LECTURE

Multimorbidity in rheumatology. From comprehensive assessment of disease to evaluation of a set of diseases

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The World Health Organization assigns cardiovascular diseases, cancers, chronic respiratory diseases, as well as diabetes mellitus and some other nosological entities, including mental and musculoskeletal disorders, to main non-communicable diseases. These are considered to be a major public health challenge of the 21st century. In this case, one patient frequently has a set of several age-related chronic diseases that develop simultaneously or sequentially. The management of these patients requires an integrated approach based on the multimorbid nature of pathology. Unlike the definition of comorbidities, which assumes to identify the underlying and related diseases, the concept of multimorbidity of such gradations fails to provide and interprets a patient's chronic diseases as equivalent.

Keywords: *multimorbidity; comorbidity; mortality; rheumatic diseases; treatment.*

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For reference: *Lila AM, Gordeev AV, Olyunin YuA, Galushko EA. Multimorbidity in rheumatology. From comprehensive assessment of disease to evaluation of a set of diseases. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2019;13(3):4-9. DOI: 10.14412/1996-7012-2019-3-4-9*

In recent years, with the accumulation of data obtained in the framework of national registers and observational studies, the problem of multimorbidity attracts increasing interest [1]. The inevitable result of the increasing life expectancy achieved in the developed countries is the growing number of elderly people, what in combination with fertility reduction leads to population aging, which in turn is accompanied by increased prevalence of chronic diseases characteristic of advanced age. In 1950, only 12% of Europeans were over the age of 65. Today, their number has reached 19.2%, and it is expected that by 2050 the proportion of such people in European countries will be 36% [2].

Aging is a normal biological process that occurs in all organisms and is accompanied by an age-related decrease in the functional activity of cells. Age-related changes in the immune system affect both innate and adaptive immunity [3]. Changes in the adaptive immunity are accompanied by a decrease in the ability to regenerate, as well as impairment of the formation, maturation and function of T and B cells. First of all, the activation of T lymphocytes declines, which, in turn, leads to a reduction of differentiation and function of B cells. Along with a decrease in the effectiveness of protective immune reactions, the aging of the immune system is accompanied by an increase in the likelihood of autoimmune diseases, including rheumatoid arthritis (RA), since the decrease in the stability of immune processes characteristic of old age predisposes to a lowering tolerance [4].

Thus, CD28 deficiency in CD4 T cells is associated with increased production of proinflammatory cytokines. In addition, changes in innate immunity induce activation of monocytes and macrophages with increased levels of tumor necrosis factor α, interleukin 6, C-reactive protein and other inflammatory products [5]. With the appearance of autoreactive T and B cells, these changes can contribute to the development of autoimmune pathology and, in particular, RA. In turn, persistent inflammatory process in RA patients can aggravate age-related changes in the immune system, contributing to the occurrence of comorbidities and, above all, cardiovascular diseases [6].

The World Health Organization classifies cardiovascular, oncological, chronic respiratory diseases, as well as diabetes mellitus and some other nosologies, including mental and musculoskeletal pathology, as the main non-communicable diseases [7]. They are considered to be a major health problem of the 21st century. Furthermore, one patient can often have a combination of several age-associated chronic diseases that develop simultaneously or sequentially. The management of such patients requires an integrated approach focused on the multi-morbid nature of the available pathology.

In contrast to the definition of *comorbid* disorders, which involves the distinction of the main and concomitant diseases, the concept of multimorbidity does not use such gradations and considers the patient's chronic diseases as equivalent [8]. The working group of the European General practice research network *believes that multi-morbidity should be understood as any combination of a chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or non-associated) or somatic risk factor* [9].

The prevalence of multimorbidity in the general population is about 25%, but this figure varies significantly depending on the age of the examined patients and methods of research. In the practice of rheumatologists, who have to supervise patients with chronic inflammatory diseases, multimorbidity is much more common [10]. It is detected in about 60% of RA patients. The combination of multi-morbidity with female sex and low socio-

economic status is described, but a detailed study of the causes and risk factors of multi-morbidity was carried out only in single studies [11, 12]. Data on the frequency of multimorbidity are presented mainly for patients with RA. For other rheumatic diseases (RD) information is very limited.

The most significant concomitant disorders for RA patients include cardiovascular diseases, depression, osteoporosis [13]. The presence of chronic inflammation and common risk factors, including smoking, obesity and sedentary life style, increases the risk of cardiovascular disease in many rheumatic diseases, including RA, psoriatic arthritis, and systemic lupus erythematosus (SLE) [14–16]. In young women with SLE, the risk of myocardial infarction was increased by 50 times compared to population control [17]. An increase in the frequency of cardiovascular diseases in ankylosing spondylitis compared to the population is described [18]. However, after adjusting for the use of nonsteroidal anti-inflammatory drugs, the statistical significance was lost [19].

Controlling inflammatory activity may play a central role in reducing cardiovascular risk. In addition to reducing the severity of inflammatory changes, disease modifying anti-rheumatic drugs (DMARD) can also improve the lipid profile of the blood [20] and reduce the risk of diabetes [21]. EULAR experts attach great importance to the influence of cardiovascular pathology on the status of patients with chronic inflammatory diseases of the joints and have prepared recommendations for the assessment and reduction of cardiovascular risk in these nosologies [22]. RD are also accompanied by an increase in the frequency of osteoporosis, which is associated with the use of glucocorticoids, decreased motor activity and the presence of chronic inflammation [23]. Thus, in patients with SLE, increased risk of osteoporosis correlates with glucocorticoid therapy, duration and severity of the disease [24]. The presence of RA is taken into account when determining the risk of fractures [25].

Mortality among patients with RD remains high, despite the widespread introduction of modern antirheumatic drugs into clinical practice, although it is decreasing in the general population [26]. Concomitant diseases are the most significant predictor of mortality. The analysis of RA patient registers showed an increase in mortality from cardiovascular and respiratory diseases, and the increase in the risk of mortality from respiratory diseases was not dependent on smoking [27, 28].

Often, RA patients do not receive sufficient treatment for comorbidities, and multi-morbid pathology can negatively affect the activity of RA [29]. At the same time, treatment with biological agents in these patients is often delayed, despite the available indications for their administration [30]. Inadequate treatment of RA, in turn, can contribute to the progression of comorbidity, while active treatment of RA can provide its improvement [31, 32]. It should be noted that the recommendations for treatment to target are based on materials that have been obtained in clinical trials, which included patients without significant concomitant disorders, so the effect of multi-morbidity was not taken into account. This greatly limits the possibility of using the available recommendations in real clinical practice, where doctors have to treat multimorbid patients. Further studies are needed to assess the possibilities of modern antirheumatic therapy in such patients.

An increase in the number of comorbidities is associated with an increase of RD activity. In the management of multimorbid patients, the recommended treatment goal of remission or low activity is much less likely to be achieved. Even after adjusting for such significant factors as age, duration of the disease, the number of DMARD used, the probability of achieving remission a year after the initiation of DMARD in multimorbid patients was 28% lower than in the absence of comorbidity [33,34]. This decrease may be due to the interaction of comorbidities, the administration of a large number of drugs or insufficient treatment of comorbidities.

It should also be noted that the presence of multimorbidity can cause a significant distortion of the result of inflammatory activity assessment. Traditionally, when determining the activity of RD, a complex of factors is used, which includes signs that are detected during an objective examination of the patient, during laboratory research, as well as parameters that are evaluated by the patient himself, such as the global patient assessment (GPA), which is used in the calculation of all main activity indices. Multimorbidity can have a great influence on the value of the parameters determined by the patient. Thus, with an increase of the number of comorbidities in RA patients, there is an almost linear increase of GPA, independent of the severity of the disease [35].

Multimorbidity also has a negative impact on the outcome of the assessment of health-related quality of life, and functional status, independent of the activity of the disease. Even in RA patients in remission, multimorbidity has a significant negative impact on status assessment [36-38]. In population studies, it was shown that the negative impact of multimorbidity on the result of determining the function and quality of life is greatest in patients with RD. Therefore, the study of the effect of multimorbidity in RD is an extremely urgent task.

There are no generally accepted ways to assess it today, and when choosing a research method, first of all, it is necessary to decide what specific diseases will be evaluated. You can take into account all the diseases available to the patient or only a select few. If only selected nosologies are registered, it is necessary to clarify the selection criteria and the list of these diseases. In addition, different diseases can be considered equivalent or ranked by importance. For example, the presence of cataracts and cardiovascular disease will affect the prognosis differently. The question of determining the severity of comorbidities is also of great importance, since more and less severe variants can change the status of the patient to different degrees.

The most accessible way to assess multi-morbidity is a simple calculation of existing diseases. This is generally an acceptable method, but it does not differentiate diseases by significance. To overcome this drawback, several indexes have been developed. Each of them is a total indicator determined by the results of the assessment of a predetermined range of diseases that may be ranked or not ranked in importance. There are quite a few similar indices developed on different populations of patients and focused on the assessment of different parameters. Indices also differ in the number of diseases that are taken into account in their calculation.

The most studied are indices that have been used for a long time. Thus, the Charlson comorbidity index (CCI) is widely used. It was developed to predict mortality during the first year of follow-up and was validated in a cohort of breast cancer patients [39]. CCI is calculated by evaluating 19 parameters (16 diseases, 3 of which are stratified in severity). Diseases are ranked by importance according to their degree of association with mortal-

ity. Despite the fact that the index was originally developed to predict mortality in clinical trials involving patients with breast cancer, it also allows predicting such parameters as hospital mortality, length of hospital stay, frequency of re-hospitalizations, use of health resources [40].

CCI has been used successfully to predict functional status, but it has not been validated for health-related quality of life (HQL). CCI has been used in rheumatology and it has been shown that multimorbidity in RA patients is associated with an increase in functional insufficiency [41]. CCI was a significant independent predictor of mortality in the cohorts of patients with osteoarthritis (OA) and RA [42]. It is widely used in clinical studies, but does not take into account such important for RD pathologies as hypertension, osteoporosis, OA, obesity, depression. Meanwhile, these diseases can significantly affect both the status of the patient and the result of assessment of inflammatory activity [43].

Of particular interest to rheumatologists may be the study of the effect of multimorbidity on functional status. The functional comorbidity index (FCI) has been developed as a tool to study this effect in the general population [44]. To calculate the index, 18 types of pathological changes are evaluated, including arthritis (RA and OA), osteoporosis, depression, anxiety, obesity, degenerative disc disease, etc. They are not ranked by significance. The index is the sum of 18 positive responses and ranges from 0 to 18. FCI can predict the dynamics of general health better than CCI and can serve as a good tool for predicting functional disorders, but is not a reliable predictor of mortality

Cumulative illness rating scale (CIRS) was created as a method of quantitative assessment of organ pathology [45]. The CIRS index is not based on the registration of any specific nosologies, but on the determination of the severity of the patient's disorders of 14 organ systems. For each of these systems, changes are scored from 0 to 4. The index is the sum of scores across all 14 systems. CIRS was a significant predictor of mortality, length of hospital stay, readmission, and functional failure [46, 47]. Fortin M. et al. who examined 238 adult patients with chronic diseases compared the results of multimorbidity assessment by CCI, FCI and CIRS with the HQL, which was determined by SF-36 [48]. CIRS explained the largest number of variations in SF-36 parameters. The authors believe that in works where HQL is of significant interest CIRS may be the best tool for assessing multi-morbidity. FIC adequately reflects the physical aspect of HQL and, considering the simplicity of its calculation, can also be applied in clinical trials. At the same time, FCI poorly correlated with SF-36 parameters and the authors do not recommend its use in studies related to the study of HQL.

In 2007, the first comorbidity index was developed in a cohort of patients with RA, OA, systemic lupus erythematosus (SLE) and fibromyalgia - rheumatic disease comorbidity index (RDCI) [49]. The basis for the development of RDCI were the data obtained by self-completion of appropriate questionnaires by patients. RDCI is calculated according to the results of the evaluation 11 related diseases, ranked according to their significance. When compared with other indices, it was shown that RDCI predicted mortality better than CCI and FCI, but FCI better reflected the functional status of the patient [50].

In 2015, the multimorbidity index (MMI) developed on a group of RA patients was proposed [51]. It includes 40 parameters as initial components. Two variants of MMI are available. The first is based on a simple calculation of existing diseases. When using the second option, nosologies are ranked by significance. Higher index values are associated with worse RA treatment outcomes [52]. MMI corresponded better to changes in EQ-5D parameters than CCI [51]. The ranked version of MMI correlated better with HQL than FCI and CCI. MMI based on a simple score performed worse, but still correlated better with HQL than CCI.

So far, there is no universal tool that would allow you to correctly evaluate all the parameters of interest. Therefore, the choice of the index depends largely on the objectives of the particular study. Thus, RDCI allows predicting satisfactorily several parameters, including mortality, need for hospitalization, disability and cost of medical care. At the same time, FCI is considered the best predictor of functional disorders. CIRS can better predict the changes of HQL than other tools. The experience of using indices developed specifically for RD is still small and older indices are often used in rheumatology.

It should be noted that no index can assess the impact of one disease on another. Meanwhile, for different nosologies, this effect can vary significantly. Thus, it has been shown that coronary heart disease, hyperlipidemia, diabetes mellitus, obesity are associated with RA activity signs to a greater extent than other concomitant diseases [53]. To date, the use of the index in the assessment of multimorbidity is not mandatory and is not proposed by official recommendations. Recently, EULAR experts have formulated the main provisions that should be taken into account in the diagnosis and prevention of selected types of comorbidities in patients with chronic inflammatory RD in everyday practice [54].

The authors believe that rheumatologists need to collect information about patients ' comorbidities, and in this work, in addition to the doctors, nurses and patients themselves can participate. A rheumatologist should not usually treat comorbid diseases, but he should interact with doctors of relevant specialties. Experts draw attention to the need for active detection of concomitant diseases, in connection with which every five years the patient must undergo a standard examination. They identify six most important for rheumatology classes of diseases. These included cardiovascular disorders, malignancies, infections, peptic ulcers, osteoporosis and depression.

The authors point out that when these diseases are detected, patients should be thoroughly examined and adequate therapy should be prescribed. It is also necessary to document anamnestic data about past relevant pathology, risk factors of these diseases, the results of screening examination performed to identify concomitant diseases, prescribed for them, drug therapy, and the patient vaccination. At the same time, the recently published EULAR recommendations for assessing the status of RA patients provide a simpler way to register comorbidities [55]. Their authors believe that only the presence or absence of the six EULAR domains mentioned above (cardiovascular disorders, malignancies, infections, peptic ulcers, osteoporosis and depression) should be documented.

Currently, multimorbidity is one of the most acute and least studied problems of rheumatology. The focus of modern medicine on the provision of highly specialized care certainly can significantly improve the effectiveness of treatment of patients with a single chronic disease. But the specialist often ignores problems beyond the scope of his specialty. At the same time, the division of diseases into main and concomitant ones leads to the fact that

the diagnosis of the latter is carried out late, their severity is underestimated, and the treatment is not adequate. The interpretation of several chronic diseases existing in one patient as equivalent within the framework of the concept of multimorbidity can contribute to a significant improvement in the quality of medical care due to the timely detection and adequate treatment of serious comorbidities developing in the patient. At the same time, the concept of multimorbidity itself also needs to be clarified, since not every concomitant disease can be recognized as equal in importance to chronic inflammatory RD. This is indicated by EULAR experts, who identified six most important classes of comorbidities for rheumatology

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Article received 06/20/2019