Prevalence of type 2 diabetes among rheumatoid arthritis patients: a large retrospective study

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To the Editor: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by an excess of cardiovascular disease (CVD) risk, estimated to be at least 50% greater than the general population.[1] CVD has been recognized as the main cause of mortality in established RA patients, but recent data confirm this trend also in earlier stages of the disease.[2] Several factors have been evoked as determinants of this additional risk, but the most consolidated theory attributes this phenomenon to the interplay between chronic high-grade inflammation and elevated prevalence of "classical" cardiovascular risk factors, including diabetes.

Diabetes mellitus (which is divided into type 2 diabetes [T2DM] and type 1 diabetes [T1DM]) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus is one of the most common metabolic diseases and has been a worldwide public health issue, and the proportion of CVDs attributable to diabetes mellitus is increasing along with socioeconomic development. The most recent data show that the overall prevalence of diabetes mellitus in the Chinese adult population is estimated to be 11.6% (95% confidence interval: 11.3–11.8%), which is far higher than the estimated global prevalence.[3] Despite the evidence that the coexistence of RA and T2DM could synergistically increase CVD risk, neither European League Against Rheumatism (EULAR) nor American Diabetes Association (ADA) guidelines[4] recommend systematic screening for diabetes in RA patients. Therefore, the aim of the present study was to explore the association between T2DM and RA, compared to a healthy population aged more than 20 years in China.

This was a population-based, retrospective study. Participants in this study were from a cohort of 6002 hospitalized patients aged >20 years from January 2015 to October 2016 in Guanghua Hospital of Traditional and Western Medicine, which satisfied the 2010 American College of Rheumatology (ACR)/EULAR classification criteria for RA.[5] A total of 10,759 healthy controls aged >20 years at the same period were involved in the physical examination center of the hospital. A standard questionnaire assessing demographic characteristics; lifestyle, such as smoking, alcohol drinking, and work-related physical activity; and family history of diseases and other risk factors, was administered by trained research staff. After the interview, all participants completed a physical examination that included an evaluation of plasma glucose after overnight fasting. Plasma glucose was measured with an automated chemistry analyzer (ADVIA@ 2400, Siemens, Deerfield, IL, USA). We excluded 28 patients with T1DM and other abnormal glucose tolerance. A total of 5992 RA cases and 10,741 controls were recruited at the same time. All subjects in two groups were divided into two gender groups, and each gender group was also divided into eight age groups (aged ≤39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, and ≥70 years). The present study was approved by the Ethics Committee of Guanghua Hospital of Traditional and Western Medicine (approval No. 2016-K-15).

Results of plasma glucose testing were categorized as follows: isolated impaired fasting glucose (IFG, fasting blood glucose concentration between 5.60 and 6.99 mmol/L) and DM (fasting blood glucose concentration ≥7.00 mmol/L), which were defined using the ADA criteria.[6]

Categorical data were represented as *n* (%). All statistical analyses were carried out using SPSS software (version

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002378

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Chinese Medical Journal 2022;135(20)

Received: 10-08-2022; **Online:** 17-11-2022 **Edited by:** Jing Ni

21.0; SPSS, Inc., Chicago, IL, USA; No. AAC2010172). Differences between groups were compared using a two-tailed Student's *t*-test for continuous variables and a chi-squared test for categorical variables; a $P < 0.05$ was considered statistical significance.

In each group, they were stratified according to gender and age based on Chinese population data from 2015. Among our participants, 73.98% ($n = 4433$) of RA patients were women, but 70.43% ($n = 7565$) of healthy controls were men. Significant differences between healthy controls and RA patients group were noted in gender ($P < 0.001$) and family history of RA ($P < 0.001$), but no statistical differences in cigarette smokers ($P = 0.058$), body mass index ($P = 0.072$), alcohol drinking ($P = 0.074$), and diabetic family history ($P = 0.807$).

The data of healthy controls are shown in Figures 1A and 1B. Among 10,741 healthy controls, 811 T2DM cases and 1309 IFG cases were observed. Among healthy controls, the overall prevalence of IFG was 12.19% ($n = 1309$), with a prevalence of 14.50% ($n = 1097$) in male and 6.68% ($n = 212$) in female ($P < 0.001$). The highest prevalence of IFG in men was at the age of 60 to 64 years (20.45%, 1547/7565), but at the age ≥70 years (17.05%, 541/3176) in women. And the overall prevalence of T2DM was estimated at 7.54% (810/10,741), with 9.53% ($n = 721$) in male and 2.80% (89/3176) in female ($P < 0.001$). So prevalences of both IFG and T2DM in male were much higher than those in female. According to Chinese population data from 2015, the age and gender-standardized prevalence of T2DM were 4.82%, and the gender-standardized prevalence of T2DM was 7.14% in male and 2.45% in female ($P < 0.001$) among healthy controls.

The data of RA patients are shown in Figures 1C and 1D. Among 5992 RA patients, 559 T2DM cases and 451 IFG cases were observed. And female RA patients with T2DM were 422 cases, which was over three times of male patients with T2DM (137 cases). The overall prevalence of IFG was 7.53% ($n = 451$), with a prevalence of 7.38% ($n = 115$) in male and 7.58% ($n = 336$) in female ($P = 0.794$). For male RA patients, the highest prevalence of IFG was also in the age range of 60 to 64 years, which was similar to the healthy controls. But for female RA patients, the highest prevalence of IFG rose at the age range of 55 to 59 years (9.31%, 413/4433), which was much different from the controls. The total prevalence of T2DM was 9.33% (559/5992), with 8.79% (137/1559) in men and 9.52% (442/4433) in women ($P = 0.393$). The age- and gender-standardized prevalence of T2DM was 5.86%, and the age-standardized prevalence of T2DM was 6.18% in male and 5.54% in female ($P = 0.355$). As a result, the prevalences of both IFG and T2DM had no gender difference.

All participants had a rising prevalence of IFG and T2DM with age growing in our study. For male, the prevalences of IFG among RA patients were much lower than those of healthy controls [Figure 1E]. But in female, the prevalences of IFG among healthy controls at the age <59 years were almost similar, with a striking upward from the age range of 60 to 64 years [Figure 1F]. In male, the prevalences of T2DM for RA patients and healthy controls had no statistical difference [Figure 1G], and the age-standardized prevalence of T2DM among RA patients was also similar to that of healthy controls (6.18% *vs.* 7.14%, $P = 0.166$). But for female, the prevalence of T2DM among RA patients significantly increased at the age of 50 to 64 years [Figure 1H]. And the age-standardized prevalence of T2DM among female RA patients was different from that of healthy controls (5.54% *vs.* 2.45%, $P < 0.001$).

In the present study, we found that prevalences of both IFG and T2DM among RA patients and healthy controls

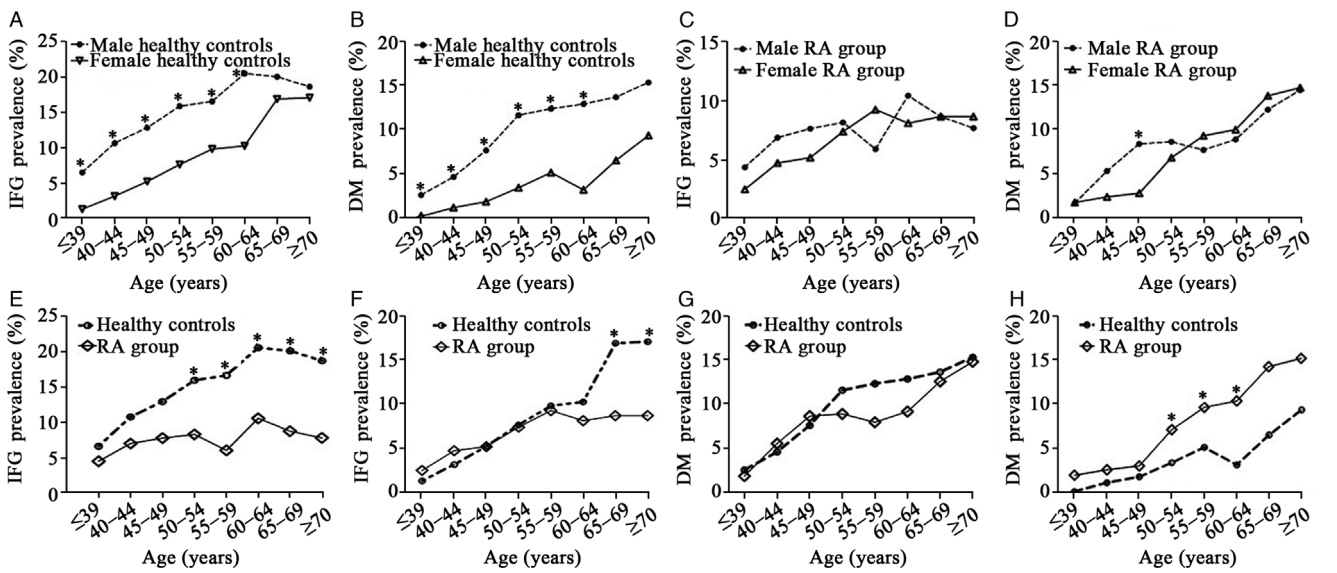

Figure 1: Prevalences of IFG and T2DM among all participants. IFG and T2DM prevalence in healthy controls (A,B) and RA group (C,D). IFG prevalence in males (E), and females (F) from healthy controls and RA group. T2DM prevalence in males (G), and females (H) from healthy controls and RA group. * $P < 0.05$. DM: Diabetes mellitus; IFG: Impaired fasting glucose; RA: Rheumatoid arthritis.

were rising with increasing age. Compared with healthy controls, the prevalences of IFG among male RA patients were much lower, but the prevalences of T2DM had no statistically significant difference. Compared with healthy controls, the prevalences of IFG among female RA patients were also lower from the age range of 60 to 64 years, but the prevalences of T2DM significantly increased, especially for the age of 50 to 64 years. So in female, the prevalences of T2DM were much higher in RA patients than those in healthy controls, and they were almost similar in male. Interestingly, the results appeared to be consistent with those obtained in prior studies. Why did RA cause the different trends among two genders with and without RA? The reason was unknown.

Patients with chronic inflammatory diseases such as RA are at higher risk of developing impaired glucose metabolism that may eventually progress to T2DM. And patients with RA whose activity is effectively controlled may experience the additional clinical benefit of improved insulin sensitivity. Clinical evidence suggests the severity and duration of RA, in addition to visceral/abdominal obesity, are important factors that influence the risk of developing T2DM. These factors require prospective consideration in studies that evaluate the risks and benefits of therapeutic strategies for the development of T2DM. Glucocorticoids are commonly used to treat RA and have effects on basic metabolic function. However, although the use of high-dose glucocorticoids often results in hyperglycemia, the anti-inflammatory effects of low daily doses may improve glycemic control through enhanced pancreatic insulin secretion and peripheral insulin sensitivity. Ozen *et al*[7] found that the incidence of T2DM was increased in RA, which was consistent with our research findings.

The present study had several limitations. First, it could only reflect the association between T2DM and RA. Therefore, it could not clarify the causality. Second, the association between diabetes mellitus and RA in the present study might be affected by some other confounding risk factors, which were not analyzed. Both RA and T2DM in patient populations should be stratified prospectively by RA severity and disease activity to reflect the systemic burden of chronic inflammation. In another word, RA severity, activity, duration, and patterns of medication use should be accounted for in the analyses.

In conclusion, the overall prevalence of T2DM was increased in RA patients. Compared with healthy controls, the prevalence of T2DM in RA patients was much higher among women but almost similar among men. Although further research was required to better understand the higher prevalence of T2DM among female RA patients, given the more frequent presence of other CV risk factors in RA patients, careful monitoring for T2DM should be considered in these patients.

Funding

This work was supported by a grant from the Shanghai Health and Family Planning Program (No. 201604303).

Conflicts of interest

None.

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How to cite this article: Han Z, Zhou Q, Han H, Qiao W, Qie Z, He D. Prevalence of type 2 diabetes among rheumatoid arthritis patients: a large retrospective study. Chin Med J 2022;135:2515–2517. doi: 10.1097/CM9.0000000000002378