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DIABETES MELLITUS AND HYPERGLYCEMIA IN PATIENTS WITH RHEUMATOID ARTHRITIS

Ergashova Madina Muxtorovna
Shichenko Olga Alexandrovna
Samarkand State Medical University, Samarkand, Uzbekistan

Abstract
Proinflammatory cytokines involved in the pathogenesis of rheumatoid arthritis (RA) can inhibit insulin production and cause insulin resistance in peripheral tissues. It is possible that with RA, the risk of developing disorders of carbohydrate metabolism (DCM) increases: diabetes mellitus (DM), fasting hyperglycemia (FH), impaired glucose tolerance. Patients with a combination of RA and DM belong to the category of the most severe patients with an unfavorable prognosis of macro- and microvascular complications.
The aim of the study was to evaluate the frequency of NUO (DM and GN) in a cohort of patients with RA and their possible effect on the course of arthritis.
Material and methods. The study included 165 patients (28 men, 137 women), with an average age of 55 [47; 61] years. 86.3% of patients were seropositive for rheumatoid factor, 78.8% for antibodies to cyclic citrullinated peptide. RA activity was low in 29.1% of patients, moderate – in 48.5%, high – in 22.4%. Glucocorticoids (HA) were received by 40.6% of patients (at an average dose of 5 [5; 7.5] mg / day), methotrexate – 72.7%, leflunomide 8.5%, genetically engineered biological drugs – 23.7%. A survey of patients was conducted to identify awareness of the presence of NUO and a study of fasting glucose levels in venous plasma for screening hyperglycemia. The height and body weight of the patients were measured, and the body mass index (BMI) was calculated.
The results of the study. NUO was present in 21 (12.7%) of 165 patients with RA. Only 11 (6.7%) of 165 patients with RA knew about the presence of DM in them (2 cases of type 1 diabetes, 9 cases of type 2 diabetes), in the remaining 10 patients with NUO (8 patients with GN, 2 patients with type 2 diabetes) were detected during laboratory examination. Patients with DM and GN had a large number of painful joints (CHBS), more high assessment of the patient's general health status (OED) and DAS28 than patients with normoglycemia, but they did not differ in the duration of RA, the level of acute phase parameters (ESR, CRP), and the number of swollen joints. Overweight was observed in 57 (34.5%), obesity in 39 (23.6%) patients. Against the background of taking HA, glucose levels were lower (5.1 [4.7; 5.5]) than in patients without GC therapy (5.4 [5.0; 5.9] mmol/L, p=0.001), and correlated with BMI (r=0.3, p=0.01).
Conclusion. The high frequency of DM and GN in RA, low awareness of patients about them, as well as the relationship have been demonstrated NUO with the activity of arthritis, mainly due to changes in subjective indicators (OOZP, BBS). Blood glucose levels in RA may be affected by taking GC and BMI.

Keywords: rheumatoid arthritis, disorders of carbohydrate metabolism, diabetes mellitus, fasting hyperglycemia, body mass index.

Introduction

The problem of rheumatoid arthritis (RA) is gaining general medical importance, since it creates prerequisites for improving the pharmacotherapy of other chronic diseases such as atherosclerosis, diabetes mellitus Type 2 (DM), osteoporosis, the development of which is also associated with chronic inflammation. The study of the pathogenesis of RA has revealed numerous "non-rheumatological" functions of proinflammatory cytokines, for example , the ability to interfere with various stages of metabolism glucose. It has been shown that tumor necrosis factor (TNF) α and interleukin (IL) 6 disrupts the synthesis and operation of insulin receptors and intracellular glucose transporter in muscles, adipose tissue, liver, along with IL1ß inhibit insulin secretion, cause apoptosis of beta cells of islets Langerhans of the pancreas. RA can be considered as a model for the study of disorders of carbohydrate metabolism (NUO). Several studies in RA patients have demonstrated a decrease in the level of functional capabilities of β-cells and an increase in insulin resistance of peripheral tissues. The mutual potentiation of inflammation and NUO (imbalance of glucose metabolism) is trying to explain that the combination of two diseases (RA and DM) to a greater extent than isolated RA or DM increases the risk of coronary heart disease, myocardial infarction, stroke,

heart failure, chronic kidney disease, dyslipidemia, lower limb ulcers, retinopathy and lesions of peripheral arteries. The progression of macro- and microvascular complications, in turn, aggravates the course of the main diseases, reduces the quality of It complicates the use of drug therapy and non-pharmacological methods, significantly increases the cost of treatment. All this makes it possible to single out patients with a combination of RA and NUO in a special group of the most severe patients with an unfavorable prognosis. However , information on the frequency of DM and other NWS in RA patients in the literature is extremely scarce and contradictory. The purpose of our study is to estimate the frequency

NUO (DM and fasting hyperglycemia – GN) in a cohort of patients with RA and their possible effect on the course of arthritis.

MATERIALS AND METHODS OF RESEARCH

The study included 165 patients (28 men, 137 women), with an average age of 55

[47;61] years old with a diagnosis of RA according to the criteria of the American College of Rheumatology (ACR), who signed an informed consent. The exclusion criteria were the age under 18 and over 85 years old, functional class IV (FC) according to the ACR classification. The standard clinical examination included counting the number of painful (CHBs) and swollen (CHPS) joints, assessment of the patient's general health (OOZ) on a visual analog scale, determination of the level of CRP, IgM rheumatoid factor (RF) by immunonephelometric method (BN Prospect, Siemens, Germany) and concentration of antibodies to cyclic citrullinated peptide (ADCP) by enzyme immunoassay (Axis-Shield Diagnostics, Great Britain), radiography of hands and feet. RA activity was assessed using the DAS28 index. Characteristics of patients and therapy with glucocorticoids (HA), basic anti-inflammatory drugs at the time of inclusion in the study (HDL) and genetically engineered basic drugs (GIBP). A survey of patients was conducted to identify awareness of the presence of NUO and a study of fasting glucose levels in venous plasma for screening hyperglycemia. According to the currently accepted WHO criteria, glucose levels <6.1 mmol/l were regarded as normal, ≥7.0 mmol/l as DM, intermediate results (≥6.1 and <7.0 mmol/l) as GN. The height and body weight of the patients were measured, and the body mass

index (BMI) was calculated using the formula: BMI= body weight (kg)/height (m)2. BMI <18.5kg/m2 corresponded to a body weight deficit, from 18.5 to 24.9 kg/m2 – normal, from 25 to 29.9 kg/m2 – overweight, and ≥ 30 kg/m2 – obesity.

Statistical data processing was carried out on a personal computer using the methods of parametric and nonparametric statistics (program Statistica 8.0, StatSoft.Inc., USA). The variables are presented as a median (Me) indicating the upper and lower quartiles [25th; 75th percentile]. The reliability of the differences between the three unrelated groups was assessed using the Kraskel – Wallace test, between the two unrelated groups using the Mann – Whitney and $\chi 2$ criteria

The relationship of the features was determined using Spearman's rank correlation criterion (r). The statistical significance of the indicators was determined as $p<0.05$.

THE RESULTS AND THEIR DISCUSSION

According to the survey, 11 out of 165 patients with RA (6.7%) knew they had diabetes. In 2 cases, we were talking about type 1 diabetes, which debuted 14 and 18 years before the onset of RA symptoms. 9 patients had type 2 diabetes, which developed on average at the age of 51 [45; 53] years. In most cases, the diagnosis of type 2 diabetes was established through 2-14 years after the diagnosis of RA, in 1 patient both diseases manifested simultaneously, in another 1 case type 2 diabetes was 28 years earlier than the appearance of arthritis. 9 out of 11 patients received antidiabetic drugs: insulin – 2 patients with type 1 diabetes, metformin – 5, derivatives sulfonylurea – 2, dipeptilpeptidase inhibitor 4 – 1 patient with type 2 diabetes. 154 patients indicated the absence of NUO, but 10 ((6.5%) of them, the concentration of glucose in blood plasma exceeded 6.1 mmol/l: in 8 patients, the glucose level corresponded to the GH gradation, in 2 more patients with glucose levels 7.27 and 7.3 mmol/l could be suspected of newly detected type 2 diabetes. Thus, in total, 21 (12.7%) of 165 patients with RA had different types of NUO during the survey and screening laboratory examination. Patients with GN turned out to be older (60 [55; 68] years old) than patients with DM (55 [54; 62] years old) and with normal glucose levels (55 [46; 60] years old), although age differences were not significant (p=0.056), possibly due to the small number of participants in the group. Patients with previously established DM, GN and normoglycemia did not differ in the duration of RA (p=0.21), the level of ESR (p=0.84), CRP (p=0.53), NPV (p=0.41). However, the patients people with diabetes assessed their condition as more severe (OOZP 60[40; 75] mm), than patients with GN (GN 45 [30; 70] mm) and normal glucose levels (GN 40 [20; 50] mm, p=0.05). In addition, patients with impaired carbohydrate metabolism had a greater BBS: with SD – 9 [6;15], with GN – 15 [6; 19], with normoglycemia – 4 [2; 7] and greater activity RA according to the DAS28 index: 4.8 [3.8; 6.0], 4.6
[4.0; 5.9] and 3.9 [3.0; 4.9] points, respectively (p=0.02). Body weight deficiency was observed in 6 (3.6%) patients, 63 (38.3%) had normal body weight, 57 (34.5%) overweight, 39 (23.6%) obese. BMI did not differ in the groups of patients with DM, GN and normoglycemia (p=0.14). In patients taking GC, the level of fasting glycemia was lower (5.1 [4.7; 5.5] mol/l) than in patients without GC (5.4 [5.0; 5.9] mmol/l, p = 0.001), and the effect on glucose concentration was not the dose of the drug (r = 0.008, p = 0.95), but BMI (r=0,3, p=0,01). In patients who did not receive HA, there was no such correlation between BMI and glucose levels (r=0.16, p=0.12).

Currently, the prevalence of diabetes is so high that they are increasingly talking about a "new pandemic", and along with obesity and hereditary predisposition, autoimmune reactions and inflammation are mentioned as possible causes. According to the circulation, it was registered 3

million 357 thousand patients with diabetes, of which 90% are patients with type 2 diabetes. An even larger number of people have other types of NUO (GN and impaired glucose tolerance) – potentially reversible "prediabetes" conditions, often associated with obesity. There is increasing evidence of the involvement of proinflammatory cytokines in the pathogenesis of NUO, which makes it relevant to study this condition in patients with RA, which is a classic model of chronic autoimmune inflammation.

Survey data and such a simple and widely available A laboratory examination method, such as the determination of fasting glucose levels in venous plasma, allowed us to identify DM or GN in every 8th patient. In different cohorts of RA patients, the prevalence of DM ranges from 7 to 17% [12-15]. It should be noted that in studies, as a rule, only cases of diabetes are taken into account Type 2, which the patients themselves know about (the so-called self-reported), or information is taken from electronic medical databases with diagnosis codes, and type 1 diabetes is an exclusion criterion and is not taken into account. About the availability of SD (both type 1 and type 2) 6.7% of RA patients reported.

Often, the absence of vivid symptoms leads to the fact that a person does not suspect for a long time about the presence of NUO, therefore, in population epidemiological studies, the prevalence of DM exceeds the registered one by 2-3 times. We also encountered 2 patients with previously undiagnosed type 2 diabetes. In addition, 8 patients with GN were identified during laboratory examination. Thus, the frequency of NUO in our cohort increased to 12.7%.

Slightly higher prevalence of DM and GN demonstrated by J. Primdahl et al., who studied risk factors for cardiovascular diseases in RA: 9% had DM, 14.3% of patients had GN. Perhaps the differences are related to the peculiarities of cohort formation and methodology: in the Danish study, patients were about 9 years older and were more likely to be overweight and obese, while fasting glucose levels corresponded to GN ≥6.0 mmol/l, not ≥6.1 mmol/L, as in our work.

CONCLUSIONS

In our work, the intake of HA was not associated with the presence of DM or GN, and the level of glycemia was higher in patients who did not receive these drugs. Similar results were demonstrated by M.G. Burt et al. in patients with various rheumatic diseases on the background of long-term HA therapy. This fact can be explained by the increased synthesis and basal secretion of insulin under the action of HA, which was observed by D. Den Uyl et al. with short-term administration of high doses of prednisone. Although they were overweight and obese In 58.1% of patients in our cohort, we noted a correlation between BMI and glucose concentration only in the case of taking HA, which seems to be associated with a combined decrease in peripheral tissue sensitivity to insulin and an aggravation of insulin resistance. Previously, an increase in the index was shown in RA HOMA-IR, reflecting insulin resistance, and its relationship with levels of proinflammatory cytokines (TNFa and IL6), acute phase parameters (ESR, CRP), RA activity (according to DAS28) and functional disorders. However, there is practically no information about the influence of NUO on RA in the literature. In our study, patients with NUO assessed their condition as more severe and had a greater BBS. This change in subjective indicators led to an increase in DAS28, although ESR, CRP, NPV in the presence of DM, GN and normoglycemia did not differ significantly. Rheumatologists should definitely take this fact into account when evaluating the activity of RA in patients with NUO. Thus, our study demonstrated a high incidence of DM and GN in RA

patients and the relationship NUO with the activity of arthritis, mainly due to changes in subjective indicators (OOZP, CBP). BMI it correlated with the presence of NUO only in patients taking GC.

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