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Невроцистицеркоза: Обзор върху психиатричната симптоматика

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Neurocysticercosis: Review of its Psychiatric manifestations

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РЕЗЮМЕ:

Невроцистицеркозата е паразитно заболяване на Централната нервна система, причинено от ларвовата форма на свинската тения, Taenia solium. При церебералната цистицеркоза обикновено има изява на психиатрична симптоматика. И двете заболявания могат да бъдат коморбидни на други неврологични синдроми, или да се проявяват самостоятелно. Тези абнормности са били предмет на широко мащабни проучвания провеждани от психиатри и невролози в началото на 20 век, полагащи основите за по–доброто разбиране на органичните психични разстройства.

Ключови думи: Taenia solium, невроцистицеркоза, клинична картина, психиатрична коморбидност

ABSTRACT

Neurocysticercosis is a medical condition of parasites investing the central nervous system. It is caused by the larval form of the pork tapeworm Taenia solium. Psychiatric disturbances are typically present as clinical symptoms of cerebral cysticercosis, both in comorbidity with other neurological syndromes or as a dominant feature. These kinds of abnormalities were a subject of extensive studies by psychiatrists and neurologists at the beginning of the 20th century, providing key preliminary insights into organic mental diseases.

Key words: Taenia solium, neurocysticercosis, clinical manifestations, psychiatric comorbidity

INTRODUCTION

Neurocysticercosis (NCC), a condition caused by the pork tapeworm T. solium, is the most common parasitic infection of the CNS (5). Nevertheless, its natural history hasn't been well documented. As regards the epidemiology of NCC, the disease is widely endemic in underdeveloped countries in Central and South America, Asia, and Africa. According to statistical data, more than 400,000 people in Latin America (1,11) and 10% of those presenting neurologic signs in developing countries (10) have NCC. NCC accounts for up to 2% of neurologic and neurosurgical admissions in southern California (15) and for more than 1000 cases per year in the United States (23). It mostly affects adults in their 30s or 40s while the infection is quite uncommon in the elderly and in children younger than 2 years owing to the long incubation period of T. solium (19).

LIFE CYCLE OF TAENIA SOLIUM

It takes approximately 2 months for the larva to evolve into a mature adult tapeworm at is capable of producing eggs (18). The fully-grown tapeworm lives in the human small intestines and consists of a scolex and strobila. The strobila consists of proglottids that contain approximately 40,000 eggs. T. solium can shed up to 300,000 eggs daily into the feces. Afterwards, the eggs are disseminated into the environment. Free-ranging pigs normally feed on human feces that are contaminated with eggs, which later develop into cysticerci (scolex containing cysts). The ingestion of undercooked infected pork containing cysticerci, whereby ingestion of T.solium eggs occurs, and the contact with carriers or contaminated food infects humans with NCC. Ingested eggs hatch in the stomach and the intestine and the then-formed oncospheres circulate in the blood and get access to various tissues. Thus cysticerci often develop in subcutaneous tissue, skeletal muscle, the brain, the eyes, heart, liver and lungs. Actually, developing cysticerci cause little host reaction. Usually only after several years, when cysticerci denigrate, inflammation develops. Ultimately, the cysts undergo necrosis and may become calcified. These calcified or dead cysts are antigenic and upon being recognized by the host, may induce an inflammatory reaction (17). The survival of the eggs is adversely affected by extreme temperature and desiccation, whereas humidity, temperatures ranging between 10°F and room temperature favor egg survival. It should be taken into consideration that wind, water, and birds help dispersing the eggs (19).

CLASSIFICATION AND PROGNOSIS

NCC is categorized according to the viability and location of the parasite in the host CNS. The classification is divided into active (vesicular), transitional (inflammatory, degenerating, or colloidal), granular nodular (healing), and inactive (calcified) stages (4). Each viability criterion is further subdivided into extraparenchymal and parenchymal. Parenchymal forms of NCC have good prognosis in terms of remission of clinical signs (7). On the other hand, the prognosis for extraparenchymal forms is unfavorable, especially in patients with hydrocephalus due to arachnoiditis (7). The viability criterion allows analysis of the parasite`s natural history and production of pathophysiologic changes in the hosts CNS. This is of prime importance as clinical manifestations and therefore therapeutic procedures vary depending on the classification (19).

DISEASE MANIFESTATIONS

The presentation of NCC in accordance with the stage, location, and amount of the cysts.11 The clinical manifestations develop upon an inflammatory response around a cysticercus that is degenerating. What triggers such degeneration hasn't been established, but the cyst seems to lose its ability to regulate the host immune response. It has been estimated that peak presentation occurs in 3 to 5 years post infection, but it might take longer than 30 years. After degenerating, the cysts become calcified and inactive. At this stage, they may no longer cause symptoms or may serve as a core for epileptic activity. Parenchymal NCC is the most common type of NCC. As a great number of cysts invade the brain parenchyma, clinical manifestations include seizures (focal or generalized), focal encephalitis, edema, and vasculitis. Any focal

neurologic deficits are usually transient, with remissions and relapses. Patients may suffer from headaches and signs of increased intracranial pressure in both the parenchymal and extraparenchymal forms. Patients having extraparenchymal disease usually develop symptoms of hydrocephalus owing to intraventricular cysts. Subarachnoid cysts may lead to visual field defects and cranial nerve palsies. Spinal cord cysticer-cosis is rare. When the spine is affected, the thoracic region is the most common location. Spinal cord cysticercosis can in turn lead to radiculopathy, paresthesias, and sphincter disturbances. Cysticerci may also develop in the eyes, heart, muscle, or subcutaneous tissue. Ocular cysticercosis is usually asymptomatic. Chorioretinitis, retinal detachment, or vasculitis may result in inflammation that occurs around degenerating cysticerci. When the heart is affected, conduction defects and arrhythmias may ensue. Subcutaneous tissue and muscle involvement will result in subcutaneous nodules and myopathy (19).

PREVALENCE OF PSYCHIATRIC DISORDERS

Most of the psychiatric knowledge on NCC has been gathered from studies carried out in mental institutions in the late 1800s and the early 1900s. These sources have provided us with detailed descriptive accountss of the patients' psychopathology. In many cases it would mimic major psychiatric syndromes such as schizophrenia and bipolar disorder (12,13, 24).

The occurence of NCC was presumed to be high in psychiatric institutions not only due to a causal relationship between the two medical conditions, but also because patients with severe forms of psychosis and dementia were prone to become secondarily infected as a consequence of poor hygiene and coprophagia.A number of psychiatric syndromes have been so far attributed to NCC. In early papers of classic research on this subject, one can come across accounts that are indistinguishable from dementia praecox, paranoia, neurosyphilis, Korsakoff's psychosis and dementia (22,27). Chronic delusions and hallucinations, as well as mood variations compatible with the diagnoses of major depressive disorder and bipolar disorder were also reported (2,21). As the etiology of these cases was seldom established in life, clinical findings were retrospectively correlated to neuropathological observations of signs of the parasitic infection. Leukart (1886), for instance, suggested that cysticerci that are located in the ventricles and basal ganglia were more liable to induce mental abnormalities than cortical lesions (14). In the majority of these cases, neuropsychiatric findings were compatible with major cognitive impairments such as delirium and dementia (14, 24).

In Europe, further interest in NCC was raised after the evaluation of cysticercosis in 450 British ex-servicemen who had acquired the disease during military placements in pre-1947 colonial India (6). 39 of these patients (8.7%) manifested mental disorders as a prominent feature – there were cases of organic deterioration, affective disorders and schizophrenia. Excluding the former cases of unequivocal organic mental disease, medical records showed divergence on the etiological relationship between the psychiatric condition and cysticercosis.

Clinicians from Brazil, Chile, Mexico, China and other countries where prevalence of the disease was high have also made important contributions to this field of scientific knowledge.

In a cross-sectional study of 38 cases at a neurology outpatient clinic in Brazil, depression was the commonest psychiatric manifestation, as shown by the Present State Examination and the Schedule for Affective Disorders and Schizophrenia – Lifetime Version semi-structured interviews (9,25,28). Signs of psychosis were observed in five patients although none had a clear-cut schizophrenic or bipolar presentation. Only 13 patients (34.2%) were classified as mentally healthy by the aforementioned psychometric methods. Thirty-two patients were assessed by the Mini-Mental State Examination and the Strub and Black's Mental Status Examination (8,26), whereby neuropsychological dysfunction was identified in the majority of the cases (87.5%). Yet, severe cognitive abnormalities were less frequent (15.6%) (9, 24). Attention deficits were detected in all the patients assessed, which has probably been influ-

enced by the effect of antiepileptic drugs(carbamazepine and barbiturates). 59.4% had mild to moderate and 40.6% manifested severe attention disturbance. Memory and language were affected in 78% of the patients and higher cognitive functions were impacted in 87.5%.Other deficits included disorders of praxis and motor functions (50%). Reading and writing skills were not so commonly impacted (28% and 0.6% of patients, respectively). There was no clear pattern of localization for the neuropsychological dysfunction in the patients. Despite the clinical heterogeneity of the test group, there was only a mild correlation between the manifestation of depression and laboratory signs of active disease (defined by the presence of parenchymal cysts, not just calcifications , as shown by computed tomography(CT) and magnetic resonance imaging(MRI) scans, and/or inflammatory cerebrospinalfluid (CSF)) (P = 0.04), and modest correlation with the occurrence of intracranial hypertension (P = 0.1). Psychosis also possibly correlated with intracranial hypertension (P =0.06) but not with disease activity (P = 0.5). No association was found between the psychiatric manifestations and the occurrence of epilepsy (P = 0.63), even when the epidemiological group of active epilepsy 29 was considered (P =0.72), nor with the current use of steroids (P =1). Previous history of depressive episodes swas strongly associated with current depression (P = 0.006) and psychosis (P = 0.04) (9).These findings come in accordance with several other studies that have addressed the etiology of organic mood disorders. Family history of depression and history of depression before the onset of the organic disease are regarded as risk factors for developing depression in patients with cerebrovascular disease and multiple sclerosis due to greater biological vulnerability (3,20). Disease activity, i.e. diffuse or localized central nervoussystem inflammation, is temporally related to organic mood disorders, as shown in other medical and neurological conditions like systemic lupus erythematosus and multiple sclerosis (16, 24).

CONCLUSIONS

The assessed mental abnormalities and cognitive dysfunctions in respectively 65.8% and 87.5%, of a cross-section of neurological outpatients with NCC presents an estimate of the high prevalence of psychiatric morbidity in the given setting. Samples of psychiatric inpatients might assist with a different profile of psychiatric findings of more severe or even specific forms of mental diseases. That is thanks to psychiatric surveys based on patients from mental institutions in the first half of the 20th century reporting up to 75% of severe mental diseases in association with cysticercosis. Such a high rate might be accounted for by a long period of the untreated underlying organic disease, since many of the aforementioned patients had previous history of neurological syndromes prior to psychiatric admission, as written in their medical records. It is possible therefore that mental disease represents one of the consequences of a deteriorating organic illness, in the setting of no effective therapeutic strategies for the parasitic infection at that time.

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Множествени първични малигнени неоплазми

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Multiple primary malignant neoplasms

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РЕЗЮМЕ:

В последното десетилетие честотата на пациентите с множествени първични малигнени заболявания нарастна значително както поради подобрените диагностични възможности, така и поради удължената преживяемост. Подобен случай е описан за първи път от Whipham (1878) при пациент с левкемия и карцином на панкреаса. Billroth (1889) формулира първите три критерия, характеризиращи подобни тумори: всеки тумор е с различен хистологичен произход; имат различна локализация (добре диференцирани макро, -микроскопски); всяка лезия има свои метастази. Warren and Gates(1932) предлагат актуални критерии: всеки тумор трябва да бъде злокачествен; да бъде категорично различен от другия; възможността единият да бъде метастатична лезия на другия се изключва. Огромното разнообразие и възможности за комбиниране на тези тумори прави невъзможно създаването на една

ABSTRACT

In recent years, the incidence of patients with multiple primary malignant tumors has increased considerably - due to the increased diagnostic capacity and prolonged survival of these patients. For the first time, such a case described by Whipham (1878) of a patient with leukemia and pancreatic carcinoma. First Billroth (1889) formulates three primary criteria for distinguishing these tumors: each tumor must have a different histological appearance; the tumors must arise in various locations (i.e., clearly differentiated macro- and microscopically); each lesion must produce its metastasis. Warren and Gates (1932) offered broader criteria: each of the tumors has a clear picture of malignancy; each must be distinct; the possibility of one being a metastatic lesion of the other must be excluded. The huge diversity and countless possibilities for combinations of these tumors make it impossible to structure them into a single classification. That is why we divide them into

класификация. Ето защо те са разделят в две групи: синхронни (две или повече неоплазми се развиват едновременно в период до 6 месеца) и метахронни (вторият карцином се появява повече от 6 месеца след първия). Според статистическите данни 5-годишната онкологична преживяемост е нарастнала до 60%. Данните показват, че броят пациенти с множествени първични малигнени заболявания ще нараства.

Ключови думи: синхронни неоплазми, метахронни неоплазми

two groups: synchronous (two or more neoplasias develop simultaneously within a period of up to 6 months and metachronous (the second carcinoma develops after 6 months compared to the first). By statistical data, 5-year oncology survival rate increased to 60%. Data show that the number of patients with multiple primary malignant neoplasias will increase.

Key words: synchronous neoplasms, metachronous neoplasms

INTRODUCTION

In recent years, the incidence of patients with multiple primary malignant tumors has increased considerably - due to the increased diagnostic capacity and prolonged survival of these patients. Patients survived a malignancy have a 20% higher risk of developing a second primary neoplasia in the same or another organ compared to the general population. Publications in this area were recognized since the late nineteenth century.

In 1888 Fenger [5] published the first report on synchronous colorectal carcinomas. Later, in 1889 Billroth [1] reported a series of cases of multiple primary breast carcinomas. Until the end of the 19th century, there was a lack of interest in the scientific circles of these isolated cases of patients with multiple neoplasias. At the beginning of the 20th century, however, it is noticeable that not only the incidence of patients progress but also the number of cases described in the scientific literature. In 1932, Warren and Gates [19] summarized 1259 cases from the worldwide publications. In the following years, over 10,000 cases have been reported globally.

In the period 1926-1931 Warren [18] and colleagues observed cases of autopsy patients with malignancies, 3.7% of all had multiple primary lesions. From the period 1932-1943 6.8 % have been demonstrated with multiple primary malignancies. Hurt and Borders [6] reported 3.3% primary malignant lesions among surgical patients at the Mayo Clinic in 1929. In 1937 Stalker [14] and associates confirm 4.5% of primary malignant neoplasia among surgical interventions in the same clinic.

It is noteworthy that the number of these patients has increased significantly over the years and they are no longer isolated cases. Due to improved treatment methods, patients who have overcome a malignant disease live long enough to have the risk of developing a second illness.

CRITERIA FOR DIAGNOSIS

At the beginning of the 20th century, it was wrongly believed that the presence of a malignant neoplasia suppressed the development of another. Hurt and Broders [6], however, noticed a trend among 71 cases that the occurrence of a second neoplasia is more likely to occur in the same organ or system as the first. Taylor, 1931 reported 18 breast cancer patients who developed a second malignancy in the genital tract [15]. A little later, other scientists (Pierce and Slaughter, Huber) sought an explanation for the relationship between estrogen-dependent organs and the occurrence of a second neoplasia. However, there is no clear evidence to support these two hypotheses [13].

All this requires the establishment of clear criteria for the diagnosis of multiple primary malignancies. Due to the specificity, variety, and unpredictability of these neoplasias, it's hard to be absolute. Multiple primary malignancies are two or more tumors that are found in the same individual at the same time or consecutively over a given period, i. e. occur synchronously or metachronically in one or different organs.

First Billroth [1] formulates three primary criteria for distinguishing these tumors:

- Each tumor must have a different histological appearance
- The tumors must arise in various locations (i.e., clearly differentiated macro- and microscopically)
- Each lesion must produce its metastasis.

Subsequently, it became apparent that due to these strict requirements, a low incidence of multiple primary malignant neoplasias was reported. This is not real because it is entirely possible that two carcinomas, independently of each other, with a similar histological characteristic, occur. In 1932, Warren and Gates [19] offered broader criteria:

- Each of the tumors has a clear picture of malignancy
- Each must be distinct
- The possibility of one being a metastatic lesion of the other must be excluded.

CLASSIFICATION

The huge diversity and countless possibilities for combinations of these tumors make it impossible to structure them into a single classification. That is why we divide them into two groups [12]:

1. Synchronous - when two or more neoplasias develop simultaneously within a period of up to 6 months.
2. Metachronous - when the second carcinoma develops after 6 months compared to the first. This division is somewhat conditional. Synchronic tumors are not relevant to the prognosis if they are diagnosed on time. But if their presence is missed, they later manifest themselves as the so-called an advanced metachronous tumor at an advanced stage.

Patients with primary malignancy had a 1.29-fold higher risk of developing a second malignant tumor with the same localization (Schoenberg) as compared to the general population. In general, we distinguish the following risk factors: genetic predisposition, exposure to environmental carcinogenic factors, prior therapy for first malignant neoplasia (chemotherapy, radiotherapy), immunocompromised status. Most likely, the etiology of a second primary malignant tumor is multifactorial **(table 1).** Other determinants include improved diagnostic tests, complicated, complex treatment, a presence of screening programs (for breast cancer, colorectal cancer, prostate cancer, etc.).

CASE STUDIES IN DIFFERENT COUNTRIES

The scientific literature has many retrospective studies evaluating the incidence of multiple primary neoplasias. Due to the advanced diagnostic methods, it ranges from 0.4% to 21% in different countries.

In a 10-year study (1944-1953) in Mayo Clinic, USA, involving 37,580 patients, 1,909 cases of histologically verified multiple primary malignancies were reported, or 5.1%. This percentage increased after 309 autopsy cases demonstrating the presence of more than one tumor left asymptomatic during the lifetime [9]. A Swedish study of 808 522 oncologists over 30 years confirms 11% of cases with second primary malignancy **(Table 2).**

SUMMARY

By statistical data, 5-year oncology survival rate increased to 60%. According to the World Cancer Registry for 2012, there are 14.1 million cancer patients, of which 8.2 million have died. The prognosis for 2030 showed 21.7 million cases of malignancies, of which 13 million will end fatally. Data show that the number of patients with multiple primary malignant neoplasias will increase. This patient pool is of interest not only because of the increasing incidence but also because of the therapeutic challenges, especially when combining a solid tumor with an on-hematologic disease. In daily clinical practice, these patients should be individually refined.

CASE STUDIES I N DIFFERENT COUNTRIES

The scientific literature has many retrospective studies evaluating the incidence of multiple primary neoplasias. Due to the advanced diagnostic methods, it ranges from 0.4% to 21% in different countries.

Table 1. ***Epidemiological factors of multiple primary tumors***

Host factors	Genetics	For example, ancestry, Li-Fraumeni, and BRCA mutations
	Hormonal factors	For example, hormonal therapy and endometrial cancer
	Prior cancer diagnosis and treatment exposures	The incidence of a second malignancy is higher in a person with a previous cancer diagnosis compared with a person of the same age group without a prior cancer
Lifestyle factors	Alcohol	These are risk factors for several cancer types and are therefore more likely to develop more than one of these predisposed cancer types compared with people without these lifestyle factors
	Tobacco	
Environmental influences	Geography	For example, cancer risk in areas of increased radon exposure
	Pathogens	For example, infections (human papillomavirus,
		Epstein-Barr virus)
	Occupation	For example, profession-associated cancer types like mesothelioma in workers with asbestos

Source: Vogt at al., 2017

In a 10-year study (1944-1953) in Mayo Clinic, USA, involving 37,580 patients, 1,909 cases of histologically verified multiple primary malignancies were reported, or 5.1%. This percentage increased after 309 autopsy cases demonstrating the presence of more than one tumor left asymptomatic during the lifetime [9]. A Swedish study of 808 522 oncologists over 30 years confirms 11% of cases with second primary malignancy **(Table 2).**

Table 2. ***Incidence of multiple primaries over all cancer sites in the literature***

Number of patients evaluated	Geographic region	Frequency of multiple primaries	Mean follow-up (years)	Definition used for multiple primaries (SEER/IACR/IARC)	*Reference*
19 252	Italy	2.4%	2.5	IACR	5
1 015 564 men	USA	15.8%	NA	SEER	6
951 022 women		14.4%		IACR	
		17.2%		SEER	
Number of patients evaluated	Geographic region	Frequency of multiple primaries	Mean follow-up (years)	Definition used for multiple primaries (SEER/IACR/IARC)	*Reference*
		14.55		IACR	
334 168	Victoria, Australia	4.3%	5	IACR	8
		7.7%	10		
		12.4%	20		
2 919 023	22 European countries	6.3%	NA	IACR	7
57 393	West of Scotland	5%	5	IACR	4
938	Netherlands	7%	NA	NA	17
1873	USA	7.2%	5	SEER	11
		11.4%	10		
		13.3%	15		
		14.8%	20		

Source: Vogt at al, 2017

In a retrospective study in China for the period 01.2010-12.2013 involving 15,398 cancer patients, reported 0.99% of cases of multiple primary malignant neoplasias [8]. They report that patients with primary head-neck and urinary tract malignancies were most at-risk of developing a second tumor, 50% of them were having no prior radiation or chemotherapy **(Table 3).**

Most studies show that male gender is more affected [8]. Patients with multiple tumors are older than those with only tumors - between 50 and 70 years of age. Most commonly, the combinations reported in men are the prostate-colorectal carcinoma, prostate-lung, prostate-chronic lymphocytic leukemia. In women: breast cancer with contralateral breast cancer or breast cancer in conjunction with hematological malignancy **(Table 4).**

SUMMARY

By statistical data, 5-year oncology survival rate increased to 60%. According to the World Cancer Registry for 2012, there are 14.1 million cancer patients, of which 8.2 million have died. The prognosis for 2030 showed 21.7 million cases of malignancies, of which 13 million will end fatally. Data show that the number of patients with multiple primary malignant neoplasias will increase. This patient pool is of interest not only because of the increasing incidence but also because of the therapeutic challenges, especially when combining a solid tumor with an on-hematologic disease. In daily clinical practice, these patients should be individually refined.

Table 3. ***Second tumor appearance depending on location***

Malignant tumor	N	MPMTs(N)	Ratio (%)
Lung cancer	3389	12	0.35
Breast cancer	3028	37	1.22
Leukemia/lymphoma tumors	2960	4	0.14
Gynecological tumors	757	15	1.98
Digestive system tumors	4014	50	1.25
Urinary tumors	334	14	4.19
Head and neck cancer	354	20	5.65
Nervous system tumors	158	0	0.00
Multiple myeloma	404	0	0.00
Total	15398	152	0.99

Source: Liu Z.,at all,2015

Table 4. ***Common risk factors for multiple primaries in women with breast cancer*** (adapted from Wood et al. 2012)

SECOND CANCER	RISK FACTORS		
Second breast cancer	Genetic (BRCA1, BRCA2)	Endocrine/hormonal factors	Obesity
Ovarian	Genetic (BRCA1, BRCA2)	Endocrine/hormonal factors	
Uterine/endometrial		Endocrine/hormonal factors	Obesity
Colorectal cancer		Endocrine/hormonal factors	Obesity
SECOND CANCER	RISK FACTORS		
Renal cell carcinoma			Obesity
Pancreatic			Obesity
Thyroid			Obesity
Gallbladder			Obesity

Source:Vogt at al, 2017

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Ефекти на триптани второ поколение – фроватриптан и алмотриптан върху локомоторната активност при експериментален модел на мигрена

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Effects of second generation triptans - frovatriptan and almotriptan on locomotor activity in an experimental model of migraine.

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РЕЗЮМЕ:

Целта на настоящето проучване е да се установят ефектите на фроватриптан и алмотриптан върху локомоторната активност на мъжки и женски плъхове с модел на мигрена. **Материали и методи:** Бяха използвани бели мъжки и женски плъхове порода Wistar (12 групи: 6 – мъжки и 6 – женски, n=8) третирани с : Контрола (физ. разтвор) субкутанно; Нитроглицерин 10 мг/кг интраперитонеално (НТГ); НТГ + Фроватриптан 2,5 мг/кг субкутанно; НТГ + Фроватриптан 5 мг/кг субкутанно; НТГ + Алмотриптан 3 мг/кг субкутанно; НТГ + Алмотриптан 6 мг/кг субкутанно. В апарата

ABSTRACT

The aim of this experiment was to evaluate effects of frovatriptan and almotriptan on locomotion in male and female rats with experimental model of migraine. **Materials and methods:** Male and female Wistar rats were used (12 groups: 6 – male, 6- female, n= 8) treated with: Control (saline) s.c; Nitroglycerin (NTG) 10 mg/kg i.p; NTG + Frovatriptan 2,5 mg/kg s.c; NTG + Frovatriptan 5 mg/kg s.c; NTG + Almotriptan 3 mg/kg s.c; NTG + Almotriptan 6 mg/kg s.c. In Activity Cage apparatus was registered horizontal and vertical activity of each rat for 5 minutes. The statistic evaluation was done

„Activity Cage" се регистрираха броя хоризонтални и вертикални движения на всяко животно еднократно за 5 минути. Статистическата обработка на данните бе направена чрез програмата SPSS (17.0). За всяка група бе изчислено средната ѝ стойност (mean) и стандартната ѝ грешка (SEM). **Резултати:** Женските плъхове третирани с фроватриптан и в двете дози, статистически значимо завишиха хоризонталната активност спрямо групата третирана само с модел, докато ниската доза фроватриптан завиши само вертикалната активност. Женските плъхове третирани с алмотриптан и в двете дози не промениха цялостната локомоторика. Мъжките групи плъхове третирани с фроватриптан 2,5 мг/кг достоверно завишиха хоризонталната и вертикална активност спрямо моделната група с нитроглицерин. Групата с алмотриптан 6 мг/кг значимо занижи хоризонталната активност, а вертикалната не бе променена. **Заключение:** Нашите резултати ни позволяват да предположим, че повишената експлораторна активност при мъжките плъхове с фроватриптан се дължи на пресинаптична регулация чрез 5-HT1A, 5-HT1B рецепторите локализирани върху мотоневроните.

Ключови думи: локомоторика, фроватриптан, алмотриптан, плъхове, модел на мигрена

by SPSS (17.0) by calculating mean and SEM for each group. **Results:** Female rats treated with frovatriptan in both doses, significantly increased the horizontal activity compared to the group treated only with NTG. The low dosage of frovatriptan increased only the vertical activity. Female groups of rats treated with almotriptan in both doses did not show significant changes in total motor activity. Male rats injected with low dosage frovatriptan increased significantly horizontal activity compared to the group treated only with NTG. Frovatriptan in both doses, applied in male rats significantly increased the vertical activity compared to the model group. Male rats treated with the high dosage almotriptan significantly decreased the horizontal activity, while vertical activity was not changed. **Conclusion:** Our results permitted to suggest that the increased exploring activity in both rat sexes, treated with frovatriptan is due to some presynaptic regulation that comes directly from both 5-HT1A, 5-HT1B receptors, localized on motoneurons.

Key words: locomotion, frovatriptan, almotriptan, rats, migraine model

INTRODUCTION

Serotonin (5-HT) is very important monoamine neurotransmitter and plays a significant role in modulating locomotor activity. Moreover, different subtypes of 5-HT receptors modulate motor functions in rodents, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} [5].

The key mechanism of frovatriptan and almotriptan action in migraine is their agonist activity on 5-$HT_{1B/1D}$ receptors and moderate affinity to 5-HT_{1A} receptors [3,6].

Different neuronal pathways participate in the regulation of locomotor activity - glutamatergic, noradrenergic, dopaminergic and serotoninergic. Most of the receptor subtypes (including 5-$HT_{1A/B/D}$) are expressed in motoneurons. [9].

The aim of this experiment was to evaluate some effects of frovatriptan and almotriptan on locomotion in male and female rats with experimental model of migraine.

MATERIALS AND METHODS

Animals

We used male and female Wistar rats with initial body weight 200-220g. The rats were housed in standard laboratory conditions (23-25°C, 50-55% humidity and 12/2h light/dark cycle) and fed with standard commercial food and given water *ad libitum.*

Experimental migraine model was induced via intraperitoneal (i.p.) injections with nitroglycerin 10 mg/kg (NTG). 1^{30} h after NTG administration, rats were treated subcutaneously (s.c.) with triptans. The rats were divided into twelve groups (6 male and 6 female groups,

n=8) as it follows: Control group – treated with saline 0.1 ml/100g s.c. Second group, treated only with NTG 10 mg/kg i.p. Third group, treated with NTG 10 mg/kg i.p and Frovatriptan 2.5 mg/kg s.c. Fourth group, treated with NTG 10 mg/kg i.p and Frovatriptan 5 mg/kg s.c. Fifth group, treated with NTG 10 mg/kg i.p and Almotriptan 3 mg/kg s.c. and sixth group, treated with NTG 10 mg/kg i.p and Almotriptan 6 mg/kg s.c.

All experiments were carried out according to the guidelines of laboratory animals in EU-guidelines/EEC Directive of 1986.

Substances

Sodium chloride solution 0.9% (saline) was purchased from B.Braun Medical EOOD (Sofia, Bulgaria). Both triptans were purchased as pure substances Frovatriptan succinate monohydrate and Almotriptan malate from Sigma-Aldrich (USA), and NTG was purchased as Nitronal solution. (G. Pohl-Boskamp GmbH & Co).

Locomotor activity test

The original automatic activity cage (Ugo Basile, Italy) with UV detector for horizontal and vertical movements was used. The rats were tested 40 min after the administration (s.c.) of triptans. Each rat had single test for 5 min. The horizontal and vertical movements were measured in relative units.

STATISTICAL EVALUATION

Data management was performed in SPSS 17.0 statistical software. All observed parameters were expressed as mean ± S.E.M for each group. A value of $P<0.05$ was considered representative of a significant difference.

RESULTS

Female rats with migraine model, i.e. the groups treated only with NTG, did not show any significant change in locomotion. The groups treated with NTG and frovatriptan in both dosages increased significantly the horizontal activity ($P<0.05$), compared to the model group, while the vertical activity was increased significantly ($P<0.05$) from the group treated with frovatriptan in low dose. In female groups, rats treated with almotriptan in both doses did not induce changes in total locomotion **(Figures 1, 2).**

On the other hand male rats treated with experimental model of migraine with NTG 10 mg/kg did not change the locomotion. Only the group treated with model and frovatriptan 2.5 mg/kg, increased significantly ($P<0.05$) the horizontal activity compared to model group. Frovatriptan 5 mg/kg did not show any significant results. Male rats treated with frovatriptan in both doses increased significantly ($P<0.05$) the number of vertical movements, compared to the group injected only with NTG. The group treated with almotriptan 6 mg/kg decreased significantly ($P<0.05$) the horizontal activity, while vertical movements were not changed **(Figure 3, 4).**

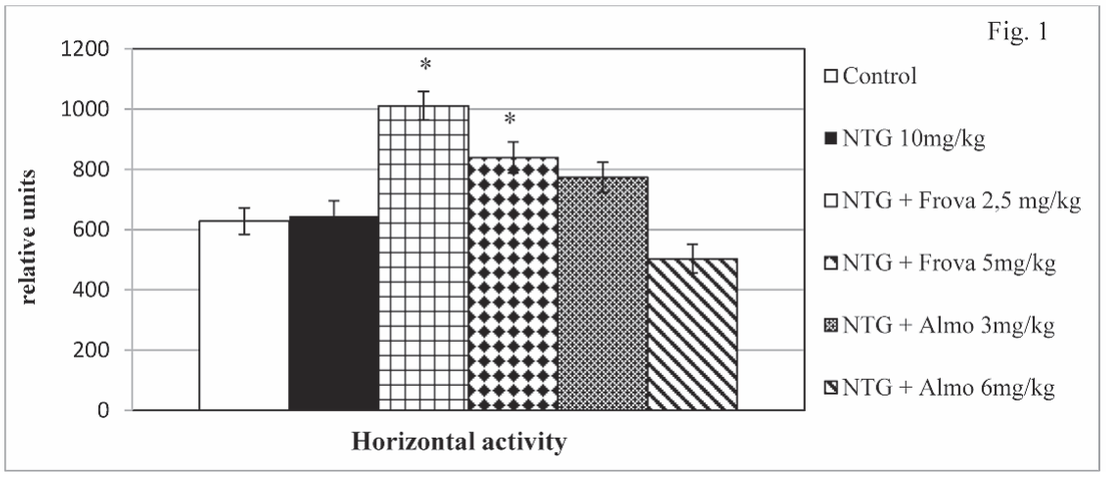

Figure 1. ***Effects of frovatriptan and almotriptan on horizontal activity in female rats with migraine model;***
**** p<0.05 compared to the model group, treated only with NTG***

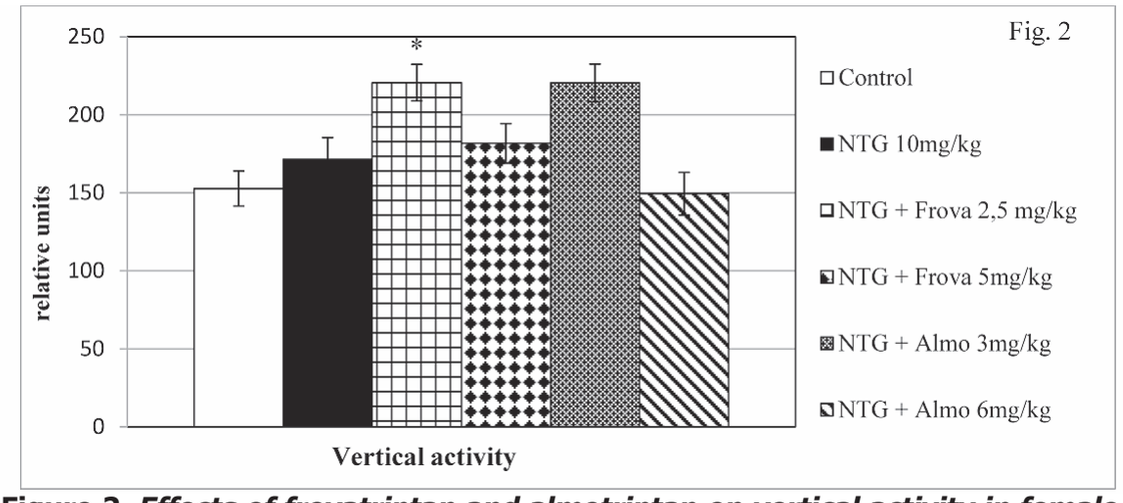

Figure 2. ***Effects of frovatriptan and almotriptan on vertical activity in female rats with migraine model;***

**** p<0.05 compared to the model group, treated only with NTG***

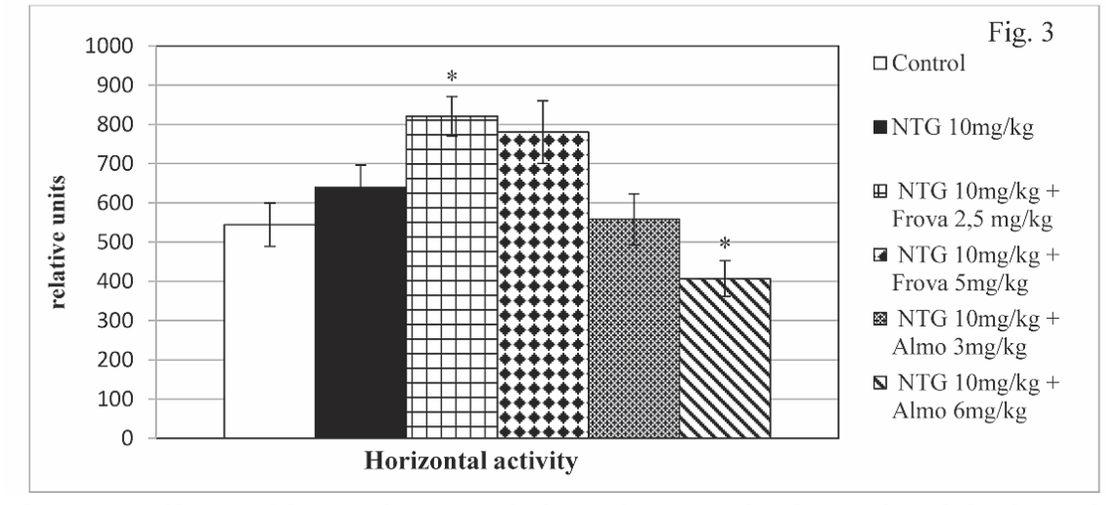

Figure 3. ***Effects of frovatriptan and almotriptan on horizontal activity in male rats with migraine model;***

****p<0.05 compared to the model group, treated only with NTG***

DISCUSSION

The abundance of 5HT1B/1D receptors in some subcortical brain regions – caudate putamen, n. accumbens, hypothalamus and also in the frontal cortex in mice, rats and guinea pigs, suggests their participation in modulating locomotor activity [10].

Other authors describe the possibility 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors to regulate dopaminergic activation, GABA neurons and serotonin projections to striatum, which in their turn, perform presynaptic serotonin regulation on dopamine release [1].

Our experiments showed that female rats treated with the NTG migraine model and frovatriptan increased the total locomotion. Frovatriptan possesses high agonist activity to 5-HT1B receptors (pKi = 8.6). The specific location of these receptors on GABA neurons in the ventral tegmentum and their influence from frovatriptan indirectly leads to increased dopaminergic transmission in these areas, respectively, and dopamine levels [11].

The above mentioned suggests that frovatriptan's high affinity to 5-HT_{1B} receptor could influence locomotor activity in male and female rats. In an experimental study Borycz et al.

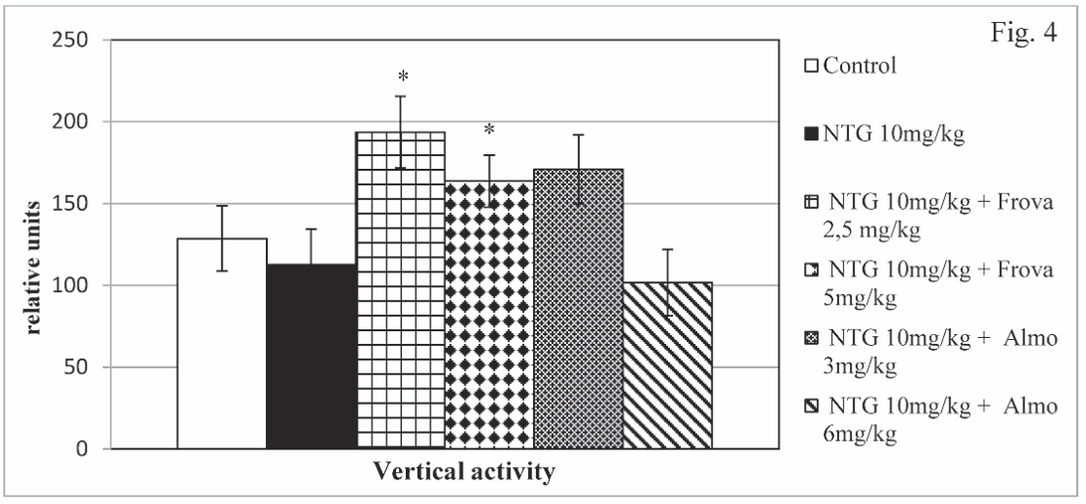

Figure 4. ***Effects of frovatriptan and almotriptan on vertical activity in male rats with migraine model;***

****p<0.05 p<0.05 compared to the model group, treated only with NTG***

(2008) explored $5HT_{1B/1D}$ receptor agonist SKF99101H activity and detected hyperlocomotive activity in guinea pigs, which is another proof of the participation of 5-HT_{1B} receptors in the motor activity at all [4]. Frovatriptan is a full agonist with moderate affinity to 5-HT_7 receptors (pKi/IC50 =6.7) [2]. A large number of immunohystochemical studies prove the location of this receptor in thalamus, hypothalamus and hippocampus. All these structures are also proven to be involved in motor activity in rodents which gives us the reason to suggest that 5-HT_7 receptors do not play a minor role in the exploratory activity in male and female rats [8]. Decreased horizontal activity in male rats treated with almotriptan 6 mg/kg probably could be due to almotriptan's agonist activity to 5-HT_{1A} receptors (pKi/IC_{50} =7.4), for which scientific data describes a possible suppressive role on locomotion in male rats, treated with NTG migraine model [7].

CONCLUSION

Frovatriptan showed better results in the „open field" test in both rat sexes, while the suppressed motor activity in the rats treated with almotriptan is a consequence of its agonist activity to 5-HT_{1A} receptors.

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Сравняване на телесното тегло, BMI, нивата на глюкоза, кръвното налягане и пулсовата честота на различни възрастови групи пациенти включени в проекта НИРДИАБО от Пловдив

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Comparison of body weight, BMI, glucose level, blood pressure and heart rate in different groups of patients included in NIRDIABO project from Plovdiv

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РЕЗЮМЕ:

Въведение: Цел на проучването е да се сравнят различни показатели (тегло, BMI, кръвна захар, кръвно налягане и пулс) в няколко възрастови групи от Пловдив и да се оцени възможния риск от развитие на диабет тип 2. **Метод:** В изследването са включени доброволци с BMI над 25, разделени на 5 възрастови групи: а) 20-29г; б) 30-39г; в) 40-49г; г) 50-59г; д) 60-69г (n=5-9). Вземането на кръвни проби е единствената слабо болезнена процедура. Първите 2 месеца пациентите са на ниско калорична диета 1200 калории дневно.

ABSTRACT

Introduction: The aim was to compare the different values in age groups in NIRDIABO project from Plovdiv region and to evaluate the possible risk to develop pre-diabetes. **Method:** The volunteers with BMI over 25 were included (male and female), divided in 5 age groups: a) 20-29 years; b) 30-39 years; c) 40-49 years; d) 50-59 years; e) 60-69 years (n=5-9). The only mild harmful procedure on the patients was taking blood samples. First 2 months the patients had low caloric diet 1200 per day. The diet included low fat, moderate protein and low carbohy-

Диетата включва ниско съдържание на мазнини и на въглехидрати, умерено на белтъци, както и прием на пробиотик. **Резултати:** Най-високо телесно тегло се регистрира в групата 40-49г. В същата група са и най-високите нива на глюкоза в кръвта сутрин на гладно. След натоварване с глюкоза същата група показа най-високи стойности над тези на гладно. Не установихме големи промени в систолното и диастолно кръвно налягане или в пулсовата честота при всички групи пациенти. **Заключение:** Настоящето изследване е малък принос към поддържането на подходящ стил на живот при хора с наднормено тегло и риск от развитие на пред-диабет и диабет тип 2 за българската популация, поради използването на ниско калорична диета, съчетана с прием на пробиотик и умерена физическа активност.

Ключови думи: ниско калорична диета, пробиотик, предпазване от развитие на диабет тип 2.

drate food and probiotics. **Results:** The body weight of the patients showed the higher value had the group 40-49 years. The higher mean values of blood glucose early morning are seen in a group of 40-49 years. After loading with glucose only the same group showed higher level. We do not register very big changes in systolic and diastolic blood pressures as well as in heart rate, in all groups of patients. **Conclusion:** The present study had important impact in management of pre-diabetic people and prevention from developing diabetes type 2 in Bulgarian population due to the usage of probiotics with appropriate low caloric diet and increasing the everyday physical activity.

Key words: low caloric diet, probiotic, prevention of type 2 diabetes.

INTRODUCTION

Diabetes mellitus type 2, also known as non-insulin dependent diabetes, is among the most rapidly spread diseases in the world. This tendency is mainly due to rise of overweight and obesity in population. Usually people at first develop the so-called pre-diabetes, which can be prevented [6].

There are several risk factors that predispose the development pre-diabetes. They are considered the same risk factors as the factors related to diabetes type 2.

Weight is one of them and it is measured mainly by body mass index (BMI). When BMI is higher than 25, the patients are at high risk for developing pre-diabetes. Especially if the patient carry a lot of extra weight in his/her abdomen, he/she may develop pre-diabetes. The excess of fat cells can cause the body to become more insulin resistant [1].

The next risk factor is the lack of physical activity. This often goes hand-by-hand with being overweight. If a person isn't physically active, he/she is more likely to develop pre-diabetes. The family history should be taken in mind, because there are also some hereditary factors. If a patient's close family member has (or had) it, he/she is more likely to develop the disease [7].

Age is also an important risk factor, because old-aged people are at high risk to develop pre-diabetes. It was found, that at the age of 45 this risk starts rising, and after the age of 65, the same risk increases exponentially [5].

Other issues like high blood pressure (hypertension) and high cholesterol level, (especially the so called "bad" LDL cholesterol) could increase very easily the risk of acquiring diabetes type 2 [4].

The aim of our study was to compare some values examined in different age groups of volunteers that took part in the project "NIR-DIABO". We have evaluated the possible risk for each group to develop pre-diabetes. The volunteers were from the Plovdiv region and they participated in the first year of the project.

METHODS

The project aimed to examine the quality of life and the effects of some non-pharmacological interventions on volunteers with obesity and high BMI. Both male and female volunteers with BMI over 25 were included in this

study, and were divided in the following groups: a) 20-29 years of age; b) 30-39 years of age; c) 40-49 years of age; d) 50-59 years of age; e) 60-69 years of age. The number of patients in each age group was relatively small (n=5-9).

All volunteers have signed a form of consent that they took part in the study. The Ethical Committee of Medical University approved the study. The written consent includes an information who of the included patients have a risk of developing pre-diabetes or diabetes type 2. If a patient followed correctly all the written instructions and kept the necessary diet he/she would have low chance to develop diabetes type 2. The results would help the patient to prevent the development of some cardio-vascular diseases. There weren't any harmful procedures on the patients excluding the weak discomfort when blood samples were taken. It was possible for a patient to become hungry, or to suffer from a weak headache, or to feel cold, but such reactions usually are weak and diminish easily in the first weeks.

We have formed the following including factors and criteria:

1. A written and signed consent for taking part in the study;
2. BMI over 25.
3. To perform a 2 hours of glucose-loading test for study glucose tolerance.
4. Motivation to take part in the study and following the necessary protocol for it.

Excluding factors and criteria:

1. Patients with diabetes type 2 diagnose.
2. Chronic diseases requiring medications that could influence the levels of blood glucose.
3. Taking part in active sport and games.
4. Specific food regimen – as vegans, etc.
5. Psychiatric diseases like anorexia or drug dependence.
6. Regular intake of alcohol over 21 Units for men and 15 Units for women per week.

The non-pharmacological interventions of the study are the following:

1. Two stages of diet performing;
2. Moderate physical activity;
3. Psychological influence.

The first 2 months of the study all the patients had to run a low caloric diet of 1200 kcal per day. This diet included 5 times of food intake during the day, but one of the nourishments had to be replaced with a product containing probiotics. The other nourishments had low fat, low carbohydrate, moderate protein containing food. The objective was for 2 months the patients to lose up to 5 % of weight compared to the basal one.

We used „TANITA C 300 BC-420 MA body composition analyzer" apparatus (USA) to make the following measurements: age, sex, body weight, BMI. The blood pressure and pulse frequency were measured on patients' forearms by Tensoval apparatus (Hartmann, Germany). To measure waist, hips, tights, we used a simple soft tailor ruler.

Statistics: all observed values were calculated and the mean for each group was estimated. Because of the small number of patients in each age group the statistical significance was not determined.

RESULTS

The results included in this study showed that the age group 40-49 years had a higher value of body weight. This group is very resistant to reduce body weight, despite the presence of the diet. Even the fact that patients had been following the instructions of the study and maintaining the new low-caloric diet, they did not decrease weight. There is not enough data to make a complete comparison of the values for statistically significant differences, but the tendency is quite clear **(Fig. 1.).**

The same tendency, we could see in the **Fig. 2** which illustrates the differences in BMI for all groups of patients. Again, the middle-aged group (40-49 years old patients) did not decrease BMI.

Patients from different age groups showed different mean values of blood glucose early in the morning on empty stomach **(Fig. 3).** The highest values are observed in the 40-49 years old patients group. After loading with glucose only the above mentioned group showed higher levels of blood glucose compared to the levels before loading.

We did not register big changes in systolic and diastolic blood pressures in all groups of patients **(Tabl. 1).** Only for the systolic pressure we found a slight tendency to decrease

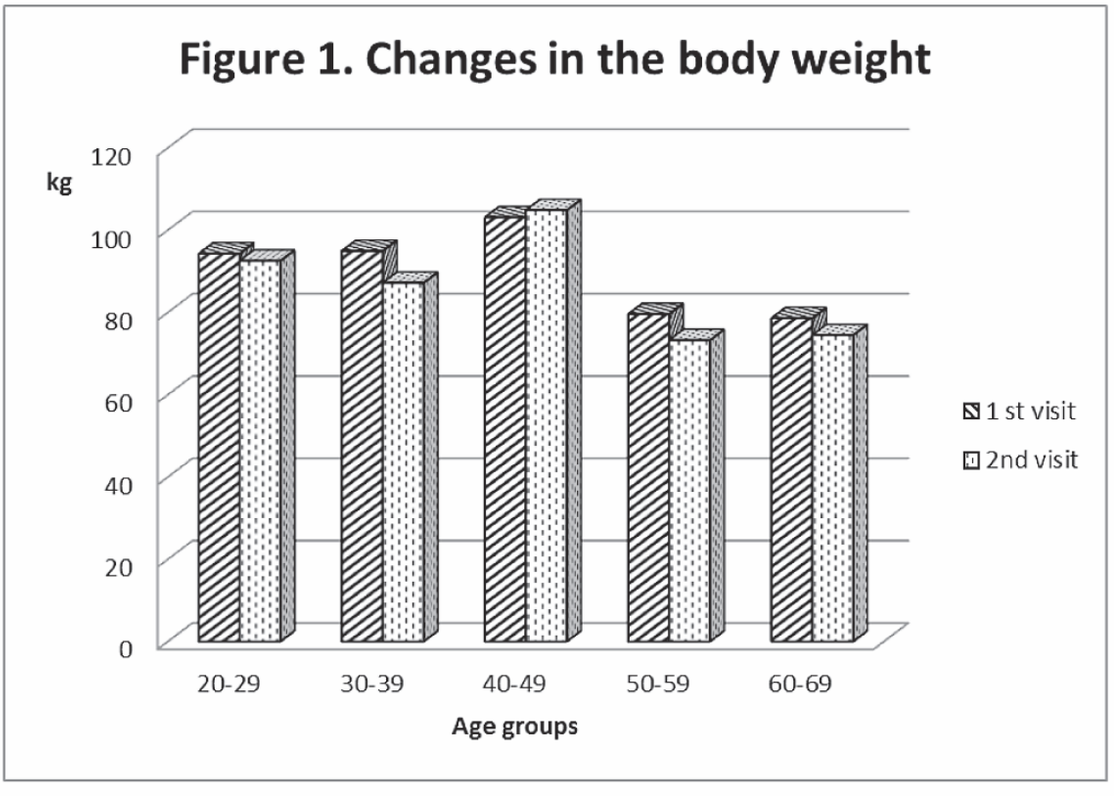


Figure 1. Changes in the body weight
kg
120
100
80
60
40
20
0
20-29
30-39
40-49
50-59
60-69
Age groups
1 st visit
2nd visit

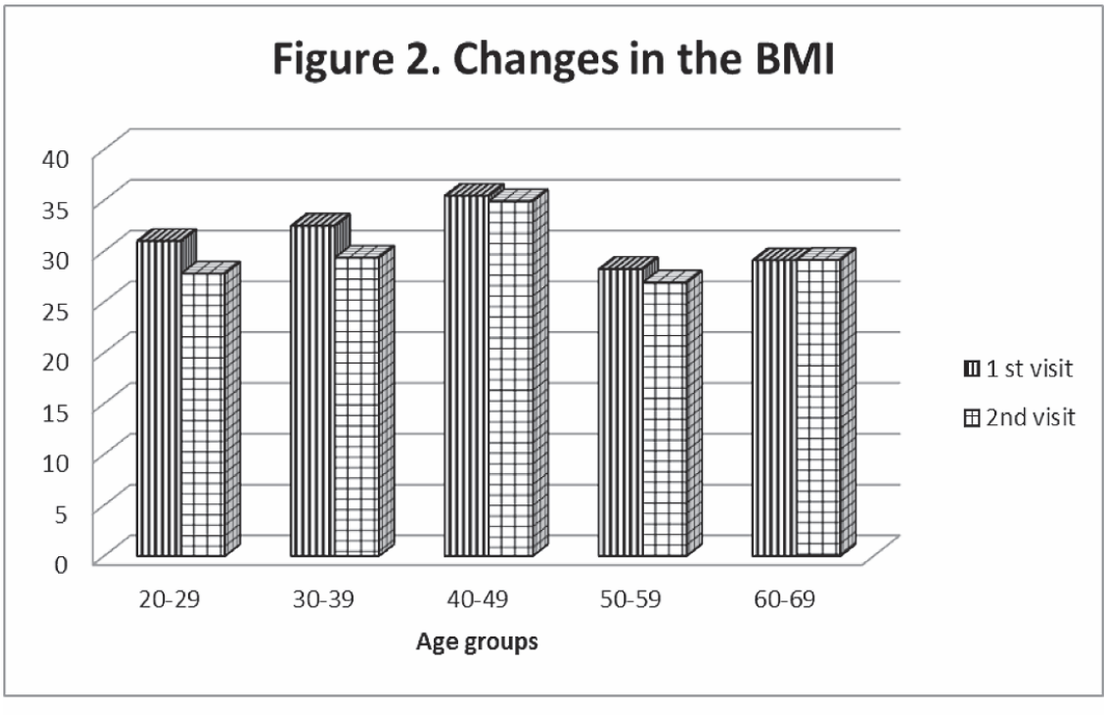
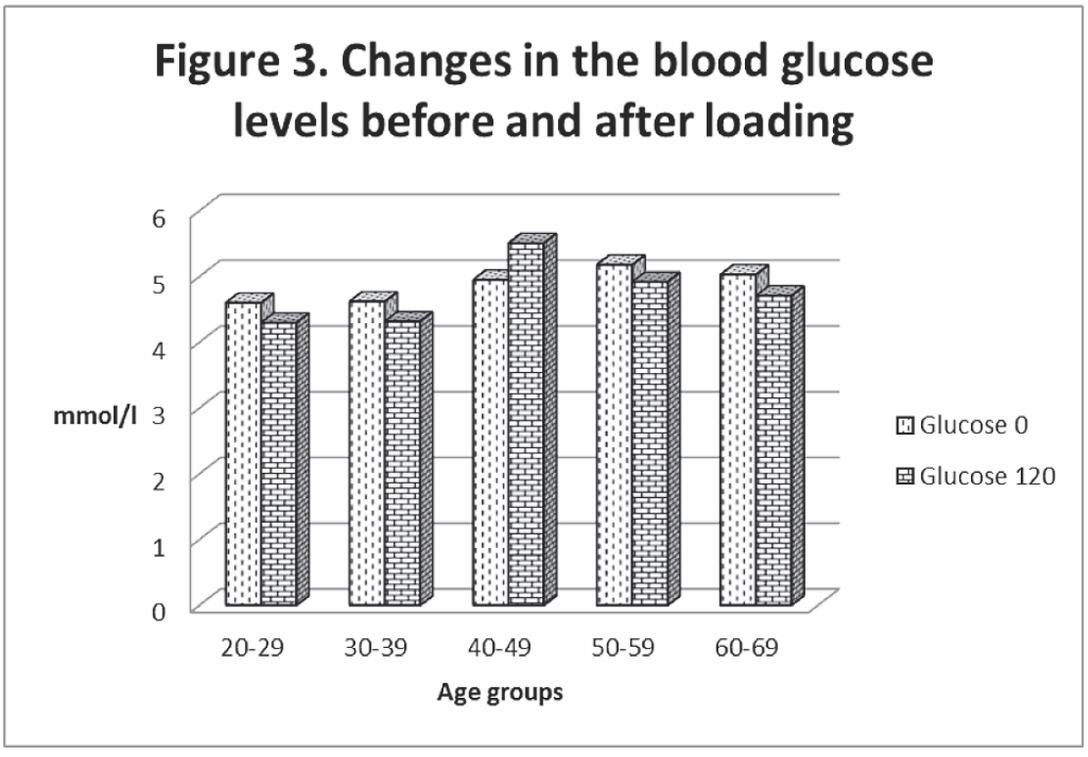


Figure 2. Changes in the BMI
40
35
30
25
20
15
10
5
0
20-29
30-39
40-49
50-59
60-69
Age groups
1 st visit
2nd visit



during the second visit, probably due to the slight increase in the every day physical activity, which was reported by the patients and the low caloric diet, especially in the age group 40-49 years. The heart rate was also not significantly changed in all groups.

DISCUSSION

Our results permit the suggestion that the main risk group is the group of 40-49 years of age. They showed higher body weight, BMI and level of blood glucose before and after the glucose loading test. The other groups showed weak decrease in their body weight and BMI after 2 months of low caloric diet, having in mind, that patients from these groups were keeping a moderate physical activity. This is in accordance with some clinical studies showing that lifestyle modification and low caloric diet are among the favorable factors contributing to the successful life without complications of diabetes type 2 for overweight people [1]. The decreased weight was not so high, but for a long term period if the patients maintain this weight or even decrease it, that would be a big success of the NIRDIABO study.

Lifestyle modifications, including both healthy eating choices and increased physical activity, are essential for weight management and diabetes prevention [2, 8]. Garber [2] found, that the designed his Program for diabetes prevention and the modulation of some parameters individually for each patient have shown repeated success and long-term maintenance. He made the conclusion that obesity is rather a metabolic disorder than a personal weakness. It may work with patients to address this condition and improve long-term health outcomes. In our study during patient's visits we talk with them on this matter.

There is strong, consistent evidence that the relationship between blood glucose levels and cardiovascular risk extends the diabetic range and obesity [7]. The same authors assumed that obesity and diabetes also increase the risk of heart failure, independent of coronary heart disease and hypertension and may cause cardiomyopathy (a frequent) and often fatal complications. In our study only middle age group (40-49 years of age) showed the tendency for none tolerance to

glucose loading. This group on our opinion is at higher risk for developing pre-diabetes and later on diabetes type 2, if the patients do not change their life style and do not keep the low caloric diet and more daily physical activity.

Some authors [9] found, that the obese people presented higher blood pressure and heart rate values at rest, compared to the eutrophic ones. They assume that probably such results may be explained by a reduction in parasympathetic activity and relative predominance of sympathetic activity. Wang et al., [10] suggest that annual blood pressure measurements are associated with increased survival and the strategy is to improve measurement frequency in obese patients which should be implemented. Our results support such view. We do not found very bug changes when we compare the blood pressure and heart rate during first and second visit, but even slight decrease in systolic values are important.

CONCLUSION

The present study has important impact in management of pre-diabetic people and prevention from developing diabetes type 2 in Bulgarian population. The use of probiotics with appropriate low caloric diet and increasing the everyday physical activity are the milestone key for prophylaxis of diabetes type 2 in our country.

Table 1. ***The values of systolic and diastolic blood pressure as well as heart rate, measured during the first and the second visits. Mean values for each group.***

Patients groups	Systolic pressure		Diastolic pressure		Heart rate	
	First visit	Second visit	First visit	Second visit	First visit	Second visit
20-29 years	112	89,5	74	73	85	79,5
30-39 years	128	117,68	86,5	85,4	84,84	82,8
40-49 years	124,43	120,77	86,45	85,86	78	77,71
50-59 years	122,78	116,3	80,8	80,56	72,4	73,67
60-69 years	115	114	76	74,33	86	74

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Персонализирана радиационна онкология - концепция, реални клинични възможности

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Personalized radiation oncology - concepts, real clinical possibilities

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РЕЗЮМЕ:

Целта на съвременната противоракова терапия е да се приложи генетична информация за тумора, която да ръководи решенията за персонализирано лечение. Този подход се отнася до комплексно лечение на рак, но в момента най-голямата и най-реалистична употреба е в химиотерапията, особено целенасочена терапия. Интегрирането на биологичната информация за подобряване на радиационната стратегия и съответно на терапевтичния отговор може да се определи като персонализирана лъчева терапия. За тази цел са необходими надеждни прогнозни биологични маркери, за да се характеризира индивидуалната ефективна радиационна реакция и възможността за радиална токсичност. Задачата е трудна и създава много въпроси, свързани с избора на типа радиотерапия, фракциониращи схеми, комбинирани модалности и др. Потенциалните маркери за пред-

ABSTRACT

The goal of modern anticancer therapy is to apply genetic information about a tumor to guide decisions on personalized therapy. This approach concerns complex cancer treatment, but currently the largest and most realistic use is in chemotherapy, especially targeted therapy. Integrating biological information to improve the radiation strategy and the therapeutic response, respectively, can be defined as personalized radiation therapy. For this purpose reliable predictive biological markers are required to characterize the individual effective radiation response and the possibility of radial toxicity. The task is difficult and creates many issues related to the choice of type of radiotherapy, fractionation schemes, combined modalities, etc. Potential predictive markers should be discussed as a hypoxia markers, markers of DNA repair, markers of different

сказване трябва да бъдат обсъдени като маркери на хипоксия, маркери за поправка на ДНК, маркери на различни отделения на туморна микросреда, маркери за ангиогенеза и противораков имунитет.

Ключови думи: лъчева терапия, персонализирана лъчетерапия, предсказващи маркери

compartments of the tumor microenvironment, angiogenesis markers and anticancer immunity.

Key words: radiation therapy, personalized radiotherapy, predictive markers

INTRODUCTION

The goal of modern anticancer therapy is to apply genetic information about a tumor to guide decisions on therapy. This personalized therapy approach is a considerable deviation from traditional combined-modality therapy, where surgery, chemotherapy, and radiation therapy (RT) are integrated in regimens tailored to the site of origin and stage of the tumor [1].

Clonal evolution and the „survival of the nastiest" remain the chief obstacles to curing cancer. But what if we could find a way to use the principles of evolution to beat evolving cancers cells at their own game? Is it possible to use Darwin;s notebook to outsmart resistance and cancer survival? May be – targeting the evolutionary trunk… truncal tumor neoantigens could allow scientists to target and destroy tumors without harming healthy tissues. The heterogeneity will nearly lead to the failure of therapies that target specific types of cell.

RADIOTHERAPY (RT)

Approximately 60% of all patients with cancer perceive RT at some point during their treatment course. The interaction of radiation and chemotherapy was prominently described in the 1970s by George Steed, who postulated four mechanisms by which combined modality treatment could improve clinical outcomes [2]. Patients show an individual response to the standard RT (fraction of 2 Gy daily for 6-7 weeks). The main guidelines for optimizing the therapeutic efficacy of radiation therapy are aimed at improving the physical and technical parameters - dose and optimization of the treatment plan.

Chemoradiation is the standart therapy for the majority of inoperable, locally advanced cancers. While there is a need to improve chemoradiation efficacy, normal tissue toxicity limits our ability to give additional chemotherapy or higher doses RT. Thus, there is excitement about the addition of molecularly targeted agents, which tend to be less toxic than chemotherapy, to chemoradiotion regimens. Unfortunately, initial empiric attempts have not been successful. We focus on the evidence that supports rational combinations of targeted agents with chemoradiation, with an emphasis on agents that target the DNA damage response and radiation-induced membrane signaling.

- Sensiting to chemoradiation by directly targeting the DNA damage response – PI3K / AKT, MEK, TGF-beta
- Sensiting to chemoradiation by alternative strategies
- Sensiting to chemoradiation by targeting radiation-induced membrane signaling – EGFR, VEGFR

Eliminating chemotherapy by a dual-targeted approach with radiation [3].

Studies of stereotactic ablative body RT, in particular, suggest improved clinical outcome compared with those previously seen with combination of conventional radiation and chemotherapy. Although ablative treatments may continue to gain traction in early-stage and oligometastatic disease, in which targets are generally smaller and often better defined, it is unlikely that further advances in physical targeting and fractionation alone will result in marked improvements in survival among patients with locally advanced disease [4].

Relatively fewer efforts of researchers are focused on including individual patients`s

characteristics in determining the treatment strategy. There are various radiobiological factors that contribute alone or in combination for the tumor response to radiotherapy. These include a number of stem cells and their irradiation, repopulating capacity and reoxygenation in the course of radiation therapy, recovery of radiation tissue damage and tumor hypoxia. These indicators were researched in experimental and clinical studies as individual irradiation factors [5].

PERSONALIZED RADIOTHERAPY

Integrating biological information to improve the radiotherapy strategy and therapeutic response can be defined as a personalized RT. To do this, reliable predictive biological markers are needed which can be used to determine optimal dose, choice of fractionation schemes, or combined modalities. Biomarkers can also be classified according to modality of assessment , and this has implication for how particular biomarker might be developed. The most common types of biomarkers according to this classification are [6]:

1. Genetic (gene mutation, gene copy number, translocations) – EGFR, HER2, BCR-abl
2. Genomic (gene expression profiles) – Mamma Print
3. Protein (serum protein assays)
4. Proteomic (analysis of serum or tumor)
5. Pathological (immunohistochemistry, histopatology)
6. Imaging (PET, Blood Oxygen Level Depend - fMRI)
7. Other (Circulating Tumor Cells)

The recent progress in this area focusing on the key stages in the biomarker development process: discovery, validation, qualification and implementation [6]. Validation of biomarker involves a systematic evatuation to assure that the technique used to assay the biomarker is reliable to perform its task. The process is guided by the established principles of bioanalytical method validation [7].

The currently used pretreatment parameters for evaluating and selecting the appropriate treatment plan currently include: histologicy, stage of differentiation, performance status and stage, but tumor associated biological parameters are not discussed. Typically, tumors are characterized by heterogeneity, which may become more pronounced during the course of complex treatment. The availability of reliable predictive early response therapies would improve and individualize RT of the patient. Typically, tumors are characterized by heterogeneity, which may become more pronounced during the course of complex treatment. The availability of reliable predictive early response therapies would improve and individualize the patient's RT. The possibilities of individualizing RT schemes should be based not only on morphological criteria but also on biological information related to the tumor. Important indicators at baseline and during radiation therapy may be hypoxic status, angiogenesis, metabolic and proliferative activity, activity of DNA repair systems in the course of applied radiotherapy. In contrast to the relatively wide use of a personalized therapeutic approach in medical oncology, RT status is more conservative.

1. Individualization of Radiotherapy based on hypoxia markers

Experimental and clinical data demonstrate the role of tumor hypoxia for malignant progression and RT resistance [5,8]. The mechanisms that can explain this association are listed above:

- Oxygen effect – three times higher radiation resistance of cells in conditions of hypoxia due to cells with normal oxygenize.
- Selection of resistant clones during carcinogenesis through hypoxic-induced acute and chronic changes in gene expression.

Identifying hypoxic tumors allows the development of strategies to potentially overcome the hypoxic condition [5]. For example: increased oxygen import before / during irradiation, use of oxygen carriers as radiosensitizers, direct cytotoxicity by using reductant compounds. Results from clinical trials have shown that some of these strategies have the potential to improve the therapeutic response. However, while the prognostic value of the various hypoxicity markers is confirmed by a number of experimental and clinical trials, their

feasibility as predictive markers for the individualization of therapy in hypoxic tumors has been studied in a small number of studies

Serum protein **osteopontin** is associated with tumor hypoxia with potential mechanism of negative correlation wich von Hippel-Lindau (VHL) gene expression [5,8]. VHL regulates oxygen-dependent uptake and proteolysis of the hypoxia-inducible transcription factor (HIF-1α). It activated transcription of genes, responsible for the adaptive response to hypoxia. Hypoxia-induced osteopontin secretion in vitro and osteopontin plasma levels correlate with oxygen partial pressure in the tumor in patients with leukemia and neck cancer. High levels of osteopontin as a marker for hypoxia are associated with therapeutic failure after radiotherapy.

2. Individualization of Radiotherapy based on markers of DNA repair

RT induces a series of DNA damage more of which can be recovered from the affected cell, but the unresolved damage causes cell death and mutations. Proteins involved in the repair of DNA damage are considered as a potential biomarkers for therapeutic response at RT [8]. One of the most studied markers is the histone protein γH2AX, which accumulates in the focus of double-stranded DNA damage and may affect other DNA proteins [9]. In patients with hypoxic tumors, a lower residual γH2AX expression was observed [9,10]. The use of DNA repair markers is useful in identifying potentially resistant tumors with effective DNA repair mechanisms. In these cases, combining radiation with an inhibitor of DNA repair mechanisms is an attractive approach to overcoming radiation resistance. As a suitable biomarker, the poly (ADP-ribose)-polymerase-1 (PARP) enzyme that protects the cell from apoptosis is considered. PARP inhibitors block DNA repair and select the tumor response to radiation in a number of pre-existing in vivo tumor models. PARP inhibition has been found to result in increased accumulation of γH2AX focuses in lung tumors. These data justify accepting that PARP may serve as a biomarker candidate for the selection of patients eligible for combined radiation / target therapy [8,9].

3. Individualization of Radiotherapy based on markers of different compartments of the Tumor MicroEnvironment (TME)

Tumor MicroEnvironment (TME) emerged as one of the key factors in therapy resistance. Tumor stroma - a complexity dictated by the hypoxic TME. RT as known to influence and modify diverse components of the TME [11]. The impact of low and high single dose, as well as fractionated RT on host cells (endothelial cells, fibroblasts, immune and inflammatory cells) and the extracellular matrix. Optimizing the schedule of RT (i.e. dose per fraction) and other treatment modalities is a current challenge. RT has a nonspecific effect, triggering both tumor and host cells.

The effect on endothelial cells depends on the dose per fraction. At a clinical single dose of 2 Gy, endothelial cell survival as favored through miRHA upregulation. Low doses RT (<1 GY) can be used as a anti-inflammatory treatment. High dose (above 10 Gy) are more likely to induce endothelial cell apoptosis and tumor vessel collapse [12]. This could explain the clinical efficacy of stereotactic body radiation therapy and stereotactic radiation surgery. With intermediate doses (5-10Gy) tumor vessel normalization and dilatation are observed and associated with reduced vascular leakage and increased tumor oxygenation [13,14].

RT can initiate inflammatory cascades by two main pathway: the nuclear and cytoplasmic pathway. NK cell mobilization following neoadjuvant RT appears crucial. Normal fibroblasts are well known to resist to high radiation dose (up to 50 Gy). Cancer-associated fibroblasts actively contribute to cancer aggressiveness by modulating different processes – angiogenesis, inflammation and extracellular matrix remodeling [11,14].

4. Radiotherapy and Cancer Immunogenic Effects

The balance between proimmunogenic and immunosuppressive effects of radiotherapy and tumor rejection is very difficult [15].. Radiation promotes the priming and effector phases of the antitumor immune response. Key molecular signals that promote priming of antitumor T cells by dendritic cells loaded with

tumor antigens include exposure of CalReTiculin (CRT) and High-Mobility Group Protein B1 (HMGB1). These signals are released by the tumor cells undergoing a radiation-induced immunogenic cell death and, together with InterLeukin 1b (IL-1b) lead to activation of tumor-specific T cells. Key molecular signals that promote the effector phase include the upregulation of chemokines CXCL9, 10, and 16, which attract activated T- cells to the tumor. Tumor infiltration by T cells produce InterFeroN y (IFN-y) and Tumor Necrosis Factor-alfa (TNF-a). The process is facilitated by upregulation of Vascular Cellular Adhesion Molecule 1 (VCAM-1) on tumor endothelium [16]. Radiation-induced upregulation of Major Histocompatibility Complex Class 1 (MHC-1) and InterCellular Adhesion Molecule-1 (ICAM-1) on surviving tumor cells improves their recognition and killing by T cells. On the other hand, radiation activates immunosuppressive Transforming Growth Factor-beta (TGF-b) and promotes accumulation of regulatory T-cells and protumorogenic M2 macrophages. Data suggest that positive effects of radiation other predominate over negative ones but are insufficient to shift the balance of the immunosuppressive tumor microenvironment to achieve tumor rejection in the absence of targeted immunotherapy [15,17].

5. Individualization of Radiotherapy based on Angiogenesis markers

Tumor blood vessels are recognized as major actors in tumor development at least through an active and passive exchange of nutrients, waste and gaz [13,16]. The effects of ionizing radiations on angiogenesis are more complex than might be expected. There are now at least three distinct ways in which radiation can affect vessel growth:

- The protons of electromagnetic radiations stimulate vessel growth at least in part, by causing the increased expression of angiogenesis factors.
- Low Linear Energy Transfer (LET) charged particles like protons inhibit angiogenesis by an unknown mechanism although decreased expression of angiogenesis factors and reduced motile tip activity is implicated.
- High LET heavy ions like Fe ions also inhibit angiogenesis by an unknown mechanism that affects the later stages of tubulogenesis.

This complexity of response opens up possibilities of greater control over angiogenesis and the resulting pathologies during coincident exposure or therapy. For exposure in space, knowledge of these mechanisms will enable more precise risk assessment and litigation strategies. For radiotherapy, treatment could be manipulated to utilize the radiation effectively. In addition, effectiveness can be increased further when used in the right combination of anti-angiogenesis drugs. Further research in this field should contribute to a great improvement in these strategies.

CONCLUSION

The hypoxia markers, markers of DNA repair, the different compartments of TME and the angiogenesis markers are closely related and contribute not only to tumor progression, but also to its treatment response. RT delivery to the primary tumor, ionizing radiation also target non tumor cells the influence tumor growth and metastatic dissemination. The TME-mediated and the other models of radioresistance is now the object of researchers [14,16]. However the impact of PERSONALIZED RT is often neglected. Here we pointed out the impact of this element of multimodal oncology treatment.

DISCLOSURE

The authors have declared no conflicts of interest.

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Вътреставни апликации с тромбоцит богата плазма за лечение на колянна остеоартроза

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Intra-articular platelet rich plasma injections for Knee Osteoarthritis

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РЕЗЮМЕ:

Въведение: Представя се метод за лечение на колянна остеоартроза с прилагане на тромбоцит богата плазма вътреставно. Съдържанието на голям брой растежни фактори обуславя нейната ефективност. **Цел:** Да се определни ефективността и безопасността от чиста Тромбоцит Богата Плазма (ТБП) при лечение за колянна остеоартроза (ОА), сравнена с други методи на терапия- хиалуронова киселина (ХК) и кортикостероиди (КС). **Материали и методи:** Не-рандомизирано, единично-заслепено проучване, което включва 96 пациента. Случайно разпределени в три групи, пациентите са получили тромбоцит богата плазма, хиалуронова киселина или кортикостероидни апликации в три поредни седмици. За оценка на ефективността от терапията преди лечението, на 1-ви, 6-ти и 12-ти месец е използван Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Отбелязани са настъпилите нежелани реакции. **Резултати:** Изходните характеристики на групите са съпоставими. На

ABSTRACT

Introduction: Treatment method for knee osteoarthritis is applications of plateler rich plasma. It consists of huge number of growing factors, which determine its efficacy. **Aim:** To determine the safety and efficacy of pure Platelet Rich Plasma (PRP) for knee osteoarthritis (OA) treatment, compared with other treatment methods-hyaluronica acid (HA) and corticosteroids (CS). **Material and Methods:** A non- randomized, single-blinded control study of 96 patients. The patients were randomly selected in three groups and received either platelet rich plasma, hyaluronic acid, or corticosteroid for a series of 3 weekly injections. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used for evaluation of the patients before injections and at 1, 6 and 12 months after the first application. Adverse events were also recorded. **Results:** The baseline characteristics of the groups are similar. At first month all treatment methods provide efficacy with no difference between groups but statistically significant difference compared with baseline. There is a clear difference in efficacy at month

първи месец всички терапевтични групи осигуряват ефективност без разлика помежду им, но със статистически значима разлика спрямо базовото ниво. Изразено различие в терапевтичната ефективност има на 6-ти месец, където ПРП и ХК показват по –добри резултати спрямо кортикостероидите. Липсва разлика между ПРП и ХК в този период. На 12 месец и двете групи все още показват сигнификантно по-добри резултати, сравнени с КС, но по-лоши спрямо тези отчетени на 6 месец. Наблюдаваните странични реакции са болка, подуване, контрактура. **Заключение:** ТБП осигурява добро повлияване на болката, намаляване на сковаността и подобряване на функцията в ежедневието. Представлява по-добър терапевтичен избор при колянна остеоартроза спрямо кортикостероиди като има съпоставим ефект с хиалуроновата киселина отчетено на 6 и 12 месец от терапията.

Ключови думи: тромбоцит богата плазма (ТБП), колянна остеоартроза, интра артикуларно

6 where PRP and HA groups illustrate better results compared with CS. There is no difference between PRP and HA at that point. At month 12 both groups still show significant results compared with CS, but worse than month 6. Adverse events are swelling, pain, temporary loss of function. **Conclusion:** PRP provide good relieve of pain, reduce stiffness and alleviate function. It is a better therapeutic choice for knee osteoarthritis. Still better one from intra-articular corticosteroids and provide similar effect as hyaluronic acid best seen at 6 and 12 month after treatment.

Key words: platelet rich plazma (PRP), knee osteoarthritis, intra-articular

INTRODUCTION

Osteoarthritis is the fourth leading cause of invalidation worldwide, and WHO 2012 classified it inside a group of 25 diseases leading to life in disability. Osteoarthritis is common worldwide with small geographic differences. Of a great interest are knee and hip osteoarthritis because of the size and money needed to be treat. The age standardized prevalence of radiographic knee OA in adults age ≥ 45 was 19.2% among the participants in the Framingham Study and 27.8% in the Johnston County Osteoarthritis Project (10). In the third National Health and Nutrition Examination Survey (NHANES III), approximately 37% of participants age >60 years or older had radiographic knee OA (10). Recent study using cadaver-derived skeletons among individuals describes osteoarthritis of the knee as a 'mismatch disease' and explain approximate doubling of knee OA prevalence that has occurred in the United States since the mid-20th century (17). The disease is no longer attributed to aging and obesity. Allels of the genes, such as GDF 5, have been shown to influence knee OA susceptibility. Also the role of environmental factors have been risen.

Gonarthrosis is a condition that affects the articular cartilage, synovial membrane and subchondral bone. All of these structures are responsible for biochemicle and biomechanical balance of the joint (14). OA is a pathology accompanied by an increased presence of inflammatory cytokines and proteolytic molecules in the tissue, which in turn lead to extracellular matrix degeneration and functional impairment. Chondrocytes and synovial cells change their quiescent phenotype in response to an abnormal microenvironment from trauma-induced inflammation (6) The main proinflammatory cytokines involved in the pathophysiology of OA are interleukin (IL)-1β, tumor necrosis factor, and IL-6. These cytokines contribute to OA pathogenesis through several mechanisms contributing to the phenotype shift of chondrocytes, through which activated cells increase the expression of catabolic and proinflammatory genes. In addition, these cytokines intensify and maintain OA disease by inducing the production of other proinflam-

matory cytokines, such as IL-8, IL-15, IL-17, IL-8, IL-21, and leukemia inhibitory factor (8,11).

The aim of treatment is reducing pain, stiffness and improve function (1). There are non-pharmacological, pharmacological and surgical methods. Approved intra-articular treatment methods are Corticosteroids (12), hyaluronic acid (3). However, ACR 2012 do not state HA's benefit (7). On the other hand, Hondroitin sulphate and Glucosamine sulphate have shown controversial results in randomized control trails (16), so they are not recommended by ACR. There are not known any disease modifying drugs for treatment of osteoarthritis.

The purpose of the study is to establish the efficacy and safety of intra-articular applications of platelet rich plasma for knee OA, compared with other methods- intra-articular hyaluronic acid and corticosteoids.

MATERIAL AND METHODS

This was designed as s prospective, single-center, non-randomized, single-blind, 3-arm group study. The study had a permission from the Ethical Comission at Medical University Plovdiv. Patient selection was based on strict inclusion/exclusion criteria **(Table 1)** All patients had a screening visit (visit 1), three treatment visits (visit 2, 3, 4, recpectively) and follow up visits at 1 month (visit 5), 6 month (visit 6) and end of study visit at 12 month

Table 1. ***Subject eligibility criteria***

Inclusion criteria:
•Signed informed consent
• Fullfilling the criteria for knee osteoarthritis according to ACR 1986
• Radiographic evidence of OA of the tibiofemoral or patellofemoral compartment of the target knee (Kellgren-Lawrence grade 2 or 3)
• Lab results within normal ranges (erythrocyt sedimentation rate, full blood count, c-reactive protein, uric acid)
Exclusion criteria:
• Kellgren-Lawrence 4 grade
• Patologyc number of platelets. Blood diseases
• Anticoagulants and antiaggregants
• Non steroidal anti-inflammatory drugs 5 days before treatmenta and 7 days after each injection
• Diagnosis of other inflammatory disease
• Previous traumas/fractures in the knee erea, luxations, arthriscopy one year before inclusion in the study. Total knee replacement
• Valgus or varus deformities (>5 °)
• Previous injection of hyaluronic acid 12 months before inclusion and systemic/local corticosteroids 3 months before inclusion
• Hip osteoarthritis
• Cardiac failure grade 3,4
• Infections
• Diabetes
• Cristal arthropaties

(visit 7). At visit 1, 5, 6 and 7 patients were evaluated by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). At all visits patient were asked and examined for any adverse events.

The study included a total of 96 patients. Baseline characteristics of the patients shown on **Table 2.**

Outcome measures

The primary efficacy outcome was the change in pain, joint stiffness, and physical function measured using WOMAC at baseline, 1 month, 6 month and 12 month. The WOMAC consist of 24 total items devided among 3 subscales: pain (0-20), stiffness (0-8) and fisical function (0-68). Higher scores

Table 2. ***Demographics and groups of treatment***

	PRP (37 patients)	HA (27 patients)	CS (32 patients)	P value
Age (mean)	68.50 (±7.91)	64.40 (±12.69)	67.47 (± 8.51)	.394
BMI	30.05 (±4.90)	31.04 (±5.84)	29.46 (±3.93)	.634
Kellgren-Lawrence Grade II Grade III	14 (36%) 25 (64%)	12 (44%) 15 (56%)	18 (56%) 14 (44%)	.229

The study group consists of 37 patients. To prepare the PRP, at each visit 2, 3 and 4 respectively, 20 cc of peripheral blood was extracted from each patient by venepuncture into extraction tube containing 3 ml Sodium Citrat as anticoagulant. The extraction tube was connected to SW-PRP kit, SAEWON, Korea. The PRP kit was centrifuged at 3850 RPM for 7 minutes at room temperature in SW-400 machine, Korea. It was followed by second centrifugation but for 8 minutes. Once the kit was centrifuged, we proceeded to physically separate the plasma fractions and receive approximally 2-3 cc of poor leucocyte, pure platelet rich plasma ready for aplication.

The first control group consists of 27 patients. They receive 3 IA injections of Sodium hyaluronate, 20 mg/2 ml. The second control group consists of 32 patients. They receive 1 IA injection of Diprophos 7 mg/1 ml. A visit 3, and 4 they receive IA injection of saline-placebo.

All intra-articular injections were applied in lateral suprapatellar recessus followed by 15 minutes rest.

are representative of greater pain and stiffnes as well as worsened physical capability. Patients answer the questions before any procedure and are not allowed to review the previous answers. The second outcome is safety of the treatment method.

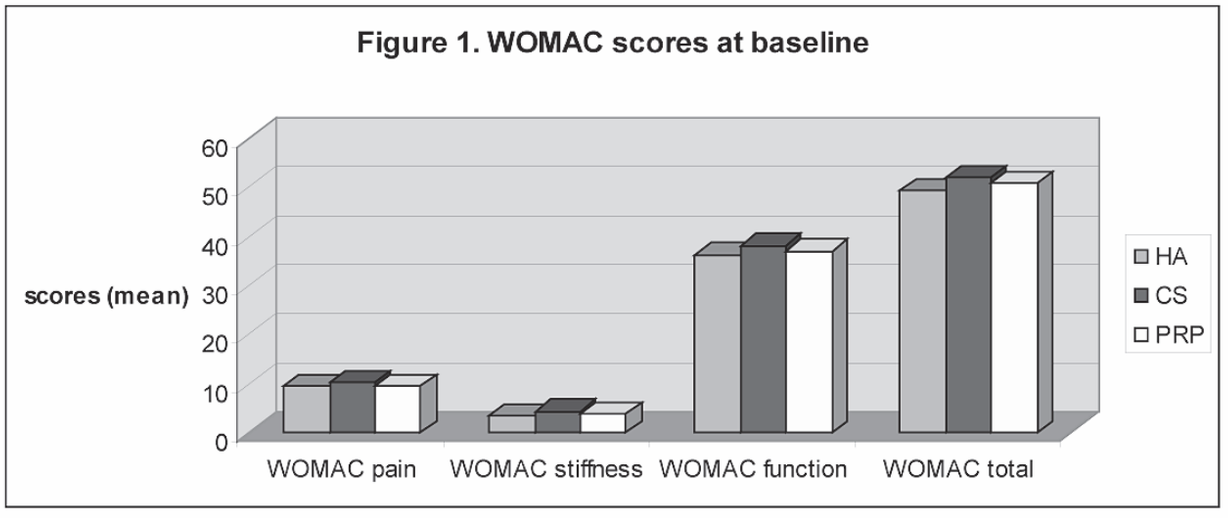
Statistical analysis was performed by the use of SPSS v17.0. Nonparametric tests of U-Mann– Whitney and Kruskal–Wallis (for continuous variables) were used.

RESULTS

1. Efficacy

No difference in baseline WOMAC parametes existed between the three groups, p > .05 (WOMAC pain, p = .532; WOMAC stiffness, p = .250; WOMAC function, *p* = .628; WOMAC total, *p* = .626).

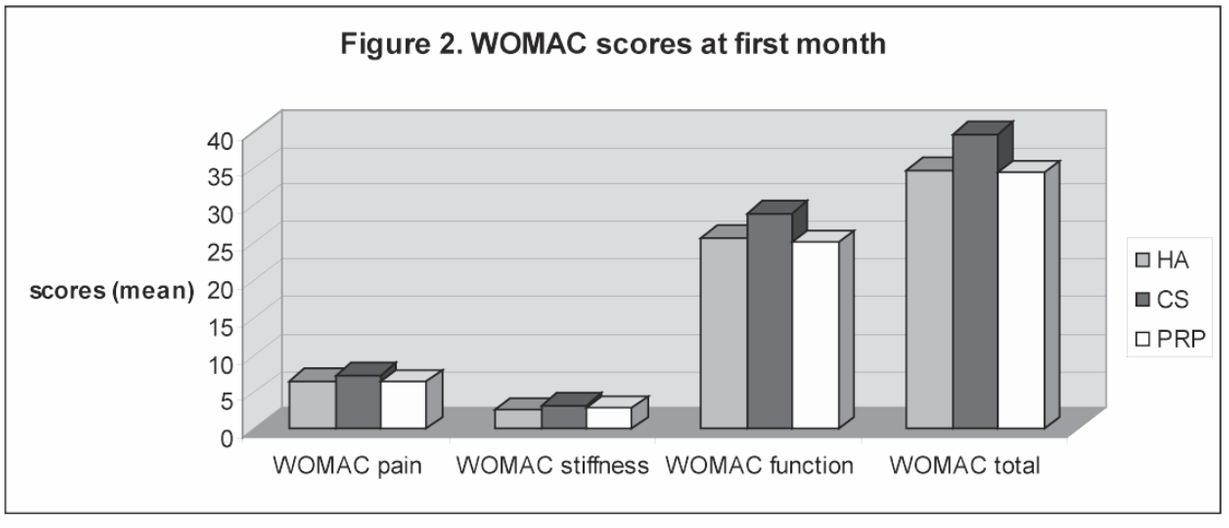
At month 1, there are no difference between the three treatment groups according to pain, stiffness, function, and total score (WOMAC pain, *p* = .679; WOMAC stiffness, p = .523; WOMAC function, *p* = .261; WOMAC total, *p* = .396). At the end of the first month there is continuating similarity in results bet-

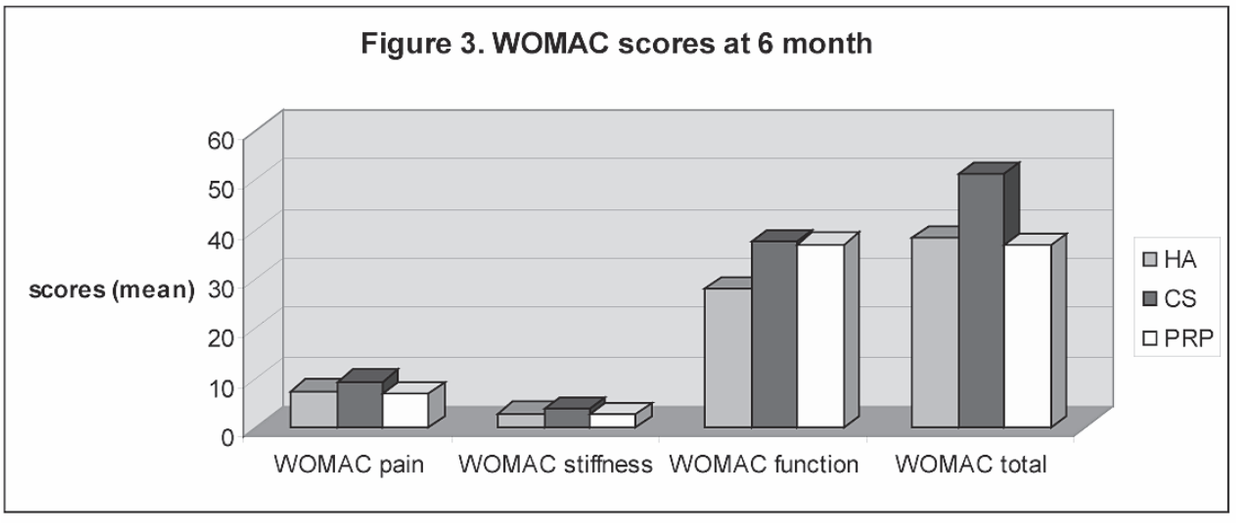


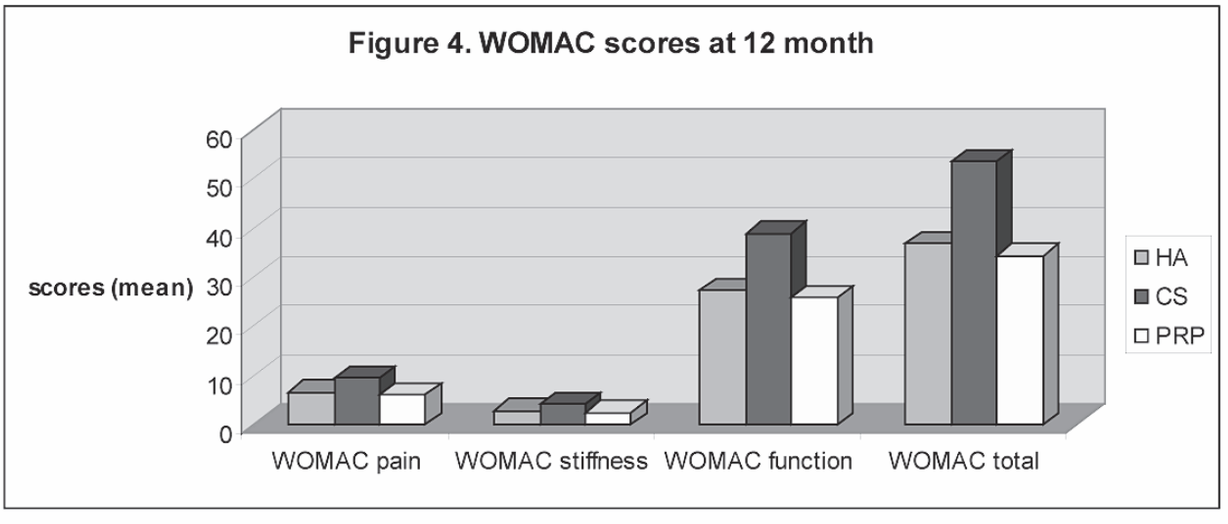
ween the treatment groups.

At month 6, there is no difference between the three treatment grups according to WOMAC pain, $p = .070$; According to stiffness, function and total score, there are statistically significant difference ($p = .009$; $p < .001$; $p < .001$, respectively). WOMAC stiffness: PRP shows statistically significant difference from CS: $p < .001$ (PRP < CS); HA has statistically significant difference from CS: $p = .011$ (HA < CS). There is no statistically significant difference between PRP and HA, $p > .05$. WOMAC function: PRP shows statistically significant difference from CS: $p = .002$ (PRP < CS); HA have statistically significant difference from CS: $p = .006$ (HA < CS). There is no statistically significant difference between PRP and HA, $p > .05$. WOMAC total: PRP shows statistically significant difference from CS: $p < .001$ (PRP < CS); HA have statistically significant difference from CS: $p = .004$ (HA < CS). There is no statistically significant difference between PRP and HA, $p > .05$.

At month 12, there are statistically significant differences between the three treatment grups according to WOMAC pain, stiffness, function and total ($p = .001$; $p < .001$; $p = .001$; $p < .001$, respectively). WOMAC pain: PRP and HA show statistically significant difference from CS: $p < .001$ (PRP < CS) and $p = .007$ (HA < CS). There is no statistically significant difference between PRP and HA, p =.548. WOMAC stiff-







ness: PRP and HA show statistically significant difference from CS: p < .001 (PRP < CS) and p = .002 (HA < CS). There is no statistically significant difference between PRP and HA, *p* =.417. WOMAC function: PRP and HA show statistically significant difference from CS: *p* < .001 (PRP < CS) and *p* = .003 (HA < CS). There is no statistically significant difference between PRP and HA, *p* =.853. WOMAC total: PRP and HA show statistically significant difference from CS: *p* < .001. (PRP < CS) and *p* = .002 (HA < CS). There is no statistically significant difference between PRP and HA *p* =.724.

2. Safety

There are statistically significant differences between study and control groups according to adverse events at the first month, p = .003. 5% of people from the PRP group reported pain after applications longer than 12 hours, effusion was reported by 14% of patients and temporary loss of function by 5%. Only 5% from HA group said they had pain after injections. At months 6 and 12 there are no adverse events and significant difference between the three groups, but 2 patients from the HA control group underwent arthroscopy compared with one patient

from PRP group. One patient had total knee replacement surgery from HA control group. All these people were excluded from the statistical analysis.

DISCUSSION

The primary porpous of the study is to evaluate the efficacy of treatment with PRP compared to other treathment methods, and the second aim was evaluating the safty. The study confirmed the hypothesis that PRP is better treatment than CS and have similar results compared to HA. This effect is seen at month 6 especially for stiffness and function, but at 12 month of the follow-up there are statistically significant differences at all parts of WOMAC (pain, stiffess and function).

The study shows similar results with prior studies comparing PRP with HA or PRP with CS.

Data from Duymus et al 2017 (5) shows similarities with our study. They perform randomized control trial with a total of 102 patients, which were treated with either PRP 2 intra-articular injections, HA single-dose of intra-articualr injection, or ozone x four times. At the end of the first month after injections, significant improvements were seen in all groups. The result was similar with our outcome.

At 6 month, while the clinical efficacies of PRP and HA were similar and continued, the clinical effect of ozone had disappeared ($p < 0.001$). Our results showed similar changes according to WOMAC compartments in PRP and HA group.

At the end of 12 month, PRP was determined to be both statistically and clinically superior to HA ($p < 0.001$) suggested the study team. Our study shows no significant differences between PRP an HA at month 12 of the follow-up period, but better significant results compared to baseline. Similar results illustrated Lana et al 2016 (9). They evaluated PRP treatment compared to HA or a combination of PRP and HA. They performed a randomized control trial with 105 patient, 36 treated with PRP three intra-articular injections, 36 with HA also three intra-articular injections. The rest of the patients were treated with a combination. The results showed greater improvement in WOMAC function at 12 month ($p=0.008$) when compared to HA group. Data from Bottegoni et al 2016 (2), observed 60 patents treated with PRP three intra-articular injections or CS single application showed worsening of the results at 6 month.

Similar results at 6 month are seen in doble randomized clinical trial of Montañez-Heredia et al 2016 (13) comparing 27 patients treated with PRP and 26 treated with sodium hyaluronate.

Cole et al 2015 (4) performed double-blinde, randomise clinical trail with a total ot 99 patients treated with PRP or HA three times during weekle interval. They discovered no statistically significant difference between the two groups at month 12 according to WOMAC score.

A meta- analysis was performed by Riboh et al 2016 (15) including 6 randomised controlled trials (evidence level 1) and 3 prospective comparative studies (evidence level 2) with a total of 1055 patients. Injection of leucocyte pour PRP (LP-PRP) resulted in significantly better WOMAC score than hyaluronic acid (mean difference, -21.14;95% Cl, -39.63 to -2.65) or placebo (mean difference, -17.84; 95% Cl, -34.95 to -0.73) No such difference was observed with leucocyte rich PRP (mean difference, -14.28; 95% Cl, -44.80 ti -16.25). The SUCRA analysis showed that LP-PRP was the highest ranked treatment for measure of clinical efficacy (WOMAC)

PRP injections resulted in a higher incidence of adverse reactionsnthan hyaluronic acid (odds ratio, 5.63; 95% CI, 1.38-22.90), but there was no difference between LR-PRP and LP-PRP (odds ratio, 0.78; 95% CI, 0.05-11.93). These reactions were nearly always local swelling and pain, with a single study reporting medical side effects including syncope, dizziness, headache, gastritis, and tachycardia (17/1055 total patients). The final analy-

sis said that PRP results in improved functional outcome scores compared with hyaluronic acid and placebo when used for treatment of knee osteoarthritis.

CONCLUSION

Treatment woth PRP showed a significantly better results compared to corticosteroids and versy similar results compared to hyaluronic acid. In addition, the data illustrate significant better results for PRP till 12 month of treatment with good safety profile.

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Изисквания към авторите

Списание Българска медицина е издание на Българската академия на науките и изкуствата (БАНИ), Отделение наука, Научен център по медицина и здравеопазване. Излиза 4 книжки годишно. Списанието е достъпно електронно на сайта на БАНИ, раздел издания.

В списание „Българска медицина" се отпечатват оригинални статии, казуистични съобщения, обзори рецензии и съобщения за проведени или предстоящи научни форуми – симпозиуми, конгреси, или други в областта на клиничната и фундаментална медицина. Списанието излиза на английски език с подробни резюмета на английски и български език. Изключения се правят за обзорни статии по особено значими теми. Заглавието, авторските колективи и надписите и означенията на илюстрациите се отпечатват и на двата езика.

Материалите трябва да се представят в два еднакви екземпляра, на шрифт Times New Roman, размер 12, разстояние между редовете 1.5 линии. Обемът на всяка статия е до 10 страници, 12 страници за обзорните статии и 3-4 страници за казуистичните съобщения. Библиографията и илюстрациите са включени в този обем. За информация за научни прояви обемът е до 4 страници, за рецензии на книги – до 2 страници. В този обем не се включват резюметата на английски и български език, чийто обем трябва да бъде до 200 думи с 3-5 ключови думи. Резюметата трябва да отразяват конкретната работна хипотеза, използваните методи, получените резултати и заключение.

Структурата на статиите трябва да отговаря на следните изисквания: заглавие, имената на авторите (собствено име и фамилия), название на научната организация или лечебното заведение, в което работят Оригиналните статии трябва да имат следната структура: въведение, методи, резултати, обсъждане и заключение или изводи. Методиките трябва да бъдат подробно описани, както и статистически методи, използвани в изследването. В теста се приемат само официално приетите съкращения, останалите трябва да бъдат обяснени.За мерните единици се използва системата SI. Илюстрациите се представят като отделни файлове и се посочва мястото им текста за улеснение при предпечатната подготовка.

Тези изисквания не важат за другите научни публикации (обзори, казуистика или съобщения и рецензии).

Книгописът се представя на отделна страница подреден по азбучен ред първо на английски език, после източниците на български език. Броят на цитираните източници не трябва да надвишава 20 за оригиналните статии, до 40 за обзорните статии и до 10 ца казуистичните случаи. Подреждането на библиографията става по следния начин:

За списание: автори, заглавие на статията, списание, година, том, страници от..до.

За книга: автори, заглавие на главата, В: заглавие на книгата, в скоби редактори, издателство, година, страници от…до.

Адрес за кореспонденция се дава в края на всяка статия и съдържа данните на кореспондиращия автор, включително адреса на електронната му поща. Всички ръкописи се изпращат с придружително писмо подписано от авторите, в което се отбелязва, че тя не е била предлагана на друго списание и не е отпечатвана у нас или в чужбина. Ръкописите не се връщат.

Процедура по рецензиране: С оглед спазване на международните стандарти, редакционната колегия е приела процедура по „двойно сляпо" рецензиране от независими референти. На авторите се предоставя възможността да предложат на вниманието на редакционния екип три имена на специалисти в тяхната област като потенциални рецензенти.

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Задължения на рецензентите: Рецензентите подпомагат редактора при вземане на решение, като те могат да подпомогнат автора за повишаване качеството на статията. Всички ръкописи, получени за рецензиране следва да се считат за поверителен материал и тяхното съдържание не следва да се разкрива пред никого, освен с разрешението на редактора. Рецензентите следва да се придържат към обективните стандарти за оценка. Лични нападки срещу авторите са неприемливи. Критичните забележки следва да бъдат подкрепени с аргументи.

Конфликт на интереси: Непубликувани материали не могат да бъдат използвани в собствени изследвания на редактора без изричното писмено съгласие на авторите. Авторите следва да обявят всички финансови или други съществени конфликти на интереси, които могат да окажат влияние върху интерпретацията на техните резултати. Всички източници на финансиране на проведените проучвания следва да бъдат обявени.

Етически съображения по отношение на самите изследвания: всички трудове, които отразяват клинични проучвания следва да имат подписано информирано съгласие от пациентите и получено разрешение за изследването от съответната Етична комисия в съответствие с Декларацията от Хелзинския комитет. Експерименталните проучвания следва да имат също разрешение от съответната Етична комисия и от Българската Агенция по безопасност на храните и лекарствата.

След положителна рецензия и одобрение на редколегията, авторите на статията дължат заплащане в размер 10 лв на страница на статията си, с оглед покриване на разноските по английската езикова редакция на текста и коректури.

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References to a book chapter:

Delange F, Endematic Cretenism. In: The thyroid (Eds. L. Braveman and R. Utiger). Lippincot Co, Philadelhia, 2001, 942-955.

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