PHYSIOLOGICAL AND HEREDITARY HYPERBILIRUBINEMIA IN ATHLETES:
ROLE IN REDUCING EFFICIENCY AND CORRECTION METHODOLOGY

1 Educational and Scientific Olympic Institute of the National Ukraine University of Physical Education and Sport, Kyiv, Ukraine
2 Vytautas Magnus University, Kaunas, Lietuva
3 Sumy State Pedagogical University named after A. S. Makarenko, Ukraine

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Gunina L. M., Mylashyus Kazys, Voitenko V. L.

Under high-intensity loads, the athlete’s bodies take place a number of biochemical reactions and physiological processes that can lead to hyperbilirubinemia. The factors that can initiate the onset of this phenomenon include the syndrome of micro-damage muscle, violation of the integrity of erythrocyte membranes, decreased blood pH, malnutrition and increase oxygen demand of the body. Degree of expression of manifestations of physiological bilirubinemias depends on the level of adaptation of the athlete to the physical activities offered. Hyperbilirubinemia in athletes can be one of the components of the deterioration of the functional state, forming the symptoms of endogenous intoxication.

The relevance of this problem in sport lies in the relatively low detection rate of hyperbilirubinemia due to the lack of regular screening studies. However, in drawing up a plan of nutritional- metabolic support for training and competitive activity and recovery measures, must not only the individual reaction of the athlete body to physical activity, but also the severity of shifts in the indicators of bilirubin metabolism and their ratio.

The article describes the reasons for the increase in bilirubin levels, which can be caused by both the effect of physical activity and by the presence of pathological processes in athletes. The factors influencing the blood serum’s bilirubin content are also highlighted, which include the state of erythrocyte cell membranes and the rate of hemoglobin destruction, the functional state of the liver, the specifics of physical loads and the use of ergogenic pharmacological agents by athletes.

Particular accent has been placed on the illumination of hereditary hyperbilirubinemias, which may have been detected at the stage of selection of athletes. The most common phenomenon is Gilbert’s syndrome, which occurs in 2-5% of cases in the general population, is characterized in the clinic by a benign flow and is manifested by episodes of jaundice and an increase in total bilirubin content to moderate values due to indirect. The frequency of detection of hyperbilirubinemias in the population of athletes is 4.68%, among which Gilbert’s disease accounts for almost half (48.7%).

Conclusion. The work highlighted the pathogenesis and diagnostic algorithm of Gilbert’s disease, and also emphasized that its drug prevention and correction in athletes to maintain functional and physical fitness should be carried out taking into account antidoping rules, which requires upon diagnosis timely receipt of a therapeutic exclusion.

Keywords: bilirubin, hereditary hyperbilirubinemias, Gilbert’s disease, hemolysis of erythrocytes, physical performance, laboratory diagnostics.

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Introduction. The high-intensity and long-term physical loads characteristic of modern sports cause changes in the concentration of / activity in the serum / blood plasma of numerous laboratory indicators [1]. Experts are constantly searching for laboratory markers that can most accurately reflect the picture of metabolic shifts in different systems, organs and tissues under the influence of physical loads [2, 3]. Important role in athletes’ ability to achieve high competitive results is played the state of the main limiting physiological systems of the organism and the metabolic response to the proposed loads. Determination of the physiological values of laboratory parameters specific to professional sports and informative in monitoring fitness activities avoids misinterpretation of survey results and optimizes the training process. It is important for a sports doctor and trainer to have objective information about the limits of changes in clinical-laboratory parameters associated specifically with locomotions, which gives valuable guidance for further dosage of physical activity. In turn, it is important for specialists in sports practice to know the limits of acceptable reference intervals for athletes...
Muscle activity is known to occur with the mandatory use of energy which is released during the hydrolysis of ATP. However, the ATP supply in the cells of muscle tissue is insignificant. Therefore, ATP resynthesis must occur to ensure a longer muscle work. Since in the aerobic pathway of adenosine triphosphate resynthesis, its capabilities are limited by the delivery of oxygen to mitochondria and their amount in muscle cells. Thus, it is possible to carry out only moderate intensity loads. At submaximal loads, the anaerobic pathway of ATP resynthesis is activated, one of the mechanisms of which is glycolysis (due to the breakdown of myocytes glycogen). As a result of this reaction, a large amount of lactate and pyruvate is formed, which diffuse into the blood and can cause a state of metabolic acidosis, which is associated with depletion of the body’s buffer reserves [11]. Adaptive ly, to compensate for metabolic lactate-acidosis with regular training, the body’s buffer reserves increase, which ensures the maintenance of blood pH, which, after intense muscular work, can decrease to 7.2–7.0, at a pH standard of 7.36–7.40. The development of resistance of tissues and blood to decreased pH is formed in highly qualified athletes in the process of many years of improvement, therefore with developing muscle fatigue, symptomatically accompanied by pain in them, as well as dizziness, nausea, athletes are relatively easily tolerate a shift in blood pH to 7.0 and below [11]. Nevertheless, acidosis, which develops under a high-intensity physical load, worsens the binding of bilirubin to albumin, resulting in an increase in the concentration in the blood of bilirubin IX-alpha, which has toxic effect [12].

A decrease in the binding of bilirubin to albumin is also caused by an alimentary deficiency of protein, which can occur with a rapid decrease in body weight of athletes before competitions (loss), to compete in a smaller weight category (judo, boxing, wrestling), as well as in athletes whose body weight must be within certain minimum limits (complex-coordination sports such as rhythmic gymnastics, figure skating, artistic acrobatics). As a result, a state of hypoalbuminemia occurs, which leads to disruption of the binding of bilirubin and an increase in its free fraction in the blood plasma [13].

The decay of myoglobin, like other heme-containing proteins that occurs when skeletal muscle cells are damaged, leads to the formation of biliverdine, which is then fermentatively restored in the liver to free bilirubin. At high-intensity loads, a state of acidosis develops, which worsens the process of binding of albumin to bilirubin and is accompanied by an intensification of the accumulation of the latter [14].

Hyperbilirubinemia, including in a number of athletes, may be one of the components of deterioration of the functional state, forming symptoms of intoxication [15, 16].

The urgency of this problem lies in the low detectability of hyperbilirubinemia, since in the early stages laboratory diagnosis of bilirubin exchange disorders in the absence of evidence and obvious clinical symptoms is practically not carried out. Thus, when drawing up a plan of training and competitive activity and rehabilitation measures, not only the individual reaction of the athlete’s body to physical load, but also the severity of the shifts in the bilirubin indices and their ratio should be taken into account [14].

Bilirubin - (from lat. bilis - bile and lat. ruber - red) bile pigment, one of the main components of bile in the human body, formed as a result of the splitting of hemoglobin and other heme-containing proteins, primarily myoglobin and cytochromes. Bilirubin is formed by the action of biliverdinreductase enzyme from biliverdine, the green pigment, which is also the product of hemme decay, which is part of the protein hemoglobin. Being oxidized, bilirubin can be converted back to biliverdin [17]. Normally, erythrocytes, having existed in the body for about 120 days, break down (programmable apoptosis, or cellular death), and this process is accompanied by the emergence of hemoglobin from them and its further transformation into bilirubin through successive biochemical reactions. As a result
of this chain of reactions, free bilirubin is formed (it is also indirect, unbound, or unconjugated), which is insoluble in water. Free bilirubin binds to albumin and is transported with the bloodstream to the liver, where it is captured by hepatocytes. Further, in the liver, free bilirubin is conjugated with glucuronic acid, and already bound bilirubin is formed (it is also direct, or conjugated). The conversion of indirect bilirubin to direct bilirubin requires normally functioning liver cells and a sufficient amount of the enzyme uridyldiphospho-glucuronyltransferase (UDPGT). The bound bilirubin is soluble in water, released from hepatocytes into the bile capillaries, and through the bile ducts ultimately enters the small intestine. In the intestine, bilirubin is turned into urobilinogen by bacteria. Some urobilinogen is absorbed in the intestine, gets into the blood and is eventually excreted with urine. Most urobilinogen is oxidized in the intestine to the brown pigment urobilin and excreted with feces [18].

In the blood serum in the clinic and under the laboratory control of athletes, the content of total, as well as direct (bound) and indirect (free) bilirubin is determined. The reference limits for the content of the total bilirubin in the human population are 5-21 mcMolxL⁻¹, bound bilirubin – not more than 3.4-4.0 mcMolxL⁻¹, free bilirubin – not more than 19-21 mcMolxL⁻¹ [19]. The serum bilirubin level in Gilbert’s syndrome, with an impaired biliary tract, and the content of total bilirubin in this case is increased precisely due to the direct one.

Factors influencing the content of bilirubin in the blood serum of athletes are the following:

1) Bilirubinemia of a prehepatic (suprahepatic) character is widespread among athletes and is the result of increased erythrocyte hemolysis under the influence of physical load factors. There is evidence that elevated hemolysis may also be due to inefficient erythropoiesis, which results in atypical erythrocytes of irregular shape or size, for example in the sickle form [20]. Such erythrocytes are subject to premature destruction and a corresponding increase in the blood bilirubin content. As a result of the accelerated hemolysis, an excessive amount of indirect bilirubin is formed, and all of it cannot bind with glucuronic acid in the liver; while the content of total bilirubin increases due to the indirect.

2) Hepatic bilirubinemia is caused by a violation of the process of binding of bilirubin in the liver. This may be due to a functional impairment or liver disease (for example hepatitis). Liver cells do not work adequately and do not transform all indirect bilirubin into a straight. In this case, the content of both direct and indirect bilirubin will be increased. In addition, hepatic bilirubinemia can be hereditary, benign, and result from a lack of enzymes involved in the metabolism of bilirubin.

3) The causes of a post-hepatic bilirubinemia are provoked by a medical problem, are pathology and are associated with blockage of the bile ducts and the inability to remove bilirubin from the body (for example, blockage of bile outflow in the form of calculus, obturation of bile ducts by tumor with subsequent development of obstructive jaundice, etc.). As a result, bilirubin accumulates in the blood, causing a specific coloration of the skin and sclera. In this case, direct bilirubin is formed, but due to the block it cannot pass further through the biliary tract, and the content of total bilirubin in this case is increased precisely due to the direct one.

Factors influencing the content of bilirubin in the blood serum of athletes are the following:

- State of erythrocyte cell membranes and hemoglobin destruction rate. When the permeability of the cell membranes of erythrocytes is disturbed, their propensity for hemolysis (destruction) increases, which can be accompanied by an increased accumulation of bilirubin and an increase in its content in the blood, primarily due to the indirect one.

- Functional state of the liver. When there are pathological processes or functional changes in the liver, the ability to bind bilirubin decreases, leading to its accumulation in the blood. The use of androgenic anabolic steroids is also accompanied by hyperbilirubinemia [21].

- Specifics of physical loads. The hemoglobin formation process is related to the rate of erythrocyte destruction (hemolysis), the intensity of which is increased by the influence of physical loads. Intravascular hemolysis during strenuous muscle activity can be caused both by the mechanical breakdown of red blood cells during continuous muscle contractions, for example in runners [22] and by cell membranes damage as a result of oxidative stress and inflammation. The most pronounced increase of bilirubin is characteristic of high intensity loads. For example, in the biochemical parameters study [23], conducted in 100 elite athletes specializing in 11 sports, the increase in the concentration of bilirubin was the second most frequent indicator, the deviation of which was detected during the screening analysis. 19 out of 37 athletes (runners in the marathon) had bilirubin levels above the interval of reference values, a consequence of the increase in erythrocyte hemolysis during overcoming the distance.

- Use of pharmacological agents. The overestimation of bilirubin in the serum is caused by the ingestion of cholestatic hepatotoxic drugs and agents causing haemolysis of erythrocytes, such as α-methyl-dopa, antibiotics (cephalosporins, penicillin, tetracycline, rifampicin), NSAID
Gilbert’s syndrome is the homozygotic (TA) 7TAA mutation in the UGT1A1 gene promoter. In population groups living outside Europe, along with (TA) 7TAA, there are also other polymorphisms the UGT1A1/A (TA) 5TAA and (TA) 8TAA gene promoter/combination thereof, while residents of the Asian region have mutations in the coding part of this gene much more frequent. Additionally, bound mutations are also possible in both parts of the UGT1A1 gene. As a result of this genetic defect, the synthesis of UGT1A1 is reduced by 70-80% and the intensity of bilirubin conjugation is reduced. Along with unconjugated hyperbilirubinemia, the deficiency of UGT1A1 is accompanied by the predominance of the transformation of monoglucurin bilirubin into diglucuronide of bilirubin in bile, making a person with Gilbert’s syndrome more susceptible to the formation of jaundice [29].

The risk of calculous cholecystitis is particularly pronounced in Gilbert’s syndrome in combination with certain haemolytic diseases such as thalassemia, congenital spherocytosis, insufficiency of dehydrogenase of glucose-6-phosphate erythrocyte, congenital ovalocytosis, etc. An additional pathogenetic factor in the occurrence of hyperbilirubinemia is the shorter lifetime of erythrocytes, which is observed in about 40% of cases, as well as the defect of absorption and transfer of unconjugated bilirubin at the level of hepatocytes. Sex hormones, especially androgens, also participate in the manifestation of Gilbert’s syndrome, which explains its rare appearance before puberty, as well as the incidence of the disease in adolescent males and adult males, 2-7 times higher than in females [30].

Due to the antioxidant properties of unconjugated bilirubin, some research suggest that Gilbert’s syndrome may constitute a positive mutation. In addition to the excluding of erythrocyte hemolysis and liver disease as the cause of unconjugated hyperbilirubinemia, the results of the clinical and laboratory diagnosis of Gilbert’s syndrome are manifested a significant increase in unconjugated bilirubinemia (more than twice as high as the initial level) as well as a significant decrease in the expression of hyperbilirubinemia or normalization of the level of bilirubin in the serum 1-3 days after taking phenobarbital (1 mg kg-1 per day) [31].

According to the results of the research of G. A. Makarova with co-authors [32], athletes with an increased level of direct bilirubin in the blood serum have Gilbert’s syndrome in 18.65% of cases. The coincidence of the peak of the release of bilirubin in the bloodstream coincides with the increased fatigue and reduced effectiveness of the training and competitive process, which requires constant monitoring of athletes and appropriate detoxification activities [23]. Hyperbilirubinemia can also be manifested, in addition to
sclera and skin coloration, by hunger, physical strain, fever, dehydration of the organism [19].

The preferred method for diagnosing Gilbert’s syndrome in athletes, which is increasingly used today, is genetic verification of this pathology. The combined laboratory biochemical confirmation of the presence of hyperbilirubinemia makes the diagnosis practically unmistakable (with timely differential diagnosis with erythrocyte pathologies). Biopsy of the liver is rare enough to confirm the low activity of UGT1A1. For the purpose of additional diagnosis of Gilbert’s syndrome, other tests can also be used, for example, with rifampicin, nicotine, etc. [29].

Gilbert’s syndrome usually does not require treatment in the practice of clinical medicine, but enterosorption, detoxification therapy, and phenobarbital doses of 50-150 mg per night can be used in the practice of training athletes. For the use of phenobarbital and phenobarbital-containing drugs (valoserdin, valosedan) in athletes with an established diagnosis of Gilbert syndrome, one should obtain TUE, as this substance belongs to the Prohibited List WADA [31].

One of the ways to reduce the metabolic effects of hyperbilirubinemia and to maintain the level of physical efficiency achieved can be the use of means, maintaining the functional state of the liver and at the same time having the possibility of improving the mechanisms of oxygen transfer to skeletal muscles, maintain the integrity of the erythrocytic membranes and inhibiting the development of the tissue acidosis and energy efficiency, on the other [33, 34]. Such agents include derivatives of succinic acid, in particular, the drug armadin (2-ethyl-6-methyl-3-hydroxypyridine succinate). The results of our researches in 47 athletes showed that the course use of armadin to a large extent (by 16.6-24.9% depending on the sport) weakens the severity hyperbilirubinemia and helps to avoid a significant reduction in physical efficiency, unwillingness to train and psychological instability at the moments of peak level of bilirubin in the blood. Such manipulations requires sufficient long-term screening monitoring to establish the frequency of hyperbilirubinemia and to start prophylaxis with armadin 5-7 days before peak.

In addition to Gilbert’s syndrome, athletes have such hereditary hyperbilirubinemias as the Crigler-Nayyar, Dabin-Jones and Rotor syndromes [25], but the frequency of their occurrence is relatively low [27, 28], nevertheless, the presence of these hereditary hyperbilirubinemias has a negative effect on the general condition of the athlete (weakness, increased fatigue, unwillingness to train on days of maximum peaks in the bilirubin content, etc.), general and special physical performance, which requires close attention to these athletes from the team doctor in terms of carrying out the appropriate medication correction.

In addition, in elite sports, it is necessary to monitor the indicators associated with the development of hyperbilirubinemia, as well as conduct additional examinations to identify possible diseases and the risks of their development that are the cause of hyperbilirubinemia. Given the data on the high frequency of this pathological condition in athletes, it is also possible total talk about insufficient of diagnosis of diseases associated with disorders of binding and excretion of bilirubin caused by genetic mutations.

**Conclusion.** The presence of hyperbilirubinemia in athletes always requires refinement and differential diagnosis, as well as comparison with the intensity and direction of the previous load. To establish the cause of hyperbilirubinemia, the entire available arsenal of diagnostic methodologies, including immunochemical and molecular genetic ones, should be used. Once it has been determined whether the identified phenomenon is a nosological form or a pathophysiological condition inherent with physical loads (erythrocyte hemolysis, protein deficiency, etc.), the sports physician must decide on the methodology for correcting bilirubin to maintain an adequate physical form of the athlete, taking into account the requirements of the anti-doping legislation.

**The prospects for further research** are to find new corrective procedures in athletes in the establishment of the diagnosis of hereditary hyperbilirubinemias and appropriate correction of the training process - in physiological bilirubinemia, particularly associated with physical loads with hemolysis of red blood cells.

**References**


11. Bazulco AS. Biochemical basis of sports muscular activity. Minsk BGUPgC; 2006. 85 p. [Russian]


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В статье описаны причины повышения уровня билирубина, которые могут быть обусловлены как воздействием физической нагрузки, так и наличием патологических процессов у спортсменов. Также освещены факторы, влияющие на содержание билирубина в сыворотке крови, к которым относятся состояние клеточных мембран эритроцитов и скорость разрушения гемоглобина, функциональное состояние печени, специфика физических нагрузок и применение спортсменами эргогенных фармакологических средств. Особый акцент сделан на освещении наследственных гипербилирубинемий, среди которых наиболее распространенным феноменом является синдром Жильбера, который проявляется эпизодами желтухи и повышением до умеренных значений содержания общего билирубина за счет непрямого, что приводит к ухудшению функционального состояния и физической и психической работоспособности спортсмена.

В работе освещен патогенез и диагностический алгоритм болезни Жильбера, а также подчеркнуто, что медикаментозная ее профилактика и коррекция у спортсменов для поддержания функциональной и физической подготовленности должна проводиться с учетом антитомбинговых правил, что требует при установлении диагноза своевременного получения терапевтического исключения (TUE).

**Ключевые слова:** билирубин, наследственные гипербилирубинемии, болезнь Жильбера, гемолиз эритроцитов, физическая работоспособность, лабораторная диагностика.

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