Research Clerkship M3

The influence of BMI and smoking at disease onset on long-term joint damage measured with the RAAD score in patients with rheumatoid arthritis

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Abstract Dutch

Introductie: na de introductie van nieuwe effectieve medicatie en op remissie gerichte behandeling is de prognose van reumatoïde artritis (RA) sterk verbeterd. Opmerkelijk is dat obesitas genoemd wordt als mogelijke voorspeller van minder gewrichtsschade op lange termijn. De literatuur is echter niet eenduidig over de relatie tussen body mass index (BMI) en lange termijn gewrichtsschade. Over het effect van roken op lange termijn gewrichtsschade is weinig bekend en resultaten spreken elkaar tegen. Bewerkelijke radiografische scoringsmethodes, zoals de Sharp van der Heijde score (SHS) en Larsen score, worden in klinische studies gebruikt ter evaluatie van gewrichtsschade. De Rheumatoid Arthritis Articular Damage (RAAD) score werd in 2002 geïntroduceerd als eenvoudig toepasbaar meetinstrument voor gewrichtsschade. De RAAD score heeft een hoge correlatie met de SHS. In deze studie is onderzocht of BMI en roken ten tijde van het stellen van de diagnose van de ziekte samenhangen met irreversibele gewrichtsschade op lange termijn, gemeten met de RAAD score.

Patiënten en methode: de onderzoekspopulatie betreft alle patiënten die behandeld zijn voor RA in de Ziekenhuisgroep Twente van januari 1996 tot en met december 2015. Uit deze populatie werden patiënten geïncludeerd met een ziekteduur van minstens vijf jaar ten tijde van de RAAD score, bepaald in de periode juli 2014 tot april 2016. Baselinekarakteristieken werden retrospectief verzameld uit gedigitaliseerde dossiers en door navraag bij patiënten. Rookstatus op baseline is ingedeeld in de groepen: nooit gerookt, gestopt met roken, rookt. Mann Whitney U testen, Spearman's correlaties, Kruskal-Wallis testen en multivariate regressie analyses zijn uitgevoerd.

Resultaten: baselinekarakteristieken studie populatie (n=521): 67.8% vrouw, gemiddelde (SD) leeftijd in jaren 49.0 (13.7), gemiddelde (SD) BMI in kg/m^2 25.7 (3.9), 79.5% reumafactor positief, 72.6% anti-CCP positief, 36.8% nooit gerookt, 28.4% gestopt met roken, 34.8% rookt. De mediane [IQR] RAAD score was 2.0 [0-6.0]. Er was een significante, zwakke correlatie tussen BMI en de RAAD score (correlatie coëfficiënt -0.14, p=0.003). Er was geen significant verschil in de RAAD score tussen de rookstatus groepen. Ziekteduur was vanzelfsprekend gecorreleerd met de RAAD score, irreversibele schade kan per definitie enkel toenemen. Ziekteduur was gecorreleerd aan BMI. Gedurende de decades was er in deze onderzoekspopulatie een toename van BMI en een geringe afname van het aantal rokers bij het begin van de ziekte. Uit multivariate analyse, waarin gecorrigeerd werd voor ziekteduur, bleek dat BMI niet gecorreleerd was aan de RAAD score.

Conclusie: BMI en rookstatus bij het begin van RA zijn niet gerelateerd aan gewrichtsschade op lange termijn zoals gemeten met de RAAD score, wanneer gecorrigeerd voor ziekteduur. Met ziekteduur is ook gecorrigeerd voor de trend in BMI gedurende de afgelopen decaden.

Abstract English

Introduction: after the development of new effective medication and the introduction of "treat-to-target" strategies directed at obtaining remission, the prognosis of RA greatly improved. Remarkably, obesity is named as a predictor of less radiographic progression. The literature is not clear about the relation between body mass index (BMI) and long-term joint damage. Little evidence about the long-term effect of smoking on joint damage is available. Time consuming radiographic scoring methods, such as the Sharp van der Heijde (SHS) and Larsen score, are frequently used in clinical research to evaluate joint damage of hands and feet. In order to have an easy applicable instrument to measure joint damage, Zijlstra et al. developed the RAAD score in 2002. A high correlation between the RAAD score and the SHS has been found. The present study investigated whether BMI and smoking at the moment of diagnosis are related with irreversible joint damage at long-term, measured with the RAAD score.

Patients and methods: the research population consists of all patients who received treatment for RA in the ZGT from January 1996 until December 2015. From this population patients with a RAAD score, determined between 2014 and April the first of 2016, and a disease duration of at least five years at the moment of the RAAD score were included. Baseline data were collected through retrospective record research and through verifying information during an outpatient visit. Smoking at disease onset was categorized in three groups: current smoker, former smoker, non smoker. Mann Whitney U tests, Spearman's correlations, Kruskal-Wallis tests and multivariate regression analysis were performed.

Results: baseline characteristics study population (n=521): 67.8% woman, mean (SD) age in years 49.0 (13.7), mean (SD) BMI in kg/m^2 25.7 (3.9), 79.5% RF positive, 72.6% anti-CCP positive, 36.8% non smoker, 28.4% former smoker, 34.8% smoker. Median [IQR] RAAD score was 2.0 [0-6.0]. A significant, weak correlation between BMI and the RAAD score (correlation coefficient -0.14, p=0.003) was found. No significant difference in RAAD score was found between patients with different smoking status. Obviously, the RAAD score was correlated with disease duration, irreversible damage can only increase. Disease duration was correlated with BMI. There was an increasing trend in BMI at disease during the decades. When corrected for this trend, through adjusting for disease duration, no significant correlation was found between BMI and the RAAD score.

Conclusion: BMI and smoking status at the moment of diagnosis of RA are not related with irreversible joint damage at long-term as measured with the RAAD score, when adjusted for disease duration. For the trend in BMI throughout the decades was corrected with disease duration.

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Introduction

Definition and epidemiology

Rheumatoid arthritis (RA) is an auto-immune disease, characterized by the presence of mostly symmetrical joint inflammation. Due to its chronic character with inflammation and erosive changes of cartilage and bone structures, RA leads to destruction and (sub)luxation of joints. Structures surrounding the joint, such as tendon sheaths, bursae and tendon insertions, can be affected as well. Because of the systemic nature of the disease, extra-articular manifestations as vasculitis, serositis and subcutanous nodules can appear. General symptoms such as fever, malaise and weight loss may occur in an active phase. RA classically affects the joints of hands and feet, but almost every joint can be affected, including the cervical spine (1) (2).

RA can have its onset at every age, but the peak-onset is between the age of 40 and 70 years. Women are two to three times more often affected than men (1). Numbers from the national information network of general practitioners in the Netherlands (Landelijk Informatie Netwerk Huisartsenzorg, LINH) confirm that women are more often affected with RA than men, at every age (3). Regarding the Dutch population, the LINH estimated a number of 116,000 RA patients registered by their general practitioner (GP) in 2011, of which 42,000 men (5.1 per 1000) and 74,000 women (8.8 per 1000). The overall prevalence of RA is higher, because of a number of patients not treated by their practitioner. In 2012 at least 59,533 RA patients received medical treatment from a rheumatologist (4).

RA can be diagnosed using the 2010 ACR/EURLAR (American College of Rheumatology/European League Against Rheumatism) criteria. The diagnosis requires the presence of synovitis in at least one joint, absence of a better explaining diagnosis and a score of at least six points achieved at the following domains: number and site of involved joints, serological abnormality, elevated acute phase response and symptom duration (5).

Measuring long-term outcome

After the development of new effective medication and the introduction of “treat-to-target” strategies directed at obtaining remission, the prognosis of RA greatly improved. Risks and costs of early intensive treatment with medication are justified by quick remission of inflammation and improvement of function. It is expected that this will also result in limitation of long term joint damage.

Disease activity, functional capacity and quality of life are important outcome measures. These parameters contribute to the making of appropriate treatment decisions focused on controlling synovitis, achieving remission and prevention of joint damage. The Disease Activity Score (DAS28) is a generally used score that combines the number of tender joints of 28 joints, the number of swollen joints of 28 joints, the erythrocyte sedimentation rate (ESR) and general health status measured on a visual analogue scale (VAS) to evaluate disease activity (6). The Stanford Health Assessment Questionnaire (HAQ) evaluates health status. One specific part of the HAQ evaluates functional capacity. This is called the HAQ Disability Index (HAQ-DI) and includes 20 questions on eight categories of activities of daily living (ADL) (7). The EuroQol Group produced an instrument for measuring generic health status, a standardized questionnaire, the EQ5D-3L (8) (9). It contains questions on dimensions of mobility, self-care, usual activities, pain and discomfort, anxiety and depression and it contains a VAS for health status.

Radiographic scoring methods, such as the Sharp van der Heijde Score (SHS) (10) and Larsen Score (11), are frequently used in clinical research to evaluate damage of cartilage and bones of hands and feet. These methods are expensive and time-consuming.

Measurements of functional outcome are relevant but reflect current disease activity. Moreover, functional capacity is influenced by comorbidities. Functional capacity is

associated with irreversible joint damage, measured with the SHS (12). An increase in SHS results in a decrease in functional capacity, although less functional decline is reported in RA patients treated with modern strategies (12).

Disease characteristics and their relation with long-term outcome

Serological status plays a role in diagnosis and prognosis of RA (5). Rheumatoid factor (RF) appears to be an important predictor of increasing severity of radiographic damage in the first five years after presentation of inflammatory polyarthritis (13). Little evidence is available about the effect of RF on long-term irreversible joint damage.
More specific than RF and informative as a diagnostic marker is the presence or absence of antibodies against citrullinated protein antigen (ACPA's) (14). The most commonly used assay for ACPA's is the assay for antibodies against cyclic citrullinated peptides (CCP). The presence of anti-CCP antibodies is associated with more severe radiographic damage (Larsen score) (15) (16). Patients with high levels of anti-CCP at onset are more likely to develop radiographic progression (SHS) (17).

Patient characteristics and their relation with long-term outcome

Whether and, if so, how gender-specific factors contribute to the cause and development of RA remains an unanswered question. Different theories try to explain this possible influence, including the role of hormones through the effects of hormonal birth control, nulliparity, pregnancy and breastfeeding (18). Women seem to have more disability, but when long-term damage (follow-up over five years) is evaluated with radiographic damage scores, there appears to be no statistically significant difference in radiographic damage between men and women (19) (20).
Regarding age at onset, the distinction is made between 'younger onset' as defined as onset before the age of 60 years and 'older onset' as defined as a diagnosis of RA at or after the age of 60 years. Conclusions about the influence of age at onset on functional ability are controversial (19). In a study about radiographic damage in relation to age at onset no difference in radiographic progression is described (21). In another study more severe joint damage at baseline in patients with older onset is reported (22).
It has been suggested that smoking is one of the most important environmental risk factors for the onset of RA (23) (24). In the literature, the hypothesis of smoking as a contributor to the production of RA-related auto antibodies, has been proposed (25). According to this hypothesis and the fact that seropositive RA patients tend to have more radiographic damage (14) (15) (16), greater disease severity in smokers is plausible and more joint damage at long-term is to be expected. However, little evidence about the long-term effect of smoking on joint damage is available. The association of smoking and more severe joint damage was found in only two cohorts, in a study that evaluated six cohorts with RA patients (26). A more recent study identified smoking as a predictor of radiographic progression in the first year of disease (27).
Overweight and obesity are globally increasing problems. If these trends continue, the global prevalence of obesity will be 18% in men and 21% percent in women in 2025 (28). There are indications for a contributing role of obesity in the development of RA (29). Differences in disease outcome have been reported between obese and non-obese RA patients. Obesity has a negative influence on disease activity and obese patients are less likely to achieve and sustain remission compared to non-obese patients (30) (31). Therefore it is reasonable to assume that there is a relation between body mass index (BMI) and radiographic joint damage. Remarkably, obesity is named as a predictor of less radiographic progression (31) (32). The possible immunomodulating and proinflammatory effect of adipose tissue on the inflammatory disease RA and the fact that obese patients are more likely to develop

seronegative RA, and therefore may a better prognosis, are some of the potential explanations (31) (33) (32).

Rheumatoid Arthritis Articular Damage (RAAD) Score

Long-term outcome has been assessed almost exclusively by measuring radiographic damage in hands and feet. Evaluating characteristics as described above using radiographic methods such as the Larsen score and SHS, is expensive and time-consuming. In 2002 Zijlstra et al. developed the RAAD score (34). The score was designed in order to have a simple, reproducible and objective scale for joint damage, not limited to the joints of hands and feet. The RAAD score can be performed in a couple of minutes. The inter-observer variation of the RAAD score was found to be small (34). A high correlation between the RAAD score and the HAQ and also between the RAAD score and radiographic damage according the SHS has been found (34). No correlation was found between the RAAD and current inflammatory activity (34). Since its introduction in 2002, the RAAD score has been applied in several studies, which confirmed these correlations (table 1).

Table 1. Published clinical research describing the RAAD score

Article	Number of patients	Study design	Mean (SD) disease duration in years (min-max range)	Mean RAAD(SD) or median RAAD[IQR] (min-max range)	Correlation disease duration	Correlation disease activity (DAS28)	Correlation functional capacity (HAQ)	Correlation radiographic damage
Zijlstra et al. 2002 (34)	47	Cross-sectional	16 (1 – 48)	10.3 (11.7) (0-51)	Significant (r=0.68, p<0.01)	Non-significant (r=0.10, p=0.51)	Significant (r=0.50, p<0.01)	Significant (Larsen) (r=0.81, p<0.01)
Beija et al. 2005 (35)	122	Cross-sectional	14 (0.1-29)	11.75	Significant (r=0.64, p=0.001)	Non-significant	Significant (r=0.59, p=0.001)	Significant (Larsen) (r=0.76, p=0.000)
Bodur et al. 2006[a] (36)	105	Cross-sectional	7.6 (6.1) (0.5 – 30)	4.3 (7.0) (0-31)	Significant (r=0.45, p<0.01)		Significant (p<0.01)	
Eksioglu et al. 2007 (37)	85	Cross-sectional	17.7 (6.3) Group 1 (10-14 years) Group 2 (15-19 years) Group 3 (>20 years)	18.98 (18.22)	*Correlation not assessed* *Significant difference in RAAD between Group 1-2, Group 1-3.*		Significant (r=0.560, p=0.000)	
Hammer et al. 2007 (38)	145	Cross-sectional	12.7 (1.1)	5 (0-36)		Significant (r=0.43, p<0.001)		Significant (SHS) (r=0.72, p<0.0010)
Gurcay et al. 2009[b] (39)	38	Cross-sectional	19.7 (12.1) (5-62) Group 1 (5-10 years) Group 2 (11-15 years) Group 3 (>16 years)	11.2 (14.8) (0-63)	*Correlation not assessed* *Non-significant difference in RAAD between groups*	Significant (r=0.43, p=0.007)	Significant (r=0.55, p=0.000)	
Hammer et al. 2010 (40)	124	Cross-sectional	2.2 (1.2) (at baseline)	5 [2-14] (after 10 years of follow-up)	Significant Univariate regression analysis with RAAD as a dependent variable (p=0.008)			Significant (r=0.70, p<0.001).

Ickinger et al. 2013 (41)	100	Cross-sectional	17.5 (8.5) (5 - 49.5)	28.2 (12.8) (3-59)	Significant (r=0.44, p<0.001) (log disease duration in months)		Significant (r=0.34, p=0.001)	

SD, standard deviation. IQR, inter quartile range. [a] Only a RAAD score for wrists, PIP joints and MCP joints was assessed with a maximum score of 44. Only the Hand Disability Index was assessed, calculated with seven items of the Turkish version of the HAQ. [b] Patients with JIA (juvenile idiopathic arthritis). JIA patients with oligoarthritis classification (1-4 joints involved) included. Only a small percentage of patients with JIA enters adolescence with severe functional disabilities.

Problem definition

Little is known about how the RAAD score progresses over time and how the score differs between patients with different baseline characteristics. Until now, the RAAD score has only been evaluated in small and selected populations.

Based on the considerations described in the introduction, associations between RF and anti-CCP and the RAAD score are expected (13) (15) (16) (17). Ickinger et al. performed the only study on BMI and smoking status in relation to the RAAD score in a population of one hundred South African RA patients (41). A negative effect of obesity on disease activity is suggested (31) (30). Patients with persistent disease activity have more pronounced radiographic damage (42), but little evidence is available about the relation between BMI and long-term joint damage or progression of joint damage. The hypothesis is that BMI has a negative effect on the RAAD score on the long-term.

Results about the relation between smoking and radiographic outcome are conflicting (26). Through possible stimulation of antibody production, the negative effect of smoking on disease activity is plausible. The hypothesis is that smoking will increase long-term joint damage.

Investigating these issues can contribute to the valuation of the RAAD score as a method for predicting long-term damage in RA patients. The score can be applied as a simple method that serves as a contributing factor in the making of treatment decisions. The following questions are studied.

Primary

- Are gender, age, body mass index and smoking status at the time of diagnosis of RA related with irreversible joint damage according to the RAAD score at follow up, in patients with a disease duration of at least five years?

Secondary

- Are 2010 ACR/EULAR criteria at the time of diagnosis of RA related with irreversible joint damage according to the RAAD score at follow up, in patients with a disease duration of at least five years?
- Is there a relation between the HAQ or EQ5D and the RAAD score?
- Is there a relation between BMI or smoking status at baseline and HAQ or EQ5D in patients with RA and a disease duration of at least five years?

Methods

Patient inclusion

The present cross-sectional study was carried out in the Ziekenhuisgroep Twente (ZGT), located in Almelo and Hengelo. The study included patients who received treatment for RA in the ZGT from January 1996 until December 2015. Only patients with a RAAD score and a disease duration of at least five years at the moment of the RAAD score were included.

Data collection

In years under study, the ZGT provided care to almost 2,100 RA patients. The department of rheumatology aims to record relevant patient and disease characteristics of all patients with RA at onset of disease. In 2014 and 2015 those data were retrieved by a retrospective review of the digitized records and have been entered on a separate electronic form in the patient records, named 'baseline RA'. The form contains the date of diagnosis, length, weight, smoking status and 2010 ACR/EULAR criteria for RA at onset of disease.

The selection of patients whose data was entered on an electronic form is based on the diagnosis register. Patients who received an administrative code for RA "101" or polyarthritis "117" were both selected, because of the variation between rheumatologists in the use of these administrative codes. In clinical practice, the diagnosis of RA is not always straightforward. Some patients meet the 2010 ACR/EULAR criteria for RA. Some present a clinical RA but do not meet the precise standards for a diagnosis as definite RA. They often receive the diagnosis undifferentiated polyarthritis. The baseline data from these electronic forms were exported to one excel file and anonymised for further analysis. Patients with a diagnosis polyarthritis were included when they had a 2010 ACR/EULAR score of six or higher at onset. This is the cut-off point for a diagnosis as definite RA (5).

As part of routine care the department of rheumatology measures functional (dis)ability using the Health Assessment Questionnaire (HAQ) and general health status using the EuroQol Group standardized questionnaire (EQ5D-3L) for every patient on a annual basis. The RAAD score is measured annually since its introduction at the outpatient clinic in 2014. RAAD, HAQ and EQ5D scores were exported to the excel database, also creating anonymised files for further analysis. When several RAAD scores from one patient were available, the RAAD score with EQ5D and HAQ scores performed within a range of one year was added to the database. In case of a larger range or no available EQ5D or HAQ scores, the most recent performed RAAD score was added to the database. The range of one year is based on the assumption that irreversible joint damage will not change significantly in one year.

During the clerkship, a short manual was written to get familiar with the RAAD score (appendix 1). Then new RAAD scores were performed until March 2016. To complete the data, HAQ and EQ5D questionnaires were distributed among the RA patients visiting the outpatient clinic who had not filled out these questionnaires in the last year. Answers of the paper questionnaires were entered in EZIS, the electronic patient record system used in the ZGT. Baseline data were completed through retrospective record research and through verifying information during an outpatient visit. For patients with a RAAD score documented in EZIS but without an electronic baseline RA form, the diagnosis was verified in EZIS and missing data were added to the database. Performing and analyzing enough radiographic scores (SHS) during the clerkship of 20 weeks, as mentioned in the research proposal, was not feasible and therefore was left aside.

The final database contained 1711 patients with a diagnosis of RA made by a rheumatologist or a diagnosis of polyarthritis in the presence of ≥ six 2010 ACR/EULAR criteria for RA. From this database patients with a RAAD score and disease duration of at least five years at the moment of the RAAD score were selected for this study.

Outcome measure and investigated variables

The primary outcome measure of this study is the association between the RAAD score and patient-specific characteristics. Second, the association between the RAAD score and functional outcome and general health status is examined. The following variables are studied:

- Gender
- Age at onset
- Body mass index at onset
- Smoking status at onset
- Disease duration
- 2010 ACR/EULAR criteria for rheumatoid arthritis at onset
    - Number and site of involved joints (1 medium/large, 2-10 medium/large, 1-3 small, 4-10 small, more than 10)
    - Serological abnormality (RF and anti-CCP normal, RF or anti-CCP increased, RF or anti-CCP increased more than three times)
    - Elevated acute phase response (CRP or BSE normal, CRP or BSE increased)
    - Symptom duration (less than six weeks, more than six weeks)
- HAQ-DI
- EQ5D-3L
- EQ5D-VAS

Statistical analysis

Microsoft Office Excel 2007 and Statistical Package for the Social Sciences (SPSS), version 23, were used for editing and merging data and for statistical analysis of the final database.

Disease duration was calculated as the difference between the date of diagnosis and the date of the RAAD score. Serology markers (RF and anti-CCP) were dichotomized into positive and negative. RF was considered positive above the cut-off value of 20 U/ml. Anti-CCP was considered positive above the cut-off value of 7 U/ml. ESR and CRP were analyzed as continuous variables. CRP values documented as <10 mg/l were analyzed as having the value one. Smoking at onset was categorized in three groups: current smoker, former smoker and non smoker. The RAAD score was calculated as the sum of all points assigned to 35 joints, with a minimum of zero and maximum of 70 points. The HAQ-DI was calculated as the sum of scores, based on a three point scale, on 20 questions. The total score divided by 20 results in a value between zero and three (7). The EQ5D was calculated using a standard SPSS syntax, resulting in a health index value between minus one and one. Negative values in the study population are possible because of the validation of the score with a reference population (43) (9) (8).

Using histograms, continuous variables were assessed for distribution. Normally distributed data are shown with a mean and standard deviation. Skewed variables are shown with a median and an interquartile range. Categorical variables are shown with the number and percentage.

The Mann Whitney U test was used to test differences between groups of skewed continuous variables (asymptotic significance ≤ 0.05). Differences between the RAAD score and polytomous variables (e.g. smoking status) were evaluated using the Kruskal Wallis test (asymptotic significance ≤ 0.05). Correlations between skewed variables were examined using Spearman rank correlation test (significance ≤ 0.05).

Linear multiple regression analysis was performed to determine the relation between different variables and the RAAD score, corrected for the variable disease duration (significance ≤ 0.10). The use of this method, despite of the skewed distribution of the RAAD score, is justified because of a normal distribution of residuals when disease duration is included in the regression model.

Results

Reference population

From the database of 1711 patients with a diagnosis of RA or polyarthritis with a 2010 ACR/EULAR criteria for RA score of six or higher, a reference population was selected. These were patients without a RAAD score and a disease duration of at least five years at the first of January 2016. Baseline characteristics of the reference population are shown in table 2. The number of deceased patients was 221 (31.7%). In 27 (3.6%) patients follow-up was ended for other reasons. Almost two thirds of the population is female, 441 (63.2%). Mean age (SD) was 60.7 (15.6). Mean BMI (SD) was 26.8 (5.3). From patients with a smoking status 172 (32.5%) were current smokers, 131 (24.7%) former smokers and 227 (42.8%) non smokers. A number of 411 (62.4%) patients had a 2010 ACR/EULAR criteria for RA score of six or higher. The number of RF and anti-CCP negative patients was higher in the reference population, suggesting a slightly milder disease and possible better outcome.

Baseline characteristics of the cohort

In this study a total of 521 patients were included. The number of patients deceased when data collection was stopped at the first of April was 13 (2.5%). Baseline characteristics of the studied population are shown in table 2. More than two thirds of the population is female, 353 (67.8%). Mean age (SD) was 49.7 (13.7) years. More than half of the population with a BMI value had overweight or obesity: 238 (53.8%). Current smokers, former smokers and non smokers were almost equally distributed in the studied population, 178 (34.8%), 145 (28.4%) and 188 (36.8%) respectively. A number of 371 (74.9%) patients had a 2010 ACR/EULAR criteria for RA score of six or higher. The majority of the population had more than three times elevated serology markers: 260 (51.0%). Rheumatoid factor was positive in 387 (79.5%) patients. Since measuring anti-CCP is relatively new, a significant part of these measurements was missing. The population counted 135 patients with an anti-CCP value. A number of 98 (72.6%) patients was anti-CCP positive. An abnormal acute phase response (elevated CRP or/and BSE) was detected in 321 (64.7%) patients.

Table 2. Baseline characteristics of the patients

	Study population (n=521)	Reference population (n=698)
Female	353 (67.8)	441 (63.2)
Age in years, mean (SD)	49.0 (13.7)	60.7 (15.6)
BMI in kg/m^2, mean (SD)	25.7 (3.9)	26.8 (5.3)
Underweight, <18.5 kg/m^2	7 (1.6)	9 (2.9)
Normal weight, ≥18.5 kg/m^2 and <25 kg/m^2	197 (44.6)	114 (36.7)
Overweight, ≥25 kg/m^2 and <30 kg/m^2	180 (40.7)	102 (32.8)
Obesity, ≥30 kg/m^2	58 (13.1)	86 (27.7)
Smoking status		
Non smoker	188 (36.8)	227 (42.8)
Former smoker	145 (28.4)	131 (24.7)
Current smoker	178 (34.8)	172 (32.5)
2010 ACR/EULAR criteria for RA score ≥ 6	371 (74.9)	411 (62.4)
Number of affected joints		
1 medium	7 (1.4)	16 (2.4)
1-3 small	103 (20.5)	155 (23.1)
2-10 medium	57 (11.3)	79 (11.8)
4-10 small	246 (48.9)	277 (41.3)
>10	90 (17.9)	143 (21.3)
Serology abnormality		
RF and anti-CCP not elevated	104 (20.4)	274 (39.9)
RF or/and anti-CCP < 3 times elevated	146 (28.6)	127 (18.5)
RF or/and anti-CCP > 3 times elevated	260 (51.0)	285 (41.5)
Acute phase response		
Abnormal CRP or/and ESR	321 (64.7)	460 (68.0)
Symptom duration		
≥ 6 weeks	487 (96.8)	636 (94.5)
RF positive	387 (79.5)	
Anti-CCP positive	98 (72.6)	
ESR, median [IQR]	25.0 [14.0-42.0]	
CRP, median [IQR]	15.0 [6.0-35.0]	

Variables are described in numbers (%), except when otherwise mentioned. SD, standard deviation; BMI, body mass index; ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor; Anti-CCP, antibodies to cyclic citrullinated peptide; ESR, erythrocytes sedimentation rate; IQR, interquartile range; CRP, C-reactive protein. Percentages relate to the number of patients with a measurement. Number of patients with missing data in the study population (n): BMI (79); smoking status (10); 2010 ACR/EULAR criteria (26); number of affected joints (18); serology abnormality (11); acute phase response (25); symptom duration (18); RF (34); anti-CCP (386); ESR (37); CRP (155). Number of patients with missing data in the reference population (n): BMI (387); smoking status (168); 2010 ACR/EULAR criteria (39); number of affected joints (28); serology abnormality (12); acute phase response (22); symptom duration (25).

Characteristics of the RAAD score in the cohort

The distribution of the RAAD score is skewed (figure 1). Median [IQR] RAAD score was 2.0 [0-6.0]. The minimum to maximum RAAD score reached from zero to 55. Median [IQR] disease duration at the moment of the RAAD score was 12.3 [7.9-19.0] years, with a range from five to 56 years. Forefeet, metacarpophalangeal (MCP) joints, wrists and proximal interphalangeal (PIP) joints were most affected, in 38.8%, 28.4%, 21.1% and 20.9% of the population (figure 2).

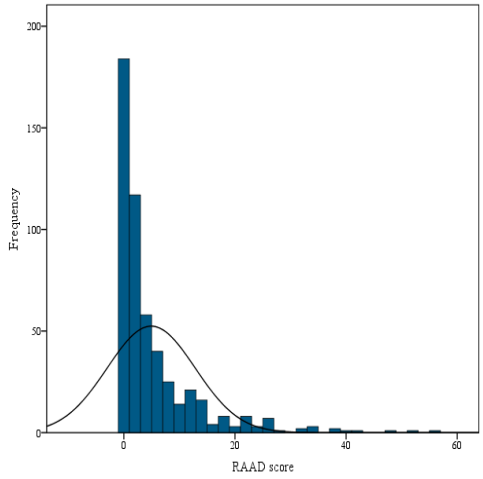

Figure 1. Distribution RAAD score

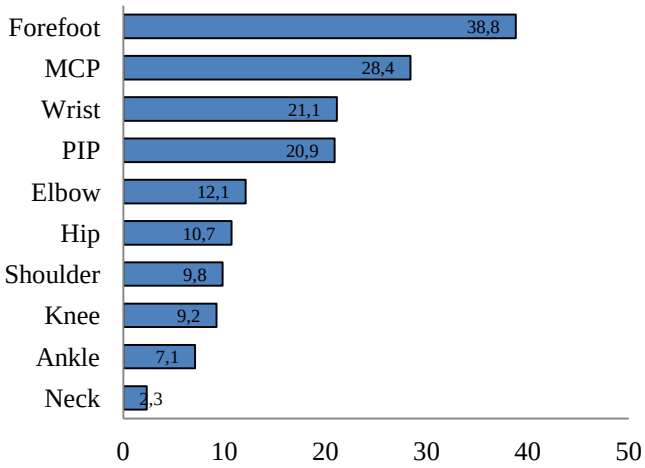

Figure 2. Percentage of patients with irreversible damage at a specific location

Table 3 (appendix 2) shows that more patients with irreversible damage in PIP joints, MCP joints and forefeet were RF positive than RF negative at the moment of diagnosis. Slightly more patients with affected elbows and wrists were RF positive. The comparison of proportions of anti-CCP positive and anti-CCP negative patients for every affected location is based on a relatively small amount of anti-CCP measurements, 135 respectively. However, patients with affected MCP joints and forefeet were more frequently anti-CCP positive than anti-CCP negative at the moment of diagnosis (table 3, appendix 2).

There is no RAAD score cut-off point for severe irreversible damage described in published research. In order to provide better insight in the frequency of joint damage as measured with the RAAD score, patients were divided in groups with a score beneath six and with scores of six or higher. For example, a score of six can represent two knee prosthesis and one other severe damaged joint, but also only multiple ulnar deviations or (sub)luxations of MCP joints. When these groups of patients were compared, a clear trend was visible (figure 3). The majority of patients with a disease duration of more than 20 years has a RAAD score of six or more.

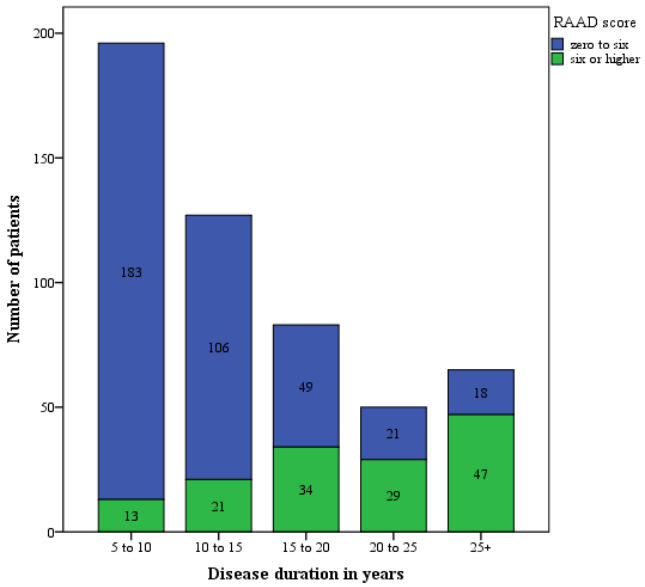

Figure 3. Proportions of severe damage in patients with different disease duration

A clear trend in BMI and a slight trend in smoking status at moment of diagnosis were noticed in the past 40 years (table 4). An overall increase in BMI at onset throughout the decades was seen in the studied population. The percentage of former smokers at moment of diagnosis slightly increased and the percentage of current smokers at moment of diagnosis slightly decreased throughout the decades.

Table 4. Trends during different periods of onset

Year of onset	Number of patients diagnosed	Median [IQR] RAAD	Mean (SD) BMI	
Before 1980	20	23.0 [8.3-31.8]	25.0 (2.0)	
1980 to 1990	38	12.5 [3.8-19.3]	24.1 (3.1)	
1990 to 2000	123	5.0 [2.0-10.0]	25.4 (3.8)	
2000 to 2010	314	1.0 [0-3.0]	26.1 (4.1)	
2010	26	0 [0-1.3]	26.4 (3.8)	
Year of onset	**Underweight**	**Normal weight**	**Overweight**	**Obesity**
Before 1980		9 (52.9)	7 (41.2)	1 (5.9)
1980 to 1990	1 (3.1)	21 (65.6)	8 (25.0)	2 (6.3)
1990 to 2000		54 (49.1)	45 (40.9)	11 (10.0)
2000 to 2010	6 (2.3)	104 (39.8)	110 (42.1)	41 (15.7)
2010		9 (40.9)	10 (45.5)	3 (13.6)
Year of onset	**Non smoker**	**Former smoker**	**Current smoker**	
Before 1980	11 (57.9)	3 (15.8)	5 (26.3)	
1980 to 1990	16 (43.2)	7 (18.9)	14 (37.8)	
1990 to 2000	40 (33.3)	36 (30.0)	44 (36.7)	
2000 to 2010	110 (35.6)	91 (29.4)	108 (35.0)	
2010	11 (42.3)	8 (30.8)	7 (26.9)	

Values are described in numbers (%), except when otherwise mentioned. Percentages relate to the number of patients with a measurement. Number of patients with missing BMI (n): before 1980 (3), 1980 to 1990 (6), 1990 to 2000 (13), 2000 to 2010 (53), 2010 (4). Number of patients with missing smoking status (n): before 1980 (1), 1980 to 1990 (1), 1990 to 2000 (3), 2000 to 2010 (5). SD, standard deviation; IQR, inter quartile range. RAAD, Rheumatoid Arthritis Articular Damage. BMI, body mass index.

Associations between the RAAD score, patient- and disease characteristics

The univariate analyses are shown in table 5. There was a weak correlation between the RAAD score and age (correlation coefficient -0.10, p=0.025). A younger age results in a higher RAAD score. There was a weak correlation between the RAAD score and BMI (correlation coefficient -0.14, p=0.003), a higher BMI resulting in a lower RAAD score. No significant difference in RAAD score was found between patients with different smoking status (p=0.105). Non smokers, former smokers and current smokers had a median [IQR] RAAD score of 2.0 [0-5.0], 1.0 [0-6.0] and 2.0 [0-7.3] respectively.

Patients with a 2010 ACR/EULAR criteria for RA score of six or higher had a slightly higher median [IQR] RAAD score compared to patients with a score beneath six (2.0 [0-6.0] versus 1.0 [0-5.0]). This difference was not significant (p=0.061).

The different criteria were also analyzed separately. There was a significant difference in RAAD score between patients with normal acute phase response at onset and patients with abnormal acute phase response at onset (p=0.011). Patients with an abnormal acute phase response had a significant higher median [IQR] RAAD score compared to patients with a normal acute phase response, respectively 2.0 [0-7.0] and 1.0 [0-5.0]. The at onset RF positive patients had a slightly higher median [IQR] RAAD score compared to at onset RF negative patients, respectively 2.0 [0-6.0] and 1.0 [0-6.0]. The difference was not significant (p=0.088).

No significant difference in RAAD score was found between anti-CCP positive and anti-CCP negative patients (p=0.677). Median [IQR] RAAD of both groups was 0 [0-2.0]. The RAAD score was moderately correlated to disease duration (correlation coefficient 0.56, p<0.001) (figure 4).

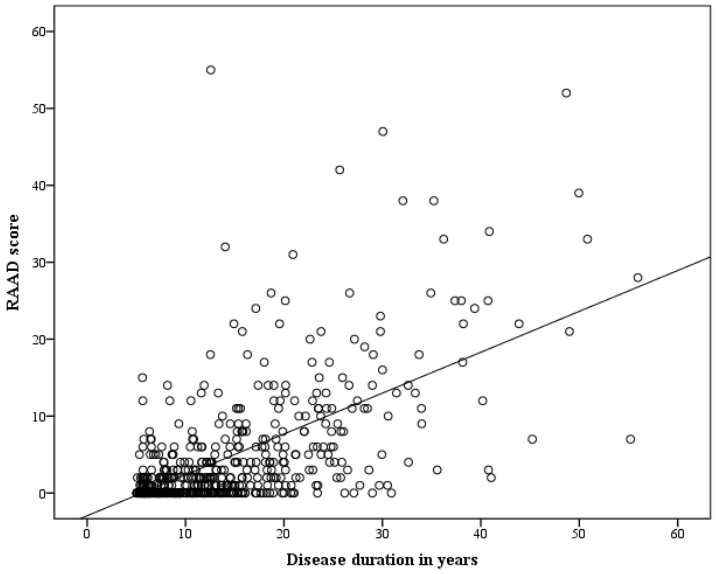

Figure 4. The RAAD score and disease duration

BMI and age were also correlated with disease duration. Therefore, disease duration was a potential confounder in both the relation between the RAAD score and BMI, as in the relation between the RAAD score and age.

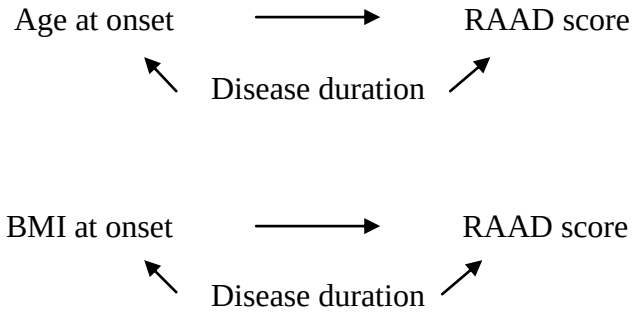

Table 5. Univariate analysis with the RAAD score and disease duration

Difference in RAAD score	
Variable	**P-value**
Gender	0.055
Smoking	0.105
2010 ACR/EULAR criteria for RA ≥ 6	0.061
Number of affected joints	0.215
Serology abnormality	0.180
Rheumatoid Factor +/-	0.088
Anti-CCP +/-	0.677
Acute phase response	0.011*
Symptom duration	0.787

Correlation with RAAD score		
	Correlation-coefficient	
Disease duration	0.56	<0.001*
Age	-0.10	0.025*
BMI	-0.14	0.003*

Difference in disease duration	
Acute phase response	0.501

Correlation with disease duration		
Age	-0.34	<0.001*
BMI	-0.11	0.018*

*significant at a 0.05 level. BMI, body mass index; ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor; Anti-CCP, antibodies to cyclic citrullinated peptide.

Multivariate analysis

Examination of the influence of age and BMI on the RAAD score while correcting for disease duration using multiple linear regression analysis, was approved through visual assessment of the residuals. They were normally distributed with the RAAD score as the dependent and disease duration as an independent variable added to the regression model (figure 5, appendix 2). Table 6 shows the explanatory models for the RAAD score with age and BMI. Age was not an explanatory variable for the RAAD score (p=0.295). BMI was not an explanatory variable for the RAAD score (p=0.332).

Table 6. Explanatory models RAAD score

	B coefficient	95.0% confidence interval	Significance
Model 1			
Disease duration	0.55	0.480 – 0.610	0.000
Age	0.02	-0.020 – 0.066	0.295
Model 2			
Disease duration	0.54	0.478 – 0.609	0.000
BMI	-0.08	-0.230 – 0.078	0.332

B, bèta. BMI, body mass index.

Associations between functional capacity and the RAAD score, patient- and disease characteristics

The population counted 330 patients with a HAQ-DI. Median [IQR] HAQ-DI was 0.4 [0.2-0.9]. The RAAD score and the HAQ-DI were significantly correlated with a correlation coefficient of 0.33 ($p<0.001$). The HAQ-DI increases when the RAAD score increases. Equal to the RAAD score, functional capacity was significantly correlated with disease duration (correlation coefficient 0.27, $p<0.001$). The HAQ-DI increases and functional capacity decreases as disease duration increases. The HAQ-DI was not correlated with BMI. A significant difference in HAQ-DI was found between patients with different smoking status ($p=0.016$). Median [IQR] HAQ-DI scores for current smokers, former smokers and non smokers were 0.6 [0.3-1.1], 0.4 [0.1-0.7] and 0.3 [0.1-0.8] respectively.

Associations between general health status and the RAAD score, patient- and disease characteristics

The population counted 316 patients with an EQ5D score. Median [IQR] EQ5D was 0.7 [0.6-0.8]. The RAAD score and EQ5D score were significantly correlated with a correlation coefficient of -0.24 ($p<0.001$). The EQ5D score decreases when the RAAD score increases. Equal to the RAAD score and functional capacity, general health status was correlated with disease duration (correlation coefficient -0.20, $p<0.001$). The EQ5D score decreases and health status is assessed worse when disease duration increases. From 316 patients who filled out an EQ5D, 305 reported a VAS score. The VAS score for general health was rated on a scale from zero to 100, with 100 representing the most optimal health status. Mean (SD) VAS score was 68.3 (17.7). The EQ5D score was not correlated with BMI. A significant difference in EQ5D score was found between patients with different smoking status ($p=0.004$). Median [IQR] EQ5D scores for current smokers, former smokers and non smokers were 0.7 [0.5-0.8], 0.7 [0.6-0.8] and 0.7 [0.6-0.8] respectively.

Explorative statistics

Some of the statistical analyses as described above were executed with subgroups of the population.

Smoking status and RAAD score

There was no significant difference in RAAD score between patients with different smoking status with a disease duration of at least ten years ($p=0.265$), at least fifteen years ($p=0.506$) or of at least twenty years ($p=0.705$) (table 7, appendix 2).

Partial RAAD score: characteristically damaged joints

An alternative RAAD score was calculated, with only the in RA typically affected peripheral joints. This “RAAD2” was calculated as the sum of all points assigned to PIP joints, MCP joints, wrists and forefeet. Median [IQR] RAAD2 was 1.0 [0-4.0].

The univariate analyses are shown in table 8 (appendix 2). There was a significant moderate correlation between the RAAD2 score and disease duration (correlation coefficient 0.55, $p<0.001$). The correlation coefficient was slightly smaller compared to the correlation coefficient of the original RAAD score (0.56). Women had a higher median [IQR] RAAD2 score compared to men (1.0 [0-5.0] versus 0 [0-3.0]). The small difference was significant ($p=0.016$). There were significant, weak correlations between the RAAD2 score and age (correlation coefficient -0.14, $p=0.002$) and between the RAAD2 score and BMI (correlation coefficient -0.17, $p<0.001$). No significant difference in RAAD2 score between patients with different smoking status was found ($p=0.175$). Patients with a 2010 ACR/EULAR criteria for RA score of six or higher had a higher median [IQR] RAAD2 score compared to patients with a score beneath six (1.0 [0-5.0] versus 0 [0-3.0]). In contrast to the original RAAD score, the small difference was significant ($p=0.006$). There was a significant difference in RAAD2 score in patients with different numbers of damaged joints at onset, one of the 2010 ACR/EULAR criteria for RA ($p=0.032$). Patients with more than ten damaged joints at onset had the highest median [IQR] RAAD2 score (2.0 [0-5.0]). When serology markers were analyzed separately, a significant but slightly higher median [IQR] RAAD2 score was found in patients who were RF positive (1.0 [0-5.0] versus 0 [0-3.8]) ($p=0.024$). Patients with an abnormal acute phase response at onset had a higher median [IQR] RAAD2 score compared to patients with a normal acute phase response at onset (1.0 [0-5.0] versus 0 [0-3.0]). The small difference was significant ($p=0.004$).
Disease duration was a possible confounder in the relation between the RAAD2 score and age, RAAD2 score and BMI, RAAD2 score and gender, RAAD2 score and RF, RAAD2 score and the 2010 ACR/EULAR criterium for RA number of affected joints. There was a difference in disease duration between men and women and between RF positive and RF negative patients. Disease duration was significantly correlated with BMI and age. Explanatory models for the RAAD2 score with disease duration added to the regression model as a independent variable were made. No significant relations were found between the RAAD2 and gender, age, BMI and RF (table 9, appendix 2).

Discussion

Controlling symptoms and improving physical function are treatment goals for patients with RA. The RAAD score has been validated as a useful instrument to evaluate joint damage before (table 1, appendix). The main purpose of this study was to investigate whether irreversible joint damage at long-term is related with patient and disease characteristics at the time of diagnosis.
The general characteristics of the study population are in line of most studies on outcome in RA. The RAAD-score appears to have been performed in a subpopulation with a somewhat more serious prognosis. This is unlikely to influence the relation between outcome and baseline characteristics. In the study population, RF positive patients had a higher RAAD score compared to RF negative patients. However, equal to results of Bodur et al. (36), no statistically significant difference in the RAAD score between RF positive and RF negative patients was found. Similarly no difference in the RAAD score was found between anti-CCP positive and anti-CCP negative patients, although a difference was expected because Syversen et al. concluded that patients with high levels of anti-CCP are more likely to develop radiographic progression (17). The current study confirmed that there is no relation between joint damage and age (37) or gender (19) (20). These observations do not exclude a possible relation between these variables and the rate of progression. Syversen et al. named anti-CCP, RF and female gender as independent predictors of radiographic progression (17). In only one of the 2010 ACR/EULAR criteria for RA, acute phase response, a small but significant difference in RAAD score was seen. Patients with an abnormal acute phase response had a slightly higher RAAD score. As expected, the RAAD score was related to general health status and functional capacity. They both decrease when joint damage increases.

The RAAD score and BMI

Despite that the reference population had a higher percentage of patients with obesity, the median BMI (SD) did not differ much from the BMI (SD) from the study population, 25.7 (13.7) and 26.8 (5.3) respectively. More than half of the study population had overweight or obesity at disease onset. The percentage (53.8%) is higher than the percentage of patients with overweight and obesity in the general Dutch population, which was 50.3% in 2015 (44). Concerning the region Twente, 50.1% of the general population had a BMI of $\geq 25 kg/m^2$ and 13.5% a BMI of $\geq 30 kg/m^2$ in 2012 (45). The increase of BMI at disease onset that was seen during the decades confirms the global trend of changes in BMI (28). The high percentage of patients with RA and overweight or obesity is remarkable. Patients with RA already have a higher risk at cardiovascular problems. The higher frequency of overweight and obesity in patients with RA is recently described by Albrecht et al. (46) They compared the BMI of patients of three large German RA cohorts with the BMI of the general German population. They concluded that patients with RA are more obese than the general population already at disease onset. Again the question arises about the odds of developing an auto-immune disease like RA when someone has got overweight or obesity. Vidal et al. concluded in their systematic review and meta-analysis that obesity in patients with RA is associated with increased disease activity and decreased functional capacity (31). The relation between BMI and the HAQ-DI was not found in the current study. Disease activity scores were not analyzed. When a high BMI results in a sustained increase of disease activity, a higher level of joint damage is expected. Svensson et al described the more pronounced joint damage in patients with persistent disease activity (42), but they were not able to find a statistically significant difference in radiographic progression between patients with persistent disease activity and non-persistent disease activity. The current study did not find a significant relation between BMI and joint damage. A negative correlation between BMI and

radiographic joint damage (31) or between BMI and the RAAD score (41) can be misleading. Vidal et al already discussed the negative correlation critically, naming different possible explanations for this relation, for example seronegativity in obese patients. Seronegativity results in a better structural prognosis compared to seropositivity. The negative correlation was found in the current study, but only when disease duration was not taken into account. In this cross-sectional study, the length of disease duration depends on the decade in which a patient was diagnosed with RA. During the decades the BMI at disease onset also changed. BMI was correlated with disease duration. Obviously, the RAAD score was correlated with disease duration. Disease duration has been found to be a confounder in the relation between BMI and the RAAD and cannot be ignored when the relation between BMI and the RAAD score is assessed. It corrects for the change in BMI at disease onset during the decades and an association between BMI and the RAAD score was no longer found.

The RAAD score and smoking status

The percentages of non smokers, former smokers and currents smokers in the reference population did not differ much from the percentages in the study population. The study population reflected the national and international trend in smoking (47). The amount of smokers slightly decreased during the decades. Although smoking has been identified as a contributing factor to radiographic damage in a few studies (26), in the current study no difference in RAAD score was found between patients with different smoking status at the moment of diagnosis. It is reasonable to think that smokers produced more RA specific auto anti bodies during time (25) and therefore were more likely to develop radiographic damage (15) (16). Even when subgroups of the population with a disease duration of more than 10, 15 or 20 years were evaluated, no difference in the RAAD score was found. It is suggested that current smokers are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors (48). An explanation could be that as a consequence, smokers have received more aggressive therapy which still protected them from the harmful effect of smoking. To evaluate the precise relation of smoking and the RAAD score, more detailed information about applied treatment strategies and smoking behavior of every patient is needed.

In this study the RAAD score was evaluated for the first time in a large cohort. BMI and smoking status had only been evaluated before in a cohort of South African patients, who have a different degree of disease expression and other locations of mostly affected joints than Caucasian patients (41). This cross-sectional study was performed with a cohort representing the whole category of RA patients treated by the rheumatologists in the ZGT. A precise illustration of the frequency of affected locations (figure 2) showed the common involvement of larger joints. It reflects the importance of recognition of disability through damage in other than the classically affected small peripheral joints.

The limitation of this study is its design. A prospective cohort study in which information is registered during follow-up of patients would give insight in progression of the RAAD score. The fact that no correlation between BMI and the RAAD score was found, does not mean that there is no relation between BMI and progression of the RAAD score. With follow-up data the hypothesis made by Eksioglu et al (37), that the rate of increase in structural damage slows down after 20 years of disease, can be evaluated. In the current study smokers were placed in one of three possible categories. However, the group with current smokers could have contained patients who just started smoking and patients who already used tobacco for a very a long time at the moment of diagnosis. The continuation of smoking after the diagnosis of RA was not evaluated. Finally, patients have received radically different treatment strategies, since this cross-sectional study included patients over a long range of time.

Further research can be performed analyzing the RAAD score during follow-up. With several RAAD scores of one patient, progression of joint damage during the years can be evaluated.

A study population with a disease onset within a smaller period will probably not be exposed to changes in BMI or smoking status at disease onset. Smoking habits can be identified registering pack years. The effect of quitting smoking during the course of disease can be evaluated. Performing RAAD scores once a year, starting at the moment of diagnosis, will possibly filter other causes of joint destruction from the RAAD score as well. However, co-existing osteoarthritis cannot be differentiated from rheumatoid arthritis as a cause of joint damage. The relation between disease activity and the RAAD score would be an interesting subject for further research as well. Annually follow-up of disease activity and the RAAD score can possibly answer a lot more questions about irreversible joint damage on the long-term.

Conclusions

There is a large variation in RAAD scores in the cross-sectional studied population with a wide range of disease duration. The RAAD score is by definition related to disease duration. There is no difference in RAAD score between men and women. There is no difference in RAAD score between patients with a different smoking status at the moment of diagnosis. Age seems weakly correlated with the RAAD score but when adjusted for disease duration, no significant correlation is found. BMI seems weakly correlated with the RAAD score. An increasing trend in BMI at disease onset is seen throughout the decades. BMI is correlated to disease duration. When corrected for this trend, through adjusting for disease duration, no significant correlation is found between BMI and the RAAD score.
Although patients with classically damaged peripheral joints are more frequently RF positive, no difference in RAAD score is found between RF positive and RF negative patients. Except for a slightly higher RAAD score in patients with an abnormal acute phase respons at disease onset, no difference in RAAD score is found concerning the 2010 ACR/EULAR criteria for RA.
Functional capacity and general health status are correlated with the RAAD score. They both decrease when joint damage increases. Current smokers had the highest HAQ-DI. The difference in EQ5D score in patients with different smoking status is significant, although median EQ5D scores in these groups are almost the same.
Further longitudinal research is needed to find out more about the effect of BMI and smoking on (progression of) long-term joint damage. Research of annually performed RAAD scores during the follow-up of a population with approximately the same period of disease onset will probably answer more questions.

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Appendix 1

Manual RAAD score (Dutch version) **03-2016**

Rheumatoid Arthritis Articular Damage (RAAD) score

Auteur: E.S. Boes

1. *Algemene gegevens*

Het meetinstrument heeft betrekking op onderstaand beschreven categorieën.

Lichaamsregio	Bovenste extremiteiten, onderste extremiteiten, cervicale wervelkolom
Aandoening (ICD-10 2016)	XIII: ziekte van het muskuloskeletale systeem en bindweefsel (M00-M99) → inflammatoire polyarthropathieën (M05-M14)
Domein (ICF)	Verslechtering van lichaamsfuncties; verslechtering van lichaamsstructuren

Korte beschrijving
De RAAD score is ontwikkeld om de irreversibele lange termijn schade aan gewrichten te meten bij patiënten met vormen van chronische artritis. Door beoordeling van deformaties van gewrichten worden punten aan deze gewrichten toegekend. Een maximum van 70 kan worden gescoord.
In vergelijking met de veel gebruikte radiologische scoring van lange termijn schade op hand- en voetfoto's zijn de voordelen van de RAAD-score: alle relevante gewrichten worden beoordeeld en de beoordeling kan poliklinisch in enkele minuten worden uitgevoerd. De RAAD-score laat een hoge correlatie met de radiologische score zien en ook met de functionele beperkingen van patiënten.

Doelgroep
Patiënten met reumatoïde artritis.

Auteurs
In 2000 ontwikkeld en in 2002 beschreven door T.R. Zijlstra, H.J. Bernelot Moens en M.A.S. Bukhari.[1]

2. *Doel instrument*

Evalueren van lange termijn gevolgen van reumatoïde artritis voor gewrichten in het gehele lichaam.

Evalueren van kwaliteit van behandeling en effect van de verschillende medicamenteuze interventies op de lange termijn.

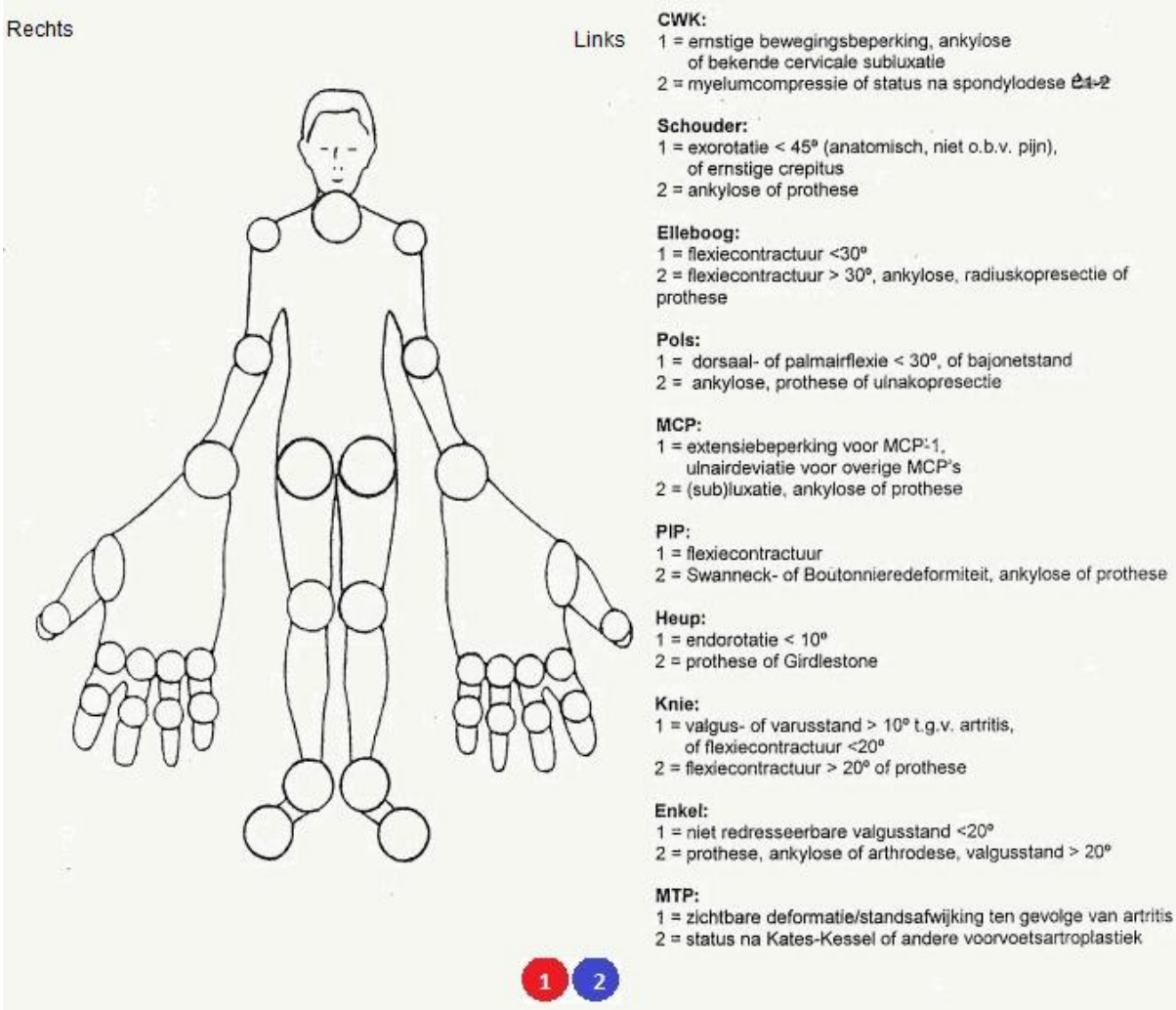
3. *Soort/vorm instrument*

Beoordeling
Door observatie, zo nodig meten en uitvoeren van passief bewegingsonderzoek van gewrichten.

Opbouw
Beoordeeld worden de volgende gewrichten: cervicale wervelkolom, schouders, ellebogen, polsen, (elk) MCP, (elk) PIP, heupen, knieën, enkels en MTP's.

De volgende scores worden toegekend aan de gewrichten:
0 → geen irreversibele schade
1 → gedeeltelijke schade
2 → ernstige schade, ankylose of prothese

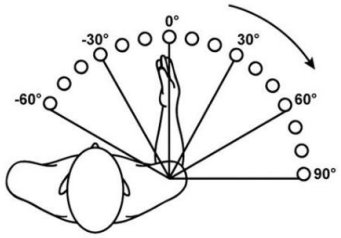
Invulinstructie



CWK
Scoren met behulp van anamnese en overige correspondentie. Alleen ernstige blijvende bewegingsbeperking (bijvoorbeeld nauwelijks naar links of rechts kunnen kijken) is door observatie en bewegingsonderzoek te beoordelen.

Schouder

De elleboog in de zij geklemd en de hand naar voren wijzend is de uitgangssituatie van 0◦. Een bewegingsrange van <45◦ dient gescoord te worden.

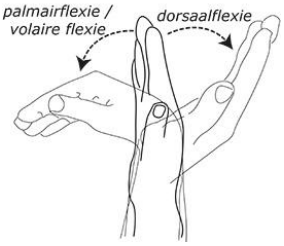


Elleboog

De elleboog volledig gestrekt is de uitgangspositie. In het geval van een irreversibele flexiestand kan met de goniometer bepaald worden of aan deze contractuur de score 1 (hoek ≤30◦) of 2 (hoek >30◦) wordt toegekend.

Pols

Indien flexie in de pols palmair (normaal ≈ 80◦) of dorsaal (normaal ≈60◦) <30◦, wordt een score van 1 toegekend. Er worden pas 2 punten toegekend indien beweging onmogelijk is.

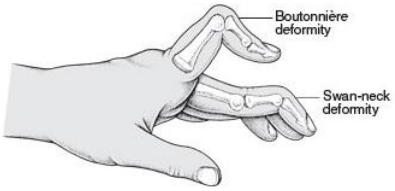


MCP

Voor de beoordeling van dig I geldt dat als de extensie beperkt is, een score van 1 wordt gegeven. De MCP gewrichten van dig II t/m dig IV zijn te beoordelen op ulnairdeviatie. Aan een (sub)luxatie van een MCP gewricht worden altijd 2 punten toegekend.

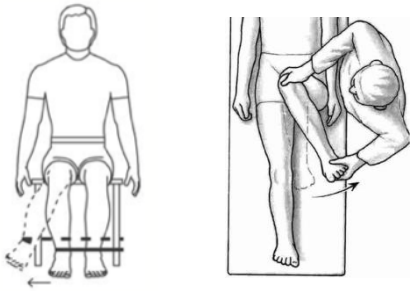
PIP

Een score van 1 wordt toegekend aan ieder PIP gewricht dat niet volledig gestrekt kan worden. Boutonnière en Swan-neck deformiteiten worden met 2 gescoord.



Heup

Endorotatie in de heup kan zittend of liggend beoordeeld worden en dient bij <10◦ gescoord te worden met een 1.

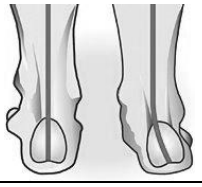


Knie

Een varus (O) of valgus (X) stand van de knie is liggend goed te beoordelen. Aan een irreversibele flexiestand ≤20◦ wordt 1 punt toegekend en 2 indien de flexiecontractuur > 20◦.

Enkel

Een valgusstand van de enkel ≤ 20◦ dient gescoord te worden mits de stand irreversibel is. Een valgusstand > 20◦ krijgt een score van 2.



MTP
Gescoord wordt zichtbare deformatie of standsafwijking ten gevolge van artritis, bijvoorbeeld diepstand van de MTP kopjes en daardoor kromstand van de tenen.
Ook deviatie van de tenen of het uit elkaar gaan staan van de tenen duidt op een verandering die gescoord moet worden.
Een hallux valgus wordt niet gescoord en bijvoorbeeld een daardoor veroorzaakte standsverandering van de 2e teen ook niet.

Algemeen

- ! Een prothese wordt altijd gescoord als 2 ongeacht de oorzaak van de vervanging van het gewricht.
- ! Gewrichten met irreversibele bewegingsbeperking door operaties vanwege andere oorzaken dan artritis worden altijd gescoord als 2.
- ! Onmogelijke volledige extensie van de MCP-1 gewrichten of PIP gewrichten dient gescoord te worden, ook bij twijfel over artritis als oorzaak.
- ! Deformaties ten tijde van het stellen van de diagnose worden gescoord, zodat progressie door de ziekte zo goed mogelijk wordt gemeten.
- ! De score dient onafhankelijk van radiologische foto's ingevuld te worden.

Meetniveau
Er zijn 35 te scoren items. Deze worden afzonderlijk gescoord met 0, 1 of 2. De score betreft de som van alle toegekende punten, waarbij het maximum dus 70 is.

4 Toepassing/hanteerbaarheid

Benodigdheden
Goniometer.

Benodigde tijd
Maximaal 5 minuten.

5 Overige gegevens

Ondanks het verschil in anatomische voorkeursplaatsen van schade door artrose en door reumatoïde artritis is niet aan te tonen welke aandoening de eventuele schade heeft veroorzaakt. Ook bij radiologische scoringsmethoden wordt bij schade aan bijvoorbeeld PIP gewrichten geen onderscheid gemaakt tussen verlies van kraakbeen door artritis of artrose.
Het is daarom van belang om bij start van de ziekte, ofwel het stellen van de diagnose, een RAAD score te bepalen. Zo is er een uitgangspositie met daarin bekende veranderingen door bijvoorbeeld artrose, operaties of protheses en kan progressie van schade door de ziekte worden gemeten.

6 Literatuur

1. *Zijlstra TR, Bernelot Moens HJ, Bukhari MA. The rheumatoid arthritis. articular damage score: first steps in developing a clinical index of long term damage in RA. Ann Rheum Dis. 2002 Jan;61(1):20-3.*

Appendix 2

Table 3. Number of patients (%) with at least one damaged joint at the described location, compared based on RF and anti-CCP status at baseline

Location	RF+	RF-	Anti-CCP+	Anti-CCP-
Neck	8 (2.1)	3 (3.0)		
Ankle	24 (6.2)	8 (8.0)	4 (4.1)	1 (2.7)
Knee	31 (8.0)	12 (12.0)	5 (5.1)	1 (2.7)
Shoulder	37 (9.6)	11 (11.0)	2 (2.0)	2 (5.4)
Hip	38 (9.8)	13 (13.0)	6 (6.1)	3 (8.1)
Elbow	45 (11.6)	9 (9.0)	4 (4.1)	1 (2.7)
PIP	85 (22.0)	15 (15.0)	5 (5.1)	5 (13.5)
Wrist	81 (20.9)	20 (20.0)	4 (4.1)	6 (16.2)
MCP	115 (29.7)	21 (21.0)	15 (15.3)	3 (8.1)
Forefoot	157 (40.6)	32 (32.0)	23 (23.5)	4 (10.8)

RF, rheumatoid factor; Anti-CCP, antibodies to cyclic citrullinated peptide. PIP, proximal interphalangeal joints. MCP , metacarpophalangeal joints.

Table 7. RAAD score and smoking status in subgroups of disease duration

Disease duration	Number of patients with smoking status	Median RAAD	Interquartile Range	Asymptotic significance Kruskal-Wallis test
≥ 10 years	318	Yes 4.0 Quit 3.0 No 3.0	1.0 – 11.0 0 – 8.0 1.0 – 10.0	p=0.265
≥ 15 years	193	Yes 7.5 Quit 6.0 No 6.0	3.3 – 14.0 2.0 – 11.0 1.8 – 17.0	p=0.506
≥ 20 years	111	Yes 11.0 Quit 8.0 No 8.5	4.0 – 17.0 3.0 – 14.0 3.0 – 21.0	p=0.705

Table 8. Univariate analysis with the RAAD2 score and disease duration

Difference in RAAD2 score		
Variable		**P-value**
Gender		0.016*
Smoking		0.175
2010 ACR/EULAR criteria for RA ≥ 6		0.006*
Number of affected joints		0.032*
Serology abnormality		0.055
Rheumatoid Factor +/-		0.024*
Anti-CCP +/-		0.061
Acute phase response		0.004*
Symptom duration		0.166
Correlation with RAAD2 score		
	Correlation-coefficient	
Disease duration	0.55	<0.001*
Age	-0.14	0.002*
BMI	-0.17	<0.001*
Difference in disease duration		
Gender		0.004*
2010 ACR/EULAR criteria for RA ≥ 6		0.273
Number of affected joints		0.039*
Rheumatoid Factor +/-		0.026*
Acute phase response		0.501
Correlation with disease duration		
Age	-0.34	<0.001*
BMI	-0.11	0.018*

*significant at a 0.05 level. BMI, body mass index; ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor; Anti-CCP, antibodies to cyclic citrullinated peptide.

Table 9. Explanatory models RAAD2 score

	B coefficient	95.0% confidence interval	Significance
Model 1a			
Disease duration	0.42	0.364 – 0.469	0.000
Age at onset	0.00	-0.034 – 0.035	0.986
Model 2a			
Disease duration	0.43	0.376 – 0.481	0.000
BMI	-0.11	-0.233 – 0.015	0.085
Model 3a			
Disease duration	0.42	0.370 – 0.467	0.000
Gender	0.29	-0.651 – 1.233	0.544
Model 4a			
Disease duration	0.43	0.381 – 0.487	0.000
RF	0.39	-0.706 – 1.485	0.485

B, beta. BMI, body mass index. RF, rheumatoid factor.

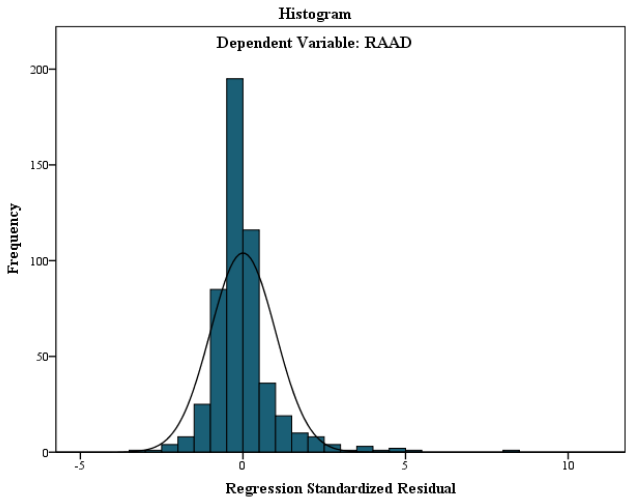


Figure 5. Normal distribution of residuals