle, screw-implants, are starting to apply in the VMA. Thanks to Professors Perovic and Kosovcevic above all, implantology begins to be studied in studies at the Faculty of Dentistry in Belgrade. Soon after, in 1981 the VMA installed the first one-piece circular leaf implant in the lower jaw [44]. Like Branemark, Schroeder, Straumann and Zarb, Dr. Skundric in Serbia is parallelly developing the B.C.T. home production implant system created as a product of years of application of different systems and acquired experience. Within the B.C.T system, this innovative scientist has also incorporated a part, a mesostructure that irresistibly resembles what 30 years later one of the leading implant houses, Nobel Biocare, will promote through its concept, on-1, which marked the beginning of an era of mucointegration.

CONCLUSION

Oseointegration is one of the most critical aspects of implant success. The history of developing and improving dental implants is a magnificent and fascinating time travel. In this field of research and learning it is only possible to stop and admire man's inventiveness over the years. Materials from which dental implants were made range from gold ligature wire, clams, ivory to chromium, cobalt, to iridium and platinum. From the spiral designs of stainless steel implants to double spiral creations and endoseal root shapes, dental researchers and clinicians worked fast and hard, creating many structures to replace positions that once had natural teeth. Dental surfaces have also been modified to reduce oseointegration time. Modified surfaces include the use of hydroxyapatites, composites, carbon, glass, ceramics and titanium oxide. To make the exterior as convenient as possible, the surfaces of the implants are further sanded, oxidated, fluorised, acid-etched and modified. The latest innovative coatings are the focus of today's implant research.

Although the importance of the surface of the implant is generally known, the surface of the abutment is subjected to far less intense research. Dense soft tissue contact with the surface of the abutment can act as a barrier that protects and preserves the subcrestal bone needed to achieve healthy integration and long-term success of dental implants.

This was the driving factor in the development of the Xeal abutment surface. To

optimize the process of mucointegration, it is important to understand the surface characteristics of abutment, especially surface chemistry and nanostructure. Still the loss of implants due to periimplantitis is a growing problem each year, so in future aspects it should be given greater importance to soft tissue health around implants.

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Vol. 46 (2021) No. 1 TIMOK MEDICAL GAZETTE Case report

IMPLANTATION OF THE PORT-A-CATH WITH ONCOLOGIC PATIENTS - USAGE AND INFLUENCE ON THE QUALITY OF LIFE

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Abstract: Central vein catheters (CVC) have very important role in the treatment of patients with malignant diseases. CVCs are used for the application of chemotherapy and also for the extended usage of liquids, blood and blood derivatives, antibiotics , total parental nutrition as well as for common blood analysis. Port-a-cath vein catheters are closed systems and their purpose is to provide access to the central vascular system. The use of these systems is associated with decreased possibility of infection, simple maintenance of the port that is not in use, esthetic benefit and improved mobility of patients. In our clinic 16port-a-cath vascular catheters were implanted to oncologic patients from January 2017 until 31st January 2018. There were no early complications and in 12,5% of patients late complications occurred. Subjective assessment of all the patients with implanted port-a -chat system is improved quality of life.

Key words: port-a-cath, oncologic patients, quality of life, chemotherapy

INTRODUCTION

Patients with malignant diseases need multidisciplinary approach and therapy that is often given intravenously. Central vein catheters (CVC) have very important role in the cure of these patients. They are used not only in the application of chemotherapy but also for the extended usage of liquids, blood and blood derivatives, antibiotics, total parental nutrition as well as for common blood analysis. There are different types of CVC: non -tunneled CVC, peripheral inserted PICC, tunneled and CVC with implantable port. For oncological patients the most adequate is CVC with implantable port due to relatively simple implantation and uses, low infection levels, safety and comfort that provides to patients [1,2,3,4]. In modern oncology these systems replace the tunneled catheters and short – term use. Chemotherapy is taken cyclically and to avoid reuse of CVC that leads to sclerosis of the blood vessel wall and as every invasive procedure takes its risks (infection, hematoma, pneumothorax…), there is a possibility of implementation port – a – chat catheter that improves lives to patients on long termed therapies [5].

PROCEDURE DESCRIPTION: PORT-A-CATH PLACEMENT

Port-a-cath is composed of the catheter and the chamber that is apart from the cytostatic treatment, antibiotics and painkillers also used for parental nutrition or for the blood sampling. The port is placed subcutaneously, mostly on the front of the chest, connected with the catheter positioned in superior vena cava above the confluence in right atrium.

Port-a-cath can stay placed for several months. To enable the route for therapy taking or blood sampling the special hollow needle (Huber needle) is implemented through the skin in silicon membrane of the port whilst the chamber is immobilized with fingers of non dominant hand. The port puncture is always done in sterile conditions with application of aseptic technique on the skin with usage of sterile gloves to prevent infection [1]. It is recommended to rinse the port after each usage with heparin solution in concentration of 10-100ij/ml . [6]

The procedure of port-a-cath catheter placement can be done in following ways: by surgery technique of the preparation of blood vessel , by the technique of direct vein puncture lead by ultrasound. The advantage of direct vein puncture is the possibility of performing the procedure in local anesthesia. Surgery placement of the port is to be done in the general or regional anesthesia. The potential places for insertion of CVC are cephalic and basilic vein, subclavian vein, vein jugular intern on the neck or vein jugular extern that can be used as the

approach at children. The choice of the place of vein puncture is usually determined on the basis of localization of the malignant disease (contralateral side at unilateral breast cancer), the presence of infection, vein thrombosis or previously placed pace – maker . The average length of the catheter to reach the wanted position (till cavoatrialjunction) when punctured jugular or vein subclavian is 18 cm on the right side and 22 cm on the left side. During the procedure EKG monitoring is necessary. After the procedure the position of the catheter is checked by the lung x-ray which excludes the presence of pneumothorax as well. [2]

The most common complication though and the most common reason of catheter explantation is infection and that is why the antimicrobial prophylaxis is necessary. [7]

Other complications can be divided according to time of origin as follows:

- complications during the intervention (puncture of artery, hematoma, air embolism, pneumothorax , heart arrhythmias, perforation of heart hollows and big blood vessels)
-complications related to catheter (dislocation, thrombosis, occlusion, rupture of catheter, narcosis of skin)
-vascular complications (thrombosis of vein vessel, arterial vein malformations)

Other division of complications related to the implantation of port-a-cath system is as follows:

-early (between 24 hours and 4 weeks from implantation)
-late (4 weeks after implatation) [3]

The purpose of the work was to present the experience of Clinical Hospital Center Bezanijskakosa related to implantation of port-a-cath catheter.

Method

Implantation of port-a-cath system presents the procedure that is performed in operation room under local anesthesia in aseptic conditions.

All the patients needed frequent parental therapy taking and blood sampling for lab analysis and the indication for implantation of S port-a-cath system was set up by an oncologist or a surgeon.

Due to compromised immunology status and prevention of the catheter infection all the patients got the prophylactic dose of antibiotics Ceftriacson 2 g an hour before the procedure.

The placement mostly was set up in the right veinsubclavian whilst with the female patients that were exposed to total mastectomy port was placed on the opposite side. In the conditions of local anesthesia catheter was placed by the technique of direct puncture of vein on the basis of anatomy points. In front of pectoral muscle the pocket in subcutaneous tissue was made where the chamber was positioned and fixed. In the end of the procedure the chamber was rinsed with the solution of heparin in concentration of 100ij/ml. After the procedure the position of catheter was verified by the x- ray.

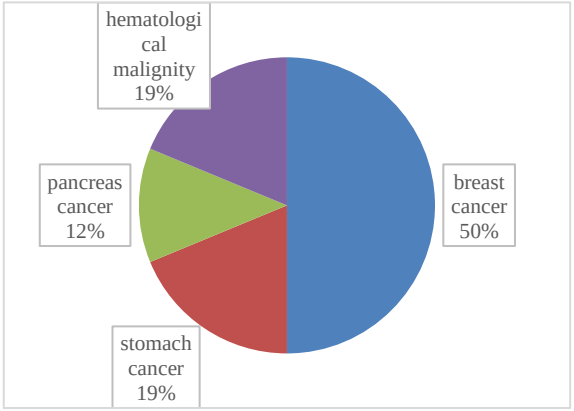
The patients and the accompanied families were educated for the usage, rinse and infection prevention of the port-a-cath system.

Results

In our institution since January 2017 until 31st January 2018., 16 port-a-cath vascular catheters were implanted to oncologic patients.

The highest percentage of the patients got the therapy for the breast cancer [8], 3 patients were treated from the stomach cancer, 2 from pancreas cancer and bile ducts and 3 patients had hematological malignity (Figure 1). The patients in average were aged 48 (27 – 75).

Figure 1: Distribution of oncologic patients underwent the port-a-cath implantation



There were no early complications during the placing of the port. Two patients had late complications - dislocation of the catheter with one that led to renewed insertion of port and the other patient had the rotation of port chamber that was solved in the local anesthesia.

DISCUSSION

In developed countries the usage of these catheters is standard in the treatment of oncologic patients whilst in developing countries the data about the usage of these catheters is poor, probably due to inaccessibility and the high costs of the catheters.

Port-a-cath systems are closed and their purpose is to provide access to the central vascular system. It gives possibility to use the skin as a natural barrier against infection and to take out a puncture needle after each usage. The advantages of such a close system are decreased possibility of infection, simple maintenance of the port that is not in use, esthetic benefit of subcutaneously positioned chamber, providing the mobility of patients as well as doing their normal daily activities and decreased possibility of complications related to central and peripheral venous catheters. [1]

Infections, hematoma, malposition of the catheter, pneumothorax, thrombosis, embolization, catheter knicking are still important complications that follow the implementation of a port – a – chat catheter. During the last decade the reports indicate that the rate of complications has been reduced significantly due to improvement of the placing technique it self as well as the material of the catheter. Previously Hicman and Borivac catheters were used and nowadays port - a - chat catheters are used due to easy accessibility and lower rate of complications. [8,9]. As the technology of producing catheters and materials has been improved, nowadays catheters with implantable port are lighter, stronger and can support higher pressure of the liquids for frequent diagnostic procedures that the malignant patients are exposed to. [10-17]

In our experience, this procedure was accompanied with late complications occurred in 12.5% of patients. Dislocation of the catheter that led to renewed insertion of port occurred in 6.25% and also, in 6.25% of patients the rotation of port chamber occurred. These complications were resolved routinely and did not significantlly affect the treatment protocol.

Advantages of this procedure were numerous. Reuse of standard CVC sometimes leads to sclerosis of the blood vessel. The veins of the patients with port-a-cath systems were protected and the reimplantation of CVC is avoided, except for one patient due to dislocation of the catherter. Also, using port-a-cath systems had benefits for medical care and other treatment procedures providing a greater comfort to medical staff by simple approach to vein route.

Subjective assessment of all the patients with implanted port-a -chat system is improved quality of life. The main advantages observed by patients were greater mobility and improved comfort.

CONCLUSION

Placing of port-a-cath system significantly improves the quality of life in the following ways:

The veins of the patients were protected from sclerosis reimplantation of CVC is avoided. Medical staff has simple approach to the vein route for therapy giving or blood sampling for the lab analysis. Patients experienced greater mobility and comfort.

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Vol. 46 (2021) No.1 TIMOK MEDICAL GAZETTE History of medicine

DOCTORS IN TIMOČKA KRAJINA AFTER WORLD WAR II

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I

This research covers the period of early post-war years 1944, 1945 and 1946. Those were very difficult years in the life of the people in Timočka Krajina, with population healthcare at a low level. Population healthcare needs by far exceeded what the state and private medical practice could offer. The urban population was in a more favourable situation because doctors, except in a few rural settlements (Salaš, Jabukovac and Andrejevac), all lived and worked in the towns. The larger rural population, especially those in remote villages, found it difficult to reach doctors and often died from diseases that were treatable or from the consequences of injuries due to the inability to timely seek and receive medical help. For the purpose of describing the life and work of doctors in the area in more detail, archival material of the Historical Archives "Timočka krajina Zaječar (1,2)" was used in this paper.

II

Doctors are the pillar of healthcare system in an area, assisted in their work by medical staff. A "List of medical personnel on the territory of the district of Zaječar on the 27th April, 1944" shows which doctors treated patients in Timočka Krajina, where, in addition to patients from the area, sick and wounded soldiers from the front, refugees and prisoners of war sought medical treatment. From the abovementioned list, one can see that at the time when it was made in the area of Timočka krajina, there were 39 doctors "on site", or one doctor per 7,387 inhabitants. One should keep in mind that given the time covered by this research, the number of doctors was constantly changing, increasing and decreasing, primarily depending on the need for doctors at the front and in the army, in the then administration, in relation to mobilization and demobilization or to those who returned from captivity.

The following doctors worked in Zajecar:

MD Milan B. Mitrović, served as the commissioner, and MD Branko P. Kosanović, as the medical officer of the Regional People's Committee. The medical officer of the command was MD Stanislav Tadić. MD Ahilo Grezo was a doctor from the Zaječar area, MD Jevrem Stanojević was a doctor at the "Serbian Balkans" mine; MD Olga Pavlović was the garrison doctor, and MD Radomir Nikolić was the doctor of the District People's Committee.

Hospital doctors in Zajecar were:

MD Ljubica Arsović, an internal medicine specialist, was head of the "internal department" of the hospital,

MD Krunoslav Popović was hospital manager and the head of the gynaecology department,

MD Miroslava Grujić-Đorđevic, was head of the department of surgery at the hospital ,

MD Desanka Đermanović-Ivanović, worked as a doctor in the health centre,

MD Cvetko Gligorijević was the town doctor and

MD Leposava Stevović was a doctor-clerk of the district office in Zaječar.

MD Mileva Kestić practiced private medicine in Zaječar.

The following doctors worked in Negotin:

MD Svetislav P. Atanasković, a malariologist, was the manager of the healthcare facility and the district medical officer of the People's Committee,

the doctors of the local command were MD Nikola Andjelković and MD Darinka Letić-Nikolić.

At the hospital, MD Midrag K. Kostić was a surgeon, hospital manager and head of the department of surgery. Head of the department of internal medicine of the hospital was MD Stanislava Ružić-Perić.

Private doctors in Negotin were MD Draginja Zdravković and MD Milan Đ. Stojković.

The following doctors worked in Bor:

MD Božidar S Ivković, served as manager of the hospital of Bratinske blagajne (a special type of social and health insurance for miners) and the district Medical Corps. Officer;

MD Georgije Pedanov, surgeon and doctor of Bratinske blagajne
MD Lepold Brnčić, dentist, doctor of Bratinske blagajne,
MD Stevan Jokanović who was a doctor of the local branch of Bratinske blagajne.
MD Mihajlo Petrovski was a doctor at the health co-operative in Zlot.

The following doctors worked in Knjaževac:
MD Leka. Djoković, served as district medical officer of the People's Committee,
MD Radmilo Janković was acting hospital manager
MD Radomir Vladić, surgeon at the department of surgery at the hospital.
MD Evgenija K. Fijošina worked as a private doctor.

In addition to those mentioned, the following doctors also worked in Timočka krajina:
MD Radmilo Jokanović, served as acting manager in Boljevac,
MD Jovan Panajotović was a doctor at the Bratinske blagajne in Majdanpek and
MD Stojan Nikolić, served as the district clerk of the People's Committee in Donji Milanovac.
The district medical officer of the People's Committee in Andrejevac was MD Jovan Zguricos while the district medical officer
doctor of the local command in Jabukovac was MD Mirko Subotić.
The duty of the district medical officer of the Municipal People's Committee in Salaš was performed by Stevan Ilić.
The private doctor in Kladovo was MD Ljutica Đ. Dimitrijević.

The abovementioned list also includes the following doctors: MD Branko Krstić, Medical Corps. major, MD Dragutin Paunović and MD Milutin Milenović, who returned from captivity and were "proposed to be taken over". MD Milić Milivoje, who lived in Gamzigradska Banja spa, ill and unable to work, was mentioned.

Most doctors in Timočka krajina served in the civil service as health commissioners and district and medical officers of regions and district, doctors of the local command and town doctors, then worked as hospital doctors, doctors of Bratinske blagajne in Bor and Majdanpek, and only a small number of them were private doctors. As doctors were few and people's needs for them were great, regardless of the functions and duties they had in the then healthcare system, they parallelly worked, as needed, in the hospital, local command, health centres, public clinics and hospitals and clinics at Bratinske blagajne and wherever it was absolutely necessary.

Given the needs of the people for treatment, in 1945, doctors were allowed to undertake private medical practice in their free time when they were not on an "official job". In an act dated on the 19th February 1945, the Health Department of the Health Commission of ASNOS in Belgrade made it clear to the District People's Liberation Committee in Zaječar that the ban for doctors to work privately was contrary to the rights of patients to "be able to choose or call for their treatment any doctor they want ". It further states that "private practice is not, nor can be prohibited by the decision of the ONO until orders are issued in that regard." Along with the act, a rulebook on the rewards they could collect from the patients was submitted for a "daily examination (from 6 am to 8 pm - 250 dinars, and in the patient's flat 350 dinars. For an intravenous injection they charged 160 dinars, for an intramuscular injection 80 dinars and for a subcutaneous one 50 dinars.

Among the doctors mentioned earlier, 30 of them were men and 9 were women. Four female doctors were single and two were widows. Among the male doctors, three were single and one was a widower. Most of the doctors were family people with a lot of children. Two doctors had four and three children respectively. Twelve doctors had two children each, and each of nine doctors had one child. Four doctors didn't have any children. Male doctors were mostly aged between 41 and 50 - 18 of them, and between 51 and 60 - 7 of them. One doctor was aged between 21 and 30, one between 31 and 40 and one between 61 and 70. When it comes to female doctors, the situation is similar. 5 of them were aged between 41 and 50, one between 31 and 40 and one between 51 and 60. Doctors made a lot of money, so it can be said that they lived better than others. Most of them had a maid.

III

One of the reasons for the changes in the number and composition of medical staff in Timočka krajina was the mobilization of doctors for army medical corps. From one act of the District People's Liberation Committee from the 2nd February, 1945, it is possible to find out

which medical staffs were mobilized from the mentioned district (3). The Health Commission of the Presidency of ASNOS in Belgrade was warned that the recruitment of medical staff, most of whom were doctors, would have "consequences in the medical organization of the District that could not be remedied and as a result of which both military and civilian medical care would suffer."

A total of 18 doctors were mobilized: MD Mićo Mićović, epidemiologist and manager of the public health centre, MD Bosiljka Popović, head of the department of tuberculosis at the hospital, MD Dimitrije Popović, paediatrics specialist from Zaječar, MD Stevan Jokanović, doctor at the mine in Bor, MD Veljko Milanović, doctor of the local command in Andrejevac, MD Stevan Ilić, district doctor in Salaš, MD Dara Letić-Nikolić, infectious disease specialist, MD Stanslava Perić-Ružić, hospital doctor and MD Draginja Zdravković, private doctor from Negotin as well as MD Slavko Pištelić, district doctor and manager of the hospital in Kladovo to the military hospital in Kruževac.

MD Mićo Mićović was mobilized as a doctor of the "14th Corps of the Hospital", and so was MD Dimitrije Popović, head of the children's department, MD Radmilo Spalajković, ear, throat and nose specialist, head of the department of otorhinolaryngology and MD Časlav Babić, surgeon and head of the department of surgery at Zaječar Hospital. Apart from the above-mentioned doctors, the following doctors were also mobilized: MD Branko S. Milosavljević, single, private doctor, MD Vladimir Kujundžić, doctor of the children's home in Negotin, MD Borivoje Ilić, traffic doctor from Knjaževac and MD Sotir Stavridis, surgeon, head of the department of surgery at Knjaževac hospital, MD Kosta Mihajlović, officer of the medical command in Boljevac, MD Aleksandar D. Anastasijević doctor of the local command in Bor, MD Milivoje S. Kosanović district doctor in Salaš, MD Miodrag Jelisijević, surgeon, major of medical service and MD Svetolik Pacić, dispensary doctor, MD Božidar Stanojević, doctor of school polyclinics from Zaječar and MD Radomir Vladić, surgeon, head of the department of surgery from Knjaževac.

The District People's Liberation Committee was particularly interested in demobilization of MD Slavko Pištelić, who enjoyed a large trust of authorities at the time and performed important public health functions of a district doctor, and the medical officer of the Command in Kladovo and at the same time ran the hospital, and mobilization, in his place, of MD Ljutica Dimtrijević a doctor, "a former MP and the best of the bunch from Stojadinović and Cvetković, who is neither capable nor trustworthy to replace the mobilized MD Pišetlić at the NLC, at the Command and to run the hospital (4), so he would be suitable for military service." It was also demanded that Mićo Mićović, epidemiologist "manager of the Public Health Centre, medical officer at the local command and one of the main administrators of the Medical School in Zaječar for military and civilian paramedics should not be mobilized (5)." His poor health and the fact that he had had a kidney removed were emphasized. It was requested that MD Stanislava Ružić-Perić, acting head of the internal department at the Negotin hospital should not be mobilized because she was in the sixth month of pregnancy, and that instead of them, a private doctor MD Milan Stojkocić, who was single and without children, be mobilized. The reply to these requests was that nothing could be done because it was "a matter for military authorities related to the needs of our army". In the early post-war years, it was difficult to find a way to secure medical personnel so that the needs of the "People's Liberation Army and the civilian needs of the district's medical services would not suffer..."

IV

On the 10th September, the Ministry of Health of the Republic of Serbia ordered that all doctors be registered - and a directory of doctors be compiled, as well as that a certificate of registration be issued to each doctor when he changed his place of residence and service. Having made the list of their doctors, the district people's committees were obliged to send it to the Ministry, which then compiled the main directory for Serbia. From the lists of doctors, basic biographical data from other sources were published along with appropriate commentary. The obligation to register doctors could not be avoided, because those doctors who did not submit to it could be punished. When a doctor was entered in the register, he received a "written confirmation", so that when he left the area where he worked, he was obliged to contact the District People's Committee to get a certificate of withdrawal without which he could

not be entered in the directory of the District Committee of the new territory.

From the preserved "Questionnaires for doctors" which were used for registering in the register of doctors in Timočka krajina, biographical data were obtained for the following doctors:

MD Jokanović Lj. Stevan, a general practitioner, serving in the hospital of Bratinske blagajne in Bor, was born on the 5th October, 1899 in Aachen, Germany. He was a Serb of Orthodox faith, a Yugoslav citizen. He was married and had four sons: Ljubomir, Živorad, Miloš and Vojislav. He graduated from the Faculty of Medicine in Belgrade in 1928, and in 1929 he acquired the right to work. He spoke Serbian and also used French and German. During the war, he worked in Brestovačka Banja spa as the manager and spa doctor and as a doctor at the hospital of Bratinske blagajne. He took part in the national liberation struggle "ideologically and propagandistically". He dwelled in ''the Bor mine'' at 10, Sarajevska Street.

MD Pedanov I. Georgije, surgeon, doctor at the hospital of Bratinske blagajne of the Bor mine, was born on the 31st March, 1887 in Neforošč, in Poltava province in Russia. He was a Russian, a "Yugoslav subject" of Orthodox faith. He was married and had a son, Evgeni, and a daughter, Katarina. He graduated from the Medical Faculty in Odessa on the 6th September, 1913. He acquired the right to practice medicine in October 1924. He spoke Russian and Serbian. After the capitulation of Yugoslavia, he got a job as a surgeon at Bratinske blagajne at the Bor mine. He participated "ideologically" in the national liberation struggle.

MD Ivković Božidar, a general practitioner, manager of the hospital of Bratinske blagajne of the Bor mine, was born in 1902 in Prokuplje. He worked part-time as a medical officer for the Bor district. He was a Serb, a Yugoslav citizen, of Orthodox faith. He had a wife Sofia and a son Danilo. He graduated from the Medical Faculty in Belgrade in 1931. He acquired the right to practice medicine in 1932. He spoke French and German. From the moment of the capitulation of Yugoslavia, on the 14th April, 1941, until the 25th August, 1942, he spent time in Germany as a Yugoslav prisoner of war, and from January 1943 he worked as a doctor in the hospital of Bratinske blagajne of the Bor mine in Bor. He participated in the national liberation struggle "ideologically". He lived in the Bor mine at 2, Ljubljanska Street.

MD Anastasijević D. Aleksandar, general practitioner in the hospital of Bratinske blagajne of the Bor mines in Bor, was born on the 16th July, 1900 in Kragujevac. He was also a doctor at the local people's committee in Bor. He was a Serb, a Yugoslav citizen, of Orthodox faith. He graduated from the Medical School in Vienna in 1927. He had had the right to practice medicine since 1929. He spoke French and German. He spent the time during the capitulation as a doctor in the hospital of Bratinske blagajne in Bor. He participated "ideologically" in the people's liberation movement. He was married, without children. He lived in the Bor mine at 5 a, Sarajevska Street.

MD Džinić Fadil, gynecologist and surgeon, doctor of the department of surgery at the hospital of local Bratinske blagajne in Bor, was born on the 28th September, 1909 in Banja Luka. He was a Croat, a Yugoslav citizen, of Muslim faith. He graduated from the Faculty of Medicine in Zagreb. He spoke French and German. From the moment of the capitulation of Yugoslavia until 1942, he spent time as an assistant at a gynaecological clinic in Zagreb, and from that year until the liberation he worked in Germany. After the Liberation for a while, he worked at the 4th ward of the Main Military Hospital in Zagreb, and after that to this moment in the hospital of Bratinske blagajne of the Bor mine. He was married and had a daughter, Farida.

MD Brenčić J. Leopold, a dentist at the hospital of local Bratinske blagajne in Bor, a specialist in oral and dental diseases, was born on the 18th October, 1905 in Petac, Slovenia. He was a Slovenian, a Yugoslav citizen, of Catholic faith. He graduated from the Medical faculty in Prague. From the moment of capitulation of Yugoslavia until the liberation, he worked as a dentist in the hospital of local Bratinske blagajne in Bor. He did not participate in the People's liberation movement. He was married, without children. He lived in the Bor mine at 1, Sarajevska Street.

MD Panajotović J. Jovan, doctor of Bratinske blagajne in Majdanpek, was born in 1877 in Belgrade. He graduated from the Faculty of Medicine in Graz, Austria. He had had the right to practice medicine since 1906. He spoke German. He spent the time from the capitulation of Yugoslavia until the liberation in Belgrade and Majdanpek, where he still worked as a doctor for Bratinske blagajne. He did not take part in the national liberation struggle due to his age and illness. He was married, without children.

MD Gligorijević I. Milan, district medical officer, was born on the 14th September, 1895 in Donji Milanovac. His "secondary service" was a doctor of Bratinske blagajne in Donji Milanovac and the Directorate of River Navigation. He was a Serb, a Yugoslav citizen, of Orthodox faith. He graduated from the Faculty of Medicine in Belgrade in 1930. He had had the right to practice medicine since 1931. He did not have a particular specialty in the profession. He spoke German, French and Romanian.

As the manager of the military hospital in Kruševac in 1941, he was captured by the Germans and released home in May as a patient. Since then, he lived in Donji Milanovac, fired from the civil service by the occupiers. On the 9th September, he voluntarily joined the units of the 25th Division, as a doctor of the 16th Brigade. He worked as a doctor in the surgical team of those units and as an epidemiologist until the 30th March, 1945, taking part in all the battles of these

units in Serbia and Bosnia. He was married and had two sons.

MD Atanasković P. Svetislav, malariologist, manager of the health centre in Negotin, was born on the 3rd May, 1895 in Mozgovo, in the Aleksinac district. His immediate service was - district medical officer and traffic doctor. He was a Serb, a Yugoslav citizen, of Orthodox faith. He graduated from the Faculty of Medicine in Paris in 1924. He had had the right to practice medicine since 1925. After the capitulation of Yugoslavia, he was in captivity for a while, only to end up as a refugee in Negotin, where he cooperated with the district people's liberation committee until the liberation. He was married and had a son (6).

MD Stojković Đ. Milan, a doctor of all medicine, a private doctor, was born on 20th 44 1889 in Negotin. He also worked as a traffic docto was a Serb, a Yugoslav subject, of Orthodox faith. He graduated from the Faculty of Medicine in 1924 in Paris, and had had the right to practice medicine since 1918. Before World War II, he was an MP and launched initiatives for the construction of water supply systems in some villages of the Negotin region. From the moment of the capitulation of Yugoslavia until the liberation, he was in captivity for some time and then found himself in Negotin. He participated in the national liberation struggle as a doctor of the command of the place and the area. He was single. He lived in Dušanova Street in Negotin (7).

MD Andjelkovic Il. Nikola, a general practitioner, who worked as a dispensary doctor-clerk, was born on the 28th December in Negotin. He completed the study of medicine in January 1924, when he acquired the right to practice medicine. On the 6th September, 1944, he was mobilized and worked as a doctor for the local and regional command. He was married and had one child. He lived at 13, Voskresenjska Street in Negotin (8).

MD Kostić K. Miodrag, surgeon, manager of the hospital in Negotin and head of the department of surgery, was born on the 4th August, 1895 in Kragujevac. He was a Yugoslav citizen of Orthodox faith. He graduated from the Faculty of Medicine on the 12th July, 1922 in Lyon, France. He acquired the right to practice medicine in 1923. He spoke French well and used English and German. After the capitulation of Yugoslavia, he was in captivity for two years, and after that he returned to Negotin. He did not take part in the national liberation struggle, except for the treatment of the wounded. He was married, without children. He lived at 4, Kraljevića Marka Street in Negotin (9).

MD Arsović S. Ljubica, an internal medicine specialist, head of the department for internal medicine of Negotin hospital, was born on the 25th December, 1900 in Belgrade. She was a Serb, a Yugoslav subject, of Orthodox faith. She graduated from the Faculty of Medicine in Belgrade on the 26th April, 1926, and had had the right to practice medicine since 1930. She spoke French and German. In the period from the capitulation of Yugoslavia until the liberation, she worked as a doctor of the internal department at Zaječar hospital, and then in the same position, from the 15th July, 1945, at Negotin hospital. She did not take part in the national liberation struggle. She was single. She lived at 3, Stanoja Nešića Street, in Negotin (10).

Apart from the abovementioned, the following doctors also worked in Timočka Krajina at the beginning of 1946: MD Radomir Nikolić, born in 1899, from Trnovac, worked as a district medical officer, MD Cvetko Gligorijević, born in 1915, from Mali Jasenovac, worked as the town medical officer in Zaječar, MD Leko Đolović, born in 1893, worked as a medical officer in Knjaževac, MD Milutin Milenović, born in 1901, from Knjaževac, worked as a doctor in Knjaževac, MD Aleksandar Pavlovcki, born in 1904 in Kiev, MD Kosta Mihajlović, born in 1883 in Trnjane and MD Stevan Ilić, born in 1898 in Donja Kamenica.

Data sources

1. Historical Archives Zaječar, ONO fund, file folder XXX/ 1945.
2. Historical Archives Zaječar, ONO fund, file folder XXXI/1946.
3. Historical Archives Zaječar, ONO fund, file folder XXX, number 1555/2/1945.
4. Historical Archives Zaječar, ONO fund, file folder XXX, number 1555/2/1945,
5. Historical Archives Zaječar, ONO fund, file folder XXXI, number 2330/14/1946.
6. Historical Archives Zaječar, ONO fund, file folder XXXI, number 2330/14/1946.
7. Historical Archives Zaječar, ONO fund, file folder XXXI, number 2330/14/1946.
8. Historical Archives Zaječar, ONO fund, file folder XXXI, number 2330/14/1946.
9. Historical Archives Zaječar, ONO fund, file folder XXXI, number 2330/14/1946.
10. Historical Archives Zaječar, ONO fund, file folder XXXI, number 2330/14/1946.

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ACKNOWLEDGEMENTS. List all contributors who contributed to the creation of the work but did not meet the criteria for authorship, such as those providing technical assistance, writing assistance, or managing a department that provides general support. Financial and material assistance, in the form of sponsorships, scholarships, gifts, equipment, medicines and more, should also be listed

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The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions**. Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the levelofsignificance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion**. For other types of papers the summary has no specific structure.

The summary must not contain any claims that are not contained in the text of the article. It must be written in such a way that even an educated nonexpert can understand the content of the article. After the summary, write 3 to 8 keywords. The words in the title should not be repeated and the keywords should be relevant or descriptive and in accordance with MESH rules (available at https://www.nlm.nih.gov/mesh).

The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, orimage,there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: http://www.nlm.nih.gov/. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

Journal articles

Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. Biol Reprod. 2003; 68 (2): 595-603.

Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

No authors listed:
Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

Books and other monographs

The author is a person (s):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.

Meeting announcements: Harris AH, editor. Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

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Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.

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Cairns RB. Infrared spectroscopy studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

Electronic material

Article in aninternetmagazine:
Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002; 102 (6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Article published electronically before the printed version:
Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002-Nov-15; 100 (10): 3828-31. Epub 2002 Jul 5.

CD-ROM:
Anderson SC, Poulsen KB. Anderson's Electronic Atlas of Hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

Online monograph:
Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

Website:
Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

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American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2screens]. Available from: http: //www.ama-assn.org/ama/pub/category/1736.html

NOTE. A paper that does not meet the requirements of this guide cannot be referred for review and will be returned to the authors for completion and correction. Adhering to the preparation instructions will significantly shorten the time of the entire process until the paper is published, which will positively affect the quality of the articles and the regularity of the publication of the journal.

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