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Diabetes Mellitus and Hyperglycemia in Patients with Rheumatoid Arthritis

Khusainova Munira Alisherovna
Toirov Doston Rustamovich
Uzokov Jurabek Baxtiyorovich
Sayfulloyeva Marjona Sobirovna
Samarkand State Medical University

Abstract: Proinflammatory cytokines involved in the pathogenesis of rheumatoid arthritis (RA) can inhibit insulin production and cause insulin resistance of peripheral tissues. Perhaps, with RA, the risk of developing disorders of carbohydrate metabolism (NUO) increases: diabetes mellitus (DM), fasting hyperglycemia (GN), glucose tolerance disorders. 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 problem of rheumatoid arthritis (RA) is becoming of general medical importance, since it creates prerequisites for improving the pharmacotherapy of other chronic diseases, such as atherosclerosis, diabetes mellitus (DM) type 2, 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 disrupt the synthesis and functioning 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 studying 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. Rheumatoid arthritis (RA) is an immuno-inflammatory disease characterized by chronic erosive arthritis and systemic damage to internal organs, which leads to an increased risk of concomitant pathology, early disability and a decrease in the life expectancy of patients.

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

Introduction

Systemic therapy with glucocorticoids (GC) leads to an increase in the number of cases of DM and other disorders of carbon- water metabolism in RA patients. The use of HA makes a significant contribution to the development of hyperglycemia due not only to the activation of gluconeogenesis, but also to the formation of insulin resistance. The development of CISD in some studies was associated with the presence of risk factors (FR) of DM Type 2 in patients who received oral GC. As the dose and duration of Gcs therapy increase, the number of cases of SIDS increases significantly. Other studies, on the contrary, did not reveal an increase in the prevalence of DM in RA patients on the background of GC therapy and did not prove the association of RA with any type of DM. 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 major diseases, reduces the quality of life of patients, complicates the use of drug therapy and non-pharmacological methods, significantly increases the cost of treatment. All this makes it possible to distinguish patients with a combination of RA and NUO into a special group of the most severe patients with an unfavorable prognosis. However, information about the frequency of DM and other NUOS in RA patients in the literature is extremely scarce and contradictory. Hyperglycemia itself provokes intracellular edema, which leads to a violation of the redox balance, an imbalance in the synthesis of components in the

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extracellular matrix by fibroblasts. But, according to modern concepts, tissue damage in DM is largely explained by the excessive formation of glycation end products (CNG). Normally, the synthesis of CNG is quite slow at a constant rate and accumulation in the body occurs gradually, but under conditions of hyperglycemia, the process accelerates. Great attention is traditionally paid to cardiovascular complications, nephropathy, retinopathy and neuropathy in DM, as they are the main causes of disability and death. However with prolonged and/or severe course of DM, other organs may also be affected, including the musculoskeletal system, which forces patients to seek help from a rheumatologist, who should be informed about various rheumatic manifestations of DM.

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.

Material And Methods

The study included 33patients (6 men, 27 women), the average age was 55 [47;61] years old with a diagnosis of RA according to the criteria of the American College of Rheumatology (ACR) in 1987, 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 (OOZP) 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 (ADC) by enzyme immunoassay (Axis-Shield Diagnostics, UK), radiography of hands and feet. RA activity was assessed using the DAS28 index. Characteristics of patients and therapy with glucocorticoids (GC), basic anti-inflammatory drugs at the time of inclusion in the study (BPVP) and genetically engineered basic drugs (GIBP) is presented in the table. A survey of patients was conducted to identify awareness of the presence of NUO in them and a study of fasting glucose levels in venous plasma for screening hyperglycemia. According to the currently accepted WHO criteria, the glucose level <6.1 mmol/l was 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, the body mass index (BMI) was calculated using the formula: BMI= body weight (kg)/height $(m)^2$. BMI <18.5kg/m2 corresponded to body weight deficiency, from 18.5 to 24.9 kg /m^2 – normal, from 25 to 29.9 kg /m^2 – overweight, and ≥ 30 kg/m^2 – 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 χ^2 criteria ; correlation of features – using Spearman's rank correlation criterion (r). The statistical significance of the indicators was determined as $p<0.05$.

Results

According to the survey, 2 out of 33 patients with RA (6.7%) knew about the presence of DM in them. In 2 cases, we were talking about type 1 diabetes, which debuted 14 and 18 years before the onset of RA symptoms. 2 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 1 case type 2 diabetes preceded the appearance of arthritis by 28 years. 2 out of 3 patients received antidiabetic drugs: insulin – 2 patients with type 1 diabetes, metformin - 5, sulfonylurea derivatives – 2, dipeptilpeptidase inhibitor 4 – 1 patient with type 2 diabetes. 33 patients indicated the absence of NUO, but 10 ((6.5%) of them, the concentration of glucose in blood plasma exceeds 6.1 mmol/l: in 8 patients, the glucose level corresponded to the GN gradation, in 2 more patients with glucose levels of 7.27 and 7.3 mmol/l, it was possible to suspect the newly detected type 2 diabetes. Thus, in total, 21 (12.7%) of 33 patients with RA had different types of NO during the survey and screening laboratory examination. Patients with GN were older (60 [55; 68] years) than patients with DM (55 [54; 62] years) and with normal glucose levels (55 [46; 60] years), although age differences were not significant (p=0.056), possibly due tofor a small number of participants in the group. Patients with previously

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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, patients with DM assessed their condition as more severe (OOZP 60 [40; 75] mm) than patients with GN (OOZP 45 [30; 70] mm) and normal glucose levels (OOZP 40 [20; 50] mm, p=0.05). In addition, patients with impaired carbohydrate metabolism had a greater BBS: with DM – 9 [6;15], with GN – 15 [6; 19], with normoglycemia – 4 [2; 7] and greater RA activity 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%) had excess body weight, 39 (23.6%) were 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). There was no such correlation between BMI and glucose levels in patients who did not receive GC (r=0.16, p=0.12).

Discussion

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 State Register of Diabetes, as of 1.01.2011, 3 million 357 thousand patients with diabetes were registered in Russia, 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 conditions of "prediabetes", often associated with obesity. There is more and more 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.

The survey data and such a simple and widely available laboratory method of examination 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 The SD ranges from 7 to 17%. It should be noted that in studies, as a rule, only cases of DM 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. The presence of DM (both type 1 and type 2) was reported by 6.7% of RA patients. 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%. A slightly higher prevalence of DM and GN was demonstrated by J. Primdahl et al. , 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 GN corresponded to fasting glucose levels≥6.0 mmol/l, not ≥6.1 mmol/l, as in our work.

In a study by J.N. Hoes et al. In which an oral glucose tolerance test was used for the diagnosis of the NUO, not the determination of glucose levels in fasting blood plasma, but an oral glucose tolerance test, 19% of patients with type 2 diabetes and 35% of patients with GN and impaired glucose tolerance were found. High cumulative and daily doses of HA were associated with the development of type 2 diabetes, however, taking into account a number of factors, including current RA activity (according to DAS28), BMI, gender and age, duration of the disease, the correlation for the total dose decreased, and disappeared for the daily dose. According to the authors, the main mechanism of the effect of HA on carbohydrate metabolism is associated with increased insulin resistance of tissues.

According to J.Al-Bishri et al., patients with RA without DM received prednisone less frequently than patients with a combination of the two diseases. Interestingly, the use of GC in this cohort was massive (prednisone was taken by 81% of the study participants), which apparently led to an unprecedented high incidence of DM (30.9%). In our work, the intake of GC was not associated with the presence of DM or GN, and the level of glycemia was higher in patients, who have not received these drugs. Similar results were

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demonstrated by M.G. Burt et al. in patients with various rheumatic diseases on the background of long-term therapy of GC. 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 overweight and obesity had 58.1% of patients in our cohort, we noted a correlation between BMI and glucose concentration only in the case of taking GC, which is apparently associated with a combined decrease in the sensitivity of peripheral tissues 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 the levels of proinflammatory cytokines (TNFa and IL6), acute phase indicators (ESR, CRP), RA activity (according to DAS28) and functional disorders.However, there is practically no information about the influence of NGOs on RA in the literature. NGOs in the RA are practically absent in the literature. In our study, patients with NUO assessed their condition as more severe, had a greater CHBS. This change in subjective indicators led to an increase in DAS28, although ESR, DRR, NPV at the presence of DM, GN and normoglycemia did not significantly differ. This fact should be taken into account by rheumatologists when assessing the activity of RA in patients with NUO. Thus, our study demonstrated a high frequency of DM and GN in RA patients and the relationship BUT with the activity of arthritis, mainly due to changes in subjective indicators (OSP, CBP). BMI correlated with the presence of NUO only in patients taking GC.

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