ZIEMIŃSKA, Daria, BURCZYK, Rafał, WARDYN, Wiktor, MICHALSKA, Martyna, WINIAREK, Karolina, MURAWSKA, Joanna, GUZOWSKI, Cezary and KĘDZIORA-KORNATOWSKA, Kornelia. Exploring Haptoglobin as a Promising Marker for Severe Liver Diseases: A Comprehensive Review. Quality in Sport. 2024;31:55911 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.31.55911
https://apcz.umk.pl/QS/article/view/55911

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 31.10.2024. Revised: 07.11.2024. Accepted: 08.11.2024. Published: 12.11.2024.

Exploring Haptoglobin as a Promising Marker for Severe Liver Diseases: A Comprehensive Review

1. **Daria Ziemińska**

Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
dziemin98@wp.pl
Orcid: 0009-0001-8240-2593
https://orcid.org/0009-0001-8240-2593

2. **Rafał Burczyk**

Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
raimer001@gmail.com
Orcid: 0000-0002-1650-1534
https://orcid.org/0000-0002-1650-1534

3. **Wiktor Wardyn**
Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
wiktor12398@gmail.com
Orcid: 0009-0002-6133-2220
https://orcid.org/0009-0002-6133-2220

4. **Martyna Michalska**
Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
martynamichalska1997@gmail.com
Orcid: 0009-0002-3467-4364
https://orcid.org/0009-0002-3467-4364

5. **Karolina Winiarek**
Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
karolinawiniarek97@gmail.com
Orcid: 0000-0001-7305-0613
https://orcid.org/0000-0001-7305-0613

6. **Joanna Murawska**
Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
joanna.murawska94@wp.pl
Orcid: 0000-0001-7564-938X
https://orcid.org/0000-0001-7564-938X

7. **Cezary Guzowski**
Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
cezary.guzowski@gmail.com
Orcid: 0000-0002-0022-9943
https://orcid.org/0000-0002-0022-9943

8. **Kornelia Kędziora-Kornatowska**
Department and Clinic of Geriatrics and Internal Medicine, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. Marii Curie-Skłodowskiej 9, 85-094 Bydgoszcz, Poland
kornelia.kornatowska@cm.umk.pl
Orcid: 0000-0003-4777-5252
https://orcid.org/0000-0003-4777-5252

Abstract
Introduction: Liver damage is a common symptom of many diseases, including metabolic disorders and cancers. Such patient condition requires effective examinations aimed at prompt diagnosis and implementation of the most appropriate treatment for a specific disease. Haptoglobin, the subject of many studies, has proven to be a protein that can be used as a biomarker of liver damage, thereby aiding not only in the diagnosis but also in the treatment, resulting in more favorable prognoses regarding patient longevity and quality of life.
Objective: The aim of this study is to elucidate the role of haptoglobin as a diagnostic and prognostic biomarker in cases of liver damage.
Methods: A review of scientific literature and analysis of clinical data regarding haptoglobin levels in liver damage were conducted to assess the reliability of haptoglobin as a biomarker. This paper primarily utilized the latest publications produced after 2015. PubMed and Google Scholar were used to find relevant publications. All cited works provided useful information to achieve the aim of our article.
Results: Analysis of the literature suggests that haptoglobin levels may be significantly associated with the development and severity of liver damage. It may serve as a suitable biomarker for diagnosing diseases that coincide with hepatocyte damage, thus improving the diagnosis of these diseases and increasing the chance of appropriate treatment, which may contribute to prolonging and improving the patient's quality of life.
Conclusions: Haptoglobin appears to be a promising biomarker in liver damage; however, further research is necessary to confirm its diagnostic and prognostic accuracy. Haptoglobin exists in various genotypic forms, each characteristic of different disease entities. Understanding the mechanisms regulating haptoglobin levels may lead to a better understanding of liver damage pathogenesis and the development of more effective therapies, increasing the chance of patient recovery and improving their quality of life.
Keywords: Haptoglobin, liver damage, haptoglobin levels in liver injury, diagnosis of liver damage, diseases associated with liver damage, acute phase reaction, liver damage biomarkers, haptoglobin measurement methods

I. Introduction

The liver, playing a key role in metabolism, detoxification and protein synthesis, is an organ of fundamental importance for maintaining the body's homeostasis. For this reason, disorders in its functioning, such as non-alcoholic steatohepatitis or cancer, may lead to a number of serious diseases, threatening the patient's health and life.

Among the diagnostic tools used to monitor liver health, haptoglobin (from the Greek haptein - "to bind"), an acute phase protein discovered in 1938 by Polonovski and Jayle's team, responsible for the uptake of free hemoglobin during hemolysis[1] - may play an important role as a potential a marker of the pathology of this organ.

In this review, we will focus on the role of haptoglobin as an indicator of severe liver disease, focusing mainly on non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and primary and metastatic liver cancers. We will investigate the relationship between haptoglobin levels and liver health, analyzing both the mechanisms of action of this glycoprotein and the results of clinical studies in humans and animals confirming its usefulness as a diagnostic tool. Moreover, we will review existing methods for determining haptoglobin and discuss the prospects for using this marker in clinical practice.

Studying the role of haptoglobin as an indicator of severe liver disease is important to improve the diagnosis and treatment of patients associated with this disease. As medical and biotechnology advances, a better understanding of pathological mechanisms and the identification of effective diagnostic markers become crucial for more effective therapeutic intervention and improved quality of health care.

II. Biological basis of haptoglobin.

Haptoglobin (HP) belongs to alpha-2-globulins synthesized by liver cells. It combines with extracellular hemoglobin (Hb), which enables its transport and prevents its decomposition. This complex reaches the cells of the reticuloendothelial system, where haptoglobin is broken down after being released [2]. Hp mainly functions to remove toxic free oxygen to prevent the formation of free radicals and their subsequent tissue damage. Hp binds to free Hb with high affinity and is then taken up by macrophages and monocytes via the CD163 receptor [4]. Human haptoglobin occurs in two allelic forms, resulting in the existence of three main genotypes such as Hp1-1, Hp2-1 and Hp2-2. They differ in terms of binding strength, degree of oxygenation or hemoglobin binding capacity [4]. Despite the fact that haptoglobin is produced mainly in liver hepatocytes, there are studies that have shown the presence of this protein also in the lungs, and mRNA in the thymus, spleen, lungs, kidneys and heart [5,6]. The determination of this alpha-2-globulin is carried out using methods

immunohistochemistry and its reference values are 70-150 mg/dl. Low haptoglobin values are used in the diagnosis of hemolytic anemias [2,7] or diseases of the liver in which it is produced [2]. Values higher than the norm are detected in cases of infections and inflammations, because haptoglobin is also an acute phase protein [8].

III. Haptoglobin determination methods

Haptoglobin testing methods, such as spectrophotometry, immunoreactive methods and gel electrophoresis, are important tools in clinical diagnosis. The above-mentioned techniques enable accurate determination of haptoglobin levels, which may be crucial in monitoring disease states and assessing the risk of complications.

The measurement of haptoglobin is based on the altered physical properties associated with hemoglobin compared to circulating as a free protein. The hemoglobin peroxidase activity in the hemoglobin-haptoglobin complex can be determined in solution, after gel filtration, spectrophotometry or after gel electrophoresis.

The three main methods used to measure haptoglobin are spectrophotometry, immunoreactive methods, and gel electrophoresis. However, the interpretation of the results requires taking into account various factors that may affect the accuracy of the measurements, such as substance interference or phenotypic differences [9].

Immunoreactive methods

Radial immunodiffusion (Mancini method) is a quantitative test based on simple gel immunodiffusion. Specific antibodies directed against a specific class of immunoglobulins are dissolved in the agar gel at a constant, known concentration. Bane sera are then placed in holes cut in this gel. During simple diffusion in a humid chamber, all soluble antigens from the test serum will diffuse from the wells, and immunoglobulins of the tested class will be bound by the antibodies present in the gel. Immune complexes precipitate around the wells in which the test sera were placed, visible in the form of precipitation circles. The resulting circles are used to read the quantitative content of antigen in the serum. The larger the diameter of the circle, the greater the content of the antigen being determined [10]. Haptoglobin along with antibodies is suspended in an agarose gel. The mixture of haptoglobin with antibodies causes precipitation of a product that can be measured by radial immunodiffusion. The hemoglobin-antibody complexes form circles, which are used to calculate the haptoglobin concentration using a standard curve. Haptoglobin phenotypes may differ in size. It has been reported that this difference in particle size can interfere with the results of a radial radiodiffusion test due to their different diffusion rates. If the haptoglobin phenotype is known, measurement corrections can be made [9].

The mechanism of action of immunoturbidimetric and immunonephelometric methods is also based on the phenomenon of precipitation of haptoglobin-hemoglobin-antibody complexes. This phenomenon leads to greater scattering of the light beam than in the case of a solution without complexes. Due to the fact that the intensity of scattered light is directly related to the concentration of scattering particles, it is possible to use these methods to determine the concentration of haptoglobin in the sample [9,11,12]

In the immunonephelometric method, the intensity of scattered light is measured through the tested solution, with the detector located at an angle of 90° to the light beam. In the ITA immunoturbidimetric technique (direct latex agglutination technique). After adding the tested protein to a suspension of latex particles coated with a specific antibody, the latex particles stick together and their turbidity increases (nephelometric or turbidimetric measurement). Then, the light intensity is measured through the tested solution, with the detector placed in front of the light beam.

Proper sample dilution is important. A sample with too high a density may result in falsely low results due to the formation of excess complexes, which in turn hinders the free passage of the light beam. The results are read based on a previously developed calibration curve [9,12].

Spectrophotometry

Spectrophotometry is an instrumental technique that uses for analytical purposes energy transitions occurring in molecules caused by the absorption of electromagnetic radiation in the ultraviolet (UV, 200-380 nm), visible (VIS, 380-780 nm) or near infrared (0.78 -30000 um). UV and Vis spectrophotometry is mainly used in inorganic analysis.

The UV-Vis spectrophotometry method can be used to determine organic and inorganic substances that absorb ultraviolet radiation, compounds that absorb radiation in the visible range, including colored organic compounds (dyes) and colored metal salts, as well as substances whose forms that absorb radiation are obtained through chemical reactions. Complexation reactions are most often used for these purposes. Many procedures have been developed for the determination of metal cations in the form of colored complexes with organic ligands [9, 14]. The principle of spectrophotometry is based on the Beer-Lambert law, which states that "the concentration of a light-absorbing substance in a sample is a logarithmic function the amount of light absorbed by this sample" [9,15].
Spectrophotometry can also be used to identify hemoglobin-haptoglobin complexes. Light absorption is measured in sodium bisulfite-reduced serum using light wavelengths of 432 and 408 nm. Analysis of differences in light absorption can be used to identify the presence of both hemoglobin-haptoglobin complexes, free hemoglobin and haptoglobin. This allows for the determination of the concentration of hemoglobin-haptoglobin complexes. This method has some limitations due to the possibility of interference with substances such as bilirubin and chylomicrons in the analyzed samples [9].

Gel electrophoresis

Gel electrophoresis is a commonly used method for the separation of proteins and nucleic acids. Both nucleic acids and proteins can be differentiated in an electric field due to their molecular mass, spatial structure and molecular charge. During electrophoresis, electromotive force is used to move molecules through the pores of the gel, leading to their separation. The most commonly used materials for the production of this matrix are polyacrylamides or agaroses [16]. Gel electrophoresis using agar gel allows the separation of free hemoglobin, haptoglobin-hemoglobin complexes and other complexes and molecules. Molecules containing heme are visualized using a heme-specific dye (o-Toliden, hydrogen peroxide). Measuring the level of haptoglobin using gel electrophoresis is often semi-quantitative, i.e. it only informs about the presence or absence of the tested substance. This method is not widely available. Due to the manual process and interpretation of results, there is a greater risk of errors than in the case of automatic measurements [9].

IV. Haptoglobin as a marker in the diagnosis of liver diseases

As already presented above, haptoglobin occurs in various allelic forms. Specific phenotypes are associated with a specific disease entity and have various functions. The Hp1-1 phenotype is associated with increased susceptibility of the body to infectious diseases, including parasitic diseases, including: Schistosoma infections [17,18]. However, the Hp2-2 phenotype is mainly associated with metabolic diseases and their consequences. It was shown that a given phenotype occurred more often in people with non-alcoholic fatty liver disease [19].
The Hp2-2 phenotype may predict the severity of HBV hepatitis. It has been proven that among people with this phenotype in the case of hepatitis B virus, the increase in Hp was accompanied by increased levels of alanine transaminase (ALT), C-glutamyl transferase (GGT), aspartate aminotransferase (AST) and a high degree of liver fibrosis [20] Fucosylated haptoglobin (Fuc-Hpt) deserves attention, among others. It is applicable to patients with non-alcoholic fatty liver disease (NAFDL) and non-alcoholic steatohepatitis (NASH).

Typical symptoms of NASH include ballooning hepatocytes and an increase in fucosylated glycoproteins in blood serum. The level of Fuc-Hpt was significantly higher in patients with NAFDL and Nash. Additionally, it was proven that the level of Fuc-Hpt showed a gradual increase proportional to the increase in hepatocyte ballooning results. NASH is a disease that can lead to serious complications such as liver cirrhosis and hepatocellular carcinoma. By testing the concentration of Fuc-Hpt in blood serum, we are able to distinguish between patients with fatty liver disease and steatohepatitis, which facilitates further management [21].

Colorectal cancer (CRC) is the second most common malignant tumor in women and the third most common in men. In Poland and in the world, this disease is in second place when it comes to the cause of death due to malignant tumors. The most common site of CRC metastasis is the liver. Early detection of their presence is very important in order to undertake appropriate medical procedures aimed at extending and improving the quality of the patient's life [2]. A correlation was demonstrated between serum Hp concentration and the presence of liver metastases in patients with CRC. Patients suffering from CRC and diagnosed with liver metastases showed significantly higher levels of Hp in the serum compared to patients with CRC without metastases [22].

Colorectal cancer is not the only cancer in which Hp can be used in the diagnosis. It has been shown that bifucosylated tetraantennary glycan of haptoglobin occurs in people suffering from hepatocellular carcinoma. The presence of this glycan is associated with the presence of HCC in patients with chronic liver disease regardless of the presence of cirrhosis. Combining the examination of this form of haptoglobin with other HCC biomarkers, such as AFP, may contribute to increasing the effectiveness of detecting cancer foci, which will translate into extending and improving the quality of life of patients. [23].

Some forms of haptoglobin can also be used to diagnose childhood cancers such as hepatoblastoma. In this case, two forms of Hp were compared. Pre-Hp which is the unprocessed form and mature Hp. Patients with hepatoblastoma had highly higher concentrations of Pre-Hp compared to mature Hp in serum [24].

Haptoglobin can exist in its numerous glycated forms. The A3G3F2 glycopeptide is divided into the glycans A3G1F2, which predominates in patients with HCC, and A3G2F2, which predominates in patients with liver cirrhosis. This has important diagnostic and prognostic significance for patients [25].

Fucosylated haptoglobin (Fuc-Hpt) is also used in assessing the degree of liver fibrosis in HCV infection. Both Fuc-Hpt and Mac-2 binding protein were used for this purpose. Levels of these two molecules increase with the severity of liver fibrosis. Fuc-Hpt and Mac-2 values were significantly high when HCC was detected in a patient with HCV. This is another example of possible diagnosis of a life-threatening disease using haptoglobin [26].

V. Prospects for future research

So far, haptoglobin has been known mainly as an object of interest for hematologists, but numerous studies have also shown different functions of this protein. There is a need to develop and validate quick and simple tests that can be used in everyday clinical practice so that the determination of haptoglobin levels can bring measurable benefits.

As a marker of liver diseases, the measurement of haptoglobin is useful in diseases such as drug-induced liver injury or liver fibrosis, also in the pediatric population[27].

The genotyping of haptoglobin in individual patients also turned out to be a breakthrough, which allows predicting various paths of potential liver damage, including cancer. The haptoglobin phenotype turns out to be as individual a feature as the blood group and the Rh factor[28]. Moreover, there is also a wide range of possibilities for haptoglobin determinations - not only pre-haptoglobin, but also proteoforms of haptoglobin alpha and beta chains can be used as biomarkers.

Nowadays, when the percentage of obese and overweight patients is increasing, the number of patients with non-alcoholic steatohepatitis (NASH) is also increasing. Since there have been reports of the successful use of haptoglobin as a biomarker of NASH in patients with various stages of liver damage[29], it is definitely an object that requires new research in this direction and perhaps, in the future, its inclusion in clinical practice. Also in the case of diagnostic difficulties between metabolic liver damage and hepatocellular carcinoma, it was possible to distinguish these two diseases using the discussed haptoglobin as a biomarker [29], which may be a report that will significantly improve future clinical practice and shorten the diagnostic path, which is extremely important for oncological patients.

VI. Summary

The above work focuses primarily on the values of haptoglobin in the perspective of the latest research as a potential diagnostic tool. We discussed not only the biological basis of this protein's action, but also various methods of its determination, allowing for its precise monitoring in the human body.

It seems that there is great potential to use this protein as a biomarker in the diagnosis of liver diseases, especially in the case of NASH, in a world where overweight and obesity are a serious health problem, new and effective diagnostic tools are crucial. The prospect of haptoglobin genotyping seems to be particularly promising because it may enable a better understanding of individual differences in the body's reactions to liver damage and predisposition to particular liver diseases.

Further research on haptoglobin appears to be crucial to improving the diagnosis and treatment of liver diseases, which could significantly impact the quality of health care for patients affected by these diseases.

Authors contribution:

Conceptualization: Daria Ziemińska, Rafał Burczyk, Wiktor Wardyn, Martyna Michalska, Karolina Winiarek, Joanna Murawska, Cezary Guzowski, Kornelia Kędziora-Kornatowska
Software: not applicable
Verification: Joanna Murawska, Daria Ziemińska, Martyna Michalska
Formal analysis: Rafał Burczyk, Wiktor Wardyn, Cezary Guzowski
Research: Joanna Murawska, Daria Ziemińska, Martyna Michalska, Rafał Burczyk, Wiktor Wardyn, Cezary Guzowski, Karolina Winiarek
Resources: Joanna Murawska, Daria Ziemińska, Martyna Michalska, Rafał Burczyk, Wiktor Wardyn, Cezary Guzowski, Karolina Winiarek
Writing-rough preparation: Karolina Winiarek
Writing-review and editing: Joanna Murawska, Daria Ziemińska, Martyna Michalska, Rafał Burczyk, Wiktor Wardyn, Cezary Guzowski, Karolina Winiarek, Kornelia

Kędziora-Kornatowska
Visualization: Daria Ziemińska
Supervision: Joanna Murawska, Kornelia Kędziora-Kornatowska
Project administration: Cezary Guzowski, Kornelia Kędziora Kornatowska
Finding acquisition: not applicable

All authors have read and agreed with published version of the manuscript

Funding statement:
This research receive no external founding

Institutional Review Board System:
Not applicable

Informed Consent Statement
Not applicable

Acknowledgments
Not applicable

Conflict of Interests Statement:
The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

References:

1. Andersen CBF, Stødkilde K, Sæderup KL, et al. Haptoglobin. Antioxid Redox Signal. 2017 May 10;26(14):814-831. doi: 10.1089/ars.2016.6793.
2. Podlak Dawidziak M, Solnica B, Hemoglobina i Hemopeksyna w Gajewski P. (red.), Interna Szczeklika. Kraków Medycyna Praktyczna 2023, s. 1777-1778.
3. Edwards O, Burris A, Lua J, et al. Influence of Haptoglobin Polymorphism on Stroke in Sickle Cell Disease Patients. *Genes (Basel)*. 2022;13(1):144. Published 2022 Jan 14. doi:10.3390/genes13010144
4. Hostettler IC, Morton MJ, Ambler G, et al. Haptoglobin genotype and outcome after spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 2020;91(3):298-304. doi:10.1136/jnnp-2019-321774
5. Kalmovarin N, Friedrichs WE, O'Brien HV, et al. Extrahepatic expression of plasma protein genes during inflammation. *Inflammation*. 1991;15(5):369-379. doi:10.1007/BF00917353
6. Yang F, Friedrichs WE, Navarijo-Ashbaugh AL, et al. Cell type-specific and inflammatory-induced expression of haptoglobin gene in lung. Lab Invest. 1995 Sep;73(3):433-40. PMID: 7564277.
7. Barcellini W, Fattizzo B. Clinical Applications of Hemolytic Markers in the Differential Diagnosis and Management of Hemolytic Anemia. *Dis Markers*. 2015;2015:635670. doi:10.1155/2015/635670

8. Raju SM, Kumar AP, Yadav AN, et al. Haptoglobin improves acute phase response and endotoxin tolerance in response to bacterial LPS. *Immunol Lett*. 2019;207:17-27. doi:10.1016/j.imlet.2019.01.002
9. Shih AW, McFarlane A, Verhovsek M. Haptoglobin testing in hemolysis: measurement and interpretation. *Am J Hematol*. 2014;89(4):443-447. doi:10.1002/ajh.23623
10. Katarzyna N., Podstawy diagnostyki immunologicznej, Bryniarski K., Siedlar M Immunologia. 2nd ed. Wrocław (Poland) Urban & Partner. 2023. s. 305
11. Brady N, O'Reilly EL, McComb C, et al. An immunoturbidimetric assay for bovine haptoglobin. *Comp Clin Path*. 2019;28(1):21-27. doi:10.1007/s00580-018-2863-6
12. Thuillier F, Demarquilly C, Szymanowicz A, et al. Turbidimétrie ou néphélémétrie: quel choix pour les dosages de l'albumine, l'ApoA, la CRP, l'haptoglobine, l'IgM et la transthyrétine? [Nephelometry or turbidimetry for the determination of albumin, ApoA, CRP, haptoglobin, IgM and transthyretin: which choice?]. *Ann Biol Clin (Paris)*. 2008;66(1):63-78. doi:10.1684/abc.2008.0192
13. Munoz CJ, Pires IS, Baek JH, et al. Apohemoglobin-haptoglobin complex attenuates the pathobiology of circulating acellular hemoglobin and heme. *Am J Physiol Heart Circ Physiol*. 2020;318(5):H1296-H1307. doi:10.1152/ajpheart.00136.2020
14. Więcek M., Metabolizm Wysiłkowy w Cięszczyk P (red.), Biochemia Sportowa. Warszawa: PZWL, 2023, s.230
15. Hasan A, Maciejewski D, Chmielniak S, et al. Medipage. Praktyczny podręcznik interpretacji równowagi kwasowo-zasadowej. Warszawa: Medipage, Cop; 2015.
16. Maciejewska-Skrendo A, Humińska-Lisowska K, Sawczu M, Techniki badań molekularnych stooswane w genetyce sportowej w Cięszczyk P., Genetyka Sportowa. Warszawa, PZWL, 2021, s. 38-40
17. Wan BN, Zhou SG, Wang M, et al. Progress on haptoglobin and metabolic diseases. *World J Diabetes*. 2021;12(3):206-214. doi:10.4239/wjd.v12.i3.206
18. Yousif AS, Elagib AA. Haptoglobin Phenotypes and Susceptibility to *Schistosoma* Parasites Infection in Central Sudan. *Mediterr J Hematol Infect Dis*. 2017;9(1):e2017042. Published 2017 Jul 1. doi:10.4084/MJHID.2017.042
19. Zhou J, Liu J, Sheng H, et al. Haptoglobin 2-2 Genotype is Associated with More Advanced Disease in Subjects with Non-Alcoholic Steatohepatitis: A Retrospective Study. *Adv Ther*. 2019;36(4):880-895. doi:10.1007/s12325-019-00902-z
20. You N, Lu Y, Yan X, et al. Haptoglobin 2-2 Genotype is Related to the Severity of Liver Damage in Hepatitis B Patients with Liver Steatosis. *Discov Med*. 2023;35(179):982-987. doi:10.24976/Discov.Med.202335179.94
21. Kamada Y, Akita M, Takeda Y, et al. Serum Fucosylated Haptoglobin as a Novel Diagnostic Biomarker for Predicting Hepatocyte Ballooning and Nonalcoholic Steatohepatitis. *PLoS One*. 2013;8(6):e66328. Published 2013 Jun 21. doi:10.1371/journal.pone.0066328
22. Sun L, Hu S, Yu L, et al. Serum haptoglobin as a novel molecular biomarker predicting colorectal cancer hepatic metastasis. *Int J Cancer*. 2016;138(11):2724-2731. doi:10.1002/ijc.29993

23. Peta V, Zhu J, Lubman DM, et al. Input of serum haptoglobin fucosylation profile in the diagnosis of hepatocellular carcinoma in patients with non-cirrhotic liver disease. *Clin Res Hepatol Gastroenterol*. 2020;44(5):681-691. doi:10.1016/j.clinre.2019.12.010
24. Naryzny SN, Legina OK. Haptoglobin as a Biomarker. *Biochem Mosc Suppl B Biomed Chem*. 2021;15(3):184-198. doi:10.1134/S1990750821030069
25. Pompach P, Brnakova Z, Sanda M, et al. Site-specific glycoforms of haptoglobin in liver cirrhosis and hepatocellular carcinoma. *Mol Cell Proteomics*. 2013;12(5):1281-1293. doi:10.1074/mcp.M112.023259
26. Tawara S, Tatsumi T, Iio S, et al. Evaluation of Fucosylated Haptoglobin and Mac-2 Binding Protein as Serum Biomarkers to Estimate Liver Fibrosis in Patients with Chronic Hepatitis C. *PLoS One*. 2016;11(3):e0151828. Published 2016 Mar 22. doi:10.1371/journal.pone.0151828
27. Gunzer S, Kraus A, Buchroth I, et al. Hypertransaminasemia and liver fibrosis associated with haptoglobin retention and anhaptoglobinemia in a paediatric patient. Liver Int. 2021 Oct;41(10):2427-2432. doi: 10.1111/liv.15029.
28. Naryzny SN, Legina OK. Haptoglobin as a Biomarker. Biochem Mosc Suppl B Biomed Chem. 2021;15(3):184-198. doi: 10.1134/S1990750821030069.
29. Lin Y, Zhu J, Zhang J, et al. Glycopeptides with Sialyl Lewis Antigen in Serum Haptoglobin as Candidate Biomarkers for Nonalcoholic Steatohepatitis Hepatocellular Carcinoma Using a Higher-Energy Collision-Induced Dissociation Parallel Reaction Monitoring-Mass Spectrometry Method. ACS Omega. 2022 Jun 22;7(26):22850-22860. doi: 10.1021/acsomega.2c02600.