Lek. Magdalena Chmielińska

Znaczenie kliniczne polimorfizmu haptoglobiny u pacjentów ze spondyloartropatią

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

Promotor: prof. dr hab. Dariusz Szukiewicz

Zakład Biofizyki, Fizjologii i Patofizjologii
Warszawski Uniwersytet Medyczny
Badania przeprowadzono w Narodowym Instytucie Geriatrii, Reumatologii i Rehabilitacji w Warszawie

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Streszczenie w języku angielskim

Title: Clinical significance of the haptoglobin polymorphism in patients with spondyloarthritis

Spondyloarthritis is a group of inflammatory joint diseases of the spine and peripheral joints with a complex pathogenesis involving genetic conditions, environmental factors and immunological mechanisms. Over recent years, the association of spondyloarthritis with the gut-joint axis has been strongly emphasised.

According to the available literature, the polymorphism of haptoglobin, which is one of the acute phase proteins whose main function is to bind free haemoglobin in the blood, may be associated with the course and treatment efficacy of autoimmune and inflammatory diseases. In my dissertation, I presented the hypothesis that different phenotypes of haptoglobin determined by its polymorphism may result in the different course of spondyloarthritis and affect the outcome of therapy. In order to comprehensively characterise the impact of haptoglobin polymorphism in this disease, in my analyses I also included a molecule described in the literature as a precursor of Hp2- zonulin, which is related to increased intestinal permeability.

Spondyloarthritis may be axial or peripheral depending on the predominant symptoms. The treatment of axial spondyloarthritis, which is the focus of my work, involves two stages: first, non-steroidal anti-inflammatory drugs (NSAIDs) are used, then, if these are ineffective, biological disease-modifying antirheumatic drugs (bDMARDs) (most commonly) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) therapy is implemented. The effectiveness of the therapy is limited and the reasons for these limitations have not yet been fully elucidated.

The first article is a review paper in which I described existing literature data on the distribution of haptoglobin phenotypes in spondyloarthritis and analysed inflammatory pathways involved in the pathogenesis of spondyloarthritis in which haptoglobin polymorphism and zonulin activity may be relevant. In this article, I presented the rationale for selecting haptoglobin polymorphism as a factor that may influence the course of spondyloarthritis. Additionally, I discussed the importance of zonulin on intestinal barrier disintegration in the context of disease progression and proposed a potential therapeutic pathway using a zonulin inhibitor.

In the second article, I described the results of an original study in which I was able to identify predictors of poor response to treatment with non-steroidal anti-inflammatory drugs in axial

spondyloarthritis. First of all, I checked whether haptoglobin, its polymorphism or zonulin were among detected predictors. The results of the analyses indicate that patients with high levels of zonulin have a significantly higher risk of poor response to standard treatment. No similar association was detected for haptoglobin and its polymorphism. Haptoglobin polymorphism alone was not associated with any of the disease activity parameters, nor was it linked to zonulin.

Importantly, my study has for the first time characterised patients with axial spondyloarthritis who have a high risk of failing to continue NSAIDs therapy. These are patients with ankylosing spondylitis, long duration of disease, sacroiliac joint involvement on X-ray, active sacroiliitis on MRI, high BASDAI, high values of subjective assessment of severity of the back pain on the VAS scale and the aforementioned high serum zonulin levels.

The third article in this series reports the results of a study on predictors of poor response to biological therapy in axial spondyloarthritis after 12 weeks of therapy. The analyses found that, again, higher zonulin concentrations were associated with treatment failure, independently of all other examined variables. In contrast, higher haptoglobin concentrations were found in patients who responded well to biological treatment. Haptoglobin concentration was significantly associated with the haptoglobin polymorphism, but the polymorphism itself was not associated with response to biological treatment or with indicators of spondyloarthritis activity. As in the previous study, zonulin was not significantly related to a specific haptoglobin phenotype and was also present in patients not carrying the Hp2 gene.

It is noteworthy that among the predictors of ineffectiveness of biological treatment, other factors besides zonulin have been identified as associated with impaired intestinal function and dysbiosis, such as older age, history of inflammatory bowel disease and frequent use of antibiotics for infections.

In conclusion, my findings in relation to axial spondyloarthritis show that the haptoglobin polymorphism is not clinically relevant in the course and treatment of this disease. My work, on the other hand, has identified predictors of failure of both standard and biological therapy in this disorder. This will help to guide more patient-specific treatment in the future and avoid prolonged standard therapy in patients where such continuation has a high risk of failure. The identification of zonulin as a factor associated with treatment response in spondyloarthritis points to new directions and treatment options using a zonulin inhibitor, regardless of the present haptoglobin phenotype. Based on my analyses, future research into the role of the gut-joint axis in the treatment of this disease is warranted.