ORIGINAL INVESTIGATIONS

The incidence of type 2 diabetes mellitus and the traditional risk factors of carbohydrate metabolic disorders in patients with rheumatoid arthritis

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Objective: *to clarify the primary incidence of type 2 diabetes mellitus (DM) in patients with rheumatoid arthritis (RA) and to compare the prevalence of traditional risk factors (RFs) in groups of patients with and without carbohydrate metabolic disorders.*
Patients and methods. *A retrospective analysis was carried out in 158 patients with RA (diagnosed at the age of 45 years and older; the disease duration was more than 12 months). The exclusion criteria were concomitant type 1 DM and type 2 DM that was diagnosed before or at the onset of RA. The patients' median age was 62 [57; 68] years. Most RA patients had moderate (41.8%) and high (39.9%) DAS28. New cases of type 2 DM and the presence of hyperglycemia were recorded at the time of the examination. The traditional RFs of type 2 DM were assessed using the Finnish Diabetes Risk Score (FINDRISC).*
Results and discussion. *The incidence rates of type 2 DM was 9.3 per 1000 patient-years. The patients with developed type 2 DM versus those without DM had a larger number of RFs according to the the FINDRISC questionnaire (6 [5; 7] and 5 [4; 5]; $p<0.01$), had more frequently experienced myocardial infarction and undergone surgery for myocardial revascularization (27.3 and 2.7%; $p<0.01$), taken beta-adrenoblockers (72.7 and 33.3%; $p<0.05$) and calcium channel blockers (36.4 and 12.2%; $p<0.05$). Fasting hyperglycemia was detected in 10.1% of RA patients. The patients with hyperglycemia versus those with normal venous blood glucose levels more often had obesity (50.0 and 29.8%) and a history of hyperglycemic episodes (43.8 and 19.1%) and less frequently used glucocorticoids (18.8 and 47.3%; $p<0.05$ for all cases).*
Conclusion. *The high incidence of type 2 DM in RA was associated with the presence of a set of traditional RFs and previous cardiovascular disease, while fasting hyperglycemia was with individual RFs for carbohydrate metabolic disorders.*

Keywords: *rheumatoid arthritis; type 2 diabetes; hyperglycemia; risk factors.*
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Rheumatoid arthritis (RA) is an immuno-inflammatory (autoimmune) rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and systemic damage to internal organs, leading to early disability and shortened life expectancy of patients [1]. Cardiovascular complications remain the most common cause of mortality in RA, which attracted the attention of researchers to the study of risk factors (RFs) for their development, one of which is diabetes mellitus (DM).

According to the international registry _ORRONA (International Registry of Longitudinal Outcomes and Associated Cardiovascular Comorbidities in Patients with Rheumatoid Arthritis), the prevalence of DM in RA ranges from 8.4% in Latin America and the United States to 12.4% in Eastern Europe and 13.5% in India [2]. Given the age of patients included in the registry, it can be assumed that most of these cases of DM are type 2 DM, but it is unclear how often endocrine disease developed against the background of already existing RA, and did not precede it.

The aim of the study was to clarify the primary incidence of type 2 DM in patients with RA and to compare the prevalence of traditional RFs in groups of patients with and without carbohydrate metabolism disorders.

Patients and methods. A retrospective analysis of case histories of patients with RA hospitalized to V.A.Nasonova Research Institute of Rheumatology from March 1 to October 31, 2015 was carried out. The study protocol was approved by the local ethics committee, all patients signed informed consent. Inclusion criteria: reliable diagnosis of RA according to ACR / EULAR 2010 criteria [3], the age at the time of diagnosis of RA at least 45 years, the duration of RA at the time of the study more than 12 months. Exclusion criteria: concomitant type 1 DM, the diagnosis of type 2 DM, established before the onset of RA or at the same time.

The study included 158 patients with RA: 136 (86.1%) women and 22 (13.9%) men. The median age of the patients was 62 [57; 68] years. Most of the patients were seropositive for rheumatoid factor (81.6%) and antibodies to cyclic citrulline peptide (81.0%), had moderate (41.8%) and high (39.9%) RA activity according to DAS28 index. Seventy-seven patients (48.7%) received methotrexate; 41 patients (25.9%) – other disease-modifying antirheumatic drugs; 47 patients (29.7%) – biological agents; 69 patients (43.7%) – glucocorticoids (GC).

New cases of type 2 DM were registered with the appropriate diagnosis in the patient's medical documents in combination with the mandatory use of sugar-lowering drugs or persistent fasting hyperglycemia of ⩾7.0 mmol / L at the time of inclusion in the study. An increase in fasting glucose concentration ⩾6.1 mmol / L,

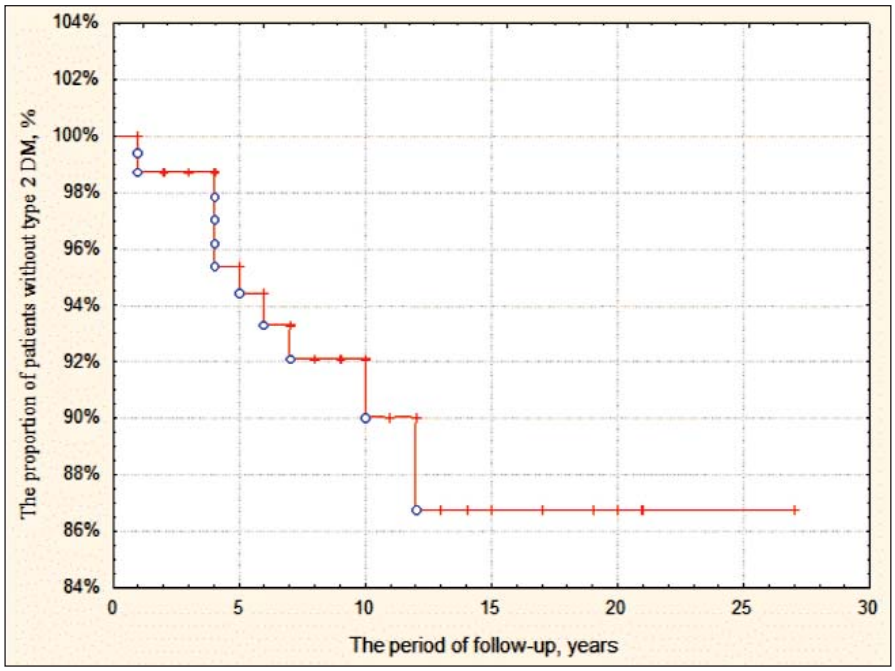

Figure 1. *Cumulative incidence of type 2 DM in patients with RA (Kaplan–Meier method)*

but <7.0 mmol / L in the absence of recorded DM diagnosis and / or specific therapy was considered as fasting hyperglycemia.

Traditional RFs of development of type 2 DM, such as age, increase in body mass index (BMI), abdominal obesity, family history, lack of physical activity, unbalanced diet, antihypertensive drugs, episodes of hyperglycemia in the past, were evaluated using a Finnish Type 2 Diabetes Risk Score (FINDRISK) questionnaire [4, 5]. The number of RFs also included male gender and administration of GC.

Statistical data processing was performed using the Statistica 6.0 program (StatSoft, USA); quantitative features were presented as median (Me) and interquartile range [25th; 75th percentile]. When comparing two independent groups by quantitative criteria, the Mann–Whitney and Kolmogorov–Smirnov criteria were used; for the qualitative criteria, χ^2 and the exact Fisher criterion were used. Differences were considered statistically significant at $p<0.05$. The Kaplan–Meier method was used to analyze the period of time until the event development (development of type 2 DM).

Results. The median duration of RA from the moment of diagnosis to inclusion in the study was 8 [3; 10] years, the total observation period of all patients was 1189 years. During this time, type 2 DM was detected in 11 (7.0%) patients, which corresponded to incidence – 9.3 cases per 1000 patient-years.

The median age of debut of type 2 DM was 57 [53; 62] years. The period from the establishment of a diagnosis of RA to the development of type 2 DM ranged from 1 to 12 years (median 4 [4; 7] years) (Figure 1).

For further analysis of traditional RFs, all patients were divided into two groups: the first group included patients with type 2 DM (n = 11), the second group included patients without DM (n = 147). At the time of inclusion in the study, the patients with type 2 DM were comparable in gender, age, duration and activity of RA, anti-inflammatory therapy, but had a greater number of RFs for the development of endocrine disease than patients without DM (Table 1).

There was a tendency to more frequent use of antihypertensive drugs by patients with a combination of RA and type 2 DM, while different groups of drugs were used with different frequencies: angiotensin converting enzyme inhibitors (ACE inhibitors) and sartans predominated in patients without DM, and beta- blockers (BB) in patients with type 2 DM (Table 2).

Myocardial infarction (MI) and associated revascularization operations (stenting of the coronary arteries, coronary artery bypass grafting) were noted in 3 (27.3%) patients with advanced type 2 DM and in 4 (2.7%) patients without DM (p = 0.008). Only 1 case of MI occurred against the background of already diagnosed RA. There were no differences in the frequency of acute cerebrovascular events (stroke) in RA patients with and without type 2 DM (Table 3).

Sixteen of 158 patients with RA (10.1%) had fasting hyperglycemia from 6.1 to 7.3 mmol / L. Patients in this group more often than patients with normal serum glucose (n = 131), had a history of obesity and episodes of hyperglycemia, and less often – history of taking GC; however, there were no differences in the total number of RFs for the development of type 2 DM per patient at the time of the examination (Table 4).

Discussion. In RA patients, the prevalence of type 2 DM exceeds population levels, which may be due to the accumulation of traditional RFs both before and during the illness, as well as exposure to RA-specific factors (e.g., inflammation) [6–8]. It should be kept in mind that the incidence of type 2 DM differs in different countries and regions due to genetic characteristics, traditional dietary preferences and lifestyle.

We calculated the incidence of type 2 DM in patients with RA over 45 years of age based on a retrospective analysis carried out in one center. It amounted to 9.3 cases per 1000 patient-years. For comparison: the officially registered incidence of type 2 DM in the Russian Federation from 2007 to 2017 did not exceed 2.4 cases per 1000 population per year [9].

Similar results were obtained in two large retrospective studies conducted in Canada and the UK [10,11]. In one of them, the incidence of type 2 DM in RA was 8.6 [10], in the other – 6.3 cases per 1000 patient-years [11]. In an Italian 12-month prospective study, type 2 DM developed in 7.1% of 439 RA patients [12]. It is worth noting that in all foreign cohorts, the average age of patients at the time of inclusion in the study was 3.5–4 years less than in the presented work; in addition, the analysis also included patients younger than 45 years old, which, of course, affected this index. So, in the study conducted by D.H.Solomon et al. [10], the incidence of type 2 DM in patients with RA under the age of 45 years was significantly lower than at the age of 45–64 years (3.4 and 9.1 cases per 1000 patient-years, respectively), and gradually increased with age.

In our patients, type 2 DM was diagnosed mainly at the age of 57, which is also characteristic of the Russian population as a whole [9]. Half of the cases of type 2 DM developed in the first 4

years after the onset of RA, and after 10 years, 10% of patients remaining under observation had this disease. In another 10% of patients with RA aged 45 years and older, the examination revealed an increase in fasting glucose in the venous blood, but the criteria necessary to establish a diagnosis of type 2 DM were absent. Interestingly, GC were less commonly prescribed to such patients, possibly due to past episodes of hyperglycemia and obesity.

In the previous studies [11,12], the most significant RFs for developing type 2 DM in RA, in addition to age, were male gender, systemic use of GC, obesity, arterial hypertension, and other comorbid diseases. We did not reveal differences in gender, drug anti-inflammatory therapy, and individual traditional RFs in patients with type 2 DM and without it, with the exception of a history of hyperglycemia, as well as a tendency to more frequent use of antihypertensive drugs, which can be considered a kind of surrogate marker for the presence of arterial hypertension. At the same time, it should be remembered that some drugs, such as BB, themselves have the ability to negatively affect carbohydrate metabolism. In our study, patients with type 2 DM, when admitted to hospital, used BB more often than patients without DM, moreover, drugs of other groups were prescribed to them much less often. This demonstrates underestimation of adverse drug reactions by primary care physicians and stresses the need for a personalized approach to the choice of not only anti-inflammatory, but also concomitant therapy. At the same time, more frequent use of calcium channel blockers in some patients with type 2 DM can be regarded as an attempt of such an individual approach.

Table 1. RFs for the development of type 2 DM in patients with RA, n (%)

Risk Factors	RA + type 2 DM (n=11)	RA without DM (n=147)
Male gender	1 (9.5)	21 (14.3)
GC	4 (36.4)	65 (44.2)
BMI, kg/m^2:		
25,0–29,9	4 (36.4)	56 (38.1)
≥30	3 (27.3)	47 (32.0)
Waist circumference, cm:		
80–88 (for women)/94–102 (for men)	4 (36.4)	20 (13.6)
>88 (for women)/>102 (for men)	6 (54.5)	99 (67.3)
Age at the time of the study, years:		
45–54	2 (18.2)	28 (19.0)
55–64	5 (45.4)	61 (41.5)
≥65	4 (36.4)	58 (39.5)
DM in relatives:		
first line	1 (9.1)	9 (6.1)
second line	3 (27.3)	22 (15.0)
Physical inactivity	9 (81.8)	100 (68.0)
Unbalanced diet	3 (27.3)	65 (44.2)
Use of antihypertensive drugs	10 (90.9)$^{\#}$	86 (58.5)
History of hyperglycemia	11 (100)*	32 (21.8)
Number of RFs for FINDRISK questionnaire $^{\#\#}$	6 [5; 7]*	5 [4; 5]
Total score for FINDRISK questionnaire $^{\#\#}$	19 [15; 20]*	13 [10; 15]

Note: * – p<0,01; $^{\#}$ – p=0,051. $^{\#\#}$ – Me [25th; 75th percentile].

The total score and the number of RFs for the FINDRISK questionnaire turned out to be higher in patients with DM, that

Table 2. Groups of antihypertensive drugs used by patients with RA, n (%)

Groups of antihypertensive drugs	RA + type 2 DM (n=11)	RA without DM (n=147)
BB	8 (72.7)*	49 (33.3)
ACE inhibitors and sartans	6 (54.5)	53 (36.1)
Calcium channel blockers	4 (36.4)*	18 (12.2)
Diuretics	2 (18.2)	20 (13.6)

Note. Here and in Table 3, 4: * – p<0,05.

Table 3. The frequency of cardiovascular complications, n (%)

Cardiovascular complications	RA + type 2 DM (n=11)	RA without DM (n=147)
MI, *including* before or at the same time as the diagnosis of RA	3 (27.3)* 2 (18.2)*	2 (1.4) 2 (1.4)
Myocardial revascularization operations without MI	0	2 (0.6)
Stroke	0	4 (2.7)

Table 4. RFs for the development of type 2 DM in RA patients with fasting hyperglycemia and with normal glucose levels, n (%)

Risk factors	RA patients with normal glucose levels (n=131)	RA patients with fasting hyperglycemia without type 2 DM (n=16)
Male gender	17 (13.0)	4 (25.0)
GC	62 (47.3)*	3 (18.8)
BMI, kg/m^2: 25,0–29,9 ≥30	 48 (36.6) 39 (29.8)*	 8 (50.0) 47 (50.0)
Waist circumference, cm: 80–88 (for women)/94–102 (for men) >88 (for women)/>102 (for men)	 20 (15.3) 83 (63.4)*	 0 16 (100)
Age at the time of the study, years: 45–54 55–64 ≥65	 27 (20.6) 51 (38.9) 53 (40.5)	 1 (6.3) 10 (62.5) 5 (31.3)
DM in relatives: first line second line	 9 (6.9) 19 (14.5)	 0 3 (18.8)
Physical inactivity	90 (68.7)	10 (62.5)
Unbalanced diet	57 (43.5)	8 (50.0)
Use of antihypertensive drugs	78 (59.5)	8 (50.0)
History of hyperglycemia	25 (19.1)*	7 (43.8)
Number of RFs for FINDRISK questionnaire #	5 [4; 5]	5 [5; 6]
Total score for FINDRISK questionnaire #	13 [10; 15]	16 [12; 18]

Note. # – Me [25th; 75th percentile].

is, the combination of traditional RFs had the greatest impact. In addition, patients with type 2 DM were more likely to have a previous MI, but not stroke. One possible explanation is that it is MI that is associated with metabolic syndrome, which also represents a certain combination of RFs common to both cardiovascular diseases and carbohydrate metabolism disorders [13].

In patients with fasting hyperglycemia, but without DM, individual RFs were of greatest importance, especially the history of hyperglycemia and obesity, due to which they had higher scores on the FINDRISK questionnaire. However, the number of RFs in patients with hyperglycemia and with a normal concentration of glucose in the venous blood was similar.

The retrospective design of the study does not preclude the loss of a certain number of new cases of type 2 DM, and does not allow to fully appreciate the significance of the above-mentioned factors, primarily the influence of drugs, which requires further research.

Conclusion. Thus, according to our retrospective analysis, type 2 DM developed in 7% of RA patients 45 years of age and older, which corresponded to the incidence rate – 9.3 cases per 1000 patient-years. A high incidence of type 2 DM in RA was associated with a complex of traditional RFs and previous cardiovascular pathology, while fasting hyperglycemia was associated with certain risk factors for carbohydrate metabolism disorders.

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