The utility of maximal oxygen uptake testing as cardiovascular disease risk marker in female patients with rheumatoid arthritis without associated lung disease

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Aim
The aim of this study was to evaluate maximal oxygen uptake (VO_2 max) as a marker of cardiovascular disease (CVD) in rheumatoid arthritis (RA) and its relation to the CVD risk factors in a cohort of female patients with RA without associated lung disease.
Patients and methods
A total of 132 female patients with RA were assessed for cardiopulmonary fitness with a VO_2 max testing. Moreover, 100 healthy female individuals were recruited as control group. Exclusion of patients with pulmonary fibrosis/nodules by using high-resolution computed tomography was done. Traditional CVD risk factors and disease characteristics and their correlation with VO_2 max level were assessed in all patients.
Results
Based on VO_2 max mean, patients were classified into three groups: unfit (<16.72 ml/kg/min), fairly fit (16.73–25.6 ml/kg/min), and with average fitness (>25.6 ml/kg/min). Patients had significantly worse VO_2 max mean (21.28 ±6.96 ml/kg/min) compared with control (30.88±7.36 ml/kg/min). Patients with poor VO_2 max level were more likely to be older, hypertensive, with family history of CVD, with high BMI, and with high mean of Framingham risk score. Significant differences were detected between the fitness subgroups in mean of carotid intima–media thickness and presence of carotid plaques. Long duration of RA, uncontrolled disease activity, high health assessment questionnaire, high C-reactive protein, and positive anticyclic citrullinated protein antibodies were correlated significantly with reduced VO_2 max level.
Conclusion
VO_2 max test can be used as a surrogate CVD marker in patients with RA. VO_2 max can be used as a noninvasive test to detect and quantify fitness defects in patients with RA at increased risk of CVD.

Keywords:
cardiovascular disease, high-resolution computed tomography, rheumatoid arthritis, maximal oxygen uptake

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Introduction

Rheumatoid arthritis (RA) affects ~1% of the general population and is associated with mortality rates ranging from 1.28 to 3 [1]. The increased mortality in RA is explained by accelerated coronary artery and cerebrovascular atherosclerosis besides other cardiovascular (CV) complications [2].

The morbidity and mortality attributed to CV risk are increased in RA. The traditional risk factors including smoking, hypertension, dyslipidemia, insulin resistance (IR), diabetes mellitus, physical inactivity, and obesity do not explain the increased CV risk in RA [3]. Inflammation is the important link between RA and cardiovascular disease (CVD), as it plays a key role in atherosclerosis [3]. RA is an autoimmune systemic disease; ~40% of patients have extra-articular manifestations during the course of the disease [4]. Pulmonary complications are directly associated with RA including, pulmonary nodules, interstitial lung disease (ILD), pleural disease, and airway disease [5]. The extra-articular pulmonary complications of RA were evaluated using open lung biopsy or high-resolution computed tomography (HRCT), which demonstrated ILD in ~40% of these patients [6]. The clinically evident RA-ILD occurs in ~10% of patients with RA in addition to considerable amount of subclinical disease [7]. The findings of HRCT in

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RA are distinct [7] and generally correlate with the histological findings.

The gold standard method for assessment of cardiorespiratory competence is the maximal oxygen uptake (VO_2 max) examination [8]. The level of VO_2 max is significantly low in patients with RA compared with the healthy individuals [9]. Nevertheless, studies cannot determine if the low level of VO_2 max is owing to the effect of RA itself, to CVD, or to the pulmonary manifestations.

Objective

The objective of this study was to evaluate VO_2 max as a marker of CVD in RA and its relation with CVD risk factors in a cohort of female patients with RA without associated lung disease using appropriate power calculations with control of several potential confounders such as sex and associated RA lung disease.

Patients and methods

Recruitment of patients with RA cohort began in 2016; 132 female patients with RA from Rheumatology Outpatient Clinic and Rheumatology In-Patient Department of Alnoor Specialized Hospital, a Tertiary Care Teaching Institutes in Makkah, Saudi Arabia, were enrolled in this prospective study. Moreover, 100 healthy female participants of matched age were recruited as a control group. Written informed consent was taken from patients with RA and volunteers after providing them with detailed verbal and written description.

Inclusion criteria were fulfillment of RA criteria according to the new American College of Rheumatology/European League against Rheumatism panel [10] and absence of any pulmonary manifestations associated with RA approved by HRCT and pulmonary function tests.

Exclusion criteria were recently diagnosed valve disease, cardiomyopathies and arrhythmias, renal disease on hemodialysis, amputation, cerebrovascular disease, known malignancy, current infection, pregnancy, recent joint surgery, and functional comorbidities incompatible with VO_2 max testing.

The participants underwent the following: Demographic data, full medical history (especially diabetes mellitus history, medication history and comorbidities), clinical examination (especially assessment of blood pressure and BMI), and Framingham risk score (FRS) were calculated to assess the 10-year risk of fatal CVD [11]. The 28-joint Disease Activity Score (DAS28) with its components [12] was recorded for each participant.

After fasting for 12 h, the following laboratory investigations were carried out for all the patients: complete blood count for hemoglobin and white cell count, fasting venous plasma glucose, fasting serum insulin level (ELISA method), serum lipids profile, rheumatoid factor, and anticyclic citrullinated protein antibody (ACCP). The homeostasis model assessment was used to evaluate IR (calculator available from http://www.OCDEM.ox.ac.uk), which is based on fasting plasma glucose and serum insulin concentrations [13]. The atherogenic index (AI), which corresponds to the ratio of total cholesterol (TC) to high-density lipoprotein (HDL), was calculated.

High-resolution computed tomography analysis

HRCT (Aquilion 16; Toshiba Medical Systems, Otawara, Tochigi Perfecture, Japan) of the chest without contrast was carried out during breath-holding and inspiration. Computed tomography images with low dose and thin section were obtained while the patient was lying in the supine position. The images were reconstructed at a 1.25-mm section thickness at 10-mm intervals with the use of a high-spatial-frequency (bone) algorithm. Images were reviewed on a Picture Archiving and Communication System screen by an experienced chest physician. Patients with abnormal HRCT findings were excluded from this study.

Carotid ultrasonography

Bilateral B-mode ultrasound examination of the carotid arteries was performed using a 12-MHz linear matrix array transducer (Mylab 70; Esaote, Genoa, Italy). Intima–media thickness (IMT) measurements were performed bilaterally in the distant wall of the common carotid artery, from ~10 mm proximal to the start of the carotid bulb [14]. Carotid artery plaques were identified bilaterally as recommended in the Mannheim consensus [15].

Maximal oxygen uptake analyses

All participants were invited to undergo an individualized VO_2 max test protocol with electrocardiography, after taking into consideration their physical abilities and the American Heart Association guidelines [16] and specific contra-indications to terminate the test [17]. The VO_2

max test was performed on a treadmill using a titrated breath-by-breath system (Metalyzer 3B; Cortex, Leipzig, Germany). A prediction equation including age, self-selected walking speed (km/h), and work heart rate was used to calculate the outcome of the treadmill test for each participant in ml/kg/min [18]. Based on the results of the VO_2 max test, patients with RA were divided into three groups: unfit, fairly fit, and with average fitness.

Statistical analysis

The collected data were tabulated and statistically analyzed using statistical package for the social sciences (SPSS) version 17.0 (Software by IBM corporation, South Africa). Quantitative variables were described as mean and SD. The unpaired *t*-test was used to compare two groups regarding quantitative variables. The χ^2-test was used to compare qualitative variables between groups. One-way analysis of variance test was used to compare more than two groups regarding quantitative variables. Spearman's correlation test was used to rank different variables against each other positively or inversely. *P* value of up to 0.05 was considered statistically significant, and *P* value of up to 0.001 was considered highly statistically significant.

Results

In total, 232 participants (132 female patients with RA and 100 matched female control participants) were included. Table 1 shows that patients and control participants did not differ regarding age and CV risk factor. However, patients scored significantly worse on VO_2 max mean (21.28±6.96 ml/kg/min), with *P* value of less than 0.001.

Based on VO_2 max mean, patients were classified into three subgroups: unfit (<16.72 ml/kg/min), fairly fit (16.73–25.6 ml/kg/min), and with average fitness (>25.6 ml/kg/min). VO_2 max mean was significantly different between the subgroups (Table 2, $P<0.001$).

Cardiovascular disease risk factors

As shown in Table 2, individuals with unfit VO_2 max were more likely be older, with hypertension, with family history of CVD, with high BMI, and with high mean of FRS (10-year CVD risk). However, there was no clear association between VO_2 max and other variables such as smoking, DM, IR, lipid profile, WBC count, and hemoglobin level. Significant differences were detected between the fitness subgroups regarding carotid IMT and presence of carotid plaques (Table 2, $P<0.001$).

Association between maximal oxygen uptake and clinical characteristics of rheumatoid arthritis

As illustrated in Table 2, most unfit and fairly fit VO_2 max patients had significantly longer duration of RA, active disease (DAS28 of >3.2) ($P<0.001$). Among these patients, 51.51% were positive for rheumatoid factor and 52.27% were positive for ACCP antibodies ($P=0.001$). Significant differences were detected between the fitness subgroups in terms of C-reactive protein (CRP), health assessment questionnaire (HAQ), and HAQ disability index. Pharmacologic therapies used in the treatment of patients with RA are presented in Table 2. There was statistically significant difference between the groups regarding NSAIDs ($P<0.001$). No significant difference emerged among the three groups in either traditional disease-modifying antirheumatic drugs (DMARDs), cumulative steroid dose, antitumor necrosis factor therapy, interlukin-6 receptor inhibitor (tocilizumab), or abatacept.

Correlation between maximal oxygen uptake levels and age, cardiovascular disease risk factors, lipid profiles, insulin resistance, and rheumatoid arthritis disease characteristics

There were inverse correlations between VO_2 max levels and age, RA disease duration, TC level, HDL levels, low-density lipoprotein

Table 1 Characteristics of patients and control participants

	Patients (*n*=132)	Control (*n*=100)	*P* value
Demographics			
Age (mean±SD) (years)	47.56±13.37	43.78±10.81	0.118
Cardiovascular risk factor CVR [*n* (%)]			
Hypertensive[a]	66 (50.00)	51 (51.00)	0.320
Diabetes mellitus	36 (27.27)	37 (37.00)	0.481
BMI (mean±SD) (kg/m^2)	28.194±6.604	27.507±5.154	0.504
Current smoker	2 (1.5)	1 (1.00)	0.201
VO_2 max (mean±SD) (ml/kg/min)	**21.28±6.96**	**30.88±7.36**	**<0.001***

CVR, cardiovascular risk. [a]Defined as systolic pressure more than 150 mmHg or diastolic pressure more than 90 mmHg. *All significance bold values were provided.

Table 2 Age, cardiovascular risk factor, disease-related characteristics, and medications of patient subgroups

Characteristics	Unfit (*n*=33)	Fair (*n*=66)	Average (*n*=33)	*P* value
Age (mean±SD) (years)	**62.939±8.821**	**49.576±8.458**	**34.394±9.918**	**<0.001***
Cardiovascular risk factor				
Hypertensive[a]	**23 (69.7)**	**36 (54.54)**	**7 (21.21)**	**<0.001***
Diabetes mellitus	**11 (33.33)**	**21 (31.82)**	**4 (12.12)**	**0.057**
BMI (mean±SD) (kg/m^2)	**30.624±5.213**	**30.985±5.549**	**26.604±4.831**	**0.001***
Current smoker	**0 (0.00)**	**2 (3.03)**	**0 (0.00)**	**0.246**
Family history of CVD	**9 (27.27)**	**5 (7.57)**	**1 (3.03)**	**0.005***
Hypercholesterolemia	**13 (39.39)**	**28 (42.42)**	**9 (27.27)**	**0.324**
TC (mean±SD) (mg/dl)	**192.52±49.28**	**191.30±39.42**	**176.455±38.85**	**0.197**
Triglycerides (mean±SD) (mg/dl)	**115.242±51.980**	**115.939±54.237**	**107.030±60.335**	**0.736**
HDL (mean±SD) (mg/dl)	**55.152±12.858**	**51.167±12.651**	**49.970±10.436**	**0.186**
LDL (mean±SD) (mg/dl)	**129.242±43.557**	**125.500±37.354**	**106.394±42.566**	**0.042**
AI (mean±SD)	**3.627±1.073**	**3.941±1.222**	**3.646±0.956**	**0.303**
FRS (mean±SD)	**5.682±3.937**	**2.212±2.186**	**0.606±1.223**	**<0.001***
Hemoglobin (mean±SD) (g/dl)	**11.841±1.627**	**11.655±1.423**	**11.503±0.985**	**0.612**
WBC (mean±SD) (10^3/UI)	**7.625±2.231**	**7.370±2.770**	**7.498±3.049**	**0.905**
FBS (mean±SD) (mg/dl)	**107.424±33.470**	**116.273±63.513**	**96.515±36.691**	**0.197**
Serum insulin (mean±SD) (μIU/ml)	**11.591±5.940**	**12.011±7.613**	**11.103±6.928**	**0.831**
HOMA-IR (mean±SD)	**3.337±2.542**	**3.499±3.051**	**2.754±2.769**	**0.472**
Carotid IMT (mean±SD) (mm)	**0.798±0.170**	**0.692±0.121**	**0.564±0.089**	**<0.001***
Presence of plaques [*n* (%)]	**16 (48.48)**	**10 (15.15)**	**0 (0.00)**	**<0.001***
Rheumatoid arthritis characteristics				
Rheumatoid arthritis duration (mean±SD) (years)	**11.242±7.267**	**7.242±5.881**	**4.182±3.423**	**<0.001***
DAS28 (mean±SD)	**4.230±0.807**	**3.969±0.902**	**2.576±0.967**	**<0.001***
CRP (mean±SD) (mg/dl)	**2.660±4.136**	**1.099±2.106**	**0.562±0.967**	**0.003***
ESR first hour (mean±SD) (mm)	**44.879±29.423**	**37.106±26.931**	**41.364±21.239**	**0.367**
HAQ (VAS) (mean±SD)	**32.727±12.814**	**26.894±9.105**	**23.030±11.315**	**0.001***
HAQ DI (mean±SD)	**1.273±0.574**	**0.848±0.614**	**0.576±0.751**	**<0.001***
Tender joint count (mean±SD)	**2.636±2.667**	**2.470±2.268**	**1.939±1.749**	**0.413**
Swollen joint count (mean±SD)	**1.697±1.960**	**1.682±1.656**	**1.515±1.661**	**0.886**
RF positive [*n* (%)]	**22 (66.66)**	**46 (69.69)**	**20 (60.60)**	**0.668**
Absence ACCP [*n* (%)]	**12 (36.36)**	**18 (27.27)**	**13 (39.39)**	
Positive ACCP [*n* (%)]	**6 (18.18)**	**26 (39.39)**	**18 (54.54)**	**0.001***
Strong positive ACCP [*n* (%)]	**15 (45.45)**	**22 (66.66)**	**2 (6.06)**	
EULAR disease activity score [*n* (%)]				
Low ≤3.1	**7 (21.21)**	**23 (34.84)**	**13 (39.39)**	
Moderate 3.2–5.1	**23 (69.69)**	**35 (53.03)**	**19 (57.57)**	**0.349**
High ≥5.2	**3 (9.09)**	**8 (12.12)**	**1 (3.03)**	
Medication [*n* (%)]				
NSAIDs	**23 (69.69)**	**35 (53.03)**	**4 (12.12)**	**<0.001***
Corticosteroids	**16 (48.48)**	**33 (50.00)**	**10 (30.30)**	**0.149**
CS dose (mean±SD) (mg)	**2.424±2.538**	**2.652±2.804**	**1.591±2.711**	**0.186**
DMARDs	**30 (88.2)**	**64 (90.1)**	**29 (87.9)**	**0.925**
Anti-TNF-α	**9 (26.5)**	**16 (22.5)**	**8 (24.2)**	**0.578**
Abatacept	**1 (2.9)**	**10 (14.1)**	**6 (18.2)**	**0.083**
Tocilizumab	**5 (14.7)**	**7 (9.9)**	**6 (18.2)**	**0.482**
VO_2 max (mean±SD) (ml/kg/min)	**13.39±12.275**	**22.40±2.444**	**30.779±3.609**	**0.001***

ACCP, anticyclic citrullinated protein antibody; AI, atherogenic index; TNF-α, tumor necrosis factor therapy; CRP, C-reactive protein; CS, corticosteroids; DAS28, Disease Activity Score in 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; EULAR, European League against Rheumatism; FBS, fasting blood sugar; FRS, Framingham risk score; HAQ DI, HAQ disability index; HAQ, health assessment questionnaire; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance; IMT, intima–media thickness; LDL, low-density lipoprotein; RF, Rheumatoid factor; TC, total cholesterol; VAS, visual analog scale; VO_2, maximal oxygen uptake; WBC, white blood cell; [a]Defined as systolic pressure more than 150 mmHg or diastolic pressure more than 90 mmHg. *All significance bold values were provided.

levels, FRS (10 years cardiovascular risk), BMI, carotid IMT, DAS28, CRP, health assessment questionnaire, and disease disability index. However, there was no significant correlation between VO_2 max levels and other variables (Table 3 and Fig. 1).

Table 3 Correlation between maximal oxygen uptake max levels and age, cardiovascular disease risk factors, lipid profiles, insulin resistance, and rheumatoid arthritis disease characteristics

Correlations	VO_2 max	
	r	*P* value
Age (years)	–0.846	<0.001*
Rheumatoid arthritis duration years	–0.494	<0.001*
Total cholesterol	–0.175	0.044*
Triglycerides	–0.096	0.272
High-density lipoprotein	–0.191	0.029*
Low-density lipoprotein	–0.212	0.015*
Atherogenic index	0.013	0.881
Hemoglobin	–0.124	0.156
White blood cell count	–0.033	0.707
Framingham risk score	–0.607	<0.001*
Fasting blood sugar	–0.111	0.207
Serum insulin level	–0.079	0.367
Homeostasis model assessment insulin resistance	–0.151	0.083
BMI	–0.294	0.001*
Carotid intima–media thickness	–0.621	<0.001*
Disease activity score in 28 joints	–0.563	<0.001*
C-reactive protein	–0.312	<0.000*
Erythrocyte sedimentation rate	–0.096	0.271
health assessment questionnaire	–0.353	<0.001*
Disease disability index	–0.418	<0.001*
Swollen joint count	–0.028	0.749
Tender joint count	–0.089	0.308

VO_2, maximal oxygen uptake. *All significance bold values were provided.

Discussion

The accurate evaluation of CV risk among patients with RA remains an area of diligent research. A significantly lower VO_2 max levels were repeatedly demonstrated in patients with RA compared with healthy counterparts, most likely attributed to their low levels of physical activity [9,19] and increased disease activity/severity. Accordingly, we also recorded that VO_2 max level found to be significantly lower in patients with RA compared with control group.

In this analysis, we eliminated the probable bias by excluding patients with pulmonary fibrosis or other significant pulmonary features. Moreover, patients with poor mobility and functional comorbidities incompatible with VO_2 max testing were excluded. This would suggest that we have chosen the most fit patients with RA here; even so, we clarified that their VO_2 max levels were significantly low.

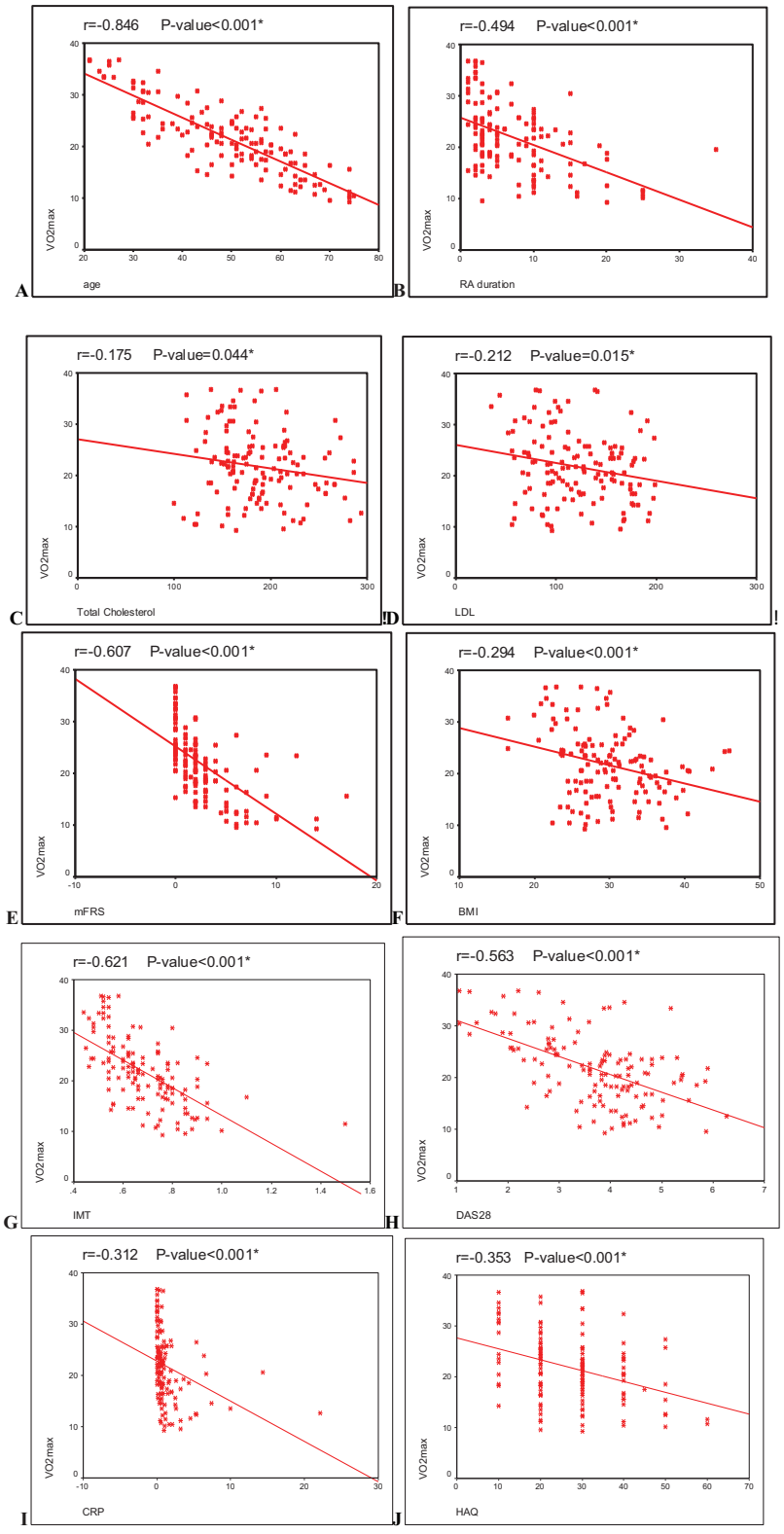
Another finding of our study was that older RA women seemed to have lower VO_2 max level, which is in accordance with previous results that state lower rates of physical fitness among women and a much larger reduction in older age [20]. One reason for these findings might be that older RA women having an inactive lifestyle and not being motivated to become more physically active [21], which represents a challenge to all health professionals.

Broad evidence demonstrates a strong inverse correlation between VO_2 max level and CVD morbidity and mortality [22,23]. In accordance to that, our results clarified the significant inverse association between cardiovascular risk profile and VO_2 max levels (TC level, HDL levels, low-density lipoprotein levels, FRS, BMI, and carotid IMT), highlighting the crucial role of fitness to conserve good health and prevent early CV morbidity in RA population. A randomized trial showed that high cardiorespiratory fitness level can be achieved through regular moderate-intensity lifestyle activities such as walking in sedentary individuals [24].

The overall explanation of low VO_2 max levels in our results only by demographic and traditional CVR measures in RA group might indicate that other factors are involved. Our results demonstrated an inverse association between VO_2 max level and clinical markers of disease activity. Patients with poor VO_2 max level had long disease duration, uncontrolled disease activity according to DAS28, high CRP level, and high score of HAQ. The low overall VO_2 max levels observed in the present study is an alarming finding that could be linked with inappropriate rheumatoid disease control. Another result in this study was the significant correlation between ACCP and lower VO_2 max level. In new research, tissue samples were obtained from lung and synovial biopsies of patients with RA. Investigating the protein proportions in these tissues discovered identical citrullinated peptides in both sites [25]. ACCP had been linked to the development of ILD, particularly when increasingly present [26,27]

Regarding comparing the line of medication, no significant difference emerged between the three groups, except for NSAIDs. Unlike other pain relievers, NSAIDs seem to be more effective in treating symptoms of RA. This is because they reduced inflammation, pain, and fever. NSAIDs enable patients with RA to perform some activities, which accelerates their fitness level. There is considerable controversy as to whether biological agents improve or worsen CV risk in RA population. To date, there have been no randomized

Figure 1



The correlation between maximal oxygen uptake (VO_2 max) mean and (a) age, (b) rheumatoid arthritis (RA) disease duration, (c) serum levels of total cholesterol, (d) serum levels of low-density lipoprotein (LDL), (e) Modified Framingham cardiovascular risk scores (mFRS), (f) BMI, (g) carotid intima–media thickness (IMT), (h) Disease Activity Score in 28 joints (DAS28), (i) C-reactive protein (CRP), and (j) health assessment questionnaire (HAQ).

controlled trials comparing biological medications for the treatment of RA associated with CV mortality and morbidity. Adverse effects of biologic DMARDs on lipids have been reported previously [28,29]. Therefore, risks and benefits of biologic DMARD must be weighed carefully.

This study is not limited by evaluating VO_2 max levels in an equivalent age-matched population and its case–control design but by the noninclusion of patients with pulmonary manifestations and patients with poor mobility possibly, introducing a positive bias in the current study.

Conclusion

This study provided a new insight into less explored test (VO_2 max test) which can be used as a surrogate CVD marker in patients with RA. VO_2 max test can be used as a noninvasive test to detect and quantify fitness defects in patients with RA at increased risk of CVD. We therefore recommend referral of patients with RA with an enhanced risk of cardiac manifestations for VO_2 max testing to better define their fitness level.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. J Rheumatol 2005; 32:430–434.

2 Nicola PJ, Crowson CS, Maradit-Kremers H, *et al.* Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum 2006; 54:60–67.

3 Van den Oever IA, Alper M, *et al.* Management of cardiovascular risk in patients with rheumatoid arthritis: evidence and expert opinion. Ther Adv Musculoskelet Dis 2013; 5:166–181.

4 Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. Respir Med 2012; 106:1591–1599.

5 Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. Curr Opin Rheumatol 2008; 20:340–346.

6 Doyle TJ, Hunninghake GM, Rosas IO. Subclinical interstitial lung disease: why you should care. Am J Resp Crit Care Med 2012; 185:1147–1153.

7 Tanaka N, Kim JS, Newell JD, *et al.* Rheumatoid arthritisrelated lung diseases: CT findings. Radiology 2004; 232:81–91.

8 Sui X, LaMonte MJ, Laditka JN, *et al.* Cardiorespiratory fitness and adiposity as mortality predictors in older adults. JAMA 2007; 298:2507–2516.

9 Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, *et al.* Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. Rheumatology 2008; 47:239–248.

10 Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010; 69:1580–1588.

11 Peters MJL, Symmons DPM, McCarey D, Dijkmans BAC, Nicola P, Kvien TK, *et al.* EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010; 69:325–331.

12 Prevoo ML, Van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38:44–48.

13 Wallace TM, Levy JC, Mattews DR. Use and abuse of HOMA modelling. Diabetes Care 2004; 27:1487–1495.

14 Homma S, Hirose N, Ishida H, Ishii T, Araki G. Carotid plaque and intima-media thickness assessed by B-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke 2001; 32:830–835.

15 Touboul PJ, Hennerici MG, Meairs S, Amarenco P, Bornstein N, Csiba L, *et al.* Mannheim carotid intima–media thickness consensus (2004–2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007; 23:75–80.

16 Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, *et al.* Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis 2013; 72:1819–1825.

17 ACSM. Guidelines for exercise testing and prescription. 7th ed. Philadelphia, PA: Lippincott Wiliams & Wilkins; 2005.

18 Minor MA, Johnson JC. Reliability and validity of a submaximal treadmill test to estimate aerobic capacity in women with rheumatic disease. J Rheumatol 1996; 23:1517–1523.

19 Tierney M, Fraser A, Kennedy N. Physical activity inrheumatoid arthritis: a systematic review. J Phys Act Health 2012; 9:1036–1048.

20 Caspersen C, Merritt R, Heath G, Yeager K. Physical activity patterns of adults aged 60 and older. Med Sci Sports Exerc 1990; 22:79–84.

21 Eurenius E, Biguet G, Stenstrom CH. Attitudes toward physical activity among people with rheumatoid arthritis. Physiother Theory Pract 2003; 19:53–62.

22 Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the lipid research clinics study. Am J Epidemiol 2002; 156:832–841.

23 Wei M, Kampert JB, Barlow CE, *et al.* Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 1999; 282:1547–1553.

24 Dunn AL, Marcus BH, Kampert JB, *et al.* Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: a randomized trial. JAMA 1999; 281:327–334.

25 Ytterberg AJ, Joshua V, Reynisdottir G, *et al.* Shared immunological targets in the lungs and joints of patients with rheumatoid arthritis: identification and validation. Ann Rheum Dis 2014; 74:1772–1777.

26 Doyle TJ, Lee JS, Dellaripa PF, *et al.* A roadmap to promote clinical and translational research in rheumatoid arthritis-associated interstitial lung disease. Chest 2014; 145:454–463.

27 Kelly CA, Saravanan V, Nisar M, *et al.* Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics – a large multicentre UK study. Rheumatology (Oxford) 2014; 53:1676–1682.

28 Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J. Insulin resistance in rheumatoid arthritis: the impact of the anti-TNFa therapy. Ann N Y Acad Sci 2010; 1193:153–159.

29 Tam LS, Tomlinson B, Chu TT, Li TK, Li EK. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol 2007; 26:1495–1498.