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ХРОНИЧЕСКИЙ ГЕПАТИТ В У СПОРТСМЕНОВ ВЫСШИХ ДОСТИЖЕНИЙ

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Chronic Hepatitis B In Elite Athletes

Резюме

Спортсмены, как и другие представители общей популяции, подвержены риску инфицирования вирусами гепатитов. **Цель исследования** — охарактеризовать клинико-вирусологическую картину хронического гепатита В (ХГВ) у спортсменов и оценить эффективность противовирусной терапии. **Материалы и методы.** В исследование были включены 42 спортсмена высших достижений с ХГВ. Проанализированы результаты клинико-лабораторных (включая вирусологические) показателей и данные инструментальных методов обследования. Эффективность противовирусной терапии оценивали по вирусологическому, серологическому, биохимическому ответам и уменьшению выраженности фиброза печени. **Результаты.** 35,7 % спортсменов периодически отмечали тяжесть в правом подреберье, 19 % — незначительную слабость. У двух третей (66,7 %) спортсменов были выявлены диффузные изменения печени, у 19,4 % — увеличение ее размеров и/или спленомегалия, у 29,0 % — умеренный или выраженный фиброз печени. Активность АЛТ была повышена у 31,0 %. ДНК вируса гепатита В была обнаружена в сыворотке крови у всех спортсменов, при этом в 73,8 % случаев ее уровень составлял ≥ 200 МЕ/мл. На фоне приема аналогов нуклеоз(т)идов была получена авиремия и нормализация активности аминотрансфераз во всех случаях (через 3,0 месяца и 4,5 месяца, соответственно), стабилизация или уменьшение выраженности фиброза печени у 90,9 % спортсменов (через 24,0 месяца). Возобновление виремии отмечено в 7/17 случаев из-за прекращения приема препарата. **Заключение.** Клиническая картина ХГВ у спортсменов отличается минимальной симптоматикой. После относительно короткого периода противовирусная терапия аналогами нуклеоз(т)идов показала высокую эффективность в достижении вирусологического и биохимического ответов, а также в уменьшении выраженности фиброза печени. Отмеченные случаи возобновления виремии связаны с прерыванием приема препаратов.

Ключевые слова: *спортсмены, хронический гепатит В, противовирусная терапия, аналоги нуклеоз(т)идов, фиброз печени*

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Abstract

Athletes, as well as other general population groups, are at risk of infection with hepatitis viruses. **The aim** of the study was to characterise the clinical and virological picture of chronic hepatitis B (CHB) in athletes and to evaluate the efficacy of antiviral therapy. **Materials and Methods.** Forty-two elite athletes with CHB were included in the study. The results of clinical and laboratory (including virological) parameters and data of instrumental methods of examination were analysed. The efficacy of antiviral therapy was evaluated by virological, serological, biochemical responses and reduction of liver fibrosis severity. **Results.** 35.7 % of athletes periodically reported heaviness in the right hypochondrium, and 19 % experienced mild weakness. Diffuse changes in the liver were detected in two-thirds (66.7 %) of the athletes. Additionally, 19.4 % exhibited liver enlargement and/or splenomegaly, while 29.0 % showed moderate or significant liver fibrosis. Elevated ALT activity was observed in 31.0 % of the athletes. Hepatitis B virus DNA was found in the blood serum of all athletes, with 73.8 % of cases showing a viral load of ≥200 IU/mL. During treatment with nucleos(t)ide analogs, aviremia and normalization of aminotransferase activity were achieved in all cases within 3.0 and 4.5 months, respectively. Stabilization or reduction in the severity of liver fibrosis was observed in 90.9 % of athletes after 24.0 months. Viremia recurrence was noted in 7 out of 17 cases due to drug discontinuation. **Conclusion.** The clinical presentation of CHB in athletes is characterized by minimal symptoms. After a relatively short period, antiviral therapy with nucleos(t)ide analogs demonstrated high efficacy in achieving virological and biochemical responses, as well as in reducing the severity of liver fibrosis. Cases of viremia recurrence were associated with discontinuation of the medications.

Key words: *athletes, chronic hepatitis B, antiviral therapy, nucleos(t)ide analogs, hepatic fibrosis.*

Conflict of interests

Co-author of the article Ilchenko L.Yu. is the editor-in-chief of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. The decision to publish the article was made by the editorial board without the participation of the editor-in-chief. The authors have not declared any other conflicts of interest

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Conformity with the principles of ethics

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ALT — alanine aminotransferase, NA — nucleoside analogues, anti-HBc — hepatitis B core antibody, anti-HBe — hepatitis B e-antigen antibody, anti-HBs — hepatitis B surface antigen antibody, HVB — hepatitis B virus, DNA — deoxyribonucleic acid, AVT — antiviral therapy, peg-IFNα — pegylated interferon alpha, TDF — tenofovir disoproxil fumarate, TE — transient elastometry, HF — hepatic fibrosis, CHB — chronic hepatitis B, ETV — entecavir, HBe Ag — hepatitis B e-antigen, HBsAg — hepatitis B surface antigen.

Introduction

High-level sports (top-class sports) are a part of sports, accounting for approximately 2 % of sportsmen and targeting high sport results during the official national and international sport competitions [1]. These competitions include world championships, Olympic and continental games, most prestigious sport leagues. High-level sports are associated with constantly rising sport results as well as new records, sometimes even phenomenal ones. At the same time, sportsmen require complete mobilisation of emotional resources and all functional capabilities of their bodies. High sports achievements are based on methodological organisation of the training system, which comprises various stages of the training and competition process.

Viral hepatitis B is associated with high morbidity and mortality in the general population. According to the World Health Organisation, in 2019, 296 million people had chronic hepatitis B (CHB) globally, and over 800,000 people die of complications, such as hepatic cirrhosis and hepatocellular carcinoma [2]. In the Russian Federation, the number of hepatitis B virus (HBV) carriers and patients with CHB is about 3 million people [3, 4].

Given the global incidence of viral hepatitis B, sportsmen are also at risk of catching this disease. In a majority of cases, HBV is transmitted during activities not related to sports, e.g. unprotected sex, drug injections, including anabolic steroids and psychoactive drugs, shared use of personal belongings, body tattoos and piercing [5].

Nonetheless, there is a risk of transmitting the virus during some types of sports. Contact sports are believed to bear the highest risk of HBV transmission [6-8]. Besides, the risk for a sportsman to catch HBV depends on the country of their origin, especially for sportsmen living in endemic regions.

The actual incidence of CHB among professional sportsmen is unknown due to the minimal amount of data in scientific literature. In a recent Russian study, HBsAg (hepatitis B surface antigen) was found in two out of 384 blood samples drawn from professional sportsmen [5]. Results of a study conducted in Tehran demonstrated that the rate of HBsAg in fighters was 1.2 %, volleyball and football players — 0.5 % [9]. At the same time, it is worth mentioning that these studies reported a high detection rate of anti-HBc (hepatitis B core antibody) (7–13.9 %), which is a surrogate marker of latent HBV infection [5, 9].

Potential effects of CHB for the health and quality of life of an infected athlete can hardly be overestimated. Although hepatic complications can be uncommon among sportsmen, physical and mental disorders can be present at early stages of the disease, interfering with reaching high results [10].

Therefore, medical professionals attending to sportsmen should be aware of the risk of infection during sport activities and should be able to consult sportsmen in this matter, know measures to prevent hepatitis, and make decision on the therapy and access of the infected sportsman to training and competitions.

The objective of this study is to characterise the clinical presentation of CHB and to assess the efficacy of the antiviral therapies in professional athletes.

Materials and methods

The retrospective prospective observational study included 42 professional sportsmen with CHB, who were followed up by the specialists of the Centre for Diagnostics and Therapy of Chronic Viral Hepatitis in 2011–2024. Sportsmen with markers of HIV infection, hepatitis C, hepatitis D were excluded from the study.

During the initial visit, all patients gave their consent for participation in the study, treatment and publication of anonymous results.

This study was approved by the Local Ethics Committee at N. I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation (Minutes No. 213 dated December 13, 2021).

Source documents were used to analyse the clinical virological, biochemical and instrumental data. Sportsmen also had their blood drawn and HBV phenotype identified.

The efficacy of antiviral therapy was evaluated on the basis of virological (HBVdeoxyribonucleic acid (DNA) < 50 IU/mL), serological (HBsAg clearance/seroconversion, HBeAg clearance/seroconversion (HBV e-antigen) in HBeAg-positive patients), biochemical (normalised activity of alanine aminotransferase (ALT)) response and reduced hepatic fibrosis (HF) activity.

Both standard laboratory and instrumental test methods were used. Serological markers of HBV (HBsAg, anti-HBs (hepatitis B surface antigen antibody), HBeAg, anti-HBe (hepatitis B e-antigen antibody)) were measured by ELISA. HBV DNA in blood was detected using polymerase chain reaction. HBV genotype was identified using a phylogenetic analysis of available nucleotide sequences or ELISA test for HBsAg subtypes in cases when no HBV DNA could be found. Aixplorer SuperSonic Imagine device (France) was used for abdominal ultrasound. HF was evaluated during transient elastometry (TE) at Fibroscan® (502 Touch Echosens, France). METAVIR classification was used to identify the stage of fibrosis (stage F0-1 — 7.2 kPa and less; F2 — 7.3 to 9.5 kPa; F3 — 9.6 to 12.5 kPa; F4 — 12.6 kPa and above) [11].

Statistical processing was performed using SPSS software (version 26.0; SPSS Inc., USA). Numerical clinical data were compared with the help of Mann — Whitney test (independent groups). Wilcoxon test was used to analyse the changes in numerical data during therapy. Parameter correlation was assessed using Spearman's correlation coefficient (r). Serum HBV and HBsAg levels were analysed after log transformation. A statistically significant value was $p < 0.05$.

Results

Clinical virological pattern

The study group included mostly male subjects (30/42; 71.4 %). The age of sportsmen varied from 15 to 45 years old (median age: 25.0 [20.0–33.0] years old). There were no statistically significant differences in the mean age between male and female subjects: 25.0 [20.0–31.0] and 25.5 [19.5–36.5] years old, respectively ($p = 0.596$).

31.0 % (13/42) of sportsmen were candidates for master of sports, 42.9 % (18/42) — masters of sports, 11.9 % (5/42) — international masters of sport. The mean sporting experience was 12.5 [7.4–21.1] years old.

Information on the first HBsAg detection was recorded during an extended medical examination; and the duration of antigen presence in blood was 6.0 [2.0–10.3] years. Sportsmen denied having a history of acute hepatitis and did not undergo hepatitis B vaccination.

Sportsmen were involved in various sports; over a half of them (52.4 %; 22/42) were contact sportsmen (Table 1).

Clinical presentations of CHB in sportsmen were minimal. Fifteen (35.7 %) sportsmen noted periodic feeling of weight in their right hypochondrium, while eight (19.0 %) mentioned mild weakness.

HBV genotype was identified in 69.0 % (29/42) of cases. Genotype D was prevailing (26; 89.7 %) as compared to genotypes A (2; 6.9 %) and C (1; 3.4 %).

During the initial visit, the majority of sportsmen (92.9 %; 39/42) were HBeAg negative. Elevated ALT values were recorded in 13/42 (31.0 %) of cases: up to three upper limits of normal (ULN) — in 11, 3–5 ULN — in 1 and over 10 ULN — in 1.

Serum HBV DNA was observed in all sportsmen, with the levels ≥ 200 IU/mL reported in 31 (73.8 %); the highest value was 10^8 IU/mL. HBV DNA levels in contact and semicontact/non-contact sportsmen did

Table 1. *Characteristics of athletes by sports affiliation*

Contact sports		**Semi-contact/ non-contact sports**	
Type of sport	n	Type of sport	n
Freestyle wrestling	6	Athletics	6
Judo	6	Ski racing	2
Taekwondo	3	Chess	2
Greco-Roman wrestling	2	Pentathlon	1
Boxing	1	Canoeing	1
Kickboxing	1	Powerlifting	1
Rugby	1	Bobsleigh	1
Sambo	1	Basketbal	1
Football	1	Badminton	1
		Mountaineering	1
		Rock climbing	1
		Stand shooting	1
		Shot put	1
Total	**22**	**Total**	**20**

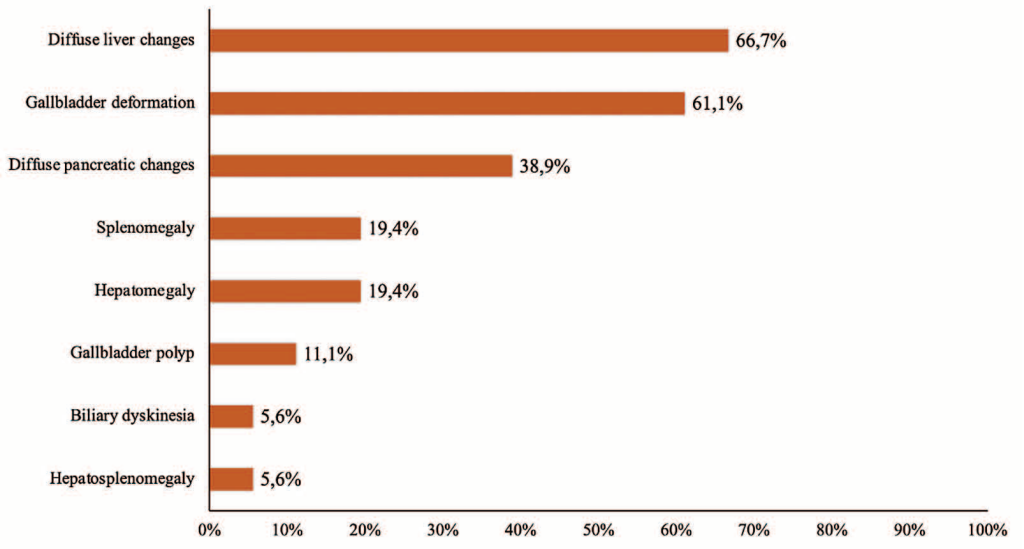

Figure 1. *Echographic signs of abdominal organ pathology in athletes*

not differ (2.8 [2.0–3.6] log_{10} IU/mL and 3.1 [2.5–3.7] log_{10} IU/mL, respectively; p = 0.350).

Abdominal ultrasound in 36 sportsmen revealed abnormal signs in the majority of cases (85.1 %; 31/36) (Figure 1).

Two thirds (66.7 %; 24/36) of sportsmen had diffuse changes in their liver. Hepatomegaly or splenomegaly was reported in 19.4 % (7/36) of cases. Over one third of sportsmen (38.9 %; 14/36) has diffuse changes in their pancreas.

Gall bladder and bile passage abnormalities were reported in 63.8 % (23/36) of cases. Of these, deformed gall bladder was observed in 61.1 % (22/36), gallbladder polyps — in 11.1 % (4/36) and biliary dyskinesia — in 5.6 % (2/36) of cases.

Liver TE was performed in 30 sportsmen, and METAVIR stage F0-1 HF was diagnosed in 22 (71.0 %) cases, F2 — in 6 (19.3 %), and F3 — in 3 (9.7 %) cases.

There were no differences in fibrosis severity between male and female athletes (6.1 [5.3–7.6] kPa and 6.1 [4.0–7.2] kPa, respectively; p = 0.527).

Comparison of semicontact/non-contact sportsmen with contact sportsmen showed more severe HF in the latter group (4.6 [4.3–6.9] kPa and 6.4 [5.6–7.8] kPa, respectively; p = 0.039).

Antiviral therapy efficacy

Eighteen sportsmen (10 male and eight female athletes) were treated with AVT. The baseline characterics of sportsmen are presented in Table 2.

The patients were treated with the following products: 9 — entecavir (ETV), 6 — tenofovir disoproxil fumarate (TDF), 1 — pegylated interferon alpha (peg-IFNα), 2 — peg-IFNα with subsequent replacement with nucleoside analogues (NA).

One out of three sportsmen treated with peg-IFNα demonstrated complete virological and biochemical response, and AVT was discontinued after 48 weeks. The other two sportsmen switched to ETV and TDF after 24 and 48 weeks of peg-IFNα therapy, respectively, because of persistent high viral load and elevated aminotransferases.

Thus, NA preparations were indicated in 17 sportsmen (ETV — 10, TDF — 7). The length of AVT with NAs was six to 118 months, mean value: 15.0 [10.0–32.0] months.

After NA therapy, all sportsmen demonstrated positive response (i.e. undetectable HBV DNA levels). The mean time from therapy initiation to this result was 3.0 [2.0–5.0] months and did not differ between sportsmen on ETV or TDF (2.5 [2.0–5.0] months and 3.0 [2.0–5.0] months, respectively, p = 0.582). The latest aviremia was recorded in one sportsman at nine months of TDF therapy.

It has been shown that the time to virologic response depends on the initial viral load: a higher HBV DNA levels were associated with a longer time to aviremia (r = 0.617; p = 0.014).

In one case, TDF therapy resulted in HBeAg seroconversion nine months after therapy initiation. No HBsAg clearance was observed; however, its level slightly dropped from 4.0 log_{10} IU/mL to 3.8 log_{10} IU/mL after 18.0 [12.0–40.0] months of therapy.

All sportsmen demonstrated normal ALT activity 4.5 [2.0–9.0] months after therapy initiation. There were no differences in the time to biochemical response with ETV or TDF therapy (5.0 [2.0–12.0] months and 4.0 [2.5–7.0] months, respectively, p = 0.748).

TE was used in 11 cases after 24.0 [12.0–30.0] months of AVT to assess changes in HF. The mean TE values reduced from 6.2 [5.5–10.5] kPa to 5.7 [4.3–7.1] kPa. The majority of sportsmen (10/11) demonstrated fibrosis stabilisation or reduction. Only one sportsman out of seven with baseline stage F0-1 developed HF stage F2.

Таблица 2. *Характеристика спортсменов на старте ПВТ*
Table 2. *Characterization of athletes at the start of antiviral therapy*

Parameters	Athletes n=18
Gender, n Male Female	 10 8
Age, years	25,0 [20,0-34,0]
Type of sport, n Contact Semi-contact/ non-contact	 9 9
HBeAg-positive, n	3
HBV DNA, log_{10} IU/mL	3,3 [3,1-4,2]
ALT, IU/L ALT>40 IU/L, n(%)	50,5 [25,0-59,4] 10 (55,6)
AST, IU/L AST>40 IU/L, n(%)	37,5 [25,0-45,0] 7 (38,9)
HBsAg, log_{10} ME/ml	4,1 [3,8-4,6]
TE, kPa	5,6 [4,3-7,8]
METAVIR stage of fibrosis, n F0-1 F2 F3	n=14 10 1 3

As for the sportsmen with baseline stage F3, there was one case of improvement to stage F2 and two cases of improvement to stage F1. Also, one sportsman with baseline stage F2 demonstrated improvement to stage F1.

Seven out of 17 sportsmen had HBV DNA on the average eight months after the therapy initiation.

The viral load varied from 150 IU/mL to 650 IU/mL, and no elevated ALT was observed. Viremia recurrence was associated with a short-term break in NA therapy during sport events (the duration of AVT suspension is unknown). Once AVT with previous drugs was resumed, aviremia was achieved on the average in 5.0 [3.0–6.0] months in all cases.

Discussion

Like the rest of the population, sportsmen are susceptible to HBV infection; however, studies of the characteristics of the clinical virological pattern and efficacy of AVT in sportsmen with CHB have never been conducted before. Our study included 42 professional sportsmen with CHB aged 15 to 45 years old.

Hepatitis B virus is justifiably included into the group of vaccine preventable diseases, the spread of which is efficiently controlled with specific prevention, i.e. vaccination. In Russia, hepatitis B vaccination was added to the National Immunisation Schedule in 2001. However, all sportsmen in the CHB study group originated from the regions, where (for some reason, primarily for religious reasons) no hepatitis B immunisation was performed. These data correlate with the results of an earlier study in 384 highly qualified athletes. According to questionnaires and medical records, only 45 (11.7 %) subjects had been vaccinated against hepatitis B [5].

The clinical presentation of CHB in sportsmen is minimal: 35.7 % of sportsmen complained of feeling of weight in their right hypochondrium and 19 % mentioned mild weakness. However, it is worth noting that an ultrasound examination revealed diffuse changes in the liver of 24 subjects, while seven had hepatomegaly or splenomegaly. Besides, there were four cases of mild to moderate HF diagnosed with TE (METAVIR stage F2–F3). Organic lesions of the liver in CHB patients can cause limitations related to the athlete's health and worsen their competitive results.

Unfortunately, there is insufficient information on the clinical characteristics of CHB in professional sportsmen in the available medical references in English (PubMed, Cochrane Library, UpToDate, Medscape, Sports Med Open, Br J Sports Med., etc.), and we are unable to compare our results with similar findings in foreign athletes.

Despite minimal clinical signs in sportsmen, CHB is a long-lasting, progressive conditions with a high risk of hepatic cirrhosis and cancer. To prevent these complications, the only option is timely AVT initiation.

There are currently no guidelines on the use of AVT in professional athletes. However, horizontal transmission of this infection via damaged skin during trainings and competitions has been reported [6, 7].

There is still no evidence of the lowest threshold of HBV DNA, below which HBV-infected athletes are considered safe to take part in competitions and protect other team members and rivals. Studies should be conducted to identify the viral load, below which the virus is not transmittable from an athlete to an athlete. Since there are no additional data, foreign scientists use the criteria applicable to medical professionals engaged in high-risk procedures, i.e. 200 IU/mL, in order to minimise the risk of HBV transmission among professional sportsmen [12]. Pending a relevant regulation, it is suggested to use it for AVT therapy in athletes with CHB [12].

During the observation, seventeen sportsmen received NA AVT (ETV or TDF). The results demonstrated high efficacy of these drugs: all patients achieved aviremia and normal ALT activity after a relatively short period of time (3.0 months and 4.5 months, respectively). As compared to other studies in non-athletes, the mean time from AVT initiation to aviremia was longer and made approximately 10 months [13]. A number of previous studies and this study established direct correlation between time to aviremia and baseline viral load [14, 15]. In athletes with CHB, AVT was initiated at lower viremia level (over 200 IU/mL), that is why they relatively rapidly achieved a non-detectable levels of HBV DNA. There were no differences in ETV and TDF therapy as to the time to virological and biochemical response. ETV and TDF also demonstrated good effects for improved liver morphology: HF stabilised or improved in the majority of athletes undergoing therapy. Timely CHB therapy considering the viral load not only reduces the risk of infection among professional athletes, but also contributes to improved hepatic enzyme levels and hepatic fibrosis status, allowing them to demonstrate high sport results.

At the same time, it is interesting to note that viremia recurred in seven patients on the average eight months after AVT initiation. ETV and TRF are known to be products with a high genetic barrier to resistance; and viremia recurred at early stages of the therapy, so drug resistance can be ruled out.

Excessive physical stress in sportsmen with CHB causes more severe damage to hepatic tissue than in athletes without CHB, and it can affect AVT efficacy [16]. Also, it can be expected that athletes may suspend NA therapy for a short period of time during trainings and competitions. In all cases, AVT was resumed with the same products and at the same doses, and in all cases aviremia was achieved in 5.0 months. It is essential that doctors in sports medicine explain to athletes that NA preparations prevent CHB complications and are not on the WADA List of Prohibited Substances and Methods; these preparations can be used on a daily basis [17].

Conclusions

Athletes with CHB have few symptoms; however, damage to their liver observed at ultrasound and TE can affect health and sport results. Antiviral therapy with NAs can efficiently inhibit virus replication, normalise cytolytic enzymes and reduce HF severity. Viremia recurrence during therapy emphasises the importance of consultations by doctors in sport, so that athletes are compliant also during their sport activities.

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Нгуен Т.Х.: концепция и дизайн исследования, сбор и обработка материала, анализ полученных данных, написание текста.

Ильченко Л.Ю.: концепция и дизайн исследования, редактирование текста.

Кюрегян К.К.: концепция и дизайн исследования, анализ полученных данных.

Мельникова Л.И.: сбор и обработка материала.

Нгуен К.К.: анализ полученных данных.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Nguyen T.H.: concept and design of the study, collection and processing of material, analysis of the obtained data, writing the text

Ilchenko L.Yu.: the concept and design of the study, editing the text

Kyuregyan K.K.: concept and design of the study, analysis of the obtained data.

Melnikova L.I.: collection and processing of material.

Nguyen C.C.: analysis of the obtained data.

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