РЕВМАТОЛОГІЯ

The most common causes of comorbidity in patients with rheumatoid arthritis

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Rheumatoid arthritis is a chronic autoimmune disease that affects the synovial membrane of the joints and leads to progressive joint damage, disability and reduced quality of life. Notwithstanding the emergence of more advanced therapeutic strategies that have improved the duration of remission, rheumatoid arthritis is associated with high rates of comorbidities, infections, malignant neoplasms, and cardiovascular pathology. It is known that some existing pathogenic inflammatory mediators in rheumatoid arthritis, such as interleukin-1β (IL-1β) and tumor necrosis factor, may play a key role in the development of cardiovascular diseases.
Various preclinical and clinical studies have shown that biological therapy, which is widely used to treat patients with rheumatoid arthritis, may be effective in treatment of cardiovascular diseases. In this context, it was proposed to study the involvement of adipocytokines. Adipocytokines are pleiotropic molecules that are primarily released from the white adipose tissue and immune cells. Adipocytokines modulate the function of various tissues and cells, and, in addition to energy homeostasis and metabolism, enhance the process of inflammation, the immune response and tissue damage. Adipocytokines can contribute to the pro-inflammatory condition in patients with rheumatoid arthritis and the development of bone tissue damage. Moreover, they may be associated with the development of cardiovascular diseases.
In the present study, we considered the already known data on the role of adipocytokines in the pathogenesis of rheumatoid arthritis, despite the fact that they are also actively involved in the pathogenesis of the cardiovascular diseases and are possible biomarkers for predicting the treatment outcomes, as well as in connection with their potential, as a possible new therapeutic target.
Keywords: *interleukin, adipocytokines, cardiovascular diseases.*

Найчастіші причини коморбідності у хворих на ревматоїдний артрит

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Ревматоїдний артрит – це хронічне аутоімунне захворювання, яке вражає синовіальну оболонку суглобів і призводить до прогресуючого ураження суглобів, інвалідності та зниження якості життя. Незважаючи на появу більш прогресивних терапевтичних стратегій, які покращили тривалість ремісії, ревматоїдний артрит асоціюється з високим рівнем супутніх захворювань, інфекцій, злоякісних новоутворень та серцево-судинної патології. Відомо, що деякі патогенні медіатори запалення при ревматоїдному артриті, такі, як інтерлейкін-1β (ІЛ-1β) та фактор некрозу пухлин можуть відігравати ключову роль у розвитку серцево-судинних захворювань.

Різні доклінічні та клінічні дослідження продемонстрували, що біологічна терапія, яку широко використовують для лікування пацієнтів з ревматоїдним артритом, може бути ефективною у лікуванні серцево-судинних захворювань. У цьому контексті були запропоновані до вивчення адипоцитокіни. Адипоцитокіни – це плейотропні молекули, які, головним чином, вивільняються з білої жирової тканини та імунних клітин. Адипоцитокіни модулюють функцію різних тканин та клітин, та крім енергетичного гомеостазу та метаболізму посилюють процес запалення, імунну відповідь та пошкодження тканин. Адипоцитокіни можуть зумовлювати прозапальний стан у хворих на ревматоїдний артрит та розвиток пошкодження кісткової тканини. Крім того, вони можуть бути пов'язані з розвитком серцево-судинних захворювань.

Відомо, що активний агоніст рецепторів адипонектину, який вводили у порожнину рота, покращив інсуліно-резистентність та порушення толерантності до глюкози у піддослідних мишей. Враховуючи, що адипонектин має протизапальні властивості, можна припустити, що адипонектин чи агоністи адипонектинових рецепторів можуть бути у перспективі досліджені для розроблення терапевтичних препаратів для лікування інсулінорезистентних станів і можливих запальних процесів.

У дослідженні було розглянуто вже відомі дані про адипоцитокіни у патогенезі ревматоїдного артриту, зважаючи на те, що вони також беруть активну участь у патогенезі захворювань серцево-судинної системи та є можливими біомаркерами прогнозу результату лікування, а також, у зв'язку з їхнім потенціалом, в якості можливої нової терапевтичної мішені.
Ключові слова: *інтерлейкін, адипоцитокіни, серцево-судинні захворювання.*

РЕВМАТОЛОГІЯ

Наиболее частые причины коморбидности у больных ревматоидным артритом
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Ревматоидный артрит – это хроническое аутоиммунное заболевание, которое поражает синовиальную оболочку суставов и приводит к прогрессирующему поражению суставов, инвалидности и снижению качества жизни. Несмотря на появление более прогрессивных терапевтических стратегий, улучшивших продолжительность ремиссии, ревматоидный артрит ассоциируется с высоким уровнем сопутствующих заболеваний, инфекций, злокачественных новообразований и сердечно-сосудистой патологии.

Известно, что некоторые патогенные медиаторы воспаления при ревматоидном артрите, такие, как интерлейкин-1β (ИЛ-1β) и фактор некроза опухолей, могут играть ключевую роль в развитии сердечно-сосудистых заболеваний. Различные доклинические и клинические исследования продемонстрировали, что биологическая терапия, широко используемая для лечения пациентов с ревматоидным артритом, может быть эффективной в лечении сердечно-сосудистых заболеваний. В этом контексте были предложены для изучения адипоцитокины. Адипоцитокины – это плейотропные молекулы, которые главным образом высвобождаются из белой жировой ткани и иммунных клеток. Адипоцитокины модулируют функцию различных тканей и клеток, кроме энергетического гомеостаза и метаболизма усиливают процесс воспаления, иммунный ответ и повреждение тканей. Адипоцитокины могут вызывать воспалительное состояние у больных ревматоидным артритом и развитие повреждения костной ткани. Кроме того, они могут быть связаны с развитием сердечно-сосудистых заболеваний.

Известно, что активный агонист рецепторов адипонектина, который вводили в полость рта, улучшил инсулинорезистентность и нарушение толерантности к глюкозе у подопытных мышей. Учитывая, что адипонектин обладает противовоспалительными свойствами, можно предположить, что адипонектин или агонисты адипонектиновых рецепторов могут быть в перспективе исследованы для разработки терапевтических препаратов для лечения инсулинорезистентных состояний и возможных воспалительных процессов.

В исследовании были рассмотрены уже известные данные об адипоцитокинах в патогенезе ревматоидного артрита, учитывая, что они также активно участвуют в патогенезе заболеваний сердечно-сосудистой системы и являются возможными биомаркерами прогноза результата лечения, а также, в связи с их потенциалом, в качестве возможной новой терапевтической мишени.

Ключевые слова: *интерлейкин, адипоцитокины, сердечно-сосудистые заболевания.*

The paper has been written within the research scientific work, entitled "The features of the course, prognosis and treatment of comorbid conditions in diseases of internal organs in respect of genetic, age and gender aspects" (State registration number 0118U004461).

Rheumatoid arthritis is associated with high prevalence of comorbidities, including infections, malignancies and cardiovascular diseases, leading to increased mortality in these patients [1]. A tight association between rheumatoid arthritis and progressive atherosclerosis is known to be due to correlation between conventional cardiovascular risk factors and pro-inflammatory pathogenetic mechanisms. Moreover, atherosclerotic process can be aggravated by the fact that conventional cardiovascular risk factors are poorly diagnosed and treated [2]. In addition, some known pathogenic proinflammatory mediators in rheumatoid arthritis, such as interleukin 1-β (IL1-β) and tumor necrosis factor, may play a key role in the development of cardiovascular diseases. In fact, common pathogenetic pathways of inflammation between atherosclerotic process and rheumatic diseases have been identified [3].

Various studies have suggested that biological disease-modifying antirheumatic drugs commonly used to treat patients with rheumatoid arthritis may be effective in ameliorating concomitant cardiovascular diseases. In this context, the contribution of adipocytokines has been proposed. Adipocytokines are pleiotropic molecules that are mainly released from the white adipose tissue and immune cells. Adipocytokines modulate the function of various tissues and cells, enhance the inflammatory process, immune response and tissue damage. In rheumatoid arthritis, adipocytokines can contribute to pro-inflammatory conditions, bone tissue damage, and accelerate concomitant atherosclerosis [4].

In the present study, we considered the already known data on adipocytokines in the pathogenesis of rheumatoid arthritis, given that they are also actively involved in the pathogenesis of cardiovascular diseases and are possible biomarkers for the prognosis of treatment outcomes, as well as their potential, as a possible new therapeutic target.

The paper was aimed at the analysis of the publications and summarize the existing data on the role of adipocytokines in the pathogenesis of rheumatoid arthritis and associated comorbid pathologies.

MATERIAL AND METHODS

We conducted a descriptive analysis of the literature aimed at reviewing the role of leptin, adiponectin, resistin and visfatin in the pathogenesis of rheumatoid arthritis, since they are involved in the active course of the disease, concomitant cardiometabolic diseases and can be biomarkers in the prognosis and treatment outcomes, due to their potential, as the new therapeutic targets. We have analyzed already known data linking the same molecule to joint damage and cardiometabolic comorbidities not only to discuss the previous studies but also to justify further ones. A search on MEDLINE (via PubMed) and the bibliography of the relevant puplications was performed manually to identify other potentially relevant studies.

RESULTS

Adiponectin is the 244-formulation protein, also known as GBP28, apM1, Acrp30 or AdipoQ, mainly

synthesized by the adipose tissue. This adipocytokine increases fatty acid oxidation and glucose uptake by the muscles, decreases hepatic glucose synthesis by acting through two AdipoR1 and AdipoR2 receptors found in the skeletal muscles and liver, respectively. Adiponectin gene ablation has an impressive effect on experimental mice on a high-fat and sucrose diet, causing insulin resistance and accumulation of lipids in the muscles [5]. In the animal mirror models, adiponectin levels are lower in obese patients and higher in patients who lose weight. On the contrary, the content of adiponectin and its receptors increases during physical activity. In addition, adiponectin secretion is inhibited by proinflammatory cytokines, indicating that inflammation may contribute to hypoadiponectinemia in insulin resistance and obesity [6].

In rheumatic diseases, adiponectin can act as a proinflammatory mediator in the joints and participate in the degradation of the matrix. During rheumatoid arthritis, the level of adiponectin and AdipoR1 in synovial fluid and tissue was relatively higher compared to the control group. In this study, many cells derived from synovial fluid and tissues in rheumatoid arthritis, including synovial fibroblasts, contained adiponectin, AdipoR1, and AdipoR2 [7]. Interestingly, the addition of adiponectin to synovial fibroblast cultures increased the production of proinflammatory cytokines such as IL-6 and IL-8. Stimulation with adiponectin also promoted the production of metalloproteinase MMP-1 and MMP-13 by synovial fibroblasts in rheumatoid arthritis. In addition, adiponectin can bind to IL-1β, which increases the production of proinflammatory mediators by the synovial fibroblasts in rheumatoid arthritis.

Adiponectin intensified bone erosion by promoting osteopoietin production in the synovial tissue in rheumatoid arthritis, indicating that adiponectin induced the expression of osteopoietin, which in turn activated osteoblasts [8]. Recently, the effect of adiponectin on the derivatives of mesenchymal adipose tissue stem cells derived from the infrapatellar adipose pad of patients with rheumatoid arthritis has been evaluated. Mesenchymal adipose stem cells were stimulated by the low-molecular and high-/medium-molecular weight isoforms of adiponectin [9]. The authors emphasized that the secretion of proinflammatory mediators was activated by the high-/medium-molecular weight isoforms, but not by the low-molecular weight isoforms of adiponectin. In addition, they highlighted that stimulation with the high-/medium-molecular weight isoforms of adiponectin reduces the proliferative effects of mesenchymal adipose tissue stem cells derived from soluble synovial fibroblast factors in rheumatoid arthritis. Summarizing these results together, we hypothesize that adiponectin has a pro-inflammatory and destructive effect on the joint during rheumatoid arthritis [10].

Increased risk for cardiovascular complications resulting from the synergy between the conventional cardiovascular risk factors and the inflammatory process itself is characteristic of patients with rheumatoid arthritis. Therefore, the role of adipocytokines, which have a possible link to obesity, inflammation and cardiometabolic diseases, has been proposed. To evaluate the likelihood of the effect of adipocytokines on insulin resistance and coronary atherosclerosis in patients with rheumatoid arthritis, a preliminary study has been conducted [11]. In this study, the authors estimated the index of coronary artery calcification according to vascular CT, a homeostatic model of insulin resistance (HOMA-IR), and blood serum adipocytokines (leptin, adiponectin, resistin, and visfatin) in 169 patients with rheumatoid arthritis. Currently, elevated leptin correlates with the insulin resistance index (HOMA-IR), even after correction for possible clinical complications, age, gender, body mass index, conventional cardiovascular risk factors, and inflammatory mediators [12].

In contrast, visfatin, adiponectin, and resistin were not associated with the HOMA-IR index. No association has been found between the coronary artery calcification index and the estimated adipocytokines [13]. Recently, adipocytokines have been additionally investigated with regard to inflammation, insulin resistance, and atherosclerosis in rheumatoid arthritis, which is associated with the pathogenic mechanisms of these diseases [14]. The study evaluated the HOMA-IR index, the thickness of the intima-media complex, the resistance index of the carotid artery and plaque of the carotid artery in 192 patients with rheumatoid arthritis. These data were correlated with adiponectin, leptin and resistin levels. The authors have noted that leptin and the leptin/adiponectin (L/A) ratio correlated with the HOMA-IR index and the thickness of the intima-media complex after taking into account cardiovascular risk factors, indicating a possible independent role of leptin in predicting cardiovascular diseases in rheumatoid arthritis [15].

With regard to adiponectin, in 210 patients with rheumatoid arthritis, a correlation between the total and high-molecular weight concentrations of adiponectin, cardiometabolic risk and markers of enhanced early atherogenesis was made [16]. The total and high molecular weight adiponectin concentrations are associated with high systolic, diastolic and mean arterial pressure, and HDL concentrations, low overall HDL/TG ratio, and TG, HDL and glucose ratios [17]. These findings reflected what was observed in the model of lipoatrophy of mice with adiponectin deficiency. In these models, adiponectin replacement improved insulin resistance, fatty acid oxidation, and energy intake, resulting in lower triglycerides in muscle tissue and liver. In addition, mice on a high-fat diet showed lower levels of adiponectin, which improved diet-induced hypertriglyceridemia [18].

Currently, the possible role of adiponectin in regulating blood pressure has been proposed. In the crossover study of patients with high arterial blood pressure, elevated blood serum adiponectin correlated with low circulating levels of the carboxy-terminal propeptide procollagen type I, and its molecule has been reported to be associated with arterial occlusion. Moreover, adiponectin has been shown to increase gene expression and activate endothelial nitric oxide synthesis by activating AMP-activated protein kinase [19]. Finally, adiponectin

has been reported to inhibit the deleterious effects of the renin-angiotensin system on blood vessels [20].

Over the last decade, the treatment options for rheumatoid arthritis have improved markedly through the use of synthetic and biological disease-modifying antirheumatic drugs. Recently, attention has been paid to finding the best therapeutic strategy to combat comorbidities in rheumatoid arthritis [21]. In this context, it has been hypothesized that the effect of blocking proinflammatory cytokines extends not only to the affected joints, but also to comorbid pathology, which improves the management of such patients. The analysis of the studies can suggest whether the exposure to adipocytokines may be effective in rheumatoid arthritis and comorbidities.

Currently, leptin antagonists have already been developed for the treatment of metabolic disorders. It should be tested whether they also have anti-inflammatory effects *in vivo*. Interestingly, the monoclonal antibody against the leptin receptor blocks the production of human tumor cell necrosis factor-alpha by monocytes, acting as an antagonist. Recently, an active adiponectin receptor agonist administered orally has improved insulin resistance and impaired glucose tolerance in experimental mice. Given that adiponectin has anti-inflammatory properties, it can be assumed that adiponectin or adiponectin receptor agonists may be investigated in the future for the development of therapeutic drugs for the treatment of insulin-resistant conditions and possible inflammatory processes [22].

CONCLUSIONS

Rheumatoid arthritis is a chronic autoimmune disease with increased mortality, mainly caused by cardiovascular diseases. Adipocytokines have been reported to play an important role in the pathogenesis of rheumatoid arthritis and related comorbidities. Further research is needed to identify new mechanisms of action of adipocytokines and to determine whether these molecules may become new possible therapeutic targets, thereby improving the management of patients with rheumatoid arthritis.

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