Clinical and epidemiological research

CONCISE REPORT

Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis

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ABSTRACT

Aim To investigate whether overweight/obesity at diagnosis affects the chances of decrease in disease activity and pain in early rheumatoid arthritis (RA).

Method We investigated incident RA cases from the population-based Epidemiological Investigation of risk factors for Rheumatoid Arthritis (EIRA) study (2006–2009, N=495) with clinical follow-up in the Swedish Rheumatology Quality Register. At diagnosis, 93% received disease-modifying antirheumatic drugs (DMARDs) (86% methotrexate). The odds of achieving a *good response* according to the DAS28-based European League Against Rheumatism (EULAR) criteria, *low disease activity* (DAS28<3.2), *remission* (DAS28<2.6) or *pain remission* (visual analogue scale ≤20 mm) at 3-months and 6-months follow-up, were calculated using logistic regression, adjusting for potential confounders.

Results Significant dose-response relationships were found between Body Mass Index (BMI) and change of disease activity as well as pain at both time points. Patients with BMI ≥25 had 51% lower odds of achieving low disease activity (odds ratio (OR=0.49 (95% CI 0.31 to 0.78)) and 42% lower odds of remission (OR=0.58 (95% CI 0.37 to 0.92)) at the 6-months visit, compared to normal-weight patients. This effect was also present at 3 months, where we also found a 43% decreased odds of pain remission (OR=0.57 (95% CI 0.37 to 0.88)). No effect modification was found for anti-citrullinated protein antibody (CCP)-status, sex, prednisolone treatment or DAS28 at diagnosis.

Conclusions Overweight at diagnosis significantly decreases the chance of achieving good disease control during the early phase of RA.

INTRODUCTION

Obesity and overweight are increasingly prevalent risk factors for many chronic diseases and also decrease the quality of life.[1] Approximately 35% of the world population is estimated to be overweight/obese.[2] Due to the immunomodulating and proinflammatory properties of adipose tissue,[3] it is of particular interest to study whether overweight may influence disease activity in rheumatoid arthritis (RA). Indeed, several studies have evaluated the effect of high Body Mass Index (BMI) on different aspects of this heterogeneous disease (reviewed in[4]). Recent reports have indicated that RA patients with high BMI have a worse long-term outcome in terms of disease activity, function and comorbidities

(BARFOT,[5]); and respond worse to tumour necrosis factor (TNF) inhibitors,[6] even the weight-adjusted infliximab treatment.[7] In an early RA trial (BeSt), BMI only associated with response to combination treatment, not methotrexate monotherapy.[8]

Our aim in this population-based cohort study of early RA was to investigate whether BMI at diagnosis affects the chance of good disease control, as measured by the 28-joint disease activity score (DAS28) and pain during the first 6 months in patients receiving standard care. The study cohort comprises extensive information about lifestyle factors that may influence the association between BMI and outcome.

METHODS

Study population

The study participants were cases with incident, disease-modifying antirheumatic drug (DMARD)–naive RA from the Swedish Epidemiological Investigation of risk factors for Rheumatoid Arthritis (EIRA) study; a population-based case-control study, described elsewhere.[9] Cases recruited between year 2006 and 2009, and who had clinical follow-up data from the Swedish Rheumatology Quality (SRQ) register (until 2010), were included (N=495). They constitute 63% of the total 786 patients included in EIRA during 2006–2009; 145 patients were excluded since they had answered an earlier version of the questionnaire, lacking our study variables, another 145 patients were excluded as they lacked data on follow-up in the SRQ register, one patient was excluded due to missing exposure information.

Definition of exposure

BMI at diagnosis (self-reported height and weight) was mainly investigated as a dichotomised measure; overweight (BMI </≥25), but was also categorised as normal-weight (BMI <25 kg/m^2), overweight (BMI 25–30 kg/m^2) or obesity (BMI ≥30 kg/m^2) according to the WHO guidelines.[10] These categories were used to investigate a potential dose-response relationship. The p value for trend was calculated. We also investigated BMI as a continuous measure.

Outcome measures

We investigated levels and changes in DAS28-based outcome measures and pain (on a visual-analogue scale (VAS-pain)) at the first two follow-up visits in

routine clinical care, 3 (2.5–5) and 6 (5–7.5) months after diagnosis. According to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations, we used low-disease activity (DAS28≤3.2), disease remission (DAS28≤2.6) and good response (DAS28 ≤ 3.2 and DAS28-decrease >1.2) as outcome measures.[11] Further, we specifically looked into the *decrease* of DAS28, defined as a decrease larger than median decrease in this population. We also investigated the effect of BMI on the components of the DAS28 measure.[12] Good disease control was further investigated in terms of pain remission (≤20 mm on a 100 mm visual-analogue scale, according to previous definition[13]) and a decrease in VAS-pain larger than the median decrease. Finally, we also investigated a decrease in activity limitation; Health Assessment Questionnaire (HAQ), larger than median decrease.

Statistical analysis

We used logistic regression to calculate the odds of each outcome (applying complete-case analysis). The analyses were adjusted for sex, calendar period of diagnosis, age at diagnosis, smoking, socioeconomic status, leisure time physical activity 5 years before diagnosis and physically demanding work 5 years before diagnosis. The analysis of DAS28 outcome was adjusted for DAS28 at diagnosis, and the analysis of pain was adjusted for VAS-pain at diagnosis. The potential effect modification by anti-citrullinated protein antibody (CCP)-status, sex, prednisolone treatment and DAS28 at diagnosis (≤/>5.1) was analysed by including interaction terms in the model. We further investigated the effect of BMI on the different DAS28 components, grouped into subjective and objective components. We calculated the OR of a decrease more than the median decrease in all three objective components (C-reactive protein, erythrocyte sedimentation rate and 28-swollen joint count) and in subjective components (tender joint count, patient global assessment), respectively.

All analyses were carried out using SAS Statistical Package V.9.3. All participants had given informed consent and the ethical review board at Karolinska Institutet, Stockholm, Sweden, approved the study.

RESULTS

Our final study population consisted of 495 RA patients. The excluded and included patients had similar BMI; median $BMI_{included\ patients}$=24.8 (95% CI 24.7 to 26.1), median $BMI_{excluded\ patients}$=25.2 (95% CI 25.4 to 26.3). Among the included patients, 86% received methotrexate at diagnosis and 6% received other DMARDs (table 1).

Patients with BMI ≥25 had 33% lower chance of achieving low disease activity at the 3-month visit (OR=0.67 (95% CI 0.45 to 1.00)), compared to normal-weight patients. This effect was further enhanced at the 6-month visit (OR=0.49 (95% CI 0.31 to 0.78)). A similar trend was found for disease remission, good response, and decrease more than the median, table 2). A statistically significant dose-response relationship was found between BMI (normal weight, overweight and obesity) and low-disease activity, good response, remission and above-median decrease, at the 6-month visit (p for each <0.01).

We further investigated the effect of BMI on the DAS28 components, grouped into subjective (tender joint count, patient global assessment) and objective (C-reactive protein, erythrocyte sedimentation rate and 28-swollen joint count) components. The odds for overweight patients, compared to normal weight patients, to have a decrease over the median decrease was significantly lower for the subjective, but not objective, measures (OR for subjective measures=0.63 (95% CI 0.42 to 0.94), OR

for objective measures=0.83 (95% CI 0.54 to 1.27) at 3 months), while none of the odds for the individual components of DAS28 was statistically significantly decreased (data not shown). At the 6-month visit, we found no significant associations.

Evaluating pain as an outcome measure (table 3), we found a 43% decreased chance of pain remission for overweight patients, compared to normal weight patients, at the 3-month visit (OR=0.57 (95% CI 0.37 to 0.88)), and a significant dose-response relationship for pain remission (p=0.01), and a decrease above median (p=0.02). Similar, but lower and non-statistically significant effects were found at the 6-month visit. In an additional analysis, we investigated the effect of overweight as compared to normal weight on the odds of experiencing a decrease in activity limitation (HAQ) above the median decrease at 3-month visit; OR=0.79 (95% CI 0.49 to 1.27)).

All analyses were adjusted for sex, calendar period of diagnosis, age at diagnosis, smoking, socioeconomic status, physical activity, physically demanding work and DAS28/pain at diagnosis, which only marginally changed the estimated ORs (see online supplementary table). Additional adjustments for vegetable intake, anti-CCP status, or treatment at diagnosis, did not change the associations. Further, we found no effect modification between BMI and anti-CCP-status, DAS28-category at diagnosis, or sex, respectively. Due to the homogenous treatment strategy at diagnosis we could only investigate effect modification by prednisolone treatment ($N_{treated}$=273, 55%). No significant difference between the groups was observed. Further, the findings were similar for the major subgroup of patients receiving methotrexate as the only DMARD at diagnosis, for example, the OR for low disease activity at 6 months were 46% decreased for overweight patients, compared to normal weight patients (OR=0.54 95% CI 0.33 to 0.87).

DISCUSSION

The results of this population-based study show that patients who are overweight at diagnosis have a statistically significant decreased chance of achieving good disease control according to standard DAS28-based measures, and regarding pain, during the initial phase of their disease. Whether these results are due to an effect of BMI on the natural progression of RA or that BMI affects the response to methotrexate, is not possible to answer due to the large proportion of patients treated with methotrexate (86%). If BMI is affecting the methotrexate response, possible mechanisms are, for example, due to intolerance or to decreased effect. The clinical implication would, however, be the same, irrespective of the underlying reason for the effect of BMI.

Strengths of the present study include its population-based setting, including an incident and unselected RA patient population, and the availability of information which made adjustments for a multitude of potential confounders possible. The self-reported exposure is likely to lead to some misclassification, which however, due to the prospective design of this study, is likely non-differential (ie, in this case not dependent on outcome status) and, thereby, underestimating the harmful effect of a high BMI, at least when comparing the extremes.

Two previous studies have investigated the effect of overweight on response to TNF-α therapy.[6][7] Both these studies showed a decreased number of good responders among overweight patients as compared to patients with normal BMI. The results in the present study are also compatible with one long-term study which demonstrated a worse outcome in individuals with high BMI after 10 years of disease.[5] Further, the BeSt trial

Table 1 Characteristics of patients included in the study, N=495, diagnosed year 2006–2009

	Normal weight (BMI <25) N (%)	Overweight/obese (BMI ≥25) N (%)	Total N (%)
Sex			
Female	189 (79)	164 (64)	353 (71)
Male	51 (21)	91 (36)	142 (29)
Age (yrs) at diagnosis			
<40	58 (24)	25 (10)	83 (17)
40–50	34 (14)	41 (16)	75 (15)
50–60	58 (24)	78 (31)	136 (27)
60–70	90 (38)	111 (44)	201 (41)
Treatment initiated at diagnosis			
No treatment	10 (4)	10 (4)	20 (4)
Only steroids	11 (5)	5 (2)	16 (3)
DMARDs (inc MTX)	219 (91)	240 (94)	459 (93)
Anti-CCP*			
Present	158 (68)	163 (65)	321 (65)
Absent	74 (32)	88 (35)	162 (34)
BMI*			
Normal weight: BMI <25	–	–	240 (48)
Overweight: BMI 25–30	–	–	170 (34)
Obese: BMI >30	–	–	85 (17)
Physical activity 5 yrs before diagnosis*			
No regular physical activity	121 (51)	144 (57)	265 (54)
Regular physical activity	117 (49)	110 (43)	227 (46)
Cigarette smoking			
Never	80 (33)	72 (28)	152 (31)
Past smoker	65 (27)	117 (46)	182 (37)
Current smoker	67 (28)	44 (17)	111 (22)
Irregular/other smoker	28 (12)	22 (9)	50 (10)
Socioeconomic status*			
High	72 (30)	57 (22)	129 (26)
Medium	116 (48)	136 (53)	252 (51)
Low	52 (22)	62 (24)	114 (23)
	Median (IQR)	Median (IQR)	Median (IQR)
Symptom duration at diagnosis (years)	0.43 (0.28, 0.68)	0.48 (0.31, 0.68)	0.46 (0.30, 0.68)
DAS28 at diagnosis	5.30 (4.5, 6.1)	5.18 (4.47, 6.18)	5.23 (4.47, 6.17)
VAS-pain at diagnosis	55 (32, 73)	56 (42, 73)	55 (36, 73)
DAS28 change: 3-month-visit	−2.28 (−1.03, −3.23)	−1.91 (−1.02, −2.90)	−2.05 (−1.02, −3.10)
VAS-pain change: 3-month-visit	−32 (−13, −52)	−28 (−8, −50)	−29 (−9, −51)
DAS28 change: 6-month-visit	−3.64 (−1.49, −2.62)	−3.16 (−0.94, −2.20)	−2.43 (−1.22, −3.37)
VAS-pain change: 6-month-visit	−29 (−10 ,−51)	−27 (−5, −45)	−27 (−8, −49)

Regarding those of the variables above measured at diagnosis, only sex, age at diagnosis and smoking differed statistically significantly between the normal weight patients and those overweight/obese.

*12 patients had missing anti-CCP -status, 3 patients had missing information of physical activity and 2 patients had missing info on VAS-pain at diagnosis.

Anti-CCP, anti-cyclic citrullinated peptide; BMI, Body Mass Index; DAS28, disease activity score 28 joints; DMARD, disease-modifying antirheumatic drug; VAS-pain, pain measured on a visual analogue scale.

showed an association between high BMI and poor response to therapy in the treatment arm combining methotrexate and infliximab, and the treatment arm combining methotrexate, sulfasalazine and prednisolone, but not for the patients treated with methotrexate monotherapy.[8] They also found that the main effect of BMI seems to be in the subjective experience (VAS-pain, tender joint count), which is supported by our DAS28-component analysis. Hypothetically; the effects of BMI on pain and inflammation may be through two different mechanisms, so that the medical antirheumatic treatment moderates the inflammation, which is reflected in the objective measures, but the subjective measures, incorporating the pain dimension, are less affected. Possibly, the somewhat larger effect of BMI on pain at the 3-month than 6-month follow-up visit indicate that pain is more inflammatory-driven early on.

The present study has not addressed mechanisms behind the association between high BMI and a less favourable early

Table 2 OR comparing patients overweight with patients of normal weight at diagnosis, with respect to DAS28-based outcome measures, at the 3-months and 6-months follow-up visits of early RA patients from the EIRA cohort

	Decrease over median		Low disease activity		Good response		Remission	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
3 months after diagnosis								
Normal weight	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Overweight	0.71	0.45 to 1.13	0.73	0.47 to 1.13	0.82	0.54 to 1.26	0.91	0.58 to 1.41
Obese	**0.37**	**0.20 to 0.68**	**0.56**	**0.32 to 0.99**	0.62	0.36 to 1.09	0.76	0.43 to 1.37
p Value for trend	**<0.01**		0.03		0.09		0.36	
Normal weight	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Overweight/obese	**0.58**	**0.38 to 0.89**	**0.67**	**0.45 to 1.00**	0.75	0.51 to 1.11	0.86	0.57 to 1.29
Effect per BMI-unit increase	**0.93**	**0.88 to 0.97**	**0.95**	**0.91 to 0.99**	**0.96**	**0.92 to 1.00**	0.97	0.93 to 1.02
6 months after diagnosis								
Normal weight	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Overweight	**0.54**	**0.32 to 0.90**	**0.50**	**0.30 to 0.81**	**0.50**	**0.31 to 0.81**	0.68	0.42 to 1.10
Obese	**0.44**	**0.22 to 0.90**	**0.48**	**0.25 to 0.94**	**0.48**	**0.25 to 0.92**	**0.36**	**0.18 to 0.74**
p Value for trend	**<0.01**		**<0.01**		**<0.01**		**<0.01**	
Normal weight	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Overweight/obese	**0.49**	**0.30 to 0.80**	**0.49**	**0.31 to 0.78**	**0.50**	**0.32 to 0.77**	**0.58**	**0.37 to 0.92**
Effect per BMI-unit increase	**0.94**	**0.89 to 0.99**	**0.94**	**0.89 to 0.99**	**0.94**	**0.89 to 0.99**	**0.92**	**0.87 to 0.97**

All models are adjusted for sex, calendar period of diagnosis (2006–2007 and 2008–2009), age at diagnosis (<40, 40–50. 50–60, 60–65, 65–70 yrs), smoking (never, past, current, irregular/other), socioeconomic status (high, intermediate, low), physically demanding work (combination of physical strain and time spent sitting, 4 levels, approximately quartiles), leisure time physical activity (regular, not regular), and for DAS28 at diagnosis as a continuous measure.
DAS28, disease activity score 28 joints; EIRA, Epidemiological Investigation of risk factors for Rheumatoid Arthritis; RA, rheumatoid arthritis.
Bold typeface indicates statistical significance.

Table 3 Odds ratio comparing patients with overweight to patients of normal weight at diagnosis, with respect to VAS pain-based outcome measures, at the 3-months and 6-months follow-up visits of early RA patients from the EIRA cohort

	At the 3-month-visit				At the 6-month-visit			
	Decrease over median		Remission		Decrease over median		Remission	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Normal weight	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Overweight	0.75	0.45 to 1.27	**0.59**	**0.37 to 0.95**	0.73	0.42 to 1.28	0.67	0.42 to 1.07
Obese	**0.43**	**0.22 to 0.85**	**0.53**	**0.29 to 0.97**	0.73	0.33 to 1.62	0.59	0.30 to 1.16
p Value for trend	**0.02**		**0.01**		0.31		0.06	
Normal weight	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Overweight/obese	0.64	0.40 to 1.03	**0.57**	**0.37 to 0.88**	0.73	0.43 to 1.25	0.65	0.42 to 1.01
Effect per BMI-unit increase	**0.93**	**0.88 to 0.98**	**0.96**	**0.92 to 1.00**	0.98	0.92 to 1.04	**0.95**	**0.90 to 1.00**

All models are adjusted for sex, calendar period of diagnosis (2006–2007 and 2008–2009), age at diagnosis (<40, 40–50. 50–60, 60–65, 65–70 yrs), smoking (never, past, current, irregular/other), socioeconomic status (high, intermediate, low), physically demanding work (combination of physical strain and time spent sitting, 4 levels, approximately quartiles), leisure time physical (regular, not regular), and for pain at diagnosis as a continuous measure.
BMI, Body Mass Index; EIRA, Epidemiological Investigation of risk factors for Rheumatoid Arthritis; RA, rheumatoid arthritis; VAS-pain, pain measured on a visual analogue scale.
Bold typeface indicates statistical significance.

disease course. However, it is previously known that adipose tissue is an endocrine/paracrine organ, it secrets bioactive substances, for example, TNF-α and interleukin-6,[3] which are important proinflammatory signals. Thus, healthy overweight individuals have higher levels of inflammatory markers than normal weight individuals.[14] However, adipose tissue can also produce cortisol; a potent anti-inflammatory substance,[15] and in line with this dualism, high BMI has in some publications been shown to protect against joint destruction,[16] or at least not to worsen it.[5 8]

Previous dietary and physical activity intervention trials in RA,[17 18] where the intervention groups have lost weight, have shown beneficial effect on disease activity, which is in line with the results of this study. However, evidence has been presented that mechanisms behind these associations may be directly

related to the diet[19] and the exercise[20] per see, rather than being an indirect effect of weight loss. The present results remained despite adjusting for level of physical activity and intake of vegetables, which may indicate that several mechanisms are in play. It is also important to keep in mind that underweight has been associated with increased mortality in RA patients,[21] highlighting the importance of maintaining muscle mass. Hopefully, future RA research on lifestyle will be able to weigh together all known factors and create a prediction model for the prognosis after RA.

In conclusion, the findings of this population-based study implicate that higher BMI at diagnosis decreases the chances of good disease control and pain control in early RA. Further studies are now warranted to investigate whether this effect can be countered by voluntary decrease of fat mass after diagnosis,

which would then be an important clinical message, highlighting the importance of lifestyle counselling. Furthermore, the present and previous studies[22] provide evidence for efforts to address overweight in individuals at increased risk for RA, and also in the general population.

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Competing interests None.

Patient consent Obtained.

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