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Are persons with rheumatoid arthritis deconditioned? A review of physical activity and aerobic capacity

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Abstract

Background: Although the general assumption is that patients with rheumatoid arthritis (RA) have decreased levels of physical activity, no review has addressed whether this assumption is correct.

Methods: Our objective was to systematically review the literature for physical activity levels and aerobic capacity (VO_{2max}) in patients with (RA), compared to healthy controls and a reference population. Studies investigating physical activity, energy expenditure or aerobic capacity in patients with RA were included. Twelve studies met our inclusion criteria.

Results: In one study that used doubly labeled water, the gold standard measure, physical activity energy expenditure of patients with RA was significantly decreased. Five studies examined aerobic capacity. Contradictory evidence was found that patients with RA have lower VO_{2max} than controls, but when compared to normative values, patients scored below the 10th percentile. In general, it appears that patients with RA spend more time in light and moderate activities and less in vigorous activities than controls.

Conclusion: Patients with RA appear to have significantly decreased energy expenditure, very low aerobic capacity compared to normative values and spend less time in vigorous activities than controls.

Keywords: Rheumatoid arthritis, Cardiovascular disease, Physical activity, Aerobic capacity, Healthy controls

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by polyarthritis and erosive synovitis and is associated with progressive impairments and activity limitations [1,2]. According to the recent EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis [3], RA should be regarded as a condition associated with higher risk for cardiovascular disease (CVD). The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden of RA [4]. Adequate control of disease activity is necessary to lower the CVD risk and evaluating the effect of

lifestyle modification on the CVD risk in inflammatory arthritis was added to the future research agenda [3]. One potentially modifiable lifestyle factor is physical activity (PA). Exercise restrictions, traditionally given to patients with RA because of concerns about aggravating joint inflammation and accelerating joint damage, may contribute to inactivity and deconditioning which is associated with a loss of aerobic capacity [5]. In addition, pain and depression associated with the disease, may result in low PA [6]. Inactivity has been shown to be associated with loss of lean mass, increases in fat mass and metabolic syndrome [6,7], contributing to CVD risk. Several studies do show that physically inactive patients with RA have a significantly worse CVD risk profile compared with physically active patients [8,9]. Conversely, patients with RA with high levels of physical activity (PA) (mean 3342 METhours/week) were shown to have a significantly better CVD risk profile than those with low levels of PA (mean 249 METhours/week), even

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when adjusting for RA disease duration, activity and severity and steroid use [10]. Recent research also shows that a moderately high or high aerobic capacity, but not high physical activity reduces metabolic syndrome and thus CVD and DM II risk even in obese persons [7].

Little is known about the level of daily PA among persons with RA. For instance, a recent meta-analysis on cardiorespiratory (aerobic) exercise in RA did not examine the influence of baseline physical activity as a confounder on either outcomes or statistical heterogeneity, as this parameter was seldom reported [11]. What is known about PA in patients with RA seems contradictory. Several studies found the proportion of patients with RA meeting national recommendations for PA similar to those of the general population [12-14] or to healthy women the same age [9]. A large international study, however, reported that the majority of patients with RA are inactive [15]. A recent systematic review on physical activity in RA concluded that methodological considerations within the reviewed studies prohibited definitive conclusions on the PA levels in this population [16]. The authors used publications on PA and energy expenditure in patients with RA (N=16) only, including studies that did not use a control group (N=9). The aim of this review did not include gathering evidence on aerobic capacity.

Data on aerobic capacity in patients with RA are hard to find. Aerobic capacity in patients with RA aged 20–65 years was found similar to normative data for the same age groups from a representative sample of the Swedish population [12], but low aerobic capacity is also reported [17]. In this study therefore, we aimed to explore whether individuals with RA are less physically active and experience a decreased aerobic capacity, compared to healthy controls. In addition, we used a healthy reference population [18] to determine the percentile of aerobic capacity for individuals with RA as healthy controls might not be representative of the general population.

Methods

Literature search

Electronic databases Medline, Cinahl, Embase, Cochrane and PsycINFO were systematically searched up to November 2010 using the following Mesh terms and text words: (motor activity OR leisure activities OR human activities OR activities of daily living OR aerobic capacity OR energy expenditure) AND rheumatoid arthritis AND healthy, to find studies comparing patients with RA to healthy persons. In order to limit results to adults, the restriction NOT (child OR adolescent) was added. Reference lists from included studies were searched manually for additional relevant studies.

Inclusion criteria

Studies were included for review when following criteria were met.

- the target population: adults with RA (18 years and older)
- outcome measures: physical activity, energy expenditure or aerobic capacity
- at baseline the outcome measures were compared to those of healthy controls and values and measures of variability were described

Exclusion criteria

- single case reports
- studies describing a direct post operative situation
- studies written in any language other than English, German or Dutch

Using the above mentioned criteria, a researcher (TM) reviewed the titles of articles in the search printouts from the databases. Abstracts from potentially relevant studies were read and included when all criteria were met. After full text reading articles were finally included when all afore mentioned criteria were met. A manual search of references from included studies was conducted to retrieve further potentially relevant studies.

Assessing trial characteristics and outcome data

The following information was systematically extracted by reviewers TM and HW: type of study, number of participating patients with RA, sex, age, setting, body composition, disease duration, classification of impairment, use of medicines and outcome measures. Based on consensus, extracted data were included in the review.

Quality assessment of studies

Although a commonly accepted valid rating instrument concerning the quality assessment of observational studies does not yet exist, there appears to be consensus about important items [19-21]. This review focuses on differences between persons with RA and healthy controls. A comparison of patients and controls at baseline was used in the case of intervention studies. This resulted in the following assessment items: selection of patients and controls, sample size calculation, adjustment for confounding, blinding of assessors and use of statistical analysis.

Results

The literature search yielded 152 studies, from which nine double hits were excluded. Another 48 studies were excluded based on the title. Eighty-two studies were excluded based on abstracts. Thirteen studies were

retrieved for full text reading, which resulted in the exclusion of another article because no data concerning afore mentioned outcome measures was given. References tracking of the included studies did not yield new studies. Finally 12 studies were included. Results of the literature search and reasons for exclusion are depicted in Figure 1.

Quality assessment

The included studies were all observational studies: ten cross-sectional studies and two cohort studies. Six studies included small groups of patients [22-27], sample size varied from 8 to 35 patients. In six other studies [13,14,28-31] sample size ranged from 67 to 232 patients.

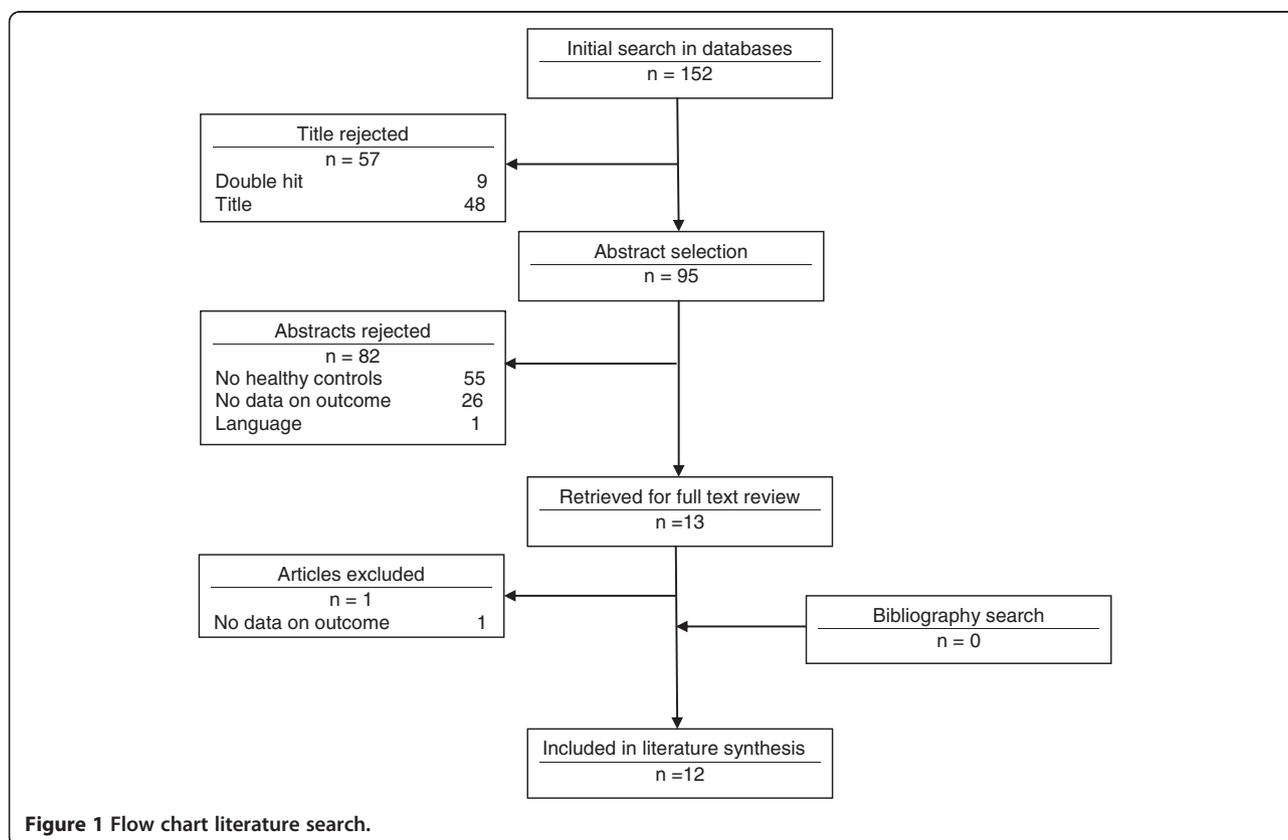
In seven studies [14,22,24-27,30] samples of patients and controls were of equal size, in the remaining 5 studies group sizes differed significantly [13,23,28,29,31]. The majority of the patients were recruited from rheumatology or arthritis clinics, in one study from a rehabilitation centre [24] and in two studies [28,29] the recruitment method was unclear. No information on the recruitment of controls was available in six of the studies [22,24-27,29]. In four studies healthy persons living in the same area were recruited [14,22,28,30], in one study healthy relatives acted as controls [31] and one study used information from the general Dutch population as reference [13].

Information about matching of patients and controls was reported in nine studies [22-24,26-31]. Different combinations of the following factors were used: race [26,27], age [22-24,26-28,30], gender [22,24,26,28,30] and body composition [22,26,27]. In one study groups were matched based on genetic and ethnic variables [31]. Having a sedentary lifestyle was a matching criterion in three [22,24,25] of the five studies [22-25,28] investigating aerobic capacity. Physically active participants were included in one study [23], whereas another study included controls to contrast with patients in terms of level of PA and body composition [29].

Three studies reported conducting sample size calculations [13,24,27]. Sample sizes were inadequate with regard to statistical analysis in two cases [13,24] and in the third study [27] adequacy of the sample size was not reported. None of the studies reported blinding of assessors. Six studies [22,24-27,31] reported that data were tested for the assumptions for parametric statistical tests or justified the use of non-parametric tests.

Patient characteristics

All patients met ACR criteria for RA [32]. Classification into Functional Class (FC) I – IV (mild to severe impairment) [33] was used in seven studies. In two studies patients were classified as FC II [24,28], in five studies patients with different levels of FC were combined in the



study population [22,23,25,26,31]. In most studies predominantly female participants were included, with percentages ranging from 62,5% to 88,6%. In three studies women only were included [23,27,31] and in one study gender of participants was not reported [24]. The mean age of patients ranged from 38.1 years to 62.6 years. The use of anti rheumatic drugs and analgesics was described in eight studies [14,23-28,31]. In six studies [14,22,24,25,27,31] patients were excluded because of severe cardio-pulmonary disease, or because they used a walking aid [27].

In three studies [14,24,31] participants with comorbidity other than cardiopulmonary disease were excluded. One study used a body mass index above 30 as an exclusion criterion [25] and exercising regularly was an exclusion criterion in another study [27]. Characteristics of patients and controls, disease parameters and results on aerobic capacity are presented in Table 1. Characteristics of patients and controls, disease parameters and results on EE and PA are presented in Table 2.

Physical activity energy expenditure

PA is defined as: "Any bodily movement produced by skeletal muscles that results in a substantial energy expenditure (EE)" [34]. EE is defined as energy expended during physical activity and measured in calories or joules per unit of time [35]. Physical activity energy expenditure (PAEE) can be calculated using the following equation: $PAEE = TEE - REE - TEF$, wherein TEE stands for Total EE, REE for resting EE and TEF stands for the thermal effect of food [35]. Three studies that measured REE, by indirect calorimetry, described similar values of REE in patients with RA and healthy controls [25-27], even when results were adjusted for body cell mass and weight [27]. However, when results were adjusted for percentage body fat, REE was higher in persons with RA compared to controls [25,26]. To calculate PAEE TEE was measured, using the doubly labeled water technique (DLW) in one study [27]. In the same study PAEE was estimated using a PA questionnaire and a PA monitor. Using these three forms of measurement PAEE was found to be significantly lower in persons with RA compared to controls. Results from the calculated PAEE correlated with results obtained with the PA monitor ($r = 0.37$) but not with the PA questionnaire.

Aerobic capacity

Aerobic capacity was examined in five studies. Two studies conducted a maximal treadmill test [22,24]. A maximal bicycle test was performed in two studies [23,25] and one study used a sub-maximal bicycle test [28].

Both treadmill studies measured oxygen uptake using the breath-by-breath method. Neither study reported significant differences in aerobic capacity between patients

and controls. One study used an incremental loading protocol to measure VO_2 at every stage of the treadmill test [22], until predicted maximal heart rate (HR_{max}) was reached (220 beats/min – age). Patients and controls were compared at the end of the last stage to determine VO_{2max} . However, 50%, 60% and 100% of patients of FC I, II and III respectively, dropped out before reaching the final stage of the test, compared to 5% of the healthy controls. EE at sub-maximal levels was higher in patients of FC II than in the control group, a difference that was not found when comparing patients of FC I with the control group. No statistical test was applied to detect differences between FC III and controls due to the small number of patients of FC III. The other treadmill study [24] used the Bruce protocol. The test was continued until voluntary exhaustion, no criteria for reaching VO_{2max} were given. VO_{2max} did not differ significantly between patients and controls, but this study had inadequate sample size.

Two studies conducted a graded bicycle test [23,25]. In the first study the test was continued until voluntary exhaustion, however, no criteria for reaching VO_{2max} were given [23]. Patients with early RA (mean disease duration 2.9 years) or long-term RA (mean disease duration 14.5 years) were compared with active healthy peers. At the end of the test mean HR_{peak} of participants fell within 5% of predicted HR_{max} and no significant differences between VO_{2max} of early RA (ERA), long-term RA (LRA) or control group were found. In the other study [25] VO_{2max} was defined as reaching one of the following three criteria: a plateau in oxygen uptake during the final stage of the test, respiratory exchange ratio > 1.0, or HR_{max} within 10% of expected goal. Patients with RA (mean age 41.8 years) were compared to groups of young and elderly controls. Persons with RA had a lower mean VO_{2max} compared to the young controls (mean age 25.8 years), whereas VO_{2max} of patients and elderly controls (mean age 69.5 years) did not differ significantly.

Finally, VO_{2max} was predicted using a submaximal Åstrand protocol during a bicycle test in one study [28]. Participants were divided in two categories (younger and older than 54 years) and bicycle test results were compared between males or females with RA and healthy controls. Persons with RA had lower estimated VO_{2max} compared to healthy control groups. Females had lower estimated VO_{2max} than males and estimated VO_{2max} decreased with age in all participants.

When comparing VO_{2max} levels of patients with RA to published normative values [18], results showed that patients in all studies scored below the 10th percentile.

Physical activity level

Six studies used questionnaires to assess PA level, focusing on different aspects of PA [13,14,26,29-31]. Classifying PA based on levels of intensity was done in two

Table 1 Studies comparing level of aerobic capacity in RA patients and a healthy reference population

| Study (ref nr) | n (% F) | Reference Population n (% F) | Patient characteristics | | | | | VO ₂ max RA patients versus reference population (ml/kg.min) p: significant difference | | |
|--------------------------|----------------------|--|-------------------------|---|--|-----------------------------------|--------------------------------------|---|------------------------------------|--|
| | | | Setting | Age [range] | Body Composition | Disease duration | Impairment (FC I-IV) | | | |
| de Carvalho 2003 MT [22] | 35 (88.6%) | 35♣ (?) hospital staff | Rheumatology clinic | 47,85 (8,29) | ? | 8 | FCI: 40% FCII: 51% FCIII: 8.6% | FC I: 24.89 (n=7) FC II: 21.86 (n=6)/ 24.28 (n=22) | NS | |
| Ekdahl 1992 SMB [28] | 67 (62.7%) | 77♥ (61.0%) personnel | ? | 53.0 (10.2) | female: 164.1 (5.6) cm female: 66.1 (11.6) kg male: 177.9 (6.8) cm male: 75.6 (10.7) kg | 10.6 (7.8) | FCII | female younger than 54 jr: 22.3±6.8 / 31.7±12.1 older than 54 jr: 18.7±3.5/ 21.9±5.3 male younger than 54 jr: 24.0±4.3/ 27.6±7.4 older than 54 jr: 18.7±4.1 / 25.1±6.1 | p<0.001 p<0.001 p<0.001 p<0.001 | |
| Häkkinen 2002 MB [23] | 23 (100%) ERA LRA | 12♠ (100%) area residence | Hospital | ERA: 41 (9) LRA: 49 (7) | ERA: 165 (9) cm 61 (13) kg fat: 30.4 (6.6) % LRA: 164 (7) cm 65 (13) kg fat: 34.3 (7.3) % | ERA: 2.9 (0.6) LRA: 14.5 (4.5) | FCI, II | ERA: 26.7±6.8/ LRA: 23.1±6.1/ controls: 24.8±2.3 | NS | |
| Kurtais 2006 MT [24] | 19 (100%) | 15♥ (100%) ? | Rehabilitation centre | 48.3 (8.4) | ? | 128.8 (85.6) months | FCI, II | 23.7±4.9 / 26.6±6.0 | NS | |
| Rall 1996 MB [25] | 8 (62.5%) | exercise young : 8 (62.5%) old: 8 (62.5%) control old: 6 (66.7%) ♦ | Rheumatology clinic | RA: 41.8±12.6 exercise young : 25.8±2.5 old : 70.3±5.0 control old 68.8±2.9 | 65.9 (15.9) kg BMI: 25.0 (4.3) | 14.6 (12.5) | FC: 2.2 (0.8) | 22.9±4.2 / young exercise group: 40.2±10.3 old exercise group: 20.7±5.0 old no exercise group: 21.7±5.7 young exercise versus other groups | p<0.001 | |

Age, body composition, disease duration are expressed as mean (standard deviation) if not expressed otherwise, VO₂max is expressed as mean ± standard deviation. Age and disease duration are expressed in years. n: number of participants with RA or in reference population, MB: maximal bicycle test, MT: maximal treadmill test, SMB: sub-maximal bicycle test, %F: percentage females, FC: Functional Class, GP: general population, BMI: body mass index, RA: rheumatoid arthritis, ERA: early RA, LRA: late RA, ml/kg.min: milliliter per kilogram per minute. Controls matched on ♣: sex, age, body mass index, ♠: age, ♥: age, sex, ♦: no information on matching.

Table 2 Studies comparing level of physical activity in RA patients and a healthy reference population

| Study (ref nr) | n (% F) | Reference populationn (%F) | Patients with RA | | | | | Physical activity RA patients versus reference population p: significant difference | |
|---------------------|-------------|------------------------------|---------------------|---------------------------------------|---------------------------------------|------------------|---|---|-----------------------------|
| | | | Setting | Age [range] | Body Composition | Disease duration | Impairment (FC I-IV) | | |
| v d Berg 2007 [13] | 232 (71.1%) | 6,428,441* (53%) GP records | Hospital based | 62.6 (9.2) 45–64 jr: 58% > 65 jr: 42% | ? | ? | ? | Light: 1297±1009 min/wk / 1495 min/wk Moderate: 369±543 min.wk / 517 min/wk Vigorous: 170±257 min/wk / 187 min/wk Light: 634±795 min/wk / 618 min/wk Moderate: 231±244 min/wk /304 min/wk Vigorous: 250±417 min/wk / 296 min/wk | p=0.01 p=0.01 p=0.01 p=0.01 |
| Lemney 2009 [29] | 73 (63.0%) | 28♦ (57%) ? | ? | 52.9 (12.9) | Fat 36.6 (12.8) % p<0.001 | ? | ? | Physical Activity Scale (0–7) 0.8±0.7 / 5.4±1.7 | p<0.001 |
| Mancuso 2007 [14] | 121 (84%) | 120 (91%) Personnel hospital | Hospital based | 49 (19–72) | ? | 14 (10) | ? | Walking: 692±610 kcal/w / 1,044±1260 kcal/w Stair climbing: 184±212 kcal/w / 185±262 kcal/w Exercise: 599±848 kcal/w / controls: 729±1210 kcal/w | p=0.002 |
| MacKinnon 2003 [30] | 143 (74.8%) | 142♥ (72.5%) area residence | Rheumatology clinic | 49.7 (11.2) | ? | ? | ? | Work 37.1±19.6 h/wk / 46.5±17.2 h/wk ADL 89.0±15.3 h/wk / 81.1±11.5 h/wk Leisure 38.4±15.4 h/wk / 37.9±15.6 h/wk | p<0.05 p<0.05 |
| Roubenoff 2002 [27] | 20 (100%) | 20♣ (100%) ? | Arthritis center | 47 (14) | BMI 25.3 (4.5) | 7.7 (6.5) | FC I FCII | PAEE 2849±1075 kJ/d / 3883±1732 kJ/d PA questionnaire 2188±1075 kJ/d / 3150±1611 kJ/d PA activity monitor 1264±992 kJ/d / 2280±1469 kJ/d | p<0.04 p<0.04 p<0.04 |
| Tourinho 2007 [31] | 71 (100) | 29♠ (100) sisters/cousins | Rheumatology clinic | 38.10 (6.62) | 1.57 (0.14) m 62.68 (12.56) kg | 30 (7,3) | FC I: 70% | Sedentarism 17.3 % / 3.4% Mild 57.7% / 35% Moderate 25% / 65% Intense 0% / 0% No exercise in leisure time 74% / 66.7% | p=0.004 p=0.004 |
| Roubenoff 1994 [26] | 23 (82.6) | 23◇ (82.6) ? | Rheumatology clinic | 50 (15) | Body cell mass 22.5 (4.3) kg p< 0.000 | 12.3±8.4 jr | FC I (n=5) FC II (n=10) FC III/IV (n=8) | Vigorous 0.1±0.2 h/d / 1.5±1.5 h/d Moderate 4.0±3.2 h/d / 5.6±2.3 h/d Light 11.6±3.4 h/d / 9.2±3.2 h/d | p<0.0001 p<0.06 p<0.02 |

Age, body composition, disease duration and physical activity are expressed as mean±standard deviation if not expressed otherwise. n: number of participants with RA or in reference population, RA: rheumatoid arthritis, FC: Functional Class, GP: general population, BMI: body mass index in kilogram per square meter, >: older than. kcal/wk: kilocalory per week, min/wk: minutes per week, kJ/d: kiloJoule per day, h/d: hours per day. Controls matched on ♣: race, age, body mass index, ♠: genetic factors, ♥: age, sex, ◇: race, age, sex, weight, ♦: controls selected to contrast on body fat, activity level, *: no information on matching.

studies [29,31]. Using a modified PA Scale to quantify intensity of PA undertaken during a normal week, patients with RA were found to be less engaged in moderate or intense recreational activities or sports [29]. When PA was classified into four levels (sedentary, mild, moderate or intense activities) [31], patients participated on a lower intensity level compared to a reference group. The patients did not engage in regular exercise and were identified to be 15% more sedentary compared to controls. There was a paucity of information on the instrument used to measure PA.

The Paffenbarger questionnaire [26] was used to measure hours per day spent in light, moderate or vigorous forms of PA. PA was defined as walking, stair climbing and sport and converted into EE per week. In another study time spent on PA was recorded during one week using an occupation log consisting of 10 different activities collapsed into 3 categories: work, activities of daily living (ADL) and leisure [30]. Results of these studies [26,30] showed that patients with RA spent an equal amount of time on PA as controls, but more time on light activities [26]. When PA was categorized as ADL, leisure and work, patients spent more time on ADL while spending less on work [30].

Finally the Short Questionnaire to Assess Health Enhancing PA (SQUASH) was used to estimate time spent on light, moderate and vigorous activities in a week [13]. PA was categorized into commuting activities, leisure time activities, household activities, and activities at work and school. Results [32] showed that the proportion of patients with RA meeting the public health recommendation for PA equaled that of the general public (58%), nevertheless younger patients (45 – 65 years) were less active in all categories than controls. Older patients (> 65 years) showed only a significant decrease in moderate PA compared to the reference group.

Modified versions of the Paffenbarger Physical Activity Questionnaire (PPAQ) were used in two trials [14,27] to calculate PAEE. Though similar proportions of patients and controls met recommended minimum levels of EE, patients with RA expended less energy in PA (24.7%), mainly due to walking less (33.7%) [14]. Roubenoff et al. [27] found comparable amounts of mean decreased PAEE in patients with RA (30.5%). Neither studies gave information on the way the PPAQ was modified and the consequences for PA assessment.

Discussion

The aim of this study was to review the literature about physical activity levels and aerobic capacity in patients with RA, compared to healthy controls and a healthy reference population.

Few studies were available that compared daily PA of persons with RA and healthy control groups. Studies

exploring aerobic capacity of persons with RA and healthy controls were even more scarce. Assessment methods, inclusion criteria and methodology of matching controls to patient were heterogeneous, complicating comparisons. No information on the recruitment of controls was available in 50% of the studies and in 25% of the studies there was no information on the matching of patients and controls. Selection bias may threaten the validity of these case-control studies and their results must be interpreted with caution.

Physical activity energy expenditure

The the gold standard measure to estimate PAEE is doubly labeled water (DLW) [36]. Only one study used DLW to assess EE. Roubenoff et al. [27] combined the use of DLW, a PA monitor and a questionnaire to calculate EE in PA. PAEE and the PA level was significantly lower in patients than controls, while REE was comparable in both groups. EE of patients in this study was comparable to normative data [1]. Results of DLW and the questionnaire did not correlate. This demonstrates a discrepancy between objective and subjective measurement.

Aerobic capacity

Studies using maximal tests reported no significant differences in aerobic capacity between persons with RA and healthy peers, except for one small sized study (n=8) [25]. Interestingly, in children, adolescents and young adults with Juvenile Arthritis, there is a large body of literature suggesting a reduced VO_{2max} in these patients [37-39]. This finding of a comparable aerobic capacity between patients with RA and healthy controls may be due to methodological issues, such as criteria for determining VO_{2max} . The use of secondary criteria of $RER \geq 1.10$ or 1.15 , $HR_{max} \pm 10$ b/min or blood lactate concentration can either lead to a significant undermeasurement of VO_{2max} or reject participants who have actually achieved VO_{2max} [40]. The criterium of reaching predicted HR_{max} calculated as $220 - \text{age}$ has little scientific basis and can under – or overestimate actual HR_{max} by more than 20 beats/min [41]. In a bicycle study VO_{2max} of patients (mean age 41.8 years) and elderly controls (mean age 69.5 years) did not differ significantly. As VO_{2max} declines with age, this means that patients had a low aerobic capacity. In the study of de Carvalho [22] HR_{max} of patients was significantly lower compared to controls and just reached 90% of predicted HR_{max} . In addition, 50%, 60% and 100% of patients of FC I, II and III respectively, dropped out before reaching the final stage of the test, whereas only 5% of healthy controls did, indicating a lower VO_{2max} in RA patients. The other treadmill study of Kurtais et al. [24] had inadequate sample size and did not report if participants reached their HR_{max} . In patients with LRA HR_{max} was lower

compared to persons with ERA and controls, but was within 10% of predicted HR_{max} in all groups [23]. Rall et al. [25] did not report if participants met preset criteria for reaching VO_{2max} .

Small samples combined with large heterogeneity of participants in lifestyle may have compromised the power of these studies [42]. Two studies used sedentary persons as controls [22,24]. Kurtais et al. [24] did not define sedentary, whereas de Carvalho et al. [22] defined sedentary as non-exercising. Hakkinen et al. [23] included physically active controls, but did not define physically active. When aerobic capacity was predicted by conducting a sub-maximal bicycle test [28] patients' VO_{2max} was decreased compared to controls. At baseline controls exercised more frequently compared to persons with RA. Results may be biased because sub-maximal tests of less fit people tend to underestimate observed values [35]. Moreover, submaximal tests use submaximal HR during exercise, which is influenced by resting HR. It is reported that resting HR is significantly higher in patients with RA [43], but correction for resting HR was not reported. Minor et al. [44,45] also showed that the correlation of predicted VO_{2max} and actual VO_{2max} diminished from 0.96 to 0.77 when a sub-maximal treadmill test, validated for use in a healthy population, was used for testing patients with RA.

Some reviewed studies included patients according to functional class. In the study that described results for separate functional classes [22], VO_{2max} decreased from FCI to FCIII and sub-maximal energy expenditure was higher in FCII and FCIII compared to FCI and controls. When VO_{2max} of persons with ERA and LRA was compared, persons with ERA experienced less disability and had higher VO_{2max} than persons with LRA and controls [23]. Although no information was available it is plausible that more persons of higher FC were allocated in de LRA group.

When comparing patients with RA VO_{2max} values to published normative data on healthy adults, patients consistently scored below the 10th percentile, indicating severe loss of aerobic capacity.

Studies with large, unselected, samples of patients with RA using rigorous exercise testing protocols and methodology are warranted [18].

Physical activity level

We found 6 studies, using 6 different questionnaires, limiting comparison across studies. In general it appears that patients with RA spend more time in light and moderate activities and less in vigorous activities than controls. Patients in the trial of de Carvalho et al. [22] expended significantly more energy than healthy controls, up to 17,9%, especially at normal walking speeds (3–5 km/h) [22]. Questionnaires using a standard

intensity categorization of PA might therefore underestimate energy expenditure of patients with RA. Some researchers report that one third of persons with RA experience cachexia [26,46], defined as a loss of muscle mass combined with higher fat mass and higher REE. Matching persons with RA and healthy controls on BMI and comparing EE based on METs may therefore lead to a biased result [47].

McKinnon et al. [30] found that patients were 20% less physically active, caused by less time spent on work. This may be due to the fact that more patients were unemployed compared to healthy controls: 43% - 86%, respectively [30]. Tourinho et al. [31] reported similar differences: 17.3% - 96.7% Patients with RA are at risk to become unemployed with increasing age and disease duration [48]. When PA level of persons with RA was compared to data from the Dutch population patients were less active. However, employed patients and controls showed comparable levels of PA (2577 min/wk vs 2433 min/wk) [13]. Mancuso et al. [14] found a decreased EE of 24.7% in patients compared to controls, even though all participants were employed at the start of the trial. Differences in results compared to other studies may have occurred because time spent at work is not assessed in the Paffenbarger Index.

Reduced vigorous activities and low VO_{2max} in patients with RA will place these patients at even greater risk for the metabolic syndrome and thus cardiovascular disease. We recommend counseling these patients on the benefits of exercise and doing research on the effect of (increased) exercise on CVD risk. Further research into factors that predict higher levels of PA in this population is to be recommended.

Conclusion

According to the gold standard persons with RA were less active compared to healthy subjects. The results of this review cannot support or refute a conclusion that persons with RA have decreased aerobic capacity compared to healthy controls. This may reflect the fact that half the general population is inactive. However, when compared to normative values patients as well as controls had very low percentile rank of aerobic capacity.

In general it appears that patients with RA spend more time in light and moderate activities and less in vigorous activities than controls. A higher functional class seems to be related to higher sub-maximal EE and lower levels of PA and aerobic capacity. Unemployment, possibly related to RA impairment, seems to contribute to a diminished physical activity level. Patients with RA suffer a 60% greater risk of CVD. Whether this risk can be reduced by a moderately high or high aerobic capacity as in healthy subjects, should be a research priority. Improving aerobic capacity in patients with RA seems of

the highest importance and vigorous physical activity can contribute to this. Aerobic training in stable RA has been shown to be safe [11] and improve aerobic capacity [49]. Future research should employ rigorous exercise testing protocols and methodology including the use of criteria for reaching VO_{2max} , differentiate between patients of different functional classes and take employment status into account.

Competing interests

The authors have declared no conflicts of interest.

Authors' contributions

TM: made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and drafting the manuscript. TT: revised the paper critically for important intellectual content; and gave final approval of the version to be published. HW: made substantial contributions to conception and design, analysis and interpretation of data, revised the paper critically for important intellectual content; and gave final approval of the version to be published. All authors read and approved the final manuscript.

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