Identifying factors hampering physical activity in longstanding rheumatoid arthritis: what is the role of glucocorticoid therapy?

M.C. van der Goes[1], J.N. Hoes[1], M.J. Cramer[2], M.J. van der Veen[3], J.H. van der Werf[4], J.W.J. Bijlsma[1], J.W.G. Jacobs[1]

[1]Department of Rheumatology & Clinical Immunology, and [2]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Rheumatology, St Jansdal Hospital, Harderwijk, The Netherlands; [4]Department of Rheumatology, Diakonessenhuis, Utrecht, The Netherlands.

Abstract

Objective

To identify factors hampering the level of physical activity in longstanding rheumatoid arthritis (RA) patients, and to evaluate the effects of glucocorticoid therapy on physical activity.

Methods

Patient characteristics, disease characteristics and cardiovascular parameters were recorded in 170 patients, who participated in a study about glucose metabolism in longstanding RA treated with or without glucocorticoids. Disease activity scores (DAS28) were calculated and x-rays of hands and feet were taken and scored according to the Sharp van der Heijde score (SHS). Participants completed the health assessment questionnaire and short questionnaire to assess health-enhancing physical activity (SQUASH), which reflect physical disability and physical activity, respectively. Adherence rates to recommendations on physical activity were calculated, and patients were categorised as fully adhering, insufficiently adhering (adherence on less than the recommended number of days per week) or inactive (adherence on none of the days).

Results

Forty-four percent of the patients showed adherence to the recommended minimum level of physical activity, and 22% were classified as inactive. Higher DAS28 and SHS, glucocorticoid therapy, and presence of cardiovascular risk factors were associated with lower total SQUASH physical activity scores univariately. In a multivariate model, higher age, higher body mass index (BMI), higher DAS28, and higher SHS negatively influenced the score significantly; cardiovascular risk factors and glucocorticoid therapy were no longer significantly influencing physical activity.

Conclusion

Physical activity in longstanding RA is hampered by higher age, higher BMI, higher disease activity, and more radiographic joint damage. Glucocorticoid therapy was not identified as independent risk factor in multivariate analyses.

Key words

rheumatoid arthritis, cardiovascular disease, physical activity, glucocorticoids

Marlies C. van der Goes, MD, PhD
Jos N. Hoes, MD, PhD
Maarten J. Cramer, MD, PhD
Maaike J. van der Veen, MD, PhD
Jacobine H. van der Werf, MD
Johannes W.J. Bijlsma, MD, PhD
Johannes W.G. Jacobs, MD, PhD

Please address correspondence and reprint requests to:
Marlies van der Goes, MD, PhD,
Department of Rheumatology & Clinical Immunology (F02.127),
University Medical Center Utrecht,
PO Box 85500,
3508 GA Utrecht, The Netherlands.
E-mail: m.c.vandergoes@umcutrecht.nl

Received on January 23, 2013; accepted in revised form on July 1, 2013.

Funding: this project was financially supported by Top Institute Pharma (project T1-106).

Competing interests: none declared.

Introduction

Worldwide there is awareness for generally rising levels of physical inactivity with major implications for the prevalence of non-communicable diseases and general health (1). Physical inactivity is within the top five leading risk factors for global mortality, together with high blood pressure, smoking, high blood glucose and obesity (2). Participation in regular physical activity reduces the risk of cardiovascular disease, some cancers, and type 2 diabetes (3). Leisure-time and mild-to-moderate occupational physical activity are associated with a reduced risk of myocardial infarction (4); even people who are physically active at levels below the minimum recommended level have significantly lower risk of coronary heart disease relative to those who are physically inactive (5).

Patients with rheumatoid arthritis (RA) have an increased risk of developing cardiovascular and cerebrovascular disease (6), probably based on elevated levels of pro-inflammatory cytokines such as tumour necrosis factor α and interleukin-6 in the systemic circulation with multiple effects on organs, including adipose tissue, and endothelium (7). These cytokines are also overproduced in dysfunctional adipose tissue of obese individuals (8). The resulting cascade of changes throughout the body driven by systemic inflammation leads to a pro-atherogenic profile: atherogenic lipid abnormalities, oxidative stress, depletion of endothelial progenitor cells associated with impairment of vascular injury repair, increased arterial stiffness, insulin resistance, endothelial dysfunction, hypercoagulable state, elevated homocysteine levels, and upregulation of atherogenic T cells (7).

Because of the increased risk of developing cardiovascular disease in RA, it is of utmost importance for health care professionals to promote physical activity, and possibly guide RA patients in achieving and maintaining a healthy lifestyle. Physical exercise is possible, even in active RA, increasing functioning (9-11), of which beneficial effects on walking speed are still present after three years (12), and decreasing the risk of cardiovascular disease (5), while not exacerbating disease activity (9, 11). In the Dutch population the proportion of RA patients meeting public health recommendations on physical activity (defined as moderate physical activity on five or more days every week) was similar to that of the general population (13). However, other studies showed decreased physical activity in RA (14, 15). The relation between glucocorticoids (GCs), often applied in the treatment of RA, and the development of cardiovascular disease is one of debate. Although randomised controlled trials have confirmed their effectiveness in terms of inhibiting progression of erosive joint damage in RA when applied in dosages up to 10 mg prednisone daily (16-22), GC exposure has been linked to adverse events and to increased carotid plaques, increased intima media thickness and arterial incompressibility in several studies (23-26). On the other hand, GC therapy in RA inhibits disease activity, hereby decreasing circulating levels of cytokines next to possibly increasing physical activity; GCs thus might decrease the risk of cardiovascular events in these patients.

Patient characteristics (*e.g.* age, gender), disease characteristics (*e.g.* disease activity, joint damage, pain, specific medications) as well as general cardiovascular risk factors may influence physical activity levels. Previously, univariate correlations between physical inactivity and cardiovascular risk factors such as suboptimal lipid levels and insulin resistance have been found in RA patients (27). However, the influence of the chronic inflammatory status in RA, possibly contributing to the increased cardiovascular risk, was not taken into account. Multivariate analyses correcting for disease activity and joint damage have not been performed before.

In this study, we assume a positive influence of physical activity on cardiovascular risk factors in longstanding RA patients and we aim to identify factors hampering the recommended minimum level of physical activity in longstanding RA patients.

Materials and methods

Patients

Patients with RA according to the 1987

American College of Rheumatology criteria (28), having a disease duration of two years or more, were recruited for a cross-sectional study on glucose metabolism and cardiovascular disease in five rheumatology clinics in the region of Utrecht, the Netherlands (29). Patients were either current and chronic (for at least three months) GC users or GC naïve. An independent ethics committee approved the study and all patients provided written informed consent before participation. The protocol was according to the Declaration of Helsinki.

Protocol

Participants visited the outpatient clinic following an overnight fast of minimally ten hours. During the visits, a physical examination including recording of height, weight, waist circumference, tender joints and swollen joints was performed and fasting blood tests were acquired (29). All participants underwent a two hour oral glucose tolerance test and a resting 6-lead electrocardiogram. Framingham scores on the 10-years risk of coronary artery disease were calculated (30). Finally, radiographs of hands and feet were made and scored for erosions and joint space narrowing according to the Sharp van der Heijde score (SHS, range 0–448) by an experienced reader blinded for patient characteristics and treatment (31).

Questionnaires

Patients completed the Stanford Health Assessment Questionnaire (HAQ) and the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) at home in the days preceding the visit, and brought them to the hospital. The HAQ is a frequently used questionnaire to measure physical disability in RA (range 0–3; 0 = no disability, 3 = severe disability) (32, 33). The SQUASH has been developed by the Dutch National Institute of Public Health and the Environment, has been designed to give an indication of the habitual activity level, and has been described as a fairly reliable tool with validity comparable to other questionnaires (34, 35). The questionnaire has been used in RA patients as well as patients other diseases, such as diabetes, cancer, multiple sclerosis, chronic obstructive lung disease and hip or knee replacement surgery (13, 36-42). The questionnaire covers items similar to those in the long-format International Physical Activity Questionnaire, which has been studied in more detail (43). The SQUASH questionnaire asks participants to recall their usual pattern of physical activity during an average week through ten questions on the number of days spent per week, the average time spent per day and the intensity regarding four activity domains: commuting activities, activities at work or school, household activities and leisure time activities including sports. The activities are categorised into light, moderate or vigorous intensity activities, and presented in multiples of metabolic equivalents (MET, kcal/kg/h) of sitting quietly (resting metabolic rate) for 1 hour (34, 44). Based on the reported effort in the questionnaire, activities are given an intensity score (ranging from 1 to 9). The total time of physical activity per week is calculated by multiplying frequency (days per week) by duration (minutes per day) for every type of activity category. Activity scores are calculated by multiplying total minutes of activity by the intensity score. The activity scores of all domains are added up, resulting in the final total SQUASH physical activity score.

Calculating prevalence of adherence to recommended physical activity

The Dutch and international guideline for recommended physical activity state that adults should be physically active at a moderate intensity for at least 30 minutes each day for a minimum of 5 days per week, or at a vigorous intensity for a minimum of 20 minutes on at least 3 days per week (45). Depending on age (for people below the age of 55 years: moderate intensity with MET 4.0 to <6.5 and vigorous intensity with MET ≥6.5; and for people of age 55 or above: moderate intensity with MET 3.0 to <5.0 and vigorous intensity with MET ≥5.0) and the reported activity, patients are scored as meeting the recommended level of physical activity, as being insufficiently physically active (less than 5 days of moderate intensity activity or less than 3 days of vigorous intensity), or as being inactive (0 days of performing the recommended activity).

Statistical analyses

Differences between two groups (*e.g.* men *vs.* women, patients aged below 65 *vs.* aged 65 and above) in means of continuous data were tested with independent samples *t*-tests or Mann Whitney-U tests, where appropriate, and differences in categorical data with Chi-square tests. For the correlation of continuous data with activity scores, Spearman's correlations were applied.

Additionally, multivariate linear regression analyses were performed to assess the influence of patient characteristics, disease severity and cardiovascular parameters on physical activity (total SQUASH physical activity score) as dependent variable. Gender, age, disease duration, current disease-modifying anti-rheumatic drug (DMARD) use, current GC use, current biological use, presence of anti-citrullinated protein antibodies, C-reactive protein, disease activity score of 28 joints (DAS28), SHS, body mass index (BMI), abdominal obesity, dyslipidemia, hypertension, and diabetes were used as independent variables. A backward selection strategy was applied.

The statistical software SPSS 18.0 was used for analyses of data. *P*-values below 0.05 were considered statistically significant.

Results

Adherence to general recommendations on physical activity

In total, 165 patients were included in this study, of which 71% were female. Forty-four percent of the patients showed adherence to the recommended physical activity, 34% were insufficiently physically active, and 22% were inactive.

Disease characteristics and cardiovascular parameters

The median disease duration was 15 years. Most patients were treated with conventional DMARDs, and therapy with biologicals or GCs was used in

respectively 36 and 43%. Thirty-five percent had low disease activity (*i.e.* DAS28 below 2.6) compared to 59% with moderate and 6% with high disease activity (*i.e.* DAS28 above 5.1). The disease characteristics and cardiovascular parameters are summarised in Table I separately for patients fully adhering to recommendations, being insufficiently active, and being inactive. Abnormal electrocardiograms were encountered in 39 patients; most frequent were repolarisation disorders (62%), followed by left ventricular hypertrophy (26%). Six of these patients had a medical history of coronary artery disease; the other 33 patients were referred to the cardiology department for additional testing; significant ischaemic heart disease was found in 1, and clinically relevant conduction problems led to pacemaker implantation in 3 patients. The patients with coronary artery disease or conduction disorders were older (mean age 70 *vs.* 57 years, p=0.001), had a greater waist circumference (100 *vs.* 90 cm, p=0.001), and a higher systolic blood pressure (137 *vs.* 125 mmHg, p<0.05) compared to those without these cardiac problems. The other 29 patients did not have clinically significant cardiovascular diseases and received preventive life style advices on cardiovascular disease and therapy to lower blood pressure or blood lipids, where appropriate.

Table I. Patient characteristics.

	Inactive n=36	Insufficiently active n=57	Adhere to recommended activity n=72
Age (years)	57 ± 12	57 ± 12	60 ± 11
Female gender (%)	83	74	64
Disease characteristics			
Disease duration (years)	18 (5–28)	17 (8–23)	11 (7–20)
Current treatment with conventional DMARDs (%)	83	81	85
Current treatment with biologicals (%)	25	44	33
Current treatment with glucocorticoids (%)	53	51	32
Tender joint count of 28 joints (n)	3 (0–8)	1 (0–4)	1 (0–3)
Swollen joint count of 28 joints (n)	0 (0–2)	0 (0–1)	0 (0–1)
ESR (mm/hour)	18 (9–41)	14 (8–23)	13 (7–22)
VAS general well-being (mm) (range 0 to 100)	43 (30–50)	30 (10–50)	20 (10–30)
DAS28	3.7 ± 1.5	3.1 ± 1.2	2.9 ± 1.3
SharpvanderHeijde score (range 0 to 448)	31 (3–178)	31 (6–142)	29 (4–121)
HAQ (range 0 to 3)	1.6 ± 0.9	1.2 ± 0.7	0.8 ± 0.6
Cardiovascular risk profile			
BMI (kg/m^2)	28 (24–32)	26 (23–29)	24 (22–27)
Increased waist circumference* (%)	56	34	25
Smoking (pack-years)	0 (0–16)	3 (0–14)	5 (0–20)
SBP (mmHg)	128 ± 18	124 ± 17	126 ± 19
DBP (mmHg)	75 ± 9	73 ± 10	73 ±10
Hypertension* or antihypertensive drugs (%)	64	56	57
Diabetes* (%)	33	11	19
IGM* (%)	39	15	25
Anti-diabetic treatment (%)	22	4	10
Dyslipidaemia* (%)	50	38	35
Statin use (%)	31	7	15
Cardiovascular events			
Transient ischaemic attack (n)	1	1	1
Cerebrovascular attack (n)	2	2	2
Coronary artery disease (n)	1	3	1

Data represent mean ± standard deviation, or median (interquartile range) when data was not normally distributed.

*VAS general well-being ranged from 0 (worst score) to 100 (best score). Sharp van der Heijde score ranged from 0 (no damage) to 448 (maximal damage). HAQ ranged from 0 (best score) to 3 (worst score). Increased waist circumference was defined as >102 cm in male and >88 cm in female. Hypertension was defined as ≥140 mmHg systolic or 90 mmHg diastolic pressure. Diabetes was defined as either fasting plasma glucose ≥7.0 or ≥11.1 mmol/L at 120 minutes of OGTT. IGM was defined as either fasting plasma glucose (<7.0 and >6.0 mmol/L) or impaired glucose tolerance (<11.1 and ≥7.8 mmol/L at 120 minutes of OGTT). Dyslipidemia was defined as triglycerides >1.7 mmol/L and/or HDL-cholesterol <0.9 mmol/L in male and <1 mmol/L in female.

DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; DAS28: disease activity score using 28 joints; HAQ: health assessment questionnaire; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; IGM: impaired glucose metabolism; OGGT: oral glucose tolerance test; HDL: high density lipoprotein.

Physical activity

Physical activity scores according to the SQUASH are presented in Table II. A mean of 48% of total activity time was reported for household activities. Leisure activities and sports took 33%. For activities at work and commuting activities this was 17 and 1%, respectively.

Influence of patient characteristics

There was no significant difference in total time spent on physical activity and total activity score between men and women (p=0.27 and p=0.47, respectively), although men spent a higher percentage of activity time on leisure and sport activities (p<0.001) and women on household activities (p<0.001). Fifty-five percent of men compared to 39% of women adhered to the general recommendations on physical activity (p=0.10). The percentage of patients adhering to recommendations was similar in the group aged 65 or above compared to the group below the age of 65 years (data not shown).

Influence of RA characteristics

Current disease activity (reflected by the DAS28) and radiographic joint damage (SHS) were negatively correlated with the physical activity score (R=-0.316, p<0.001 and R=-0.158, p<0.05), as was disease duration (R=-0.164, p<0.05). Use of conventional DMARDs or biologicals did not significantly influence physical activity levels. In contrast, GC therapy and the cumulative GC dose both had a significant negative impact on the physical activity level (p<0.01 and R=-0.194, p=0.02).

Influence of cardiovascular risk factors

In univariate analyses, decreased physical activity was associated with presence of the cardiovascular risk factors abdominal obesity, hypertension, diabetes, elevated triglycerides, metabolic

Table II. Physical activity in longstanding RA.

Physical activity	Minutes / week		Activity score	
Commuting				
Walking	0 (0–0)	5 ± 27	0 (0–0)	9 ± 54
Bicycling	0 (0–0)	12 ± 51	0 (0–0)	61 ± 254
Activities at work				
Light	0 (0–480)	402 ± 748	0 (0–960)	804 ± 1495
Intense	0 (0–0)	48 ± 283	0 (0–0)	238 ± 1412
Household activities				
Light	450 (90–1050)	729 ± 856	1080 (200–2100)	1494 ± 1717
Intense	0 (0–30)	42 ± 112	0 (0–150)	215 ± 563
Leisure time				
Walking	60 (0–180)	112 ± 134	120 (0–290)	205 ± 273
Bicycling	30 (0–120)	82 ± 186	135 (0–600)	420 ± 945
Gardening	0 (0–60)	63 ± 163	0 (0–300)	302 ± 804
Odd jobs	0 (0–0)	42 ± 137	0 (0–0)	76 ± 231
Sports	0 (0–90)	63 ± 107	0 (0–420)	322 ± 648
Total	1500 (540–2355)	1579 ± 1235	3650 (1320–5910)	4016 ± 3288

The SQUASH activity scores give an indication of the habitual activity level. Participants were asked to recall the number of days spent per week, the average time spent per day and the intensity regarding four activity domains: commuting activities, activities at work or school, household activities and leisure time activities. Based on the reported effort in the questionnaire, activities were given an intensity score (ranging from 1 to 9). Activity scores were calculated by multiplying total minutes of activity by the intensity score. Minutes/week and activity scores are in median (interquartile range) and mean ± SD.

Table III. Multivariate model for physical activity in longstanding RA.

Linear regression (backward strategy, entry p=0.05, removal p=0.1)
Outcome: physical activity score

R^2 0.247	Absolute beta (95% CI)	p-value	Standardised beta
Constant	14638 (11208 to 18068)	<0.001	
Age (years)	-76 (-117 to -36)	<0.001	-0.272
BMI (kg/m^2)	-142 (-237 to -46)	<0.01	-0.221
DAS28	-610 (-1011 to -208)	<0.01	-0.226
SHS	-6 (-11 to -1)	0.02	-0.175

Excluded from model: gender, disease duration, current conventional DMARD use, current GC use, current biological use, presence of anti-citrullinated protein antibodies, C-reactive protein, presence of metabolic syndrome according to US National Cholesterol Education Program Adult Treatment Panel III definition (2001) or its separate parameters abdominal obesity, dyslipidaemia, hypertension and diabetes, because of non significance.
CI: confidence interval; BMI: body mass index; DAS28: disease activity score using 28 joints; SHS: Sharp van der Heijde score; DMARD: disease-modifying anti-rheumatic drug; GC: glucocorticoid.

syndrome, and cardiovascular disease. The calculated Framingham scores on the 10-years risk of coronary artery disease (based on gender, age, low and high density lipoproteins, blood pressure, diabetes and smoking) as a surrogate marker for cumulative cardiovascular risk correlated negatively with physical activity (R=-0.282, p=0.001).

Multivariate model

Combining patient characteristics, RA characteristics and cardiovascular parameters in a multivariate regression model showed that higher age, higher BMI, higher DAS28, and higher SHS significantly negatively influenced the total activity score (see Table III). Cardiovascular parameters (*i.e.* abdominal obesity, dyslipidaemia, hypertension, diabetes, or these taken together as metabolic syndrome) and GC therapy were no longer significantly correlated with physical activity.

Discussion

This study shows that physical activity in RA patients is hampered by higher age, higher BMI, higher DAS28 and higher SHS. With correction for age and disease activity, univariate associations of cardiovascular risk factors and GC therapy with physical activity disappeared. This indicates that GC therapy itself does not contribute to diminished physical activity but that the negative impact of active RA, for which GCs probably have been prescribed (channeling bias), is important on physical activity. The strengths of this study are the detailed examination of RA including cardiovascular risk factors, and the integration of patient characteristics, disease characteristics and cardiovascular risk factors in multivariate analyses. Validated questionnaires have been used to assess physical activity and functioning (32-34). Remarkable findings are the small amounts of time spent on commuting and activities at work, which are probably explained by the majority of patients being women with a mean age of 58 years. The rate of adherence to recommended physical activity in our study was lower than that in an earlier study in RA showing adherence, comparable to that found in the general Dutch population, of 58%. (13). Higher inactivity rates were also found in other studies (14, 15), and a recent meta-analysis suggested physical activity may be lower in RA compared to healthy controls (46). Low physical activity has been associated with increased cardiovascular risk factors in RA, but the influence of radiographic joint damage, which was statistically significant in our study, was not corrected for in earlier analyses (47). Although physical activity was limited by age in the multivariate analysis, adherence rates were similar for people aged over and age below 65 years, based on different definitions of adherence for these age groups. Multivariate analyses showed stronger influence of age and radiological joint damage than of disease duration, indicating that disease severity (*i.e.* development of joint damage) has higher influence than disease duration. A negative impact of GC therapy was identified at univariate analysis, but multivariately, after correcting for age, BMI, and disease activity, the influence of GC therapy was no longer significant.

It is difficult to estimate the exact im-

pact of decreased physical activity on daily functioning on the risks of cardiovascular disease in RA patients. Our findings that older patients (mean age 70 versus 57 years, p=0.001) with an increased waist circumference (100 versus 90 cm, p=0.001) were predominantly the ones with clinically significant heart disease seem to indicate that the previously described elevated cardiovascular risk in RA may largely be attributed to patients with severe RA, who become inactive and develop (abdominal) obesity. The ongoing inflammation and the accompanying limitation in physical functioning can put especially these patients at risk; the low level of physical activity in these patients is probably insufficient to counteract endothelial dysfunction, atherogenic effects, and inflammatory effects (48).

Physical inactivity and disease activity are also important predictors of the number and length of hospital admissions of RA patients. The combination of lifestyle changes, particularly increased physical activity, along with effective pharmacological therapy may improve multiple health outcomes as well as cost of care for RA patients (49) without increasing disease activity or joint damage (50-52). Stronger beliefs that physical activity can be helpful for managing disease and increased motivation to engage in physical activity are related to higher levels of physical activity participation (53). Nevertheless, although rheumatologists, nurses, and physical therapists are aware of the positive effects of physical activity, they rated their competency to promote physical activity as low to medium; of these health care workers, 54%, 85%, and 72% respectively expressed a need for additional education regarding this topic (54). So, specific physical activity programmes improving the physical functioning of patients may be of additional value.

A limitation of this study is the cross-sectional design, thus follow up information on the development of cardiovascular risk factors or disease is absent. Although the association between high BMI and low physical activity levels is clear and has been described before (55), it is impossible to determine the mutual interactions of these two factors as cause and consequence. Additionally, this study was based on self-reported levels of physical activity, which may be subject to response bias – due both to recall bias and social desirability (56), leading to reporting of desired levels or highest levels of physical activity instead of the actual level (57). However, the reported physical activity was lower than in an earlier study with RA patients (13), and roughly corresponds with other studies among European populations, while lower physical activity rates have been described for inhabitants of the United States (55).

In conclusion, physical activity in longstanding RA is hampered by higher age, higher BMI, higher current disease activity, and radiographic joint damage.

References

1. Global recommendations on physical activity for health. Geneva, World Health Organization 2010.
2. GLOBAL HEALTH RISKS: mortality and burden of disease attributable to selected major risks. Geneva, World Health Organization 2009.
3. The World Health Report 2002. Reducing Risks, Promoting Healthy Life. Geneva, World Health Organization 2002.
4. HELD C, IQBAL R, LEAR SA *et al*.: Physical activity levels, ownership of goods promoting sedentary behaviour and risk of myocardial infarction: results of the INTERHEART study. *Eur Heart J* 2012; 33: 452-66.
5. SATTELMAIR J, PERTMAN J, DING EL *et al*.: Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011; 124: 789-95.
6. WOLFE F, FREUNDLICH B, STRAUS WL: Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol* 2003; 30: 36-40.
7. KU IA, IMBODEN JB, HSUE PY, GANZ P: Rheumatoid arthritis: model of systemic inflammation driving atherosclerosis. *Circ J* 2009; 73: 977-85.
8. HAJER GR, VAN HAEFTEN TW, VISSEREN FL: Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008; 29: 2959-71.
9. DE JONG Z, MUNNEKE M, ZWINDERMAN AH *et al*.: Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. *Arthritis Rheum* 2003; 48: 2415-24.
10. NEUBERGER GB, AARONSON LS, GAJEWSKI B *et al*.: Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 943-52.
11. WESTBY MD, WADE JP, RANGNO KK, BERKOWITZ J: A randomized controlled trial to evaluate the effectiveness of an exercise program in women with rheumatoid arthritis taking low dose prednisone. *J Rheumatol* 2000; 27: 1674-80.
12. LEMMEY AB, WILLIAMS SL, MARCORA SM, JONES J, MADDISON PJ: Are the benefits of a high-intensity progressive resistance training program sustained in rheumatoid arthritis patients? A 3-year followup study. *Arthritis Care Res* (Hoboken) 2012; 64: 71-5.
13. VAN DEN BERG MH, DE BOER IG, LE CESSIE S, BREEDVELD FC, VLIET VLIELAND TP: Are patients with rheumatoid arthritis less physically active than the general population? *J Clin Rheumatol* 2007; 13: 181-6.
14. SOKKA T, HAKKINEN A, KAUTIAINEN H *et al*.: Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. *Arthritis Rheum* 2008; 59: 42-50.
15. LEE J, DUNLOP D, EHRLICH-JONES L *et al*.: The public health impact of risk factors for physical inactivity in adults with rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2012.
16. BAKKER MF, JACOBS JW, WELSING PM *et al*.: Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012; 156: 329-39.
17. CHOY EH, SMITH CM, FAREWELL V *et al*.: Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 656-63.
18. KIRWAN JR: The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. *N Engl J Med* 1995; 333: 142-6.
19. KIRWAN JR, BIJLSMA JW, BOERS M, SHEA BJ: Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev* 2007: CD006356.
20. SVENSSON B, BOONEN A, ALBERTSSON K *et al*.: Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005; 52: 3360-70.
21. VAN EVERDINGEN AA, JACOBS JW, SIEWERTSZ VAN REESEMA DR, BIJLSMA JW: Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002; 136: 1-12.
22. WASSENBERG S, RAU R, STEINFELD P, ZEIDLER H: Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3371-80.
23. DEL RINCON I, O'LEARY DH, HAAS RW, ESCALANTE A: Effect of glucocorticoids on the arteries in rheumatoid arthritis. *Arthritis Rheum* 2004; 50: 3813-22.

24. KUMEDA Y, INABA M, GOTO H *et al*.: Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 1489-97.
25. PARK YB, AHN CW, CHOI HK *et al*.: Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum* 2002; 46: 1714-9.
26. SOLOMON DH, KARLSON EW, RIMM EB *et al*.: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003; 107: 1303-7.
27. ELKAN AC, HAKANSSON N, FROSTEGARD J, HAFSTROM I: Low level of physical activity in women with rheumatoid arthritis is associated with cardiovascular risk factors but not with body fat mass--a cross sectional study. *BMC Musculoskelet Disord* 2011; 12: 13.
28. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
29. HOES JN, VAN DER GOES MC, VAN RAALTE DH *et al*.: Glucose tolerance, insulin sensitivity and {beta}-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. *Ann Rheum Dis* 2011; 70: 1887-94.
30. WILSON PW, D'AGOSTINO RB, LEVY D *et al*.: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837-47.
31. VAN DER HEIJDE DM, VAN RIEL PL, NUVERZWART IH, GRIBNAU FW, VAN DE PUTTE LB: Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989; 1: 1036-8.
32. FRIES JF, SPITZ PW, YOUNG DY: The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982; 9: 789-93.
33. BOERS M, JACOBS JW, VAN VLIET VLIELAND TP, VAN RIEL PL: Consensus Dutch health assessment questionnaire. *Ann Rheum Dis* 2007; 66: 132-3.
34. WENDEL-VOS GC, SCHUIT AJ, SARIS WH, KROMHOUT D: Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003; 56: 1163-9.
35. WAGENMAKERS R, VAN DEN AKKER-SCHEEK I, GROOTHOFF JW *et al*.: Reliability and validity of the short questionnaire to assess health-enhancing physical activity (SQUASH) in patients after total hip arthroplasty. *BMC Musculoskelet Disord* 2008; 9: 141.
36. BOSSENBROEK L, TEN HACKEN NH, VAN DER BIJ W *et al*.: Cross-sectional assessment of daily physical activity in chronic obstructive pulmonary disease lung transplant patients. *J Heart Lung Transplant* 2009; 28: 149-55.
37. WAGENMAKERS R, STEVENS M, GROOTHOFF JW *et al*.: Physical activity behavior of patients 1 year after primary total hip arthroplasty: a prospective multicenter cohort study. *Phys Ther* 2011; 91: 373-80.
38. WAGENMAKERS R, STEVENS M, ZIJLSTRA W *et al*.: Physical activity behavior of patients 1 year after primary total hip arthroplasty: a prospective multicenter cohort study. *Phys Ther* 2008; 88: 1039-48.
39. GROEN JW, STEVENS M, KERSTEN RF, REININGA IH, VAN DEN AKKER-SCHEEK I: After total knee arthroplasty, many people are not active enough to maintain their health and fitness: an observational study. *J Physiother* 2012; 58: 113-6.
40. KERSTEN RF, STEVENS M, VAN RAAY JJ, BULSTRA SK, VAN DEN AKKER-SCHEEK I: Habitual physical activity after total knee replacement. *Phys Ther* 2012; 92: 1109-16.
41. VAN WAAS M, WIJNEN M, HARTMAN A *et al*.: Daily life physical activity in long-term survivors of nephroblastoma and neuroblastoma. *J Pediatr Hematol Oncol* 2013.
42. ADMIRAAL WM, VAN VALKENGOED IG, JS LDM *et al*.: The association of physical inactivity with Type 2 diabetes among different ethnic groups. *Diabet Med* 2011; 28: 668-72.
43. CRAIG CL, MARSHALL AL, SJOSTROM M *et al*.: International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35: 1381-95.
44. AINSWORTH BE, HASKELL WL, HERRMANN SD *et al*.: 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011; 43: 1575-81.
45. HASKELL WL, LEE IM, PATE RR *et al*.: Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007; 39: 1423-34.
46. TIERNEY M, FRASER A, KENNEDY N: Physical Activity in Rheumatoid Arthritis: A Systematic Review. *J Phys Act Health* 2011: [Epub ahead of print].
47. METSIOS GS, STAVROPOULOS-KALINOGLOU A, PANOULAS VF *et al*.: Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. *Eur J Cardiovasc Prev Rehabil* 2009; 16: 188-94.
48. METSIOS GS, STAVROPOULOS-KALINOGLOU A, SANDOO A *et al*.: Vascular function and inflammation in rheumatoid arthritis: the role of physical activity. *Open Cardiovasc Med J* 2010; 4: 89-96.
49. METSIOS GS, STAVROPOULOS-KALINOGLOU A, TREHARNE GJ *et al*.: Disease activity and low physical activity associate with number of hospital admissions and length of hospitalisation in patients with rheumatoid arthritis. *Arthritis Res Ther* 2011; 13: R108.
50. NORDEMAR R, EKBLOM B, ZACHRISSON L, LUNDQVIST K: Physical training in rheumatoid arthritis: a controlled long-term study. I. *Scand J Rheumatol* 1981; 10: 17-23.
51. HAKKINEN A, HAKKINEN K, HANNONEN P: Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. *Scand J Rheumatol* 1994; 23: 237-42.
52. HAKKINEN A, SOKKA T, KOTANIEMI A, HANNONEN P: A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 515-22.
53. EHRLICH-JONES L, LEE J, SEMANIK P *et al*.: Relationship between beliefs, motivation, and worries about physical activity and physical activity participation in persons with rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2011; 63: 1700-5.
54. HURKMANS EJ, DE GUCHT V, MAES S *et al*.: Promoting physical activity in patients with rheumatoid arthritis: rheumatologists' and health professionals' practice and educational needs. *Clin Rheumatol* 2011; 30: 1603-9.
55. BASSETT DR, JR., PUCHER J, BUEHLER R, THOMPSON DL, CROUTER SE: Walking, cycling, and obesity rates in Europe, North America, and Australia. *J Phys Act Health* 2008; 5: 795-814.
56. SHEPHARD RJ: Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med* 2003; 37: 197-206.
57. MOTL RW, MCAULEY E, DISTEFANO C: Is social desirability associated with self-reported physical activity? *Prev Med* 2005; 40: 735-9.