

ASSOCIATION BETWEEN TYPE 2 DIABETES AND SERONEGATIVE REUMATOID ARTHRITIS

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The rheumatoid arthritis (RA) is a chronic disease characterized by systemic inflammation and persistent synovitis. The association between type 2 diabetes mellitus (T2DM) and RA can be partially explained by the inflammatory process that occurs in both conditions. We describe the clinical case of 53-years old caucasian men diagnosed with T2DM in 2013 and seronegative RA during the same year. The family history of the patient is negative for RA but positive for diabetes, past medical history includes hypertension, dyslipidemia, obesity. The patient is also an active smoker. The majority of patients with RA are young or middle aged women but the disease can occur at any age and gender. There is an influence of gender in this disease—the women report more numerous and intense symptoms than men, but increased treatment responses and remission rates occur in male patients. The patient is an active smoker and previous studies have highlighted that smoking is a consistent predictor of RA in males. The association between these two diseases was found to be strongest for patients with the shortest time interval between the diagnosis of both diabetes and RA. Association between RA and diabetes in men is a relatively rare condition. With the recommended treatment the evolution was favourable for both diseases. The short time interval between the onset of these two diseases suggests that T2DM and RA are related.

Keywords: diabetes, rheumatoid arthritis, smoking, gender.

INTRODUCTION

The RA is a chronic disease characterized by systemic inflammation and persistent synovitis. The disease is typical in women and the prevalence varies between 0.5% and 1%¹. Epidemiological studies demonstrated the presence of inflammation in T2DM and obesity^{2,3,4}. Biomarkers of inflammation such as tumor necrosis α , interleukin-6, C reactive protein are according to the results of several studies elevated in T2DM as well in preclinical phase of RA^{5,6}. The association between T2DM and RA can be partially explained by the inflammatory process that characterizes both conditions. Smoking can generate the alteration of the cytokine and modifications of autoantigenes and may be involved in development of RA⁷.

CASE REPORT

A 53-year-old caucasian men diagnosed with T2DM in 2013 and seronegative RA during the same year was hospitalized in the Clinical Hospital “Dr. I. Cantacuzino” Bucharest for clinical and biological evaluation. The symptoms of RA started in 2013 with fever, painful swelling and erythema in the ankles and finger 1 of right hand. Biological evaluation revealed leukocytosis, significant inflammatory syndrome, normal uric acid. The results were negative for rheumatoid factor, blood cultures, anti-cyclic citrullinated peptide (CCP) antibodies and human leukocyte antigen (HLA) B27. Initially the diagnosis was acute infectious oligoarthritis complicated with gout arthropathy for which antibiotics, glucocorticoids and uric acid lowering therapy was initiated. After the above-mentioned treatment, the symptoms did not

improve by persisting joint swelling and inflammatory biological syndrome. Furthermore, the antibodies anti-double-stranded deoxyribonucleic acid, anti-cardiolipin, antinuclear, anti-Sjögren's-syndrome-related antigen A, also called anti-Ro, anti Shigella, anti Yersinia, anti Samonella, anti Borelia were also negative. The musculoskeletal ultrasound of the antepicior revealed second grade synovial proliferation in the talo-navicular and naviculo-cuneiform joints. The diagnosis of seronegative RA was established and treatment with methotrexate 15mg/ week and sulfasalazine 3 gr/day was initiated. The patient showed a favourable evolution without hip or joint swelling. The family history is negative for RA but positive for diabetes, past medical history includes hypertension, dyslipidemia, T2DM, obesity, social history-active smoker. Clinical examination: height 174 cm, weight 102 kg, normal skin and mucous membranes without palpable superficial adenopathies, normokinetic, normotone muscular system, no articular swelling, bilateral vesicular murmur, no rallies, blood pressure 120/60 mmHg, heart rate 78 beats per minute, abdomen increased in volume through excess fat, liver with the lower rim at the rebord, non-palpable spleen, bilateral Giordano test-negative. Laboratory analysis outside the reference range: glucose 164 mg/dl, alanine aminotransferase 46.07 UI/l. The right ankle musculoskeletal ultrasound did not reveal synovial proliferation. There have been observed complex modifications-erosions, synovial proliferation in the metatarsalphalangeal joint I.

T2DM diagnosis preceded that of RA with baseline blood glucose of 280 mg/dl. Treatment with Metformin has been initiated in combination with lifestyle optimization. The patient had a good glycemic control, glycated hemoglobin (HbA1c) values varying between 6% and 6.5%.

DISCUSSION

The majority of patients with RA are young or middle aged women although the disease can occur at any age and gender. The influence of gender on severity of disease has been investigated in numerous studies. In a review published in 2001 in *Journal of General Internal Medicine* in which were analyzed the results of 174 articles, Barsky AJ *et al.* show that women report more numerous and intense symptoms than men. The differences in perception of symptoms between the two sexes (mainly in terms of pain that is the most studied

symptom) is not fully elucidated but women and men may differ in the central control processing of pain⁸. A large multinational cross-sectional cohort study in patients with RA evaluated the association of sex with disease characteristics. The study included 6004 patients with RA seen in seventy sites from twenty-five countries. The study explored associations of gender, disease activity and clinical characteristics. It was observed that rheumatoid polyarthritis activity appears to be worse in women than in men, erosions were more prevalent among women than among men but men had rheumatoid nodules more often than women⁹. Several studies report higher treatment responses and remission rates in male^{10,11,12}.

Smoking is a consistent predictor of RA in males¹³. Heliövaara M and coworkers evaluated the association between smoking and incidence of seropositive and seronegative RA. In the study were included 512 patients with RA, 348 patients with seropositive RA (229 women and 119 men) and 164 patients with seronegative RA (112 women and 42 men). The authors suggest that exposure to tobacco smoke can initiate the production of rheumatoid factors which in men contribute to the development of clinically manifest RA¹⁴. Smoking gender and risk for RA were evaluated in 1095 patients with RA. The results of the study confirmed that smoking is a risk factor for RA in men but not in women^{15,16}.

The association between T2DM and RA was found to be strongest for patients with the shortest time interval between the diagnosis of diabetes and RA. A nationwide case-control study that investigate the risk of RA in Taiwanese patients with T2DM suggested that the association between T2DM and RA is important when there is a short time interval (<4 years) between the diagnosis of T2DM and the RA. Conversely, in patients whose RA appears 11 years or more after the diagnosis of T2DM there is no significantly association between the two diseases¹⁷.

CONCLUSIONS

Association between RA and diabetes in men is a relatively rare condition. With the appropriate treatment for both diabetes and arthritis the results are favourable. The short time interval between the onset of both diseases suggests that T2DM and RA are related. Smokers patients with RA will be advised to quit smoking.

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