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Clinical science

Improving our understanding of the paradoxical protective effect of obesity on radiographic damage: a large magnetic resonance imaging-study in early arthritis

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Abstract

Objective: Obesity conveys a risk for RA development, while paradoxically, associating with less radiographic progression after RA diagnosis. Using MRI we can study this surprising association in detail from MRI-detected synovitis and osteitis to MRI-detected erosive progression, which precedes radiographic progression. Previous research suggested obesity associates with less osteitis and synovitis. We therefore aimed to (i) validate the previously suggested association between BMI and MRI-detected osteitis/synovitis; (ii) study whether this is specific for ACPA-positive or ACPA-negative RA or also present in other arthritides; (iii) study whether MRI-detected osteitis associates with MRI-detected erosive progression; and (iv) study whether obesity associates with MRI-detected erosive progression.

Methods: We studied 1029 early arthritis patients (454 RA, 575 other arthritides), consecutively included in Leiden Early Arthritis Clinic. At baseline patients underwent hand-and-foot MRI that were RAMRIS-scored, and 149 RA patients underwent follow-up MRIs. We studied associations between baseline BMI and MRI-detected osteitis/synovitis (using linear regression), and erosive progression (using Poisson mixed models).

Results: In RA, higher BMI associated with less osteitis at disease onset ($\beta = 0.94$; 95% CI: 0.93, 0.96) but not with synovitis. Higher BMI associated with less osteitis in ACPA-positive RA ($\beta = 0.95$; 95% CI: 0.93, 0.97), ACPA-negative RA ($\beta = 0.97$; 95% CI: 0.95, 0.99) and other arthritides ($\beta = 0.98$; 95% CI: 0.96, 0.99). Over 2 years, overweight and obesity associated with less MRI-detected erosive progression ($P = 0.02$ and 0.03, respectively). Osteitis also associated with erosive progression over 2 years ($P < 0.001$).

Conclusions: High BMI relates to less osteitis at disease onset, which is not confined to RA. Within RA, high BMI and less osteitis associated with less MRI-detected erosive progression. This suggests that the protective effect of obesity on radiographic progression is exerted via a path of less osteitis and subsequently fewer MRI-detected erosions.

Keywords: RA, BMI, obesity, MRI, MRI-inflammation, erosive progression, radiographic progression, disease progression, ACPA, other arthritides

Rheumatology key messages

- High BMI conveys risk for RA development; paradoxically in RA patients obesity associates with less radiographic progression, which is insufficiently understood.
- In this large MRI study, high BMI associates with less MRI-detected osteitis in early arthritis patients (ACPA-positive and -negative) and other arthritides.
- High BMI associated with less MRI-detected erosive progression, suggesting that the protective effect of obesity on radiographic progression is exerted via less osteitis and subsequently fewer MRI-detected erosions.

Introduction

Paradoxical associations are found between obesity and RA. High BMI associates with increased risk of RA development, higher disease activity and lower odds of achieving disease remission [1, 2]. However, in patients diagnosed with RA, high BMI associates with less severe erosive radiographic progression of hands and feet. This seemingly paradoxical association is poorly understood [3–5]. Regarding disease development, obesity is reported as a risk factor for development not only of RA, but also of other inflammatory diseases such as psoriasis and inflammatory bowel disease. These associations are in line with the assumption that adipose tissue has immunomodulating and proinflammatory properties [6]. Interestingly, the contradictory association of obesity with

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radiographic erosive progression within established RA is also consistently reported in literature and was observed in five independent longitudinal cohorts [3, 7, 8, 9]. However, it is still unclear whether this association results from a true biological effect, a diagnosis subgroup effect, or is an epidemiological phenomenon (called index event bias).

A possible theory for a biological explanation was described by a previous cross-sectional MRI study in 354 patients, of whom 195 had RA. This study suggested that MRI-detected osteitis and synovitis might play a role in the association of high BMI with less radiographic progression, as at disease presentation obese RA patients had less severe MRI-detected osteitis and synovitis [4]. Thus far this association has not been validated. Moreover, it is unknown whether the association of obesity with less osteitis/synovitis is confined to RA or present in a variety of arthritides. Furthermore, even though it is known that osteitis is more prevalent in ACPA-positive RA, it remains unknown whether this association can be found in both ACPA-positive RA and ACPA-negative RA [10, 11]. Additionally, it remains to be explored if obesity also associates with less progression of erosions as (more sensitively) detected with MRI in RA.

Alternatively, a selection bias called index event bias might explain the BMI paradox in RA. This bias could either result in finding inverse associations due to selection of the population (RA patients), or could bias associations to the null if another (unknown) risk factor for RA is more strongly associated with the outcome [12, 13]. ACPA could be this unknown risk factor, as ACPA strongly associates with MRI-detected osteitis and erosive progression. Presence of this bias can be explored by studying the association between high BMI and less MRI-detected osteitis/erosive progression in patients with other arthritides and in ACPA subgroups and could be assumed less probable if the association is also found within these patients.

With the ultimate goal to increase our understanding of the paradoxical association between high BMI and less radiographic progression, we performed a large MRI study in a population-based inception cohort. We aimed to (i) validate the association between high BMI and less MRI-detected osteitis and synovitis; (ii) study whether this association is a subgroup effect in ACPA-positive or -negative RA only, and if this association is a general effect in early arthritis or confined to RA; (iii) study whether increased MRI-detected osteitis at diagnosis associates with MRI-detected erosive progression during follow-up; and (iv) study whether increased BMI associates with less MRI-detected erosive progression in RA [14, 15].

Methods

Patient selection

All patients consecutively included in the Leiden Early Arthritis Clinic (EAC) from August 2010 until March 2020 were evaluated for RA diagnosis or diagnosis with other arthritides (Fig. 1). The EAC is an inception cohort of patients with recent-onset arthritis with symptom duration <2 years. RA was defined as fulfilment of 1987 and/or 2010 RA classification criteria [16, 17]. Both 1987 and 2010 RA classification criteria were considered, since the 1987 criteria identify autoantibody negative RA patients earlier when compared with the 2010 criteria and the 2010 criteria identify autoantibody positive RA patients earlier compared with the 1987 criteria [18].

For validation of the previously described association of high BMI with less MRI-detected osteitis and synovitis (our first aim), we confined our study population from October 2014 until March 2020, since RA patients included between August 2010 and October 2014 were already assessed in the previous study that we aimed to validate (Fig. 1) [4]. For all other analyses, patients included between August 2010 and March 2020 were studied.

At baseline, physical examination (including weight and height) and laboratory procedures were performed—including ACPA (EliA CPP [anti-CCP2], Phadia, Nieuwegein, the Netherlands, considered elevated if ≥10 U/ml), IgM RF (in-house ELISA, considered elevated if ≥5.0 IU/ml) and CRP (mg/l). BMI (kg/m^2) was categorized according to WHO definitions into underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) and obese (BMI >29.9). Furthermore, at baseline an MRI of hand and foot was obtained from all patients. Between August 2010 and February 2015 MRIs were also performed during follow-up visits at 4, 12 and 24 months in RA patients. Clinicians and patients were blinded for MRI images and scoring results. Some patients had unknown baseline BMI or no baseline MRI (of sufficient quality) and were not studied; their baseline characteristics did not differ from the studied patients (Supplementary Table S1, available at *Rheumatology* online). All patients provided written informed consent. Ethical approval was provided by the Medical Ethics Committee ('Commisie Medische Ethiek') of the Leiden University Medical Centre (B19.008).

MRI scanning and scoring

MCP (2–5), wrist and MTP (1–5) joints were scanned using a 1.5-T MRI after administration of intravenous gadolinium. At baseline, joints of the most affected side were scanned and in cases of equally affected joints the dominant side was scanned. Follow-up MRI scans were obtained from the same side as scanned at baseline. Patients were asked to stop NSAIDs 24 h before the MRI scan. MRIs were scored for erosions, osteitis and synovitis according to the RA MRI Scoring (RAMRIS) method and for tenosynovitis according to Haavardsholm and colleagues [19, 20]. Erosion, osteitis, synovitis and tenosynovitis scores were calculated per feature per patient. Total MRI-detected inflammation was the sum of the osteitis, synovitis and tenosynovitis scores. Baseline MRIs were scored by three pairs of experienced readers with an excellent inter-reader reliability of ≥0.95, as reported previously [21]. Follow-up MRIs were scored by one reader with known time order. Intrareader reliability for follow-up MRIs was assessed for both baseline MRI scans and the change of MRI score between baseline MRI and MRI at 1 year, and was excellent: single measures intraclass correlation coefficient of 0.98 and 0.97. All readers were blinded for clinical data. Supplementary Data S1 (available at *Rheumatology* online) provides detailed information about scanning and scoring.

Statistical analyses

Associations between baseline BMI and MRI inflammation scores (osteitis, synovitis and tenosynovitis separately and summed as total MRI inflammation) were analysed using linear regression with the different MRI scores as dependent variable. MRI scores were log-transformed to obtain normally

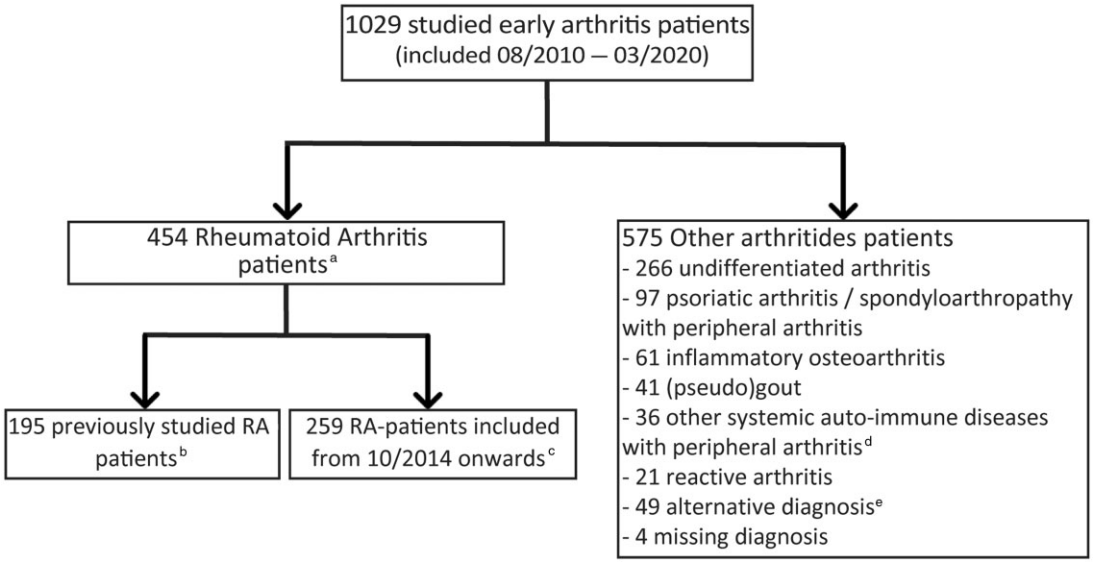

Figure 1. Subgroups within the studied early arthritis patients of the EAC cohort. Overview of the studied subgroups from the EAC cohort. Patients with unknown baseline BMI or baseline MRI of insufficient quality were excluded; baseline characteristics were similar to studied patients ($n = 663$, Supplementary Table S1). [a]RA-patients included between August 2010 and March 2020, used for all analyses except the validation of the previously described association between high BMI and less MRI-detected osteitis and synovitis. [b]Patients previously studied by Mangnus *et al.* [4]. [c]Patients studied for validation of the previously described association between high BMI and less MRI-detected osteitis and less MRI-detected synovitis. [d]Other systemic auto-immune diseases with peripheral arthritis includes SLE ($n = 4$), MCTD ($n = 11$), sarcoidosis ($n = 9$) and other systemic diseases ($n = 12$). [e]Alternative diagnosis includes RS3PE ($n = 22$), para-malignant ($n = 5$), and none of the above specified diagnoses ($n = 22$). EAC: Leiden Early Arthritis Clinic

distributed residuals (formula: ln[MRI score + 1]). The obtained effect sizes were back-transformed to normal scale (formula: e^{β}) and interpreted on a multiplicative scale.

Poisson mixed models were used to analyse the effect of both osteitis and BMI separately on the course of MRI-detected erosions (erosive progression during 2 years' follow-up). Mixed models are suitable for longitudinal measurements since they adjust for within-patient effects. Poisson regression is used to predict an outcome that consists of count data, such as the erosion score. In the first model erosion score was the dependent variable, osteitis and time in months were the independent variables. In the second model erosion score was the dependent variable and BMI (categorized as normal weight [reference], overweight and obese) was the independent variable. An interaction between BMI and time in months was added to assess the increase of erosive progression per BMI category. Since Poisson mixed models incorporate log-transformation, results were represented on a multiplicative scale as an incidence rate ratio (IRR). An IRR <1 indicates less erosive progression compared with the reference group (normal weight); an IRR >1 indicates more erosive progression compared with the reference. All analyses were corrected for age. SPSS Statistics v25 (IBM Corp., Armonk, NY, USA) and Stata v.16 (StataCorp, College Station, TX, USA) were used.

Results

Study population

In the period August 2010 to March 2020, 1029 consecutively included early arthritis patients were studied (Fig. 1); 454 patients were classified as RA and 575 patients had another diagnosis (e.g. undifferentiated arthritis, psoriatic arthritis, systemic auto-immune diseases with peripheral arthritis, reactive arthritis).

Table 1 presents the baseline characteristics of the study population. The mean age of the RA patients was 59 years and 64% were female. Median BMI was 26.0 and respectively 41% and 20% of the patients were suffering from overweight and obesity. Supplementary Table S2 (available at *Rheumatology* online) presents the characteristics of the ACPA-positive and ACPA-negative RA patients separately. Patients presenting with other arthritides had a mean age of 55 years, 51% were female and median BMI was 26.0 (42% overweight and 19% obese, Table 1). Of the total 454 RA patients, 259 RA patients were included between October 2014 and March 2020. These patients were studied for validation of the previously found association between high BMI and less synovitis and osteitis. Patient characteristics of these 259 RA patients were comparable to the 454 RA patients included from August 2010 until March 2020 (Supplementary Table S3, available at *Rheumatology* online).

High BMI associates with less MRI-detected osteitis

Our first aim was to validate the previously found association between high BMI and less synovitis and osteitis [4]. Higher BMI associated with a lower total MRI-detected inflammation score (osteitis, synovitis and tenosynovitis scores summed) with adjustment for age ($\beta = 0.98$; 95% CI: 0.96, 1.00; $P = 0.014$; Table 2), meaning that a patient with one point increase in BMI, had a 0.98 times lower total MRI-detected inflammation score at disease presentation. Regarding the individual MRI features, BMI only significantly associated with osteitis ($\beta = 0.94$; 95% CI: 0.92, 0.97), while no association was observed with synovitis, tenosynovitis and erosions (Table 2). BMI remained inversely associated with osteitis, independent of synovitis and tenosynovitis scores

Table 1. Baseline characteristics of RA patients and patients with other arthritides

	All RA patients ($n = 454$)	Other arthritides ($n = 575$)
Age, mean (S.D.), years	59 (14)	55 (16)
Female patients, *n* (%)	289 (64)	293 (51)
BMI, median (IQR), kg/m^2	26.0 (23–29)	26.0 (24–29)
Normal weight (BMI 18.5–24.9), *n* (%)	175 (39)	217 (38)
Overweight (BMI 25–29.9), *n* (%)	186 (41)	244 (42)
Obese (BMI >29.9), *n* (%)	90 (20)	109 (19)
SJC (68 joints), median (IQR)	5 (2–10)	2 (1–4)
TJC (71 joints), median (IQR)	8 (4–13)	3 (1–7)
CRP, median (IQR), mg/l	9 (4–24)	5 (3–14)
ACPA-positive, *n* (%)	209 (46)	6 (1)
RF-positive, *n* (%)	241 (53)	40 (7)
MRI scores, median (IQR)		
Total MRI inflammation	17 (8.0–27.0)	8.5 (3.0–17.0)
Total osteitis	4.0 (1.5–9.0)	2.5 (0.5–5.5)
Total SYN	6.5 (3.5–10.0)	3.5 (1.0–6.5)
Total TS	5.0 (2.0–8.5)	1.5 (0.0–5.0)
Total erosions	3.25 (1.5–6.0)	2.5 (1.0–5.0)

Baseline characteristics of early arthritis patients included in the EAC between August 2010 and March 2020. Within the RA population $n = 3$ patients had a BMI < 18.5; within other arthritis $n = 5$ patients had a BMI <18.5. Other arthritides consist of: undifferentiated arthritis ($n = 266$); psoriatic arthritis/spondyloarthropathy with peripheral arthritis ($n = 97$); inflammatory osteoarthritis ($n = 61$); (pseudo)gout ($n = 41$); reactive arthritis ($n = 21$); SLE/MCTD/sarcoidosis/other systemic disease ($n = 36$); alternative diagnosis ($n = 49$); and unknown diagnosis ($n = 4$). IQR: interquartile range; SJC: swollen joint count; SYN: synovitis; TJC: tender joint count; TS: tenosynovitis.

Table 2. Associations between BMI (independent variable) and MRI features (dependent) at baseline in RA patients and patients with other arthritides

	β (95% CI) per unit BMI increase				
	Univariable analyses[b]				Multivariable analysis[c]
	Outcome total MRI-inflammation	Outcome osteitis	Outcome synovitis	Outcome tenosynovitis	Outcome osteitis
RA patients[a]	0.98 (0.96, 1.00)*	0.94 (0.92, 0.96)*	1.00 (0.98, 1.01)	0.99 (0.97, 1.02)	0.94 (0.93, 0.96)*
ACPA$^+$ RA	0.97 (0.94, 0.99)*	0.94 (0.91, 0.96)*	0.99 (0.97, 1.01)	0.99 (0.97, 1.02)	0.95 (0.93, 0.97)*
ACPA$^-$ RA	0.98 (0.96, 1.00)	0.96 (0.94, 0.98)*	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.97 (0.95, 0.99)*
Other arthritides	1.01 (0.995, 1.03)	0.98 (0.97, 0.996)*	1.02 (1.01, 1.03)*	1.01 (0.998, 1.03)	0.98 (0.96, 0.99)*

The association of BMI with all MRI-features in RA patients, ACPA-subgroups and patients with other arthritides. Associations were analysed using linear regression; MRI scores were the dependent variable, BMI (continuously) and age were independent variables. MRI scores were log-transformed for regression analyses (ln[MRI score + 1]). Regression coefficients and confidence intervals were back-transformed (e^{β} and $e^{95\%CI}$), and therefore effect sizes should be interpreted as multiplicative. Effect sizes <1 indicate a β-fold decrease in MRI feature per unit increase in BMI and effect sizes >1 mean β-fold increase in MRI feature per unit increase of BMI, i.e. in RA patients 1 point increase in BMI leads to a 0.98 times decrease in osteitis score.

[a] Validation in RA patients included from October 2014 onwards.
[b] Outcome adjusted for age only.
[c] Outcome adjusted for age, synovitis and tenosynovitis scores.
* $P < 0.05$.

(multivariable analysis β = 0.94; 95% CI: 0.93, 0.96), meaning that per point increase in BMI, osteitis scores were 0.94 times lower. This validated the inverse relationship between BMI and MRI-detected osteitis at disease-onset, but not between BMI and MRI-detected synovitis.

High BMI associated with less osteitis in ACPA-positive and ACPA-negative RA

To study if the inverse association between BMI and MRI-detected osteitis is present in both ACPA subgroups, ACPA-positive and ACPA-negative RA patients were assessed separately. In ACPA-positive RA, a higher BMI associated with less MRI-detected osteitis independent of age (β = 0.94; 95% CI: 0.91, 0.96; Table 2) and also independent of MRI-detected synovitis and tenosynovitis scores (β = 0.95; 95% CI: 0.93, 0.97). This association was also present in ACPA-negative RA (β = 0.96; 95% CI: 0.94, 0.98; Table 2) and was independent of synovitis and tenosynovitis scores as well (β = 0.97; 95% CI: 0.95, 0.99). In both ACPA subgroups, BMI was not associated with MRI-detected synovitis, tenosynovitis or erosions. Thus, similar associations were found in ACPA-positive and ACPA-negative RA patients.

High BMI associated with less MRI-detected osteitis in other early arthritides

To study whether the association between obesity and less MRI-detected osteitis was specific for RA or also present in other early arthritides, 575 patients with other arthritides were studied (diagnoses shown in Fig. 1). Similarly, in these patients, high BMI associated with less MRI-detected osteitis (β = 0.98; 95% CI: 0.97, 0.996; Table 2), also independent of MRI-detected synovitis and tenosynovitis scores (β = 0.98; 95% CI: 0.96, 0.99). Supplementary Table S4 (available at *Rheumatology* online) shows the association in subgroups of patients with other arthritides: the association was significant in patients presenting with undifferentiated arthritis and a

similar trend was found in patients with psoriatic arthritis, several systemic auto-immune diseases with peripheral arthritis (i.e. SLE, MCTD, sarcoidosis) and reactive arthritis, although these groups were smaller in size. Thus, the association between high BMI and less MRI-detected osteitis was not specific for RA.

Osteitis associates with MRI-detected erosive progression

Previous research showed that osteitis strongly correlates with MRI-detected erosive progression in the same bone [14]. As we observed that patients with a high BMI have less osteitis at baseline, our next aim was to study the association of baseline osteitis with MRI-detected erosive progression. Therefore, we assessed 149 RA patients with serial MRIs during a 2-years follow-up. Their baseline characteristics were similar to the rest of the studied RA patients (Supplementary Table S5, available at *Rheumatology* online). MRI-detected osteitis associated with more severe erosive progression; per point increase in baseline osteitis, erosive progression increased 3% during the entire follow-up (IRR 1.03; 95% CI: 1.02, 1.05; $P < 0.001$). Thus in the same patient, higher baseline osteitis significantly associated with more erosive progression.

Obese RA patients show less MRI-detected erosive progression compared with normal weight patients

Knowledge of the correlation between osteitis and MRI-detected erosive progression, both in the same patient (this study) and in the same bone (previously shown), combined with our observation of less osteitis in RA patients with a high BMI, prompted us to assess whether increased BMI also associated with less MRI-detected erosive progression [14].

We evaluated the three BMI groups (38% normal weight, 40% overweight and 22% obese) in RA patients with serial MRIs. Normal weight RA patients had most erosive progression over time (Fig. 2; for raw data see Supplementary Fig. S1, available at *Rheumatology* online). When comparing the three BMI groups with normal weight as reference, patients with overweight and obesity had significantly lower MRI-detected erosive progression than normal weight patients (Fig. 2, IRR of respectively 0.989 [95% CI: 0.98, 0.998; $P = 0.017$] and 0.989 [95% CI: 0.980, 0.999; $P = 0.027$]). This indicates that the MRI-detected erosive progression was 0.989 times lower per month in both overweight and obese

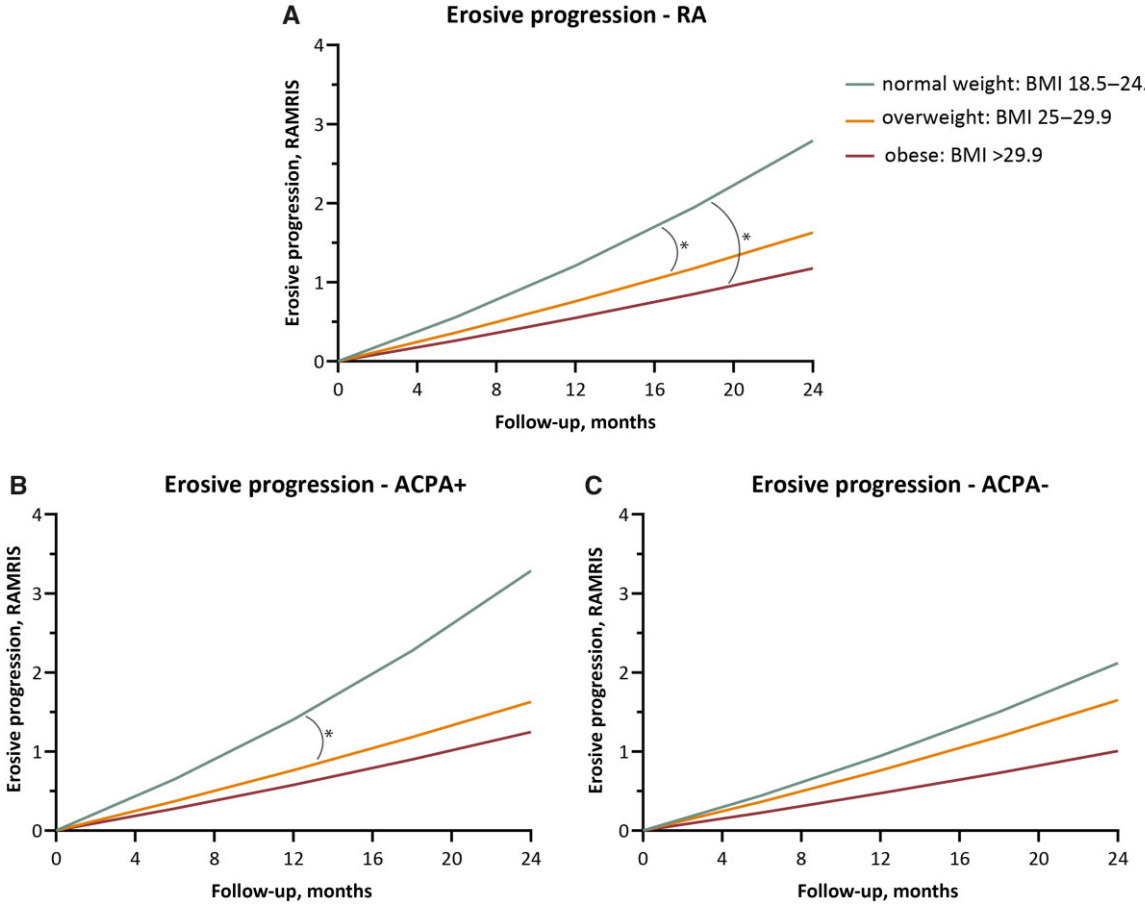

Figure 2. Trajectories of MRI-detected erosive progression in patients: obesity associates with less MRI-detected erosive progression compared with normal weight. Trajectories of MRI-detected erosive-progression during follow-up in (**A**) all RA patients with follow-up MRI, (**B**) ACPA-positive and (**C**) ACPA-negative RA patients per BMI category. (**A**) Overweight and obese patients have significantly less severe erosive-progression compared to normal-weight RA (overweight IRR 0.989, $P = 0.02$; and obese IRR 0.989, $P = 0.03$). (**B**) Within ACPA-positive patients ($n = 77$) similar results were found: overweight patients had significantly less erosive progression(IRR 0.986, $P = 0.007$) and a similar trend was found in obese patients (IRR 0.988, $P = 0.092$). (**C**) Within ACPA-negative patients ($n = 72$) similar trends were seen, but not significant (IRR for overweight patients 0.99, $P = 0.50$; and IRR 0.99, $P = 0.35$ for obese patients). Patterns were visualized based on estimated marginal means resulting from Poisson mixed models, per BMI-category baseline erosions were substracted from all marginal means to show the erosive progression more clear. *$P < 0.05$

patients, or 23% lower over a period of 2 years (IRR for 1 month 0.989, thus $0.989^{24\text{months}} = 0.77$, and thus erosive progression times 0.77 over 2 years).

Although sample sizes became lower after ACPA-stratification, the same tendency was found in ACPA-negative and ACPA-positive RA during 2 years follow-up. In ACPA-negative RA both patients with overweight and obesity had 0.99 times less erosive progression per month than normal weight patients (IRR 0.99; 95% CI 0.99, 1.01 and IRR 0.99; 95% CI 0.98, 1.01, respectively as shown in Fig. 2). These IRRs of 0.99 per month corresponds with 21% less erosive progression over 2 years ($0.99^{24\text{months}} = 0.79$). Similarly, ACPA-positive patients with overweight and obesity had less erosive progression compared with ACPA-positive patients with normal weight (IRR 0.986 [95% CI: 0.98, 0.996; $P = 0.007$] and IRR 0.988 [95% CI: 0.97, 1.00; $P = 0.09$], respectively). This IRR ACPA-positive patients with overweight corresponds to 29% less erosive progression over 2 years and the IRR of 0.988 for ACPA-positive patients with obesity corresponds to 25% less erosive progression over 2 years, compared with normal weight ACPA-positive RA patients (Fig. 2). Thus, obesity is not only associated with less MRI-detected osteitis at baseline, but also with less MRI-detected erosive progression in RA patients and the same tendency is seen in both ACPA-positive and ACPA-negative RA.

Discussion

Paradoxical associations are found in RA patients regarding BMI: high BMI associates with increased risk of RA development, higher disease activity in RA and lower odds of achieving disease remission. Contradictory, multiple studies have undeniably reported that within RA, obesity is related to less severe radiographic erosive progression. We aimed to increase understanding of this unexpected association, by studying the intermediate steps between obesity and radiographic progression. Our study included 1361 MRIs in 1029 patients and revealed that high BMI associated with less severe MRI-detected osteitis in RA at disease onset, both in ACPA-positive and -negative RA, and in other arthritides. Furthermore, we showed that MRI-detected osteitis at disease onset associates with MRI-detected erosive progression, which precedes radiographic erosive progression. Additionally, RA patients with overweight and obesity had less MRI-detected erosive progression compared with normal weight RA patients (Fig. 3). Although a causal relationship cannot be implied from these analyses, the data do suggest that the paradoxical effect of high BMI on less severe radiographic erosive progression is connected via an intermediate path with less osteitis and less MRI-detected erosive progression [14].

A previous MRI study in 354 patients from our research group suggested an association of BMI and MRI-detected osteitis and synovitis at disease presentation [4]. In an independent dataset of consecutively included RA patients, we here replicated the association of obesity with osteitis. In addition, we revealed in both ACPA-positive and ACPA-negative RA that a high BMI associated with less MRI-detected osteitis and with less erosive progression. Therefore, the associations found with high BMI were not restricted to one ACPA subgroup.

At the start of the study, we considered whether an epidemiological phenomenon (index event bias), caused by an (unknown) risk factor or selection of the study population, could explain the beneficial association of an increased BMI [12, 13]. ACPA could be this risk factor as ACPA strongly associates with presence of osteitis and radiographic progression [22, 23]. This bias would imply that there is no true beneficial effect but that this supposed effect would occur due to patient selection. However, the data showed that effects of BMI on osteitis were present in both ACPA subgroups, and likewise in other early arthritides. Hence this makes the presence of this index event bias highly unlikely. This, combined with repeated findings from previous studies and the current study, makes a 'true inverse association' between obesity and radiographic joint destruction in RA more probable.

Possible biological processes underlying the association of obesity and less severe erosive progression are still to be elucidated. In general, obesity is considered a pro-inflammatory state as adipose tissue secretes adipokines that are involved in regulation of inflammation. Adiponectin is an adipokine and could be part of the underlying biological processes: adiponectin is increased in RA patients compared with the general population, both in plasma and in the synovium [24, 25]. Additionally, adiponectin positively associates with radiographic progression in RA [26, 27]. The precise mechanism involved is not completely clear, but previous research showed that adiponectin is able to up-regulate matrix metalloproteinases and IL-6 in RA and could increase the production of VEGF [25, 26, 28]. Thus, an increase in adiponectin (as shown in RA patients) could contribute to disease progression in the joints. Obese patients generally have lower adiponectin levels compared with normal weight patients, which

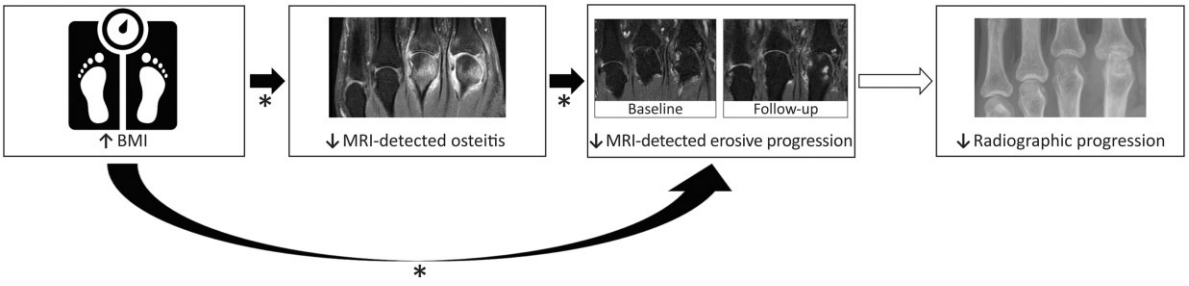

Figure 3. Overview of the findings and suggested association of BMI with radiographic progression. High BMI associates with less severe MRI-detected osteitis in RA at disease onset. MRI-detected osteitis at disease onset associated with MRI-detected erosive progression and high BMI associated with less MRI-detected erosive progression, which precedes radiographic erosive progression. A causal relationship cannot be implied with these analyses, but the data do suggest that the beneficial effect of high BMI on less severe joint damage progression is related via an intermediate path with less osteitis and less MRI-detected erosive progression. Black arrow with *: significant finding in the current study, $P < 0.05$. White arrow: not assessed in this study, known from previous studies [3, 5, 7, 8, 9]

could (partially) explain the paradox [27, 29, 30]. However, other processes could also be involved and further translational research is needed to fully comprehend underlying biological mechanisms.

Patients received treatment by their rheumatologist in line with international recommendations, and these guidelines do not recommend different treatment depending on BMI. The possibility that patients with normal weight and patients with overweight or obesity were treated differently by rheumatologists was further disproved by our observation that the treatment rates of corticosteroid use, conventional and biologic DMARDs were similar in all groups (Supplementary Table S6, available at *Rheumatology* online). It is therefore unlikely that the severity of erosive progression could be explained by differences in DMARD treatment.

BMI is a convenient measure as it is a simple ratio of weight to height. However, BMI does not account for body composition and might not be an accurate representation of the distribution of (excessive) body fat. Furthermore, BMI does not take age, sex and ethnicity into account, which could influence the relationship between BMI and body fat. Hence its use could be considered a limitation. Alternative methods that are possibly more adequate are, for example, waist circumference, waist-to-height ratio, waist-to-hip ratio, bioelectrical impedance analysis or MRI. Ideally, our findings would be validated in a study where BMI would be replaced by a direct measure of body composition or fat mass. However these data were not available and BMI is a commonly used measure in clinical practice, can be easily and objectively obtained, is easy to replicate, and can be applied in clinical practice without difficulty.

An important strength of this study is the large sample size of both RA patients and patients with other arthritides, included over a period of 10 years. Due to the large sample size and the fact that both ACPA-positive and -negative patients were included, we could properly investigate both ACPA-positive and -negative patients separately. This is of importance, as previous research suggested differences in underlying inflammatory pathways and outcomes in ACPA-positive and -negative patients [10, 22, 31]. To the best of our knowledge this is the first study assessing MRI-detected erosive progression over a time span of 2 years (instead of cross-sectionally looking at high/low MRI scores on several points in time and/or dichotomizing MRI scores).

In conclusion, this large prospective MRI study showed that early arthritis patients with high BMI have less MRI-detected osteitis at disease onset. This finding is not confined to RA, but also seen in patients with other arthritides. Within RA, obesity is also related with less severe MRI-detected erosive progression. Although previous research showed differences in outcomes between ACPA-positive and ACPA-negative patients, associations were similar in both ACPA subsets [10, 22, 31]. Our findings suggest a pathway of high BMI, via less MRI-detected osteitis, to less MRI-detected erosive progression, thereby explaining the effect of obesity on less radiographic progression (Fig. 3). Therefore this study increases our understanding of less severe radiographic joint damage in RA patients with higher BMI, which is essential in a time in which obesity keeps increasing.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information. Additional data are available upon reasonable request.

Contribution statement

All authors contributed to the conception and study design. N.K.dH. contributed to acquisition of the data and analysed the data. All authors contributed to interpretation of the data and the development of the manuscript. All authors approved the final version of the manuscript.

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