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SPECIFIC BIOCHEMICAL INDICATORS AND INFLAMMATORY MARKERS IN RHEUMATOID ARTHRITIS (RA)

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Abstract. It is acknown that Rheumatoid inflammation is a chronic systemic autoimmune disease developing on the background of infection. Damages mainly the heart, blood vessels, musculoskeletal system and other internal organs. Multiple joints may be affected, primarily the knee, ankle and elbow undergoing destruction leads to pain, mainly symmetrical. Damaged joints swollen and skin in these foci reddens; joint morning stiffness lasts for an hour or more, this sign is accompanied by low fever and fatigue. As a result of the rheumatic process, the heart is damaged, leading to cardiovascular manifestations. Analysis of blood parameters allows the severity of the disease to be determined based on a relatively new method using Das28. The obtained results for ESR and CRP are used to calculate DAS28, which also allows monitoring of RA treatment. Most patients with rheumatoid arthritis (RA) are seropositive—they have abnormally high levels of rheumatoid factor (RF) or anti-citrullinated peptide antibodies (anti-CPP) in the blood.
The article examines aspects of synthetic, chemical and alternative medicine impact on treating patients with RA as well. The article discusses comparative aspects of pharmacological and herbal medicine in the therapeutics. According to the literature, patients who have not received the expected results after treatment with pharmacological preparations successfully use herbal remedies as a means of body restoring and healing. To date, the success of traditional medicine is ahead of those of conventional using synthetic drugs.

Keywords: *ASO (anti-streptolysin-O), anti-cyclic citrullinated peptide (anti-CCP), CRP (C-reactive protein), Disease Activity Score (DAS28), East Asian herbal medicine, rheumatoid arthritis (RA), rheumatoid factor (RF).*

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1. Introduction

Rheumatoid arthritis (RA) is a connective tissue mainly of the joints, progressive erosive polyarthritis type damage associated with excessive antibody production (Guo *et al.*, 2018). In many industrialized countries, rheumatoid arthritis is spread with a frequency of 24–45/100,000 person-years affecting 0·5–1·0% of adults (Alamanos *et al.*, 2006).

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2. Rheumatoid arthritis risk-factors

Particulate matter pollution has long been implicated as a cause of many diseases, including RA. Air pollution triggers innate immune responses by stimulating the release of proinflammatory cytokines and the production of reactive oxygen species rising adaptive immune responses. It has been found that the incidence of RA is higher in more polluted urban areas and living near sources of air pollution increases both the risk of RA developing and RA-specific autoantibodies production (Sigaux *et al*., 2019).

Genetic predisposition makes a significant contribution to the development of RA in the population as well. Studies using analysis of genotype variability in twins with RA conducted in Finland and the UK showed, that the heredity role in the RA development was 65% in Finnish patients and 53% in the UK. It was also revealed that at least 40% contribution in the RA development comes from the general family environment (MacGregor *et al*., 2000).

Studies have been conducted regarding the role of heredity in the development of anti-CCP-positive RA, which was found to be almost the same as for anti-CCP-negative RA. Study including 148 pairs of twins, in which at least one from each pair had RA, tested for the presence of anti-CCP antibodies and HLA-DRB1 genotypes showed that the role of heredity in the development of RA among twin pairs was approximately 66%. Thus, for anti-CCP-positive RA, the role of genetics was 68% and for anti-CCP-negative RA - 66% (Van der Woude *et al*., 2009).

Persistent synovial systemic inflammatory process is accompanied with rised autoimmune markers, such as rheumatoid factor, ASO, CRP (Mellana *et al*., 2012) and cyclic citrullinated peptides, the indicators of immune system's attack on the joints (Wahab *et al*., 2013). Along with genetic factors, an important role in the spread of RA has a way of life, nutrition, as well as ecology (Abhishek *et al*., 2017). Sex differences in the prevalence of RA according recent studies demonstrates worst levels of RA activity in female compared to men (van Vollenhoven, 2009). A study conducted on 564 patients with RA found that the average age of first symptoms is 45 years in women and 50 in men, i.e. RA starts in women on average 5 years earlier than in men and the incidence of the disease in the Femail: Men ratio was 2,3, which means there are 2 times more women with RA than men. However, after the 6th decade of life this ratio becomes 1:1 (Goemaere *et al*., 1990).

RA is a multifactorial disease in which neuroendocrine factors are also involved. RA is characterized by striking age-sex differences. The disease is rare in men under 45 years of age, but incidence increases rapidly in older men and thus approaches the frequency indicator in women. This suggests that androgens play a protective role in RA; add to this that most men with RA have reduced testosterone levels. Interestingly, although testosterone suppresses immune responses, both cellular and humoral, most likely protecting against autoimmune processes, but it mediates protection against RA most likely via protein synthesis, helping to restore the body after damage. In women, RA usually subsides during gestation, a process characterized by increased levels of corticosteroids, estrogens and progesterone, which indicates that increased levels of steroids, namely adrenal and gonadal hormones, undoubtedly suppress RA development (Wilder, 1996).

Due to the cytokines IL-6 and TNF-alpha, stress and inflammatory conditions activate the hypothalamic-pituitary-adrenal glands, due to which adrenal hypofunction plays a direct role in the pathogenesis of RA. IL-6 and IL-12 have been found to act

together on the hypothalamic-pituitary-adrenal axis. Low-dose of adrenocorticotropic hormone (ACTH) in older women and low secretion of adrenal hormones predict susceptibility to RA. Clinical and biochemical improvement after glucocorticoid therapy in patients with RA may be explained by the suppression of mentioned above proinflammatory factors by hypothalamic-pituitary-adrenal axis hormones (Cutolo *et al*., 2002).

Current literature confirms that smoking exhibits a negative impact on rheumatic diseases and that moderate or high alcohol consumption is associated with an increased risk of RA outbreaks (Wieczorek *et al*., 2022; Marchand *et al*., 2022). Lifetime cigarette smoking has been found to be positively correlated with the risk of RA developing, even among smokers with low cigarette use. So, after analyzing 4,552 cases of RA, Di Giuseppe and co-authors concluded that the risk of RA developing increases by 26% in smokers between 1 and 10 pack-years vs never smokers. Not only that: the risk of RA developing even doubles in smokers for more than 20 pack-years. In addition, the RA risk was statistically significantly higher with positive RF vs RF-negative [13>15; 14>16]. A fever at RA is caused by throat infection with Streptococcus pyogenes and an autoimmune response to bacterial intervention [15>17]. Due to the fact that disease development is based on a streptococcal infection and that the immune system weakens with age, age is also an aggravating disease course factor [16>18]. According to Goronzy et al. RA is accompanied by expression of antibodies against IgG, as well as citrullinated peptides, self-anthienes or neoantigenes, which are differently expressed. To date, RA can occur at any age, more in probably, in the middle age group. The age accumulation of T follicular helper (TFH cells) can play a decisive role in an increased phenotype of autoimmune disease in middle age [17>19]. Nevertheless, there are scientific results that RA is initially observed in the age group and a more sharp activation of RA in the elderly is associated with a higher state of activation of peripheral blood CD4+ T cells [18>20].

As for observations regarding the genetic factor and external environment pollution role in the RA incidence, it was found out that the risk of RA incidence in a group with the highest genetic risk and air pollution point is almost twice as much as with the lowest genetic risk and a group of air pollution[19>21]; [20>22].

Change in intestinal microbiota is an indirect mechanism of RA onset and progression. Some dietary models, for example the Mediterranean diet, vitamin D and probiotics, can become additional therapy for the RA treatment. Due to this, in patients with RA, it is necessary to encourage a healthy lifestyle and nutrition [21>23].

According to Marchand et al. the long-term weight gain is closely associated with increased RA risk in female. So, an increase in weight ≥20 ***arhthritis***life quality, uncontrolled active rheumatoid arthritis results in joints, heart, system damage, disability and musculoskeletal system disorders (Scott *et al*., 2010).

3. Rheumatoid arthritis diagnostics

To determine the degree of activity of the rheumatic process, a series of rheumatological tests are performed. For this:

1) Clinical symptoms;
2) X-ray examination;
3) Electrocardiographic symptoms;
4) Serological tests;

5) Increased capillary conductivity should be considered as well (Egerer *et al*., 2009).

Finally, RA is diagnosed using clinical, immunological, ultrasound, MRI, radiological, ultrasound examination of joints, as well as laboratory and morphological results. Stages of RA are determined radiographic scoring (Heijde *et al*., 1992). In addition, it is systematic signs of osteoporosis may also be detected.

Widely used sensitive to RA biochemical analyzes include RF, ASO, CRP. In the blood, the sedimentation rate of erythrocytes (SRE) should also be taken into account. RF-rheumatoid factors are designed against the Fc region of immunoglobulin G (IgG). Rheumatoid factor first discovered 70 years or more ago in all individuals with/without autoimmune disease, even in healthy individuals. This indicator is useful in differential diagnosis of arthropathies. Therefore, rheumatoid factor alone cannot be used in diagnosis of RA, so for correct diagnosis, anti-CCP and rheumatoid factor both are determined in clinical practice. It is recommended to evaluate these factors jointly. Because anti-cyclic citrullinated peptide antibodies as a single parameter is moderate, that is why the processing of two biomarkers in joint form increases the diagnostic accuracy in the case of early RA diagnostics. The positive anti-CCP antibodies are associated with an increased risk of early-onset RA (Diaz *et al*., 2011).

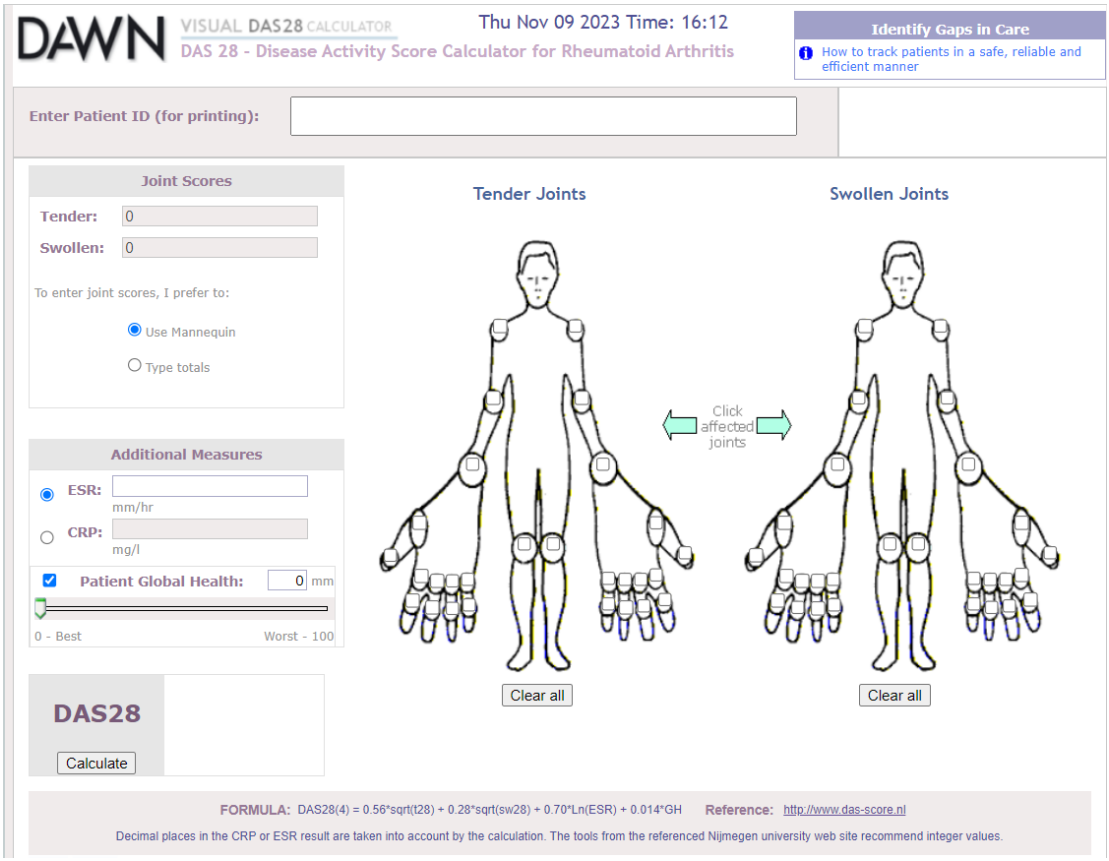
There is evidence in the literature (152 Colombian patients) that antibodies against CCP and the presence of protective ^{70}DERAA^{74} sequence in a family of genes termed the human leukocyte antigen (HLA) DRB1 can significantly influence the age of onset of RA. The HLA-DRB1 gene instructs the translation of protein, which has a crucial role in the immune system and helps distinguish self-proteins from foreign ones. So, the presence of the protective sequence ^{70}DERAA^{74} in this gene is associated with delayed onset of the disease (Ingegnoli *et al*., 2013).

Besides, different RF isotypes alone or in combination with other RA markers may be helpful for screening and selection of therapeutic strategy (Ingegnoli *et al*., 2013) along with biomarker ASO. ASO is a biomarker identifying antibodies against IGs caused by β-hemolytic streptococci of groups A, C and G intervention. The resulting antibodies can attack the left atrioventricular valve of the heart cross-recognized as streptococcus bacteria. When attacks are directed against the heart, it is termed rheumatism (Crowson *et al*., 2013), while disease attacking the joints is termed RA. When exposed to streptococci, ASO indicator is elevated during first 1-3 weeks, while ASO reference range of is mainly accepted as <100-150 IU/ml in children and <200 -250 IU/ml in adults (Steer *et al*., 2009).

RA activity degree, that is, how far it has progressed, is measured by disease activity severity -28 (DAS28, see picture below, McWilliams *et al*., 2018).

First of all, the pain that occurs, in which joints is examined to find the intensity of RA. Then the difficulty of joints movement, as well as loss of joints mobility, shackles feeling in extremities, especially in the morning is counted. ESR and CRP increase are crucial for DAS28 measurement (Inoue *et al*., 2007). The obtained ESR and CRP results are used for DAS28 calculation. After DAS28 calculation, suitable treatment method is applied to the patient. Only one indicator in rheumatoid patients is not informative, due to that, to find patients' DAS28 in America, RA patients swollen and sensitive joints number, as well as ESR and patient health information are taking into account to determine the disease development degree. Based on international Das28 results, a value 2,6 is counted as remission, 2.6-3.2 – as relatively low level, 3.2-5.1 is considered a moderately severe level of RA (Hansen *et al*., 2017).

Among methods for blood serum and joints synovial fluid immunological examination it is helpful to determine the rheumatoid factor complement levels. Therefore, the RF latex test, the Waaler-Rose reaction and the dermatol test help to identify RA patients. For more sensitive RA determination and to rise the effectiveness of assay result as well as to avoid the false-positive reactions, blood serum should be diluted in 1:20 or more ratio. It is considered more informative to perform Waaler-rose and latex-test reactions in parallel. By this method the first 6-18 months of the disease, RF can be detected earlier in 70-80% of patients (Nikolaisen *et al*., 2005).



In RA patients proteinogram, the biochemical examination shows decline in the albumin fraction and tendency to increase in globulins. The increase in fibrinogen levels, as well as in seromucoid, the indicator of direct immunofluorescence and finally presence of CRP confirms the activity of the inflammatory process and the need for medical intervention.

4. RA Treatment ways

There are many therapeutic pathways of RA treatment with pharmacological preparations that can alleviate the symptoms of RA by targeting inflammation, fibroblast-like synoviocytes, oxidative stress, immunoregulation, angiogenesis, osteoclasts, microRNAs, etc. To date, flavonoids, phenolic acids, alkaloids and triterpenes are considered as the main compounds contributing to the RA recovery and symptoms reduction (Wang *et al*., 2021). Most of the compounds mentioned above are obtained in their pure form, as they are used in scientific medicine. However, as the experience of

treating physicians shows, not only the active substances themselves, but also those accompanying them in the plant world can enhance the therapeutic effect. They sometimes help by improving the absorption of the main components and sometimes providing a synergistic effect. As a result, the use of plant raw materials as a whole and not its ingredients separately, helps to improve the healing process and speed up the patient's recovery. For instance, there are evidences in the literature, that randomized controlled trials comparing East Asian herbal medicine with conventional medicine in eleven databases have indicated a preference for the use of medicinal plants in the treatment of RA (Jo *et al*., 2022).

It is declared that East Asian herbal medicine has undeniable advantages over conventional medicine and this is primarily due to the fact that this medicinal leanage always tries to block or take something away from the body, disrupt some enzymatic or even worse, genetic processes, whereas treatment with the help of plants provides the body with what it lacks and the rest the body, perfectly created from the beginning, improves itself. Studies involving 19,716 patients with RA showed that the best effect of East Asian herbal medicine was observed on both the intensity of persistent pain and the number of painful joints and response rate. Patients treated with East Asian herbal medicine experienced significantly fewer side effects due to the low toxicity of medicinal plants compared to conventional medicine. Moreover, the main candidate herbs selected as a result of the study act in several directions at once and are expected to accelerate the analgesic effect and suppress the inflammatory process, restore balance in immune regulation and help prevent joint destruction, therefore can be used in combination with pharmacological preparations to facilitate the therapeutic effect.

Pro-inflammatory components, the cytokines interleukin-1 (IL-1), IL-6, IL-7, IL-8 and tumor necrosis factor-α (TNF-α) are directly involved in the development of the RA process. For this reason, one of RA treatment ways is based on blockade of TNF-α, IL-1 and IL-6 paths and therapy through the B-cell activity regulation, as well as inhibition of angiogenesis. Treatment is carried out with both synthetic and natural compounds. The group of synthetic drugs includes cyclophosphamide, sulfasalazine, methotrexate; symptomatic treatment includes non-steroidal anti-inflammatory drugs for intramuscular administration. However, these agents cause gastrointestinal disorders, including gastric ulcer, hepato-renal effects, hypertension, etc. (Akram *et al*., 2021). Let's add to this that in addition to adverse side effects, allopathic therapy is quite expensive. A review of electronic data bases of scientific material from journals published in PubMed, Elsevier, Science Direct, Web of Science and Google Scholar between 2016 and 2021 concluded that the active ingredients of conventional herbal therapies for RA can relieve symptoms by improving immune regulation, reducing inflammation, effects on fibroblast-like synoviocytes, microRNAs, angiogenesis, oxidative stress and even osteoclasts (Wang *et al*., 2021).

Thus, treatment of RA should be based not so much on reducing the pathogens titer with the help of antibiotics and easing symptoms, but on restoring the body's immune balance via supply of ingredients potentially involved in the restoring the regulation of cellular response signaling pathways.

5. Conclusion

Diagnosis of RA based on the methods available in the medical arsenal, including DAS28, needs further refinement. When treating patients with RA, it is advisable not to

limit yourself to synthetic drugs and painkillers, but to use herbal preparations that help restore homeostasis and normalize immune auto-regulation as well.

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