Patients with newly diagnosed rheumatoid arthritis are at increased risk of diabetes mellitus: an observational cohort study

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ABSTRACT

Aims: To reveal the prevalence of diabetes mellitus (DM) in patients with newly diagnosed rheumatoid arthritis (RA) and evaluate the association between clinical characteristics of RA and DM, as well as, treatment response in newly diagnosed RA patients with DM.

Methods: Newly diagnosed, adult, RA patients, who were registered in Danish Danbio since 1st January 2010, were included. Patients' demographics, serology results including rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP) and antinuclear antibody (ANA), as well as, disease activity score in 28 joints-C-reactive protein (DAS28-CRP), at the time of diagnosis and after 4 months (±1-2 months) of treatment initiation, were extracted from Danbio Registry. To reveal the presence of DM, patients' electronic medical records were reviewed. The prevalence of DM in our patients was compared (using an age- and gender-matched analysis) with that expected from Danish population.

Results: of 439 included patients, 60.1% were female, mean of age 64.6±15.0 years and RA disease duration 2.6±1.7 years. Prevalence of DM was 57/439 (12.9%), herein type II DM 52 (91.2%) and type I DM 5 (8.8%). Except for two patients, diagnosis of DM was established prior to the diagnosis of RA. The prevalence of DM in newly diagnosed RA patients of all ages was significantly increased versus that expected from Danish population (RR=2.21, CI=1.40-3.42, P <0.001). In addition, prevalence of DM was significantly increased with more than twice of the expected for RA patients aged 65-84. Both genders showed increased risk of DM after subgroup analysis. The presence of DM in RA patients was significantly associated with age (P <0.001) and RA disease duration ≥4 years (P =0.05). We did not find any significant associations between presence of DM and gender, RF, anti-CCP, as well as, ANA. Additionally, presence of DM in the RA patients was not a negative predictor of treatment response measured by the European League Against Rheumatism (EULAR) response criteria and ΔDAS28-CRP.

Conclusion: Newly diagnosed RA patients are at higher risk of DM (13% versus 5.7% in Denmark), and a high index of suspicion must be kept.

Keywords: Rheumatoid arthritis; Diabetes mellitus; DAS28; RF; Anti-CCP

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, autoimmune disease, characterized by articular and, in some cases, extra-articular manifestation, with a prevalence of 0.5-1% in the general population. It has been generally accepted that RA should be diagnosed and managed promptly. The ultimate goal of treatment is to prevent or control joint destruction and subsequent functional loss[1]. There has been a major improvement in the long term prognosis of RA, since the introduction of highly effective disease modifying anti-rheumatic drugs (DMARDs) and by improved management strategies such as tight control and treat-to-target[2,3]. However long-term prognosis can be affected by different comorbidities, leading to increased rate of mortality in comparison with the general population. Cardiovascular disease, infections and certain kinds of malignancies, are the main causes of excess mortality rate in RA patients[4-6]. Comorbidities may be related to the disease characteristic itself or occur as a results of treatment.

Diabetes mellitus (DM) is a metabolic disease caused by deficiencies in insulin secretion, action or both, re-

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sulting in disturbances of carbohydrate, fat, and protein metabolism. The vast majority of DM cases consist of type I, characterized by absolute insulin deficiency, and type II, characterized by insulin resistance and relative insulin deficiency[7]. There is no consensus regarding the prevalence of DM in RA, how-ever most of the previous studies support the increased prevalence of DM or insulin resistance in RA, caused by immune system activation and/or RA treatment[8,9]. Tumor necrosis factor alpha (TNF) is a mediator of insulin resistance and play a significant role in the pathogenesis of RA[10,11]. On the other hand, TNF inhibitors reduce the risk of developing DM in RA patients, which suggests a role for TNF in the pathogenesis of RA and DM[12]. Co-occurrence of DM among RA patients is associated with increased risk of cardiovascular disease[13].

Considering the possible relationship between RA and DM, an early diagnosis of DM can substantially improve long-term prognosis, and moreover reduce the economic burden and mortality rate of RA patients. The primary objective of this study was to investigate the prevalence of DM in newly diagnosed RA patients. The secondary objectives of this study were to evaluate the association between clinical characteristics of RA and DM, as well as, treatment response in RA patients with diagnosed DM.

MATERIALS AND METHODS

DANBIO

The Danish Danbio registry was established in 2000 and approved by the National Board of Health (file no. 7-201-03-12/1) and Danish Data Protection Agency (file no. 2007-58-0014 and file no. 2007-58-0006). It provides national data on the disease course of patients with inflammatory rheumatic disease including RA, ankylosing spondylitis and psoriatic arthritis, via personal identification code. In addition to its value in routine clinical care, it provides an effective and powerful research database at the same time. Data in Danbio are categorized to baseline variables (e.g. demographic data, diagnosis, diseases duration) and longitudinal/follow-up data (e.g. treatment, functional status and disease activity scores) and collected by online registration from patients and health personnel at every consultation.[14] All departments of rheumatology in Denmark are required to register every newly diagnosed RA patient in Danbio, however each department has only access to its own patients. At our department, all patients with diagnosis of RA are registered in Danbio, at every consultation.

STUDY DESIGN AND SETTING

This is an observational, cohort, single center study. The whole parts of the study were performed at the rheumatology outpatient clinic, Svendborg Hospital, Denmark, in December 2015. Ethical approval was obtained from Danish Data Protection Agency (file no.14/50243) and Danish Patient Safety Authority (file no.3-3013-1542/1/).

PARTICIPANTS

The diagnosis of RA was made according to the new 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA. All our RA patients registered in the Danbio database were considered to enter into the study[15]. The following inclusion criteria were applied: 1) Patients who were registered at the rheumatology outpatient clinic and 2) Adult patients who were diagnosed with RA since 1st January 2010 according to the new criteria. Patients who passed away or were referred to the other departments were also included in the study. Exclusion criteria were patients who diagnosed with RA before 1st January 2010 and those with juvenile RA.

INITIAL RHEUMATOID ARTHRITIS TREATMENT

At our rheumatology outpatient clinic, patients with newly diagnosed RA are treated with methotrexate, which may be increased to 25 mg per week, depending on disease monitoring using disease activity score in 28 joints-C-reactive protein (DAS28-CRP), as an index of disease activity. Additionally, hydroxychloroquine, sulfasalazine as well as prednisolone (given Intramuscular, intraarticular or orally) can be added in case of persistent disease activity. The treatment goal is to achieve remission i.e. DAS28-CRP less than 2.6 (or low disease activity i.e. DAS28-CRP≤3.2) as quickly as possible.

DATA COLLECTION

For each patient data on demographics (age, sex, year of RA diagnosis), serology test results including rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP) and antinuclear antibody (ANA) were collected. DAS28-CRP at the time of di-

agnosis and after 4 months (±1-2 months) of treatment initiation were also gathered. The actual dosage of prednisolone was obtained, if patients received prednisolone.

The electronic medical records of the patients were reviewed for a positive history of DM as well as prescribed antidiabetic medications and abnormal lab tests (fasting blood sugar (FBS) and hemoglobin A1C (HbA1C)) to identify if the patients had been diagnosed with DM as well. Types of DM and year of DM diagnosis were extracted from Fyns Diabetes Database. Diagnosis of DM was made at the department of endocrinology according to international standards[7].

To compare the prevalence of DM in the group of patients with newly diagnosed RA at our outpatient clinic with prevalence of DM in Danish population, we calculated expected number of DM for our cohort study based on available data from Statens Serum Institut[16].

VARIABLES

Demographic data were extracted from Danbio. The results of RF (normal range: <15 IU/mL), anti-CCP (normal range: <20 EU/mL) and ANA (normal range: <1/0 IU), were collected and analyzed both quantitative and qualitative (positive/negative). DAS28-CRP and ΔDAS28-CRP were also calculated:[17]
ΔDAS28-CRP =$DAS28_1$-CRP (at the time of diagnosis) – $DAS28_4$-CRP (after 4 months of treatment initiation ±1-2 months). The lower reporting limit of CRP was considered as <10mg/L.[18]

We considered following reference values for FBS (<126 mg/dl) and HbA1C (<6.5%).

THE EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) RESPONSE CRITERIA

The EULAR response criteria classify the RA patients as non-, moderate or good responders dependent on the change and the level of the disease activity score during the time[19]. In the present study additionally to ΔDAS28-CRP, EULAR response criteria were used to assess the treatment response in the RA patients.

STATISTICAL ANALYSIS

We used Microsoft Excel 2010 to perform statistical analysis. Continuous data were presented as mean ± standard deviation (±SD), categorical data as frequencies and respective percentages. Student's t-test was used to compare the above mentioned variables, between RA patients with and without DM. When comparing two binary variables the Chi-square test was performed.

The expected number of patients with DM for our cohort was estimated by multiplying the Statens Serum Institut's rate of DM for each age group, as well as, gender by the number of RA patients within those subgroups. Subsequently, relative risk (RR) for each subgroup was expressed as the ratio of observed to expected cases. P value was considered as significant if $P \leq 0.05$. In case of missing data we used pairwise deletion to keeps as many cases as possible for each analysis.

RESULTS

Of 974 RA patients registered in the regional part of Danbio, 439 patients, who were diagnosed according to the new criteria, met the inclusion criteria and had none of the exclusion criteria. 535 patients were excluded from the study since RA diagnosis was established before 1st January 2010. Demographics, disease characteristics and response to treatment of included patients are summarized in Table I.

The prevalence of DM, in the present cohort study, was 57/439 (12.9%), of which 52 (91.2%) and 5 (8.8%) patients were diagnosed with type II and type I respectively. Of 57 patients, 9 patients had HbA1C ≥6.5% without receiving antidiabetic medication and 11 patients were prescribed prednisolone with an average of 6.8±2.4mg/day. All 11 patients who received prednisolone had type II DM. RA patients with type I (n=5) were all positive for RF.

Using an age- and gender-matched analysis, prevalence of DM in our cohort was compared with the prevalence of DM expected based on available data from Statens Serum Institut (Table II). For patients of all ages with newly diagnosed RA, there was a significant increase in the prevalence of diabetes, with more than twice the expected number of patients with DM (RR=2.21, 95% confidence interval =1.40-3.42, P <0.001)). Statistically significant differences were found in RA patients aged 65-84, irrespective of the gender.

As expected, RA patients with DM were significantly older than patients with isolated RA. The results of our study revealed that RA disease duration ≥4 years

TABLE I. DEMOGRAPHIC AND DISEASE CHARACTERISTICS OF THE INCLUDED PATIENTS

Number of patients (n) =439		
Age (years), Mean ± SD:		64.6±15.0
0-24	n=5	20.6±0.5
25-34	n=14	29.7±3.2
35-44	n=26	39.3±3.3
45-54	n=58	50.9±2.9
55-64	n=94	59.4±2.9
64-74	n=121	70.0±2.7
75-84	n=91	78.9±2.8
85+	n=30	88.3±2.9
Gender (%)		
Female		264 (60.1%)
RA disease duration (years), Mean ± SD:		2.6±1.7
DAS281-CRP, Mean ± SD:		4.4±1.3
DAS284-CRP, Mean ± SD:		3.0±1.2
ΔDAS28-CRP, Mean ± SD:		1.4±1.4
IgM RF (%)		
Positive		244 (55.6%)
Negative		195 (44.4%)
Anti-CCP (%)		
Positive		197 (44.9%)
Negative		241 (54.9%)
No data		1 (0.2%)
ANA (%)		
Positive		85 (19.4%)
Negative		327 (74.5%)
No data		27 (6.1%)

a) RA: rheumatoid arthritis b) DMARDs: disease modifying antirheumatic drugs c) DAS281-CRP: disease activity score in 28 joints-C- reactive protein at the time of diagnosis d) DAS284: disease activity score in 28 joints-C-reactive protein after 4 months of treatment initiation ±1-2 months e) ΔDAS28-CRP: DAS281-CRP (at the time of diagnosis) – DAS284-CRP (after 4 months of treatment initiation ±1-2 months) f) RF: rheumatoid factor g) Anti-CCP: anti-cyclic citrullinated peptide antibody and h) ANA: antinuclear antibody

TABLE II. PREVALENCE OF DIABETES IN PATIENTS WITH NEWLY DIAGNOSED RHEUMATOID ARTHRITIS COMPARED TO THE PREVALENCE OF DM EXPECTED FROM DANISH POPULATION

	Observed number of patients with DM	Expected number of patients with DM	Relative Risk	95% CI	P value
All patients	57	26	2.21	1.40-3.42	<0.001
Age (y)					
45-54	2	2	1.19	0.15-6.86	1.00
55-64	9	5	1.80	0.63-5.17	0.26
65-74	22	9	2.35	1.17-5.09	0.01
75-84	19	8	2.39	1.10-5.15	0.02
85+	5	2	2.75	0.52-11.89	0.22
Gender					
Male	28	13	2.62	1.15-4.02	0.01
Female	29	13	2.63	1.19-4.19	0.01

DM: Diabetes mellitus, CI: Confidence Interval

was significantly associated with higher prevalence of DM, since patients who were diagnosed before 2012 had higher prevalence of DM in comparison with patients who were diagnosed within 2012 and later. There were no statistically significant associations between presence of DM and gender, RF, anti-CCP, ANA, ΔDAS28-CRP as well as EULAR response to treatment (Table III).

In two RA patients with DM, diagnosis of RA was made prior to the diagnosis of DM, in which one of them was prescribed prednisolone 10 mg/day. In rest of the patients, diagnosis of DM was established before patients were diagnosed with RA (to the extent that data were available) (Figure 1).

DISCUSSION AND CONCLUSION

This is the first cohort study, evaluating the association between clinical characteristic of RA and DM as well as treatment response in newly diagnosed RA patients with DM. The main results of this study can be summarized as follows: 1) considering the prevalence of DM in Danish population (5.7%), DM was more prevalent among RA patients (12.9%), 2) there was an increased prevalence of diabetes in newly diagnosed RA patients of all ages, after age- and gender-matched analysis, 3) both genders showed a higher risk of DM compared to the expected from Danish population, 4) elder RA patients with disease duration ≥4 years were at increased risk of DM compared to younger patients with disease duration <4 years and 5) Presence of DM in the RA patients was not associated with worse initial treatment response measured by the EULAR response criteria and ΔDAS28-CRP compared to the patients with isolated RA.

The overall prevalence of DM among RA patients was estimated to be about 13% in this study; however, with respect to the prevalence of DM in RA patients there were still controversies in the previous studies. Han et al, in a cross sectional study of 28,208 RA patients compared with controls matched 4:1 for age, sex, geographic region, and length of time in plan found a significantly increased prevalence of DM in RA patients (10.4% versus 7.6%, P value: 0.01)[9]. A recent meta-analysis by Jiang P et al, including 11 case control and 8 cohort studies, revealed the increased risk of DM (both type I and II) in RA. The pooled risk estimate of case-control and cohort studies demonstrated a statistically significant higher prevalence of DM among RA individuals (Odds ratio=1.40, 95% Confidence interval: 1.34-1.47 and Risk ratio =1.43, 95% confidence in-

TABLE III. ASSOCIATION OF DIABETES MELLITUS WITH GENDER, DISEASE DURATION, RF, ANTI-CCP, ANA, ΔDAS28-CRP AND EULAR RESPONSE CRITERIA IN RHEUMATOID ARTHRITIS PATIENTS IN EACH GROUP

N=439	With diabetes: n=57	Without diabetes: n=382	P value
Age, Mean±SD	72.2±9.0	63.5±15.4	<0.001
Gender (%)			
Female	29 (50.9%)	235 (61.5%)	0.50
Disease duration			0.05
≥4 years (%)	27 (47.4%)	130 (34.0%)	
<4 years (%)	30 (52.6%)	252 (66.0%)	
RF positive (%)	33 (57.9%)	211 (55.2%)	0.84
Anti-CCP positive (%)	25 (43.9%)	172 (45.0%)	0.91
ANA positive (%)	10 (17.5%)	75 (19.6%)	0.75
DAS281-CRP, Mean±SD	4.6±1.4	4.3±1.2	0.17
DAS284-CRP, Mean±SD	3.1±1.2	3.0±1.1	0.43
ΔDAS28-CRP, Mean±SD	1.5±1.5	1.4±1.4	0.64
Eular response criteria			0.84
Good response	19 (33.3%)	121 (31.7%)	
No response	14 (24.6%)	88 (23.0%)	

a) RF: rheumatoid factor; b) Anti-CCP: anti-cyclic citrullinated peptide antibody; c) ANA: antinuclear antibody; d) ΔDAS28-CRP: DAS281-CRP (at the time of diagnosis) – DAS284-CRP (after 4 months of treatment initiation ±1-2 months); e) DMARDs: Disease Modifying Antirheumatic Drugs; f) Eular: European League Against Rheumatism; g) SD: Standard Deviation

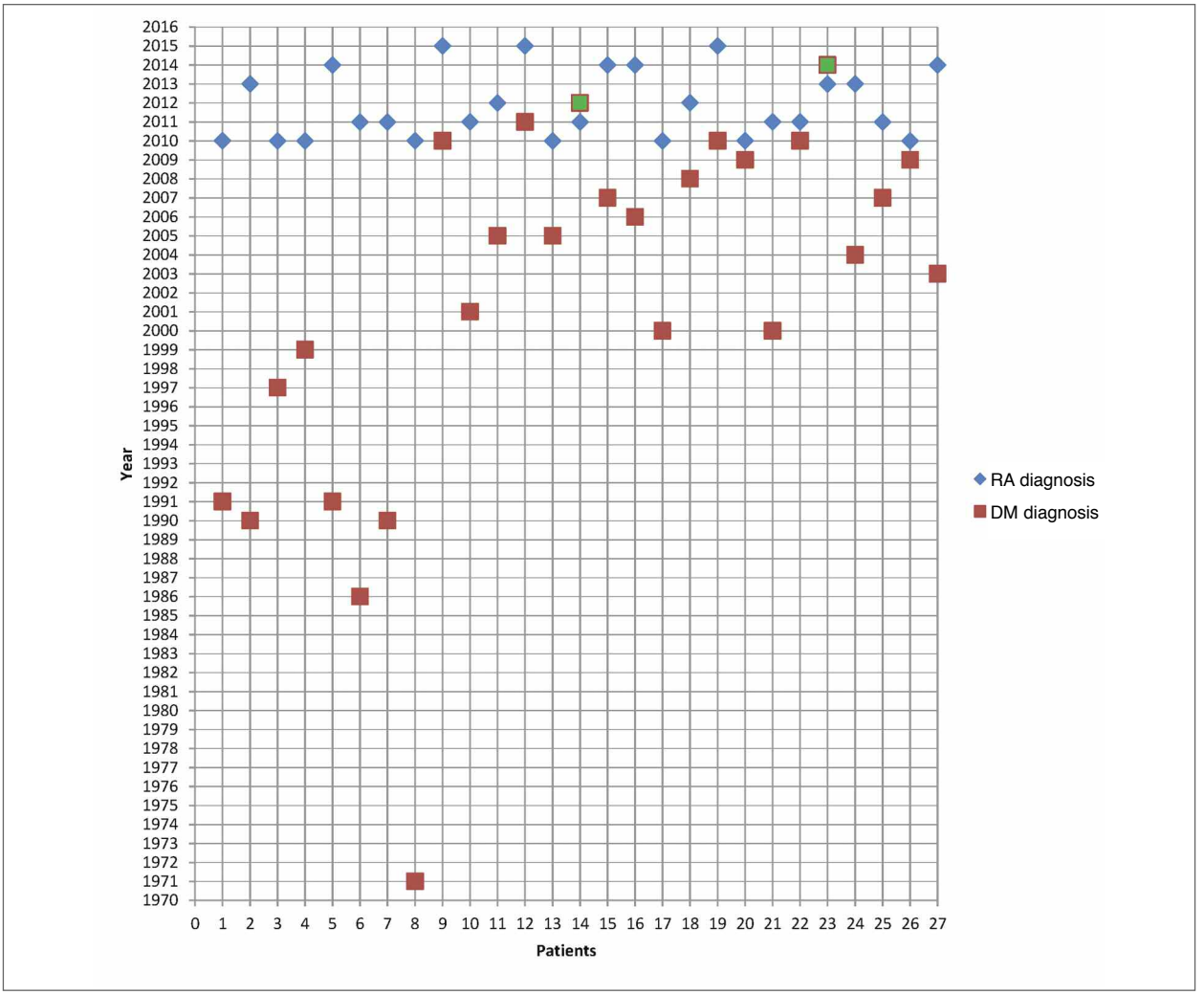

FIGURE 1. Rheumatoid arthritis (RA) and Diabetes (DM) years of diagnosis for each individual RA patient with DM (to the extent that data were available). As shown, in two patients diagnosis of RA was made prior to the diagnosis of DM (green squares)

terval: 1.38-1.47 respectively)[8]. On the contrary, Solomon et al in a prospective longitudinal cohort study did not find any significant difference in the prevalence of DM among women with RA (n=287) and without RA (n=87,019) participating in the nurses' health study (4.8% versus 4.4%)[20]. These controversies might be due to diversity of study populations mainly ethnicity or other factors related to disease characteristic e.g. disease duration.

There was a significant association between age and presence of DM in RA patients. This finding is consistent with the fact that prevalence of DM increases with age[21]. Aging has been reported as to be associated with deterioration in glucose tolerance[22,23]. Based on our results older RA patients, who tended to have longer disease duration were more likely to have diabetes. These results were in line with a cohort study by Ranganath VK et al examined 1548 RA subjects with varying disease duration for 33 comorbidities including diabetes. In Ranganath VK's study, the prevalence of diabetes was reported as 9.3%. They also found that aging was significantly associated with longer disease duration and greater number of comorbidities (P value ≤0.001)[24].

Diagnosis of RA at initial presentation and starting treatment at earlier stage is extremely important to prevent further joint destruction. The first few months of treatment initiation has significant impact on the long term prognosis[25]. Previous studies demonstrated that patients with lower disease activity achieved in the 6 months of treatment initiation had better long term

outcome and a clinical remission within 3 to 6 months of treatment initiation, halts the progression of joint damage[26,27]. The authors implemented the concept of ΔDAS28-CRP, representing treatment outcome after 4 months, on the importance of the first few months after treatment initiation. In this study, however, we did not find any association between presence of DM and DAS28-CRP at time of diagnosis or after 4 months (±1-2 months) of treatment initiation and subsequently, ΔDAS28-CRP had no significant difference between RA patients with and without diabetes. Besides, assessment of treatment outcome according to the EULAR response criteria was also in favor of that presence of DM in this RA population was not a negative predictor of treatment response.

The exact pathophysiology of DM among RA patient is not clearly understood, however the role of immune system activation and proinflammatory mediators (e.g. TNF, interleukin 1 and Interleukin 6) are well documented in RA.[28] In obese patients, excess lipid accumulation may cause low grade inflammatory process, resulting in increased production of inflammatory cytokines e.g. TNF and interleukin 6, which can lead to insulin resistance, impaired glucose tolerance as well as diabetes. Additionally, liver immune cells produce proinflammatory cytokines in response to inflammatory mediators secreted by adipose tissue. Certain number of these proinflammatory cytokines play key roles in the pathogenesis of RA[29]. In this study, we included only newly diagnosed RA patients based on 2010 classification criteria. However, further research, with inclusion of all RA patients regardless of which classification criteria is used, should be performed to elucidate the link between RA and DM considering the other risk factors such as body mass index or other features of metabolic syndrome.

Steroids are commonly used in the treatment of patients with RA. Though steroids conventionally cause increase in plasma glucose, the anti-inflammatory effect of steroids may theoretically increase the secretion of insulin pancreatic cell and improve peripheral insulin sensitivity[30]. Toms TE et al on a cross sectional study of 398 RA patients did not find any association between long-term steroid exposure and higher prevalence of the metabolic syndrome, however Dessein PH et al demonstrated that high oral prednisolone (cumulative dose 4.8 g (range 2.0-8.5)) and high doses of pulsed glucocorticoids is related to decreased insulin sensitivity in RA patients.[31,32] Based on our results the authors cannot assuredly rule out the role of steroid treatment in the development of DM, but in almost all patients, DM was diagnosed before starting steroids. Short term use of steroids in early RA patients allows better disease activity control without significant increase in the risk of DM development, which may be explained by an improvement in insulin resistance as suggested by Svenson KL et al[33].

Both RA and DM are risk factors for cardiovascular disease[34]. Considering the higher prevalence of DM among RA patients found in this study, the authors propose routine screening for DM i.e. either measurement of HbA1C or FBS at diagnosis and with yearly interval thereafter in all RA patients.

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