

Original article

The impact of diabetes mellitus on treatment and outcomes of rheumatoid arthritis at 5-year follow-up: results from a multi-ethnic Asian cohort

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Abstract

Objectives We evaluated the impact of type 2 diabetes mellitus (T2DM) on RA treatment and outcomes in a longitudinal RA cohort.

Methods We analysed data collected in the period 2001–2013 involving 583 RA patients, including demographics, diabetes diagnosis, clinical features, treatment, ACR functional class, HAQ, and quality-of-life measurement using the Short-Form 36.

Results Seventy-seven (13.2%) of the RA patients had T2DM. DAS28 was not different in patients with T2DM at 5 years post-RA diagnosis. Fewer T2DM patients received MTX than those without T2DM (51% vs 80%, $P < 0.001$). Using univariate analysis, T2DM patients were more likely to experience poorer outcomes in terms of ACR functional status ($P = 0.009$), joint surgery ($P = 0.007$), knee arthroplasty ($P < 0.001$) and hospital admissions ($P = 0.006$). Multivariate regression analyses showed more knee arthroplasty ($P = 0.047$) in patients with T2DM.

Conclusion Fewer patients with T2DM received MTX compared with those without T2DM. Patients with RA and T2DM were at higher risk of knee arthroplasty than RA patients without T2DM.

Key words: rheumatoid arthritis, diabetes mellitus, outcomes, treatment

Key messages

- This study investigated the impact of type 2 diabetes mellitus on treatment and outcomes of RA patients in a multi-ethnic Asian cohort.
- Fewer patients with type 2 diabetes mellitus received MTX than those without.
- Type 2 diabetes mellitus is an independent risk factor for knee arthroplasty in patients with RA.

Introduction

RA is a chronic systemic inflammatory disorder affecting ~1–1.5% of the population worldwide [1–3]. The concept of treating to target in RA [4] and the availability of efficacious agents [5] have improved the control of

disease in the past three decades. However, metabolic co-morbidities complicating RA treatment are increasingly being encountered. The EULAR proposed specific recommendations for the detection and management of specific co-morbidities for patients with RA and other forms of inflammatory arthritis [6, 7]. The impacts of diabetes mellitus on treatment and outcomes have not been well investigated, although there are some studies based on questionnaire survey and electronic health record-based registry [8, 9].

Type 2 diabetes mellitus (T2DM) is a substantial global burden. Systemic chronic inflammation is recognized as the underlying aetiology of a variety of diseases, such

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as diabetes mellitus, autoimmune diseases and neurodegenerative diseases [10]. The central role of metabolism in the modulation of immune responses is increasing being recognized in autoimmune disease [11]. The hyperglycaemic status can influence both innate and adaptive immune responses [12]. The concomitant systemic chronic inflammation and altered immune response in diabetes mellitus might alter the disease characteristics of RA. Moreover, the microvascular and macrovascular complications from diabetes mellitus might influence patients' functional status and choices of treatment. Besides cardiovascular complications, diabetes mellitus also causes a variety of musculoskeletal complications [13].

It is important to address the impact of T2DM on RA, given their shared underlying systemic chronic inflammation and overlapping propensity to cause cardiovascular and musculoskeletal complications. Our previous studies demonstrated that RA is an important cause of quality-of-life impairment, disability and premature death in Singapore, a multi-ethnic Asian society [14–16]. The aim of this study was to investigate whether the presence of T2DM among patients with RA leads to differences of clinical features and outcomes in a multi-ethnic Asian cohort.

Methods

Study population

The Tan Tock Seng Hospital (TTSH) RA Registry has been following patients longitudinally since 2001. All the patients are managed by doctors in the Department of Rheumatology, Allergy and Immunology at TTSH, Singapore, a public hospital that is a tertiary rheumatology referral centre. The data in this study were extracted from the TTSH RA registry. All patients fulfil the 1987 ACR revised criteria for RA or the 2010 ACR/EULAR criteria [17, 18]. The diagnosis of T2DM is physician reported, based on Singapore clinical practice guidelines of diabetes mellitus [19]. Patients who entered the study provided written informed consent according to the Declaration of Helsinki. The Registry is approved by the institutional review board (National Healthcare Group's Domain Specific Review Board Reference Number: 2014/01141).

Data collection

The disease registry collected the following at baseline and thereafter 6-monthly: socio-demographic data, clinical data including the presence of co-morbidities, extra-articular features, physician's global assessment of RA activity, damaged joint counts, Disease Activity Score of 28 joints (DAS28), visual analog scale score for patient-reported general health, drug treatment, ACR functional class, HAQ, quality-of-life measurement using the Short-Form 36 (SF-36), and selected laboratory tests. Details of the Registry have been published [15]. To investigate the long-term impact of T2DM on patients with RA, 583

patients with outcomes at 5 years after diagnosis were selected for analysis.

Statistical method

We displayed descriptive data of demographic characteristics, clinical features and outcomes of RA, categorical variables by frequency and percentage, and continuous variables by median and interquartile. We compared differences in demographics, serology, clinical features, co-morbidities and outcomes between T2DM and non-T2DM RA patients using Pearson's χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for non-parametric continuous variables. After adjustment of patient's background variables (i.e. age, gender (male or female), ethnicity, smoking, hypertension, hyperlipidaemia and use of medications), we performed logistic multivariate regression analyses for categorical outcomes and linear multivariate regression for continuous outcomes. We used STATA software v.15 (Stata Corp., College Station, TX, USA). Complete case analysis was used for missing data. All tests were conducted at the 5% level of significance, reporting the odds ratio (OR), β coefficient value, *P*-value and corresponding 95% CI reported where applicable.

Results

Baseline demographic characteristics

Data were collected from 583 RA patients with outcome metrics documented 5 years after diagnosis, among whom 77 (13.2%) had T2DM. Of these 77 patients, 26 were diagnosed to have T2DM after the onset of RA. The median duration of T2DM was 6 years. There were 11 patients on insulin and 52 patients on oral hypoglycaemic agents. The T2DM patients were older (69 vs 55 years, $P < 0.001$), and the prevalence was higher in Malays (26%) and Indians (24%) when compared with Chinese (11%; $P = 0.005$). There was no difference in gender or smoking history (Table 1).

Differences of clinical features, co-morbidities and outcomes between diabetic and non-diabetic RA patients

A lower proportion of patients with T2DM received MTX (39 of 77, 51%) compared with those without T2DM (406 of 506, 80%; $P < 0.001$), although there was no difference with regard to cumulative doses of MTX (1447 mg vs 1809 mg, $P = 0.052$; Table 2). There was numerically less use of LEF (5% vs 13%, $P = 0.058$; Table 2). Hypertension, hyperlipidaemia, cardiovascular events and renal disease occurred more commonly in T2DM patients (Table 2). The T2DM patients were more likely to experience poor ACR functional status ($P = 0.009$), joint surgery (10% vs 4%, $P = 0.007$), knee arthroplasty (9% vs 2%, $P < 0.001$) and hospital admission (44% vs 29%, $P = 0.006$; Table 3).

There was no statistical difference in serological results or disease activity. The use of prednisolone,

TABLE 1 Demographic characteristics of diabetic and non-diabetic RA patients

Characteristic	T2DM (n = 77)	Non-T2DM (n = 506)	P-value
Age, median (IQR), years	60 (54–68)	55 (48–64)	<0.001
Female, n (%)	64 (83)	426 (84)	0.811
Ethnicity			0.005
Chinese, n (%)	52 (68)	422 (83)	
Malay, n (%)	12 (16)	35 (7)	
Indian, n (%)	12 (16)	38 (8)	
Others, n (%)	1 (1)	11 (2)	
Smoking			0.895
Ever, n (%)	10 (1)	63 (1)	
RF positive ^a	60 (78)	406 (80)	0.742
Anti-CCP positive ^b	49 (64)	357 (71)	0.688
Disease duration, median (IQR), years	5.6 (5.3–7.0)	5.5 (5.3–7.1)	0.537
Duration of T2DM, median (IQR), years	6 (4–10)	–	

Values are given as the median (IQR) for non-parametric continuous variables and *n* (%) for categorical variables. The χ^2 test for categorical variables and Mann–Whitney *U*-test for non-parametric continuous variables were performed for statistical analyses. ^aThree cases with unknown status. ^bFifty-eight cases with unknown status. IQR: interquartile range; T2DM: type 2 diabetes mellitus.

TABLE 2 Clinical features and co-morbidities of diabetic and non-diabetic RA patients at 5 years after diagnosis

Characteristic	T2DM (n = 77)	Non-T2DM (n = 506)	P-value
Deformity of joints, median (IQR)	0 (0–2)	0 (0–2)	0.697
DAS28, n (%)			0.771
DAS28 ≤ 2.6	35 (45)	251 (50)	
2.6 < DAS28 ≤ 3.2	17 (22)	95 (19)	
3.2 < DAS28 ≤ 5.1	22 (29)	145 (29)	
5.1 < DAS28	3 (4)	15 (3)	
Medication use, n (%)			
Prednisolone	72 (94)	478 (94)	0.734
Cumulative prednisolone per patient, median (IQR), mg	3661 (2037–7221)	3611 (1652–6013)	0.227
MTX	39 (51)	406 (80)	<0.001
Cumulative MTX per patient, median (IQR), mg	1447 (0–2572)	1809 (382–3115)	0.052
HCQ	33 (43)	241 (48)	0.434
SSZ	56 (73)	330 (65)	0.194
LEF	4 (5)	65 (13)	0.058
Gold	2 (3)	17 (3)	>0.999
Penicillamine	2 (3)	15 (3)	>0.999
AZA	3 (4)	14 (3)	0.481
CSA	2 (3)	3 (1)	0.132
Biologics	1 (1)	5 (1)	0.574
Drug adherence, n (%)	66 (86)	419 (83)	0.525
Subcutaneous nodules, n (%)	3 (4)	24 (5)	>0.999
Interstitial lung disease, n (%)	0 (0)	14 (3)	0.234
Hypertension, n (%)	54 (74)	157 (31)	<0.001
Hyperlipidaemia, n (%)	38 (49)	132 (26)	<0.001
Cardiovascular event, n (%)	10 (13)	32 (6)	0.035
Cancer, n (%)	1 (1)	13 (3)	>0.999
Liver disease, n (%)	9 (12)	37 (7)	0.185
Renal disease, n (%)	11 (14)	16 (3)	<0.001
Osteoporosis/fracture, n (%)	20 (26)	97 (19)	0.171

Values are given as the median (IQR) for non-parametric continuous variables and *n* (%) for categorical variables. The χ^2 test for categorical variables and Mann–Whitney *U*-test for non-parametric continuous variables were performed for statistical analyses. IQR: interquartile range; T2DM: type 2 diabetes mellitus.

TABLE 3 Outcomes for diabetic and non-diabetic RA patients 5 years after diagnosis

Outcome	T2DM (n = 77)	Non-T2DM (n = 506)	P-value
ACR status, n (%)			0.009
1	56 (73)	421 (83)	
2	13 (17)	69 (14)	
3	4 (5)	12 (2)	
4	4 (5)	4 (1)	
PGA, median (IQR)	10 (0–30)	4 (0–25)	0.243
DGA, median (IQR)	2 (0–12)	2 (0–9)	0.350
VAS, median (IQR)	5 (0–28)	0 (0–31)	0.534
HAQ, median (IQR)	0.125 (0–0.5)	0.25 (0–1.125)	0.106
PF score, median (IQR)	80 (55–95)	75 (37.5–90)	0.100
RP score, median (IQR)	100 (25–100)	75 (0–100)	0.267
BP score, median (IQR)	74 (51–84)	74 (51–100)	0.293
GH score, median (IQR)	62 (45–77)	62 (40–74.5)	0.614
VT score, median (IQR)	60 (45–75)	60 (50–77.5)	0.506
SF score, median (IQR)	87.5 (62.5–100)	93.75 (62.5–100)	0.818
RE score, median (IQR)	100 (67–100)	100 (50–100)	0.730
MH score, median (IQR)	76 (60–88)	76 (64–92)	0.653
RAI, median (IQR)	38 (34–43)	39 (35–44)	0.450
Joint surgery (arthroplasty, arthrodesis), n (%)	8 (10)	18 (4)	0.007
Arthroplasty (hip), n (%)	0 (0)	5 (1)	>0.999
Arthroplasty (knee), n (%)	7 (9)	8 (2)	<0.001
Arthroplasty (others), n (%)	0 (0)	4 (1)	>0.999
Arthrodesis, n (%)	1 (1)	1 (0.2)	0.247
Infection, n (%)	4 (5)	21 (4)	0.559
Admission, n (%)	34 (44)	145 (29)	0.006

Values are given as the median (IQR) for non-parametric continuous variables and *n* (%) for categorical variables. The χ^2 test for categorical variables and Mann–Whitney *U*-test for non-parametric continuous variables were performed for statistical analyses. BP: bodily pain; DGA: doctor global assessment; GH: general health; IQR: interquartile range; MH: mental health; PF: physical functioning; PGA: patient global assessment; RAI: rheumatology attitudes index; RE: role emotional; RP: role physical; SF: social functioning; T2DM: type 2 diabetes mellitus; VAS: visual analog scale; VT: vitality.

other DMARDs, including HCQ, SSZ, gold, penicillamine, AZA and CSA, and biologics, was similar in both groups (Table 2). There was also no difference in the frequency of other co-morbid conditions (osteoporosis, fracture and infections) and drug adherence (Table 2).

Multivariate analyses of the impact of T2DM on outcomes of patients with RA

We performed multivariate regression analyses, adjusting for age, gender, ethnicity, smoking status, hypertension, hyperlipidaemia and use of medications. The results showed a higher risk for knee arthroplasty (adjusted OR: 3.480, 95% CI: 1.016, 11.920, *P*=0.047; Table 4). There was no statistically significant difference in disease activity, ACR functional status, HAQ score, infection rate and admissions (Table 4). The outcomes, including ACR functional status, HAQ and joint surgery, were independent of the duration of T2DM upon further analyses by regression test (data not shown).

Discussion

We found that T2DM is more prevalent in Malays and Indians than Chinese patients. Fewer T2DM patients

received MTX. They might have a higher risk of knee surgery.

The overall prevalence of T2DM was 13.2% in patients with RA in our cohort. The prevalence of T2DM in the general population (age range: 18–69 years old) in Singapore is 11.3% [20], with differences in age and gender compared with patients in our cohort. An Italian cross-sectional study showed that the prevalence of diabetes mellitus in patients with RA is 13.6%, which is higher than the age- and gender-matched population, which is 8.4% [21]. A meta-analysis including a total of 11 case-control studies and 8 cohort studies also confirmed that RA is associated with increased risk of diabetes mellitus [22]. It has been established that underlying inflammation, characterized by elevated CRP and IL-6, plays a role in development of T2DM [23]. In addition, the use of corticosteroids might predispose the development of T2DM.

MTX remains the anchor drug in RA therapy [5]. The benefits of MTX are not limited only to the control of RA, but include the reduction of cardiovascular events [24, 25]. The combination of MTX and biologic therapy is associated with a lower rate of large joint replacement than with biologic agents alone, supporting the hypothesis that low-dose MTX is chondroprotective [26, 27]. The

TABLE 4 Multivariate regression analysis of the impact of T2DM on RA outcomes

Outcome	Non-T2DM	T2DM	P-value
DAS28	Reference	0.923 (0.566–1.503)	0.744
ACR status	Reference	1.802 (0.968–3.353)	0.063
PGA	Reference	–1.497 (–7.467 to 4.472)	0.622
DGA	Reference	–1.998 (–6.310 to 2.314)	0.363
VAS	Reference	2.446 (–3.962 to 8.855)	0.454
HAQ, median	Reference	0.129 (–0.010 to 0.267)	0.068
PF score, median	Reference	–1.661 (–8.323 to 5.001)	0.624
RP score, median	Reference	–1.886 (–13.129 to 9.358)	0.742
BP score, median	Reference	–0.492 (–6.978 to 5.994)	0.882
GH score, median	Reference	–1.977 (–7.595 to 3.642)	0.490
VT score, median	Reference	1.625 (–3.867 to 7.116)	0.561
SF score, median	Reference	–1.338 (–7.975 to 5.299)	0.692
RE score, median	Reference	–1.328 (–11.909 to 9.254)	0.805
MH score, median	Reference	–1.158 (–5.988 to 3.672)	0.638
RAI, median	Reference	0.582 (–1.387 to 2.550)	0.562
Arthroplasty (knee)	Reference	3.480 (1.016–11.920)	0.047
Infection	Reference	0.994 (0.305–3.240)	0.993
Admission	Reference	1.332 (0.771–2.302)	0.304

Logistic multivariate regression for categorical variables and linear multivariate regression for continuous variables, respectively. T2DM as a risk factor was adjusted to the patient's background variables (i.e. age, gender, ethnicity, smoking, hypertension, hyperlipidaemia and medications). The β -coefficient is shown for continuous variables and odds ratio for categorical variables. BP: bodily pain; DGA: doctor global assessment; GH: general health; MH: mental health; PF: physical functioning; PGA: patient global assessment; RAI: rheumatology attitude index; RE: role emotional; RP: role physical; SF: social functioning; T2DM: type 2 diabetes mellitus; VAS: visual analog scale; VT: vitality.

probable reason why proportionately fewer patients with T2DM received MTX is the concomitant renal disease in T2DM. There were significantly fewer MTX prescriptions for patients with renal disease (59%) than for those without (82%) in our cohort ($P=0.03$). T2DM is a risk factor for MTX hepatotoxicity in patients with arthritis [28, 29].

Unsurprisingly, the co-morbid conditions of cardiovascular disease and renal disease were more prevalent in T2DM. Proportionately more T2DM patients underwent joint surgery; in particular, knee arthroplasty. T2DM is known to be associated with multiple musculoskeletal complications, such as limited joint mobility, stenosing flexor tenosynovitis, Dupuytren's contractures, and diabetic sclerodactyly, adhesive capsulitis, rotator cuff tendinopathy and neuropathic arthropathy [13], which may be indications for joint surgery. Hence, optimal management of T2DM can potentially reduce the risk of arthroplasty and its complications. Although MTX is suggested potentially to be chondroprotective in RA, our analysis showed that the higher risk of arthroplasty in T2DM patients is independent of MTX use (data not shown) [26, 27].

Many patients have substantial physical disability in spite of achieving disease remission [30]. Previous studies showed that the functional impairment in patients with RA might be attributable not only to the joint disease, but also to co-morbidities [31–33]. A recent publication showed poor functional status in RA patients with T2DM [9]. Indeed, the finding that co-morbidities contribute to disability in spite of quiescent RA highlights

the importance of managing such conditions, especially T2DM [30–33].

The strength of our study is the large number of patients with long-term follow-up in an Asian context. One limitation of our study is its observational nature; hence, we cannot evaluate the direct impact of T2DM on outcomes of RA patients. A second limitation is that obesity or BMI might be an important potential confounder, but these data are available for only 313 of 582 patients. Third, the diagnosis of T2DM was physician reported, and an oral glucose tolerance test was not performed on every patient. Fourth, although it is independent of the duration of T2DM, we are not certain whether the poorer outcomes in patients with T2DM are dependent on the glycosylated haemoglobin A_{1c} level, which, unfortunately, is largely unavailable.

In summary, the prevalence of T2DM in RA patients is higher than that in the general population, with an inter-ethnicity difference. MTX was used less in patients with T2DM. T2DM might be an independent risk factor for a higher risk of knee arthroplasty. More studies are warranted to investigate whether good control of T2DM improves outcomes in patients with RA.

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Data availability statement

The datasets generated for this study are available from the corresponding author upon request.

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