CLINICAL LABORATORY DIAGNOSTICS

MYOCARDIAL DAMAGE BIOMARKERS AND THE FIRST CASE OF MACROTROPONIN I DETECTION IN ENDURANCE ATHLETES

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ABSTRACT

Background. *High levels of cardiac troponin in the blood indicates myocardial injury, including those caused by intense exercises. Recent studies have shown that an elevation in the troponin concentration in the patients can be caused by the macrotroponin circulation. There is no data in the scientific literature describing this problem in athletes.*
The aim. *To identify the cases and possible causes of high blood levels of cardiac markers in athletes before and after endurance exercises.*
Materials and methods. *The study was conducted on 11 male cross-country skiers aged 15–21 years. The study included two stages: the first was conducted at the end of the preparatory period (November, 2020–2021), the second – in the middle (March) of the 2020–2021 competitive period. At each stage, two blood samples were taken from a vein: the first – in the morning on an empty stomach after a day of rest, the second – 12–14 hours after a high-intensity exercise. In the blood serum, the activity of total creatine kinase (CK), weight concentration of the cardiac isoenzyme of creatine kinase (CK-MB), and concentration of high sensitive troponin I (Tn) were measured.*
Results. *The activity of CK in athletes exceeded the upper limit threshold, and decreased from the preparatory (November) to the competitive (March) period. The concentration of CK-MB in response to exercise increased by 2 times and was not accompanied by the signs of myocardial injury. The most sensitive indicator, responsive to physical activity, was troponin I. However, the highest elevation of Tn in blood of one athlete, both before and after the exercise, was associated with the presence of macrotroponin without signs of myocardial injury.*
Conclusions. *An increase of muscle tissue injury biomarkers in blood, including the heart muscle (CK, CK-MB, and Tn), by 2–4 times is a typical reaction for the body of a cross-country skier to an intense exercise. High levels of troponin in the blood, both before and after training or competition, may be associated with the presence of macrotroponin.*

Key words: *cross-country skiing, troponin I, macrotroponin, creatine kinase, myocardial injury*

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БИОМАРКЕРЫ ПОВРЕЖДЕНИЯ МИОКАРДА И ПЕРВЫЙ СЛУЧАЙ ВЫЯВЛЕНИЯ МАКРОТРОПОНИНА I У АТЛЕТОВ, ТРЕНИРУЮЩИХСЯ НА ВЫНОСЛИВОСТЬ

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РЕЗЮМЕ

Обоснование. *Высокий уровень тропонина свидетельствует о повреждении миокарда, в том числе вызванного интенсивными тренировками. Исследования последних лет показали, что у больных увеличение концентрации тропонина может быть вызвано циркуляцией макроформ. В научной литературе нет данных, описывающих данную проблему у атлетов.*

Цель исследования. *Выявить случаи и возможные причины высокого уровня кардиомаркеров в крови у атлетов до и после физической нагрузки на выносливость.*

Материалы и методы исследования. *Обследовано 11 лыжников-гонщиков мужского пола (15–21 лет). Эксперимент включал 2 этапа: первый – в ноябре 2020–2021 гг.; второй – в марте 2020–2021 гг. На каждом этапе проводили два забора крови из вены: первый – после дня отдыха, второй – через 12–14 ч после высокоинтенсивной тренировки. В сыворотке определяли активность общей креатинфосфокиназы (СК), концентрацию сердечной изоформы креатинфосфокиназы (СК-МВ) по массе и тропонина I (Тн), определённого высокочувствительным методом.*

Результаты исследования. *Активность СК превышала верхнюю границу нормы и снижалась от ноября к марту. Концентрация СК-МВ в ответ на тренировку повышалась в 2 раза и не сопровождалась признаками повреждения миокарда. Наиболее чувствительным показателем, реагирующим на тренировку, оказался Тн. Однако самое высокое повышение тропонина в крови у одного атлета было связано с наличием макротропонина без наличия признаков миокардиального повреждения.*

Заключение. *Повышение в крови уровня биомаркеров повреждения мышечной ткани, в том числе миокарда, в 2–4 раза является характерной реакцией для организма лыжника-гонщика в ответ на интенсивную тренировку. Высокий уровень тропонина в крови как до, так и после тренировки может быть связан с наличием макроформ протеина.*

Ключевые слова: *лыжные гонки, тропонин I, макротропонин, креатинкиназа, повреждение миокарда*

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OBJECTIVES

Moderate physical activity has a positive effect on human health, which is not the case for professional sports, in which physical activity is extreme. The athlete's body works at its limits during competition. Changes in athletes' biochemical indicators are often beyond normal values for ordinary people. First of all, the levels of muscle tissue biomarkers – creatine kinase and cardiac troponin – are increased.

High sensitive troponin I (Tn) has been the "gold standard" in the diagnosis of acute myocardial infarction in all developed countries since 2018, as it is a completely specific marker for heart muscle. The 99th percentile of this marker being repeatedly exceeded in the blood usually indicates the development of an acute myocardial infarction or other myocardial injury. Blood levels of Tn can remain increased up to 7 days after damage [1]. In recent years, a growing amount of data has been accumulating that suggest that Tn is increased in various diseases accompanied by myocardial injury [2]. An increase in cardiac troponin levels can be induced by intense and prolonged exercise [3, 4]. The increase of Tn level in blood is associated with its release from cardiomyocytes as a result of increased permeability of the sarcolemma [5]. As well, exceeding reference values of Tn in athletes indicates myocardial injury due to insufficient myocardial adaptation to a certain level of physical activity [6]. Determination of Tn after exercise in recreational long-distance runners or sport walkers may have predictive significance in the development of cardiovascular complications, especially after the age of 50 years [7].

Increased Tn levels caused by a novel coronavirus infection (COVID-19), including in athletes, have recently been reported in international forums [8–10]. High blood Tn concentration is prevalent in hospitalized patients with COVID-19 and is associated with decreased survival and development of complications [11]. Tn elevation mechanism in COVID-19 patients is associated with myocardial injury due to thromboembolism, acute respiratory distress syndrome (ARDS) combined with systemic inflammatory reaction [12]. The increase in marker levels during COVID-19 disease may be the result of direct myocardial injury by the virus [11].

However, there are a certain number of false-positive Tn assays due to the presence of so-called «macrotroponins» in the bloodstream rather than cardiac damage [13]. Macrotroponin is a complex formed by endogenous autoantibodies to Tn and circulating cardiac troponin I in the blood [14]. The molecular mass of these complexes varies from 340 to 900 kDa and indicates the participation of immunoglobulins A or G in their formation [15]. Accumulation of macrotroponins may lead to macrotroponinemia by analogy with macroprolactinemia (macroprolactin is an immune complex of the pituitary hormone molecule prolactin with autoantibodies) [16]. Detection of high blood troponin levels associated with macrotroponinemia can lead to false-positive diagnosis of acute myocardial infarction, hospitalization and unnecessary, dangerous and expensive manipulations in a medical institution, such as contrast-enhanced coronary angiography [17]. We did not find a description of this problem in athletes in the scientific literature.

THE AIM OF THE STUDY

To identify the cases and possible causes of high blood levels of cardiac markers in athletes before and after endurance exercises.

MATERIALS AND METHODS

The study was conducted as part of the research work "Development of full assessment of performance and damage to vital organs in competitive sportsmen based on innovative laboratory-biochemical automated methods", approved by the local ethics committee of the Lesgaft National State University of Physical Education, Sport and Health, St. Petersburg (protocol No. 4, registration number No. 0089 dated 30.12.2017). The study included 11 male cross-country skiers of St. Petersburg aged 15–21 years with different sports qualifications (First-Class Sportsmen, Candidates for Master of Sport, Masters of Sport), trained by a coach in one group and following the same training and competition plan, which was the reason for their allocation into one group (Table 1).

TABLE 1

ANTHROPOMETRIC CHARACTERISTICS OF CROSS-COUNTRY SKIERS (*n* = 11)

Parameters	Me	min	max
Age, years	17	15	21
Height, cm	179.0	164.0	185.0
Weight, kg	72	61.0	80.0
BMI, kg/m^2	22.4	19.4	25.0

The experimental part of the study included two stages: the first (I) – at the end of the preparatory period, the second (II) – in the middle of the competitive period of cross-country skiers 2020–2021. At each stage, after signing informed voluntary consent (for minors – by their legal representatives) for medical intervention, two blood samples were taken from a vein into vacuum systems. The first blood sampling was performed in the morning on an empty stomach after a day of rest. At stage I, the second blood sampling was performed 12–14 hours after a high-intensity exercise (10 km cross-country skiing) in the evening, as close as possible to the competitive load. At stage II, the second blood collection was performed after a 10 km competitive ski race at the same time.

Biochemical and immunochemical analyzers of Architect line were used to perform the analyses using reagents and control materials of the equipment manufacturer (Abbott, USA). The activity of total creatine kinase (CK), weight concentration of the cardiac isoenzyme of creatine kinase (CK-MB) and concentration of high sensitive troponin I (Tn) were measured (the 99th percentile for the indicated method of analysis in men is 34 ng/L). Important to note that immunochemical methods for CK-MB and Tn determination are method-dependent, and absolute values expressed in ng/L may differ by several times when using equipment or reagents from another manufacturer.

The obtained data were processed using Statgraphics 19 program (Statgraphics Technologies, Inc., USA). The sample was assessed for conformity to a normal distribution using standardized skewness and standardized kurtosis. For normal distribution of traits, the mean ± standard deviation (mean ± SD) was used; for distributions not conforming to normal, the mean and 25th and 75th percentiles (mean [Q_1; Q_3]) were used. The statistical significance of differences between blood sampling results was assessed using Student's t-test for related samples with normal distribution of variables or using the Wilcoxon signed-rank test for related samples. Statistical significance of differences in the values of the studied parameters was established at $p \leq 0.05$.

RESULTS AND DISCUSSION

Total CK activity at the end of the preparatory period of cross-country skiers after a day of rest was 290.1 [192.9; 330.4] u/l; it increased to 393 ± 164.8 u/l 12 hours after a high-intensity exercise ($p < 0.05$). In clinical practice, 190 u/l is considered the upper limit of normal for men, but this threshold value is not recommended for professional athletes [18]. The increase in total CK activity in blood is mainly due to an increase in myocyte cell membrane permeability, which is explained by acidosis and accumulation of strong organic acids in cells during intense physical activity [19]. It is believed that the increase in enzyme activity in the blood of endurance training athletes can be up to 800 u/l without serious consequences [18]. There are also scientific data showing multiple excesses of normal CK activity in individual athletes associated with mechanical damage to skeletal muscle [20]. The intensity of CK release from muscles into the vascular bed is an individual characteristic, and the dynamics of the level of this enzyme in blood serves as an integral indicator of the delayed effect of physical activity [21] and depends on the type of sport [22].

Before competition, athletes' CK activity significantly decreased (219.7 ± 129.6 u/l) compared to the preparatory period ($p < 0.01$). After the race, enzyme activity still decreased slightly in most athletes (204.6 ± 47.8 u/l); data are shown in Figure 1. We can assume that athletes recovered faster due to the change in the nature of physical activity. We hypothesize that competitive activities of cross-country skiers have a less damaging effect on skeletal muscles than intense/long training loads of 2 workouts per day.

Any physical activity affects the cardiovascular system of the human body. The effect of exercise on cardiac muscle can be assessed by changes in the concentration of cardiac-specific markers in the blood. Weight concentration of CK-MB during the preparatory period in cross-country skiers before and after training were 5.4 [3.2; 6.4] and 6.4 ± 2.7 ng/ml, respectively ($p < 0.01$). Changes in blood troponin I levels during the same period showed a higher sensitivity in response to exercise: 8.6 [4.5; 37.9] ng/L before exercise and 18.3 [7.6; 29.0] ng/L after exercise. It is reasonable to conclude from these results that assessing the effect of exercise on the cardiac muscle by changes in Tn concentration is preferable to using weight concentration of CK-MB. However, the Tn results were more variable than CK-MB, which supports the assumption of an individual response in each athlete (Table 2).

The data presented in Table 2 shows that 6 athletes had an increase in Tn level and this increase was statistically significant. In other cross-country skiers the change was insignificant: for example, in athlete #7 the marker concentration decreased from 3.2 to 1.4 ng/L, but these figures are at the limit of method sensitivity and when using the laboratory method of the previous generation even of the same manufacturer (before 2016) corresponded to the digital value 0 (the indicator in the blood is not determined). Two athletes exceeded the upper reference level threshold (34 ng/L) at both blood collection points.

In the competitive period, the blood Tn level remained at the level of the preparatory period after exercise. Pre-race CK-MB and Tn values were 7.7 ± 3.8 ng/ml and 18.8 [11.0; 99.3] ng/L, respectively; post-race values were 5.8 ± 2.3 ng/ml and 14.1 [9.7; 33.1] ng/L. CK-MB concentration after the competition decreased to the level of the preparatory period before exercise. CK-MB levels exceeded the upper reference level at all-time points of blood sampling (Fig. 2).

Blood Tn levels increased in individual cross-country skiers throughout the study. We hypothesized that competitive load influences the increase in Tn concentration to a greater extent than exercise load. However, given the high variation of results within the group, no statistically significant differences between the indicators were found (Table 3).

An increase in Tn concentration after the race was detected in the majority of athletes, as in the preparatory period. Unfortunately, not all athletes were able to participate in stage II of the study: 2 athletes (blood samples #6 and #9) finished their sports career, and one athlete was ill for a long time (sample #7) and showed the worst race time. It should be noted that a significant increase in the level of the marker was recorded in two athletes both before and after the competition. We also noted a high level of Tn in these athletes during the preparatory period. There was a multiple increase in Tn levels in ath-

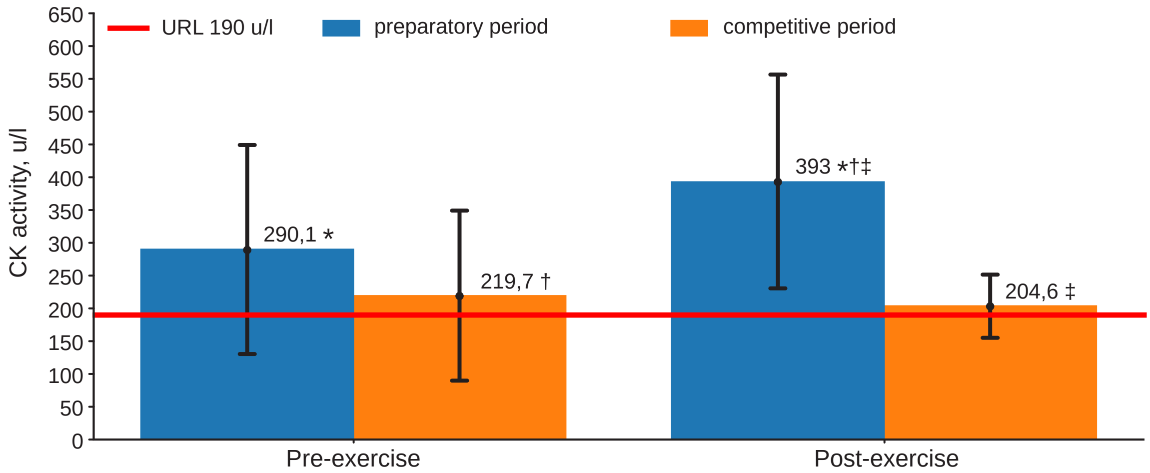

FIG. 1.

*Creatine kinase activity in cross-country male skiers before and after exercise in different training periods (mean ± SD): URL – upper reference level for men over 17 years old – 190 U/l (Abbott, USA); * – p < 0.05 compared to pre-exercise values in the preparatory period; † – p < 0.01 compared to post-exercise values in the preparatory period; ‡ – p < 0.05 – compared to post-exercise values in the preparatory period*

TABLE 2

INDIVIDUAL CHANGES IN BLOOD TROPONIN CONCENTRATION IN CROSS-COUNTRY SKIERS AT STAGE I OF THE STUDY (*n* = 10)

Sample #	Tn level before exercise, ng/L	Tn level after exercise, ng/L	ΔTn, ng/L	Level change, in % of baseline
1	98.9	118.4	+19.5	+19.7
2	5.0	17.9	+12.9	+258.0
3	4.5	4.1	–0.4	–8.9
4	8.6	18.7	+10.1	+117.4
5	81.5	94.1	+12.6	+15.5
6	3.9	7.6	+3.7	+94.9
7	3.2	1.4	–1.8	–56.3
8	37.9	29.0	–8.9	–23.5
9	7.3	–*	–*	–*
10	9.3	11.5	+2.2	+23.7
11	30.4	27.4	–3.0	–9.9

Note. * – Athlete #9 results were excluded due to the presence of hemolysis in the post-exercise sample.

lete #1 that did not fit the overall picture of what was going on. Any increased biomarker value, in our opinion, should be analyzed in combination with other indicators of the athlete's health status. Thus, the increase in troponin I in athlete #1 was not associated with the other laboratory parameters studied (Fig. 3).

Analyzing these graphs, it can be noted that the increase in CK as well as CK-MB is within the normal range of changes during sports training and does not exceed 3-fold of the upper limit of normal. The state of skeletal muscles is normal for this athlete. An increase in Tn level by more than 10 times (such changes are interpreted in clinical cardiology as an indicator of mass death of cardiomyocytes) may mislead a sports physician in diagnosing myocardial injury. In this study, an electrocardiogram (ECG) was performed to rule out myocardial pathology, which showed no pathologic changes. On ECG, only slight sinus bradycardia (heart rate – 50 bpm) was registered, which in most cases is typical for athletes of this sport [23]. According to the latest scientific data, it is not possible to identify the initial pathological characteristics of myocardial injury in athletes based on ECG or echocardiography findings alone. During further examination in the Almazov National Medical Research Center, delayed contrast-enhanced MRI of the heart was performed in athlete #1 [24]. The study results showed no myocardial integrity abnormalities, no thickened pericardium, no pathologic effusion in the pericardial cavity, no ventricular dilatation, no dilated atria, no signs of myocardial edema. Thus, the repeated increase in troponin I in this athlete is not associat-

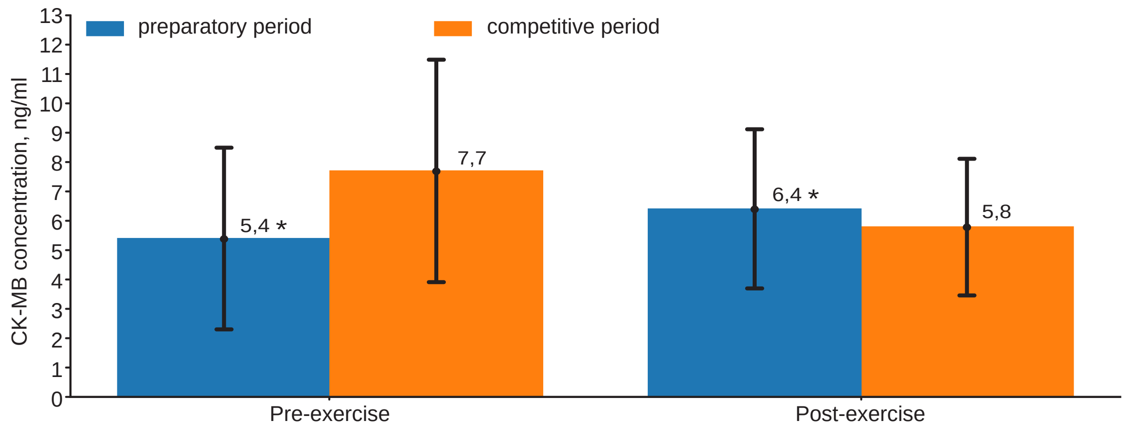

FIG. 2.

*Concentration of cardiac isoenzyme of creatine kinase in cross-country male skiers before and after exercise in different training periods (mean ± SD): * – p < 0.05 compared to pre-exercise values in the preparatory period*

TABLE 3

INDIVIDUAL CHANGES IN TROPONIN CONCENTRATION IN CROSS-COUNTRY MALE SKIERS BEFORE AND AFTER THE RACE (*n* = 9)

Sample #	Tn level before the race, ng/L	Tn level after the race, ng/L	ΔTn, ng/L	Level change, in % of baseline
1	613.4	772.6	+159.2	+26.0
2	35.8	9.7	–26.1	–72.9
3	11.9	18.7	+6.8	+57.1
4	10.0	33.1	+23.1	+231.0
5	162.7	243.2	+80.5	+49.5
7	–*	5.4	–*	–*
8	24.6	13.3	–11.3	–45.9
10	9.5	8.4	–1.1	–11.6
11	12.9	14.1	+1.2	+9.3

Note. * – Athlete #7's sample was excluded before the race for technical reasons.

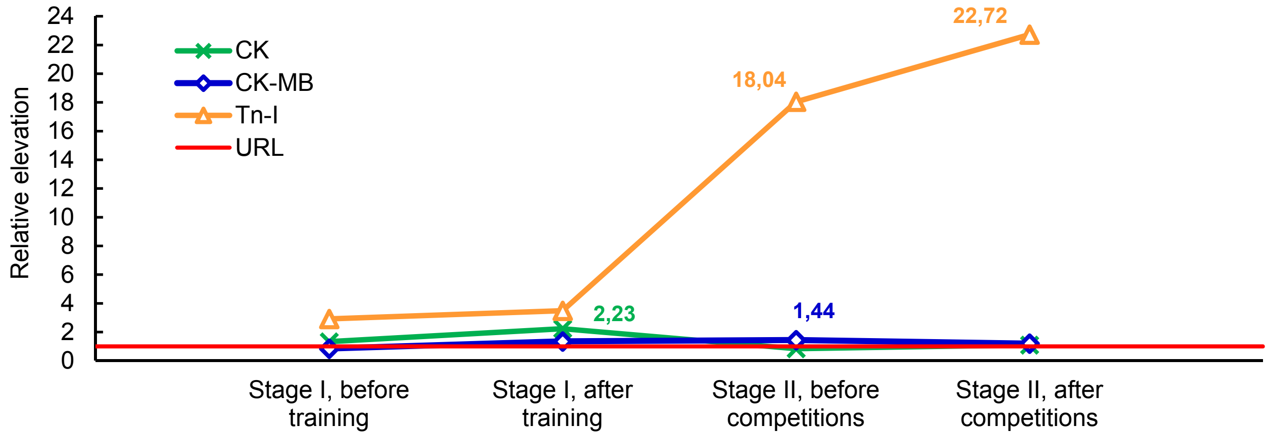

FIG. 3.

Relative increase in injury markers as related to the upper normal level in sportsman No. 1: URL – upper reference level

ed with the development of abnormal myocardial changes. Further strategy of our study was aimed at establishing the cause of such a significant increase of Tn in blood. In the course of reviewing the scientific literature of recent years, we hypothesized the presence of macrotroponin in this athlete. In a study by J.V. Warner et al. it was shown that in 5 % of patients with increased high sensitive Tn levels, high molecular weight complexes containing immunoreactive troponin I and immunoglobulins (macrotroponin) are detected in the blood. The researchers also noted that patients with myocarditis and Tn macrocomplexes have higher and more prolonged marker increases compared to patients without the presence of macrotroponin. In most subjects with macrotroponins, high sensitive Tn levels did not exceed 100 ng/L [15]. In a study by P.A. Kavsak et al. it was shown that increased blood levels of Tn are associated with the presence of troponin I macrocomplexes, which can be determined by polyethylene glycol precipitation. The results of assays using Beckman (USA) equipment and reagents are slightly less susceptible to changes in the presence of macrotroponins I in the blood [25]. L. Lam et al. found the differences between samples with and without macrotroponins to be statistically significant ($p < 0.001$) using gel permeation chromatography (GPC). The authors also noted the effect of autoantibodies to Tn on troponin immunoassay results [26]. Autoantibodies to Tn may possibly potentially influence cardiac remodeling [27]. Animal experiments have shown that decreased levels of autoantibodies to troponin and other cardiac-specific proteins (alpha-actin 1 and beta-myosin 7B) may be an indicator of cardiomyocyte adequacy and adaptation to exercise stress [28].

To determine the presence or absence of Tn macrocomplexes in the serum of athlete #1, we used the proven method of precipitation of high molecular weight protein complexes using a 25 % aqueous solution of polyethylene glycol 6000 (Sigma, Germany). After incubation of serum and polyethylene glycol in a 1:1 ratio, the mixture was centrifuged at 5000 g for 20 min. Tn immunochemical determination was performed in the supernatant, taking into account the dilution of the sample. Assay results confirmed precipitation of macrotroponin complexes; less than 10 % of the original Tn remained in the supernatant. After precipitation of macrotroponin complexes in other athletes with polyethylene glycol, which was performed in the II (competitive) stage of our study, less than 20 % of macrotroponin of the baseline amount of troponin I were detected in the sera of all skiers except athlete #1. Thus, it can be assumed that the high blood Tn level in the athlete is a false positive, not related to myocardial injury, but is due to the development of an autoimmune process. In addition, we can assume that troponin I levels in athletes with autoantibodies to Tn will be significantly higher than in ordinary people with low physical activity and the presence of such pathology. We believe that the situation with macrotroponins will be much the same as the laboratory phenomenon of "macroprolactinemia" and the development of the phenomenon of high levels of thyroperoxidase antibodies. Unfortunately, such patients do not have clinical manifestations of immune pathology for lots of months, which leads to diagnostic errors in the work of endocrinologists, oncologists and medical officers of other specializations. High-intensity and prolonged myocardial exercise in professional athletes leads to increased cardiomyocyte permeability and increased entry of intracellular proteins into the blood, which may induce an immune response. The effect of COVID-19 can be especially dangerous to the athlete who continues to train, as muscle cells are quickly affected by the coronavirus. For example, athlete #1 had the highest level of immunoglobulin G to the virus in the second stage of the study compared to the other athletes after the December 2020 illness.

CONCLUSION

A 2–4-fold increase in blood levels of biomarkers of muscle tissue damage, including cardiac muscle (CK, CK-MB and Tn), is a typical reaction for a cross-country skier in response to intense exercise. The most sensitive indicator responsive to physical activity of a cross-country skier is high sensitive troponin I. Significant increase of troponin I concentration in blood (5 times and higher in relation to the upper reference interval), in our opinion, requires in-depth laboratory analysis and deeper medical examination to exclude possible myocardial pathology. In some cases, multiple troponin increases may be associated with the presence of macrotroponin in the blood. The phenomenon of blood macrotroponin detection in athletes requires further study to better understand its clinical and predictive significance.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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