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C-reactive protein versus procalcitonin. Simillar but different biomarkers in the assessment of an infection

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ABSTRACT:

Markers of systemic inflammation and bacterial infection such as C-reactive protein (CRP), and procalcitonin are commonly evaluated parameters in everyday medical practice. They are useful in quick assessment of patients condition, and the utility of CRP and procalcitonin as a marker of infection has been confirmed. An ideal marker of an inflammatory reaction should take into account many features. It should be remembered that we can not always choose one, more valuable biomarker. Interpretation of the results depends on numerous factors such as clinical status, weight and age. Both markers have their limitations. Early inflammatory disease diagnosis, properly implemented effective antibiotic therapy can contribute to the reduction of mortality.

Keywords: C - reactive protein, procalcitonin, inflammatory response, infection

Introduction:

An inflammatory reaction is the defence of the body which develops under the influence of a damaging factor and is characterised by an increased biochemical, haematological and immunological response at the local or systemic level. The strength of the inflammatory reaction is directly proportional to the potency of the irritant and duration of its effect. Inflammation can be caused by exogenous and endogenous factors, among which chemical, physical or biological factors are distinguished. Exposure to a given factor leads to the disturbance of homeostasis and the emergence of an inflammatory reaction, which is a defensive response of the body, aimed at neutralising the damaging factors and restoring the pnormal state. As a result of the response to the inflammatory process, under the influence of inflammatory mediators such as TNF, interleukin IL-1 and IL-6, IL-8, the rate of synthesis of the group of plasma proteins produced in the liver, which collectively are called acute phase proteins, changes. The major glycoproteins produced by hepatocytes include C-reactive protein (CRP). It is one of the most frequently evaluated markers of inflammation. In 1993, Assicot et al. described another marker of inflammation, which is procalcitonin (PCT). Both parameters are used in confirming the body's defensive response to the damaging factor. The value of their concentration and the rate of rise are different depending on the clinical condition of the patient. Therefore, it is necessary to know how to assess and interpret the results of the above-mentioned parameters in different clinical situations.

CRP:

C-reactive protein was discovered by Tillet and Francis in 1930. Its increase in serum has been observed in patients with *Streptococcus pneumoniae* aetiology [1]. The name derives from the ability of the protein to bind to the pneumococcal capsule C polypeptide. CRP is made up of 206 amino acids and is characterised by a pentameric structure. The gene for this protein is located on chromosome 1. The correct concentration of C-reactive protein in healthy people should not exceed 5 mg/l. However, under the influence of cytokines, in particular IL-6 and other mediators of inflammation, it is excessively synthesised in hepatocytes. It reaches its maximum concentration after 24 - 48 hours. Normalisation of the CRP concentration value occurs after 7-12 days. The uniqueness of this protein lies in the fact that its concentration is only slightly modified by hormones, biological substances and anti-inflammatory drugs [2]. The most important task of C-reactive protein is its participation in the immune response of the body. Different factors such as genetic factors, physical activity, age, long-term medication and cigarette smoking can affect the serum concentration of the protein [3]. In the course of necrosis or inflammation, the concentration of CRP increases very rapidly. When determining the C-reactive protein, the result suggesting slightly elevated CRP values may indicate inflammatory process withinin the vascular wall. Infections with Gram-negative bacteria usually cause much greater changes in C-reactive protein

concentration than do the Gram-positive or fungal infections [4].

Several publications report that CRP is not only a marker of the ongoing inflammatory reaction. The relationship between C-reactive protein and hypercholesterolaemia, obesity and diabetes is increasingly discussed. Lipotoxicity associated with obesity is considered an inflammatory process, so it can generate elevated values of acute phase proteins, including CRP. Patients with dyslipidaemia and advanced coronary artery disease who are undergoing statin therapy have a better prognosis if there is a clear decline in CRP regardless of changes in the lipidogram. There is also a hypothesis that C-reactive protein, through opsonisation of the LDL cholesterol fraction and endothelial dysfunction, facilitates their penetration into macrophages, which leads to the formation of foam cells and early atherosclerotic lesions. Higher CRP levels are observed in the hypertensive population, whereas its multiple increase is observed in myocardial infarction. A relationship was observed between IL-6 and CRP levels and the risk of developing type 2 diabetes. Several studies have demonstrated that the concentration of CRP protein is significantly higher in patients meeting the criteria of the metabolic syndrome, compared with people without the characteristics of this syndrome. Attention is also paid to the elevated level of CRP in patients with autoimmune diseases such as systemic lupus erythematosus or Crohn's disease. There are also reports that C-reactive protein is the best indicator of cancer metastasis [2,5].

Procalcitonin:

Procalcitonin was described by Assicot et al. in 1993. Its increase in serum has been observed in patients with sepsis. It is a polypeptide consisting of 116 amino acids. The gene for CALC-1 is located on chromosome 11. The products of this gene are calcitonin and procalcitonin, which have the same 32 amino acid sequence, but their induction is regulated differently. After translation of the CALC-1 gene, preprocalcitonin is formed, followed by translocation of procalcitonin, which under almost physiological conditions is enzymatically converted to CT. For this reason, in the state of health PCT concentration is virtually indistinguishable. During the inflammatory reaction, by hydrolysis of the N-terminal end of procalcitonin by DPP IV, creates the so-called 114 amino acid "inflammatory" procalcitonin . It is synthesised by blood cells and neuroendocrine cells of many organs, including the lungs, intestines, kidneys and pancreas [6,7]. During inflammation, pro-inflammatory mediators and bacterial toxins induce expression of the CALC-1 gene. During viral infection, INF-γ is produced which inhibits the activity of inflammatory mediators and, at the same time, the synthesis of procalcitonin. Therefore, during the viral infection, the serum concentration of procalcitonin is significantly lower compared to infections with bacterial aetiology, so procalcitonin is an important differentiating indicator. Compared with other markers of inflammation, procalcitonin is characterised by high sensitivity, specificity and speed of reaction. It is produced less than two hours from the moment the damaging factor activates. It is determinable in the serum after 3 - 4 hours from the occurrence of infection; the maximum concentration occurs after about 14 hours. Procalcitonin is a stable protein that is characterised by a wide biological range and a long half-life [7].

In which clinical situations should procalcitonin and CRP be considered?

Both parameters are used in confirming the body's defensive response to the damaging factor. The value of their concentration and the rate of rise are different depending on the clinical condition of the patient. Therefore, it is necessary to know in which situations to mark the above-mentioned parameters and how to interpret the results. The increase in the concentration of procalcitonin may be caused by bacterial infections, but also by serious injury, some autoimmune diseases or even a cardiogenic shock. The systemic nature of stimulation of procalcitonin production in contrast to CRP makes its value not increase significantly during local bacterial infection as, for example, during tonsillitis [7]. Below various clinical conditions and the justification for which parameter it is better to choose in a given situation will be presented.

Hospitalised adults with acquired pneumonia or exacerbation of asthma / Chronic obstructive pulmonary disease (COPD)

It has been proven that by determining procalcitonin or CRP, patients with pneumonia can be distinguished from patients with exacerbation of asthma/COPD. We can thus protect a large number of patients with asthma and COPD who are given antibiotics contrary to the recommendations. The studies show that CRP is at least equal to the accuracy of detecting pneumonia and can be used in a similar way to procalcitonin to assess the need for antibiotic therapy. However, as the authors themselves have admitted, to support their conclusions a randomised study is required [8]. Moreover, Johannes M.A. Daniels et al. reported, contrary to the current literature, that patients with acute exacerbations of COPD with low procalcitonin values benefit from antibiotic therapy, therefore CRP may be a more valuable marker in these patients.[9] Ashraf Abd El Halim and Manal Sayed in their study found an increased serum concentration of procalcitonin among exacerbated patients with COPD, and suggest the role of procalcitonin in predicting bacterial infections and their needs in the support of ventilation [10].

Biomarker of sepsis in the ICU patient

The speed of identification of patients with sepsis in Intensive Care Units (ICUs) significantly affects the course, procedure and prognosis. Both the markers - procalcitonin and CRP - showed limited diagnostic value in terms of identification of infectious origin. However, in this case procalcitonin with its properties far outweighs the C-reactive protein. Only an early diagnosis of the developing infection allows for achieving satisfactory therapeutic results. Changes in body temperature, respiration rate and heart rate are not very characteristic in the initial phase of clinical symptoms. That is why laboratory testing is so important. A fast marker that additionally allows you to follow the response to treatment is

procalcitonin. The authors recall the existing correlation between the decrease in the concentration of procalcitonin and the efficacy of antibiotic therapy [6.11]. Hoeboer and Groeneveld, observing 72 patients in a critical condition with a new fever symptom, marked the procalcitonin and CRP levels at regular intervals. In their publication, they concluded that CRP may be a better marker than procalcitonin in assessing the response to the implemented antibiotic therapy. However, they underestimate the value of procalcitonin in detecting the risk of complications such as bacteraemia, septic shock, multi-organ failure and death. Therefore, the concentration of procalcitonin should be taken into account before the end of antibiotic therapy [15]. In a large American study, in which thirteen American emergency departments and intensive care units participated, the concentration of procalcitonin and the consequences of not decreasing it by more than 80% from the baseline, which was a significant predictor of mortality, were monitored in patients meeting the criteria of severe sepsis or septic shock [16].

Diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department:

Among children, procalcitonin has a greater diagnostic accuracy than CRP (AUC 0.95 for PCT and 0.81 for CRP). However, it should be taken into account that this applies to severe bacterial infections of high invasiveness, among them a high rate of meningitis and septicaemia. In their publication, Barbara Andreola et al.'s observation included paediatric non-critically ill patients, where ca. 50% were discharged home. In this population, procalcitonin and CRP showed similar diagnostic accuracy. However, it was found that the concentration of procalcitonin was significantly higher than that of CRP. Therefore, procalcitonin appears to be a more accurate predictor at the beginning of infection. However, due to the lower cost of marking, greater availability and longer practice, it is allowed to use CRP in emergency situations [12].

Markers of bacterial infection:

It was observed that procalcitonin is a more accurate marker of bacterial infection than C-reactive protein. This applies to the differentiation of bacterial infection from non-infectious causes of inflammation and bacterial and viral infection. Procalcitonin is characterised by high sensitivity and specificity. The production of procalcitonin starts within 4 h and reaches the maximum concentration after 8 h, where in the case of CRP the increase will start after 4 - 6 h, and the peak reaches the marker only after 36 h. Procalcitonin is a stable protein and the result is available within 2 h, unfortunately the cost of the test is twice as high as the C-reactive protein determination. However, the determination of procalcitonin is important in differentiating infection with bacterial and viral aetiology, which is an extremely common problem in everyday medical practice. Therefore, in the era of the abuse of antibiotic therapy, the cost of the marker of bacterial infection which is procalcitonin is twice as high as the low price for limiting the use of antibiotics and consequently promoting drug resistance among pathogens [13].

Suspicion of blood infections in children with cancer:

Sepsis is the leading cause of morbidity and mortality in paediatric patients with cancer. Very often there is a fever in this clinical situation in paediatric patients. It should be distinguished whether it is caused by infection or inflammation caused by cancer, which is why it is very important to choose a reliable biomarker in the identification of blood infections that will allow for rapid diagnosis and implementation of appropriate treatment. There are many reports comparing CRP and procalcitonin in patients with cancer. C-reactive protein is definitely an inferior marker for identifying sepsis in oncological patients (AUC for procalcitonin was 0.78, and CRP 0.64). Hattori et al. showed that the cut-off value for bacteraemia is 0.9 ng / ml for procalcitonin [14].

Early sepsis marker in newborns:

Research conducted by Seth Kwabena Amponsah et al. shows that in the first twelve hours of life, procalcitonin is the most reliable acute phase protein in the diagnosis of sepsis. In the observation of 62 newborns under 12 years of age with suspected sepsis, the sensitivity for procalcitonin and CRP was respectively (87.5% vs. 50%), specificity (63.0% vs. 72.2%), positive predictive value (44.1% vs. 37.5%), and negative predictive value (93.8% vs. 81.3%, respectively). However, the role of procalcitonin and C-reactive protein in the diagnosis of sepsis remains controversial. CRP is a valuable marker, however its concentration depends on the physiological condition of the newborn (body weight, gestational age). It should be remembered that in the first two days of the newborn's life, the values of procalcitonin are physiologically increased. However, in critically ill newborns with suspected sepsis, procalcitonin should be the test of choice [7,17].

Sepsis and septic shock in senior patients:

Zhang et al., who attempted to determine the role of procalcitonin and high-sensitivity CRP in the assessment of sepsis and septic shock in patients > 85 years old, stated that CRP is not a worse biomarker in the assessment of sepsis and septic shock than procalcitonin. In comparison with other age groups, senior patients have less severe signs of infection and multi-organ failure is more likely to develop. Therefore, it is important to quickly diagnose sepsis or septic shock. It has been observed that high-sensitivity CRP is more useful in the diagnosis of lung infection. It should be borne in mind that the concentration of procalcitonin is lower in the elderly, and concentration at the level of 0.2 ng / ml may suggest bacteraemia [18].

Conclusions:

Markers of inflammation such as C-reactive protein and procalcitonin are commonly evaluated parameters in daily medical practice. These studies bring a number of benefits. Thanks to them, we can quickly assess and control the health of patients. Is there an ideal biomarker? The search for the ideal marker in inflammatory reactions should take into account many features, including the possibility of identifying the etiological factor that causes the infection, whether it is a viral or bacterial infection, help to implement adequate treatment in a timely manner, and monitor the progression of the disease as well as predict the consequences. Currently, there are no unambiguous recommendations, and the high weight attached to finances makes C-reactive protein a more popular and more frequently evaluated marker. However, the cited clinical situations in which the vast majority of procalcitonin use is greater than C-reactive protein, and a number of recent reports prove that it is a mistake to not routinely mark procalcitonin. The very benefit of reducing the frequency of unnecessary antibiotic therapy, while reducing the drug resistance of pathogens, is invaluable. By repeating the quoted question and trying to give an exhaustive answer, we must state clearly that we cannot always choose the best biomarker. It depends on many factors such as clinical status, body weight and age. Be sure to conduct a very thorough interview and approach each patient individually so as not to use schematic diagnostics, marking only one inflammatory biomarker. Early diagnosis of the disease and properly implemented effective antibiotic therapy can contribute to the reduction of mortality.

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