Chapter 6

High BMI is associated with decreased treatment response to combination therapy in recent onset RA patients- a subanalysis from the BeSt study

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ABSTRACT

Objective To assess the association between high body mass index (BMI) and treatment response in recent onset RA.

Methods In the BeSt study, 508 patients were randomized to initial monotherapy or combination therapy with prednisolone or infliximab (IFX). Response to disease activity score (DAS)≤2.4- steered treatment (first dose and after 1 year) was compared between patients with a BMI <25 and ≥25, using relative risk regression analyses. DAS, components of DAS and functional ability during the first year were compared using linear mixed models.

Results High BMI was independently associated with failure to achieve DAS≤2.4 on initial therapy, RR 1.20 (95% CI 1.05;1.37). The effect for combination therapy with prednisolone was RR 1.55 (95% CI 1.06;2.28) and for combination therapy with IFX 1.42 (95% CI 0.98;2.06). The RRs for failure after one year were 1.46 (95% CI 0.75;2.83) and 2.20 (95% CI 0.99;4.92) respectively. High BMI was also associated with failure on delayed combination therapy with IFX, after adjustment for selection bias related to previous failure on DMARD. No significant association was observed in the initial monotherapy groups. In the first year, patients with a high BMI had higher DAS and worse functional ability, with more tender joints and a higher VAS global health, but not more swollen joints and similar systemic inflammation.

Conclusions High BMI was independently associated with failure to achieve low DAS on initial combination therapy with prednisolone and on initial and delayed treatment with infliximab. Patients with a high BMI experienced more pain, but not more swelling or systemic inflammation.

INTRODUCTION

An association between treatment response to TNF-blockers and BMI was described in a group of patients with established RA who had failed on disease modifying anti-rheumatic drugs (DMARD) treatment. Patients with a high BMI responded less well to treatment with a fixed dose of TNF-blocker infliximab (IFX).[1] This finding was replicated in patients who had failed on methotrexate and were treated with a fixed dose of adalimumab, etanercept or infliximab.[2] Patients with a high BMI and thus a higher fat mass might show more inflammation.[3,4] Yet, clinical synovitis might be less easy to assess in RA patients with a high BMI. It has also been described that patients with various conditions and a high BMI report more pain than patients with normal or low BMI.[5-7]
In the BeSt trial, a treat to target trial in early RA patients, treatment response in terms of Disease Activity Score (DAS) and patient reported outcomes was assessed every 3 months and yearly radiographs were taken. Because different treatment strategies were used, we could analyze the association between BMI and different components of treatment response not only to TNF-blockers, but also to conventional DMARD mono- or combination therapy.

METHODS

Patients from the BeSt cohort, a study originally designed to compare four different treatment strategies in early DMARD-naïve rheumatoid arthritis patients, were analyzed. Patients were randomized to sequential monotherapy (group 1) or step-up combination therapy (group 2) starting with methotrexate (MTX), initial combination therapy (group 3) with the COBRA scheme: MTX, sulfasalazine (SSA) and high dose tapered prednisolone or a combination of MTX and IFX (group 4).
Treatment was a disease activity score (DAS)-steered and aimed at a DAS≤2.4 resulting in treatment adjustments every three months as long as the DAS was >2.4. Thus, In groups 1-3, delayed infliximab treatment was initiated if patients had failed on at least 3 synthetic DMARD, including methotrexate, sulfasalazine, leflunomide (in arm 1) or hydroxychloroquine (in arm 2) and prednisolone (in arms 2 and 3). In all arms, DMARD treatment was changed or added to at least twice in case of insufficient response (DAS>2.4), before MTX+IFX combination therapy was started. Patients treated with MTX+IFX started IFX in a dose of 3 mg/kg/8weeks, but if the DAS remained >2.4, the IFX dose was escalated from 3 mg/kg/2 months to 6, 7.5 and finally 10 mg/kg if necessary. If the highest dose did not lead to a low DAS, MTX+IFX were abandoned and the next treatment initiated. At any stage of the protocol, if patients achieved a DAS≤2.4 for ≥6 months, treatment was tapered to maintenance dose: MTX monotherapy in groups 1

and 2, sulfasalazine monotherapy in group 3 and MTX+IFX 3mg/kg/2 months in group 4. More details on the treatment protocol were published previously.[8]

Treatment response (failure defined as not achieving a DAS ≤2.4) was compared between patients with a normal weight (BMI<25) and overweight or obese patients (BMI ≥25).[9] Both height and weight were assessed at baseline and were measured by a research nurse. Weight was measured on professional, calibrated scales, height with wall based measure rods. Treatment response was assessed at two time points. First, we looked at whether or not patients achieved a DAS≤2.4 after the first three months of treatment. Second, we looked at failing (DAS>2.4) in year 1, on treatment step 1 and 2: methotrexate monotherapy (15 mg/week, if necessary increased to 25 mg/week) in groups 1 and 2, on combination therapy with prednisolone (methotrexate 7.5, if necessary increased to 25 mg/week) in group 3, and on treatment steps 1, 2 or 3 (methotrexate plus infliximab increased from 3, 6 to 7.5mg/kg/2 months) in group 4. The different cut-off for group 4 was chosen because based on DAS evaluations before each infliximab dose, treatment could be intensified every 2 months, compared to every 3 months in the other groups. We also looked for a relation between BMI and clinical response to treatment with MTX plus infliximab in patients who had failed on previous synthetical DMARD in groups 1-3. After 8 years of treatment, the number of protocolized treatment steps patients had failed on was recorded in the initial treatment groups. Radiological damage progression was assessed using the Sharp-van der Heijde score (SHS), taking the mean of the scores of 2 independent readers who evaluated all the radiographs of hands and feet in non-chronological order, blinded for patient identity.

Statistical analysis

Statistical analyses were performed with the software program SPSS version 17.0 and STATA 12. Baseline characteristics were compared between patients with normal and high BMI, using the Student's t test, Mann Whitney U test or Chi square test. To determine whether a higher BMI was associated with impaired response to therapy according to the definitions above, a relative risk regression model was used, where the parameters were estimated using a modified Poisson regression approach with robust standard errors.[10] These analyses give risk ratios, which are easier to interpret than odds ratios. The analyses were adjusted for gender, age, smoking habits, rheumatoid factor (RF) and baseline DAS. Then the regression analyses for treatment response were repeated stratified for treatment group (groups 1&2, group 3 and group 4). The association between BMI and failure to achieve a DAS≤2.4 on delayed IFX was examined in patients from group 1-3 who received MTX+IFX after failing on several DMARD. Differences in baseline characteristics in this group, associated with response to DMARD, were observed between patients with low or normal and high BMI, indicating that there might be a selection bias. Therefore propensity scores, with age, RF, alcohol use (yes/no), treatment group, baseline ESR, number of swollen joints, visual ana-

logue scale global and morning stiffness (VAS) as predictors and high BMI as outcome were calculated using logistic regression. Then to correct for the differences between patients with normal and high BMI, a relative risk model was fitted with the weighting based on the estimated propensity score, i.e. 1/propensity score for patients with high BMI and 1/(1-propensity score) for patients with normal BMI. Weights larger than 5 were truncated at 5. We repeated the analyses with BMI as a (linear) continuous variable. There was no evidence of a non-linear association (tested by comparing likelihoods of different models and by using fractional polynomials). To find out whether there was a difference in disease manifestation in the first year of treatment, between the BMI categories in the various DAS components or in patient reported outcomes, linear mixed models were fitted. The following dependent variables were used in the different models: tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patients' assessment of global health (VAS global), and of pain (VAS pain) and Health Assessment Questionnaire (HAQ) score. In each of the models time and BMI category were entered as categorical covariates and the baseline value of the dependent variable as continuous covariate. The interaction between time and BMI was not significant in any of the analyses, therefore it was not included in the final models. The estimates were adjusted for gender, age, RF and smoking habits.
The number of treatment steps patients had failed on after 8 years was compared using the Mann Whitney U test.

RESULTS

Patients with a BMI≥25 were older than patients with a BMI<25: 56 versus 53 years (p=0.03) and were less often smokers (31 versus 41%, p 0.01).(*table 1*) No other significant differences in baseline characteristics were observed. A BMI ≥30 was observed in 15% of all patients.
High BMI was an independent predictor of failing (not achieving a DAS ≤2.4) on the first treatment step with a RR of 1.20 (95% CI 1.05;1.37).(*table 2*) A minor effect was observed for failing on treatment steps in year 1 (step 1 and 2 in groups 1-3 or steps 1, 2 and 3 in group 4) with a RR of 1.15 (95% CI 0.92;1.43). Analyses were repeated with BMI as a continuous variable and these results confirm the findings of the dichotomized analyses. High BMI was again an independent predictor of failing on the first step (RR 1.03, 95% CI 1.01;1.06) and for failing on treatment steps in year 1 (RR 1.02, 95% CI 1.01;1.04).(*table 3*)
After 8 years of DAS-targeted treatment, the median (IQR) number of treatment steps patients had failed on was 1 (0-3) for patients with a BMI<25 and 2 (1-4) for patients with a BMI≥25, p<0.001. The percentage of patients who after 8 years were no longer treated according to protocol due to failing on all treatment steps was not different: 26% vs 22%, p=0.4.

Table 1: baseline characteristics for patients with normal and high BMI

	BMI<25 (n=216)	BMI≥25 (n=292)	p-value
Female n(%)	155 (72)	188 (64)	0.08
Age	53 ± 15	56 ± 13	0.03
BMI	23 ± 2	29 ± 3	<0.001
Symptom dur. median (IQR)	23 (13-57)	23 (14-47)	0.7
ACPA-positive n(%)	131 (65)	160 (59)	0.2
RF positive n(%)	149 (69)	180 (62)	0.09
DAS	4.4 ± 0.8	4.4 ± 0.9	0.4
HAQ	1.4 ± 0.6	1.4 ± 0.7	0.4
CRP median (IQR)	20 (8-55)	21 (9-50)	0.96
ESR median (IQR)	38 (20-56)	34 (18-56)	0.4
TJC median (IQR)	13 (9-17)	13 (9-19)	0.3
SJC median (IQR)	13 (10-19)	14 (9-18)	0.8
VAS global health	51 ± 20	54 ± 20	0.09
VAS physician	58 ± 18	57 ± 18	0.6
VAS pain	54 ± 21	55 ± 22	0.3
Smoking n(%)	88 (41)	89 (31)	0.02

ACPA anti-citrullinated protein antibodies, *RF* rheumatoid factor, *DAS* disease activity score, *HAQ* Health Assessment Questionnaire, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *TJC* tender joint count, *SJC* swollen joint count, *VAS* visual analogue scale
Unless indicated otherwise, values are mean ± SD

Table 2: risk of not achieving a DAS ≤2.4 (on the first dose and during year 1) in patients with a high BMI

	Crude RR	Adjusted RR*
Fail on initial treatment step (all)	1.20 (1.04;1.38)**	1.20 (1.05;1.37)**
Fail on first dose MTX monotherapy	1.10 (0.96;1.25)	1.10 (0.97;1.25)
Fail on initial dose MTX+SSA+prednisolone	1.57 (1.02;2.41)**	1.55 (1.06;2.28)**
Fail on initial dose MTX+infliximab	1.37 (0.93;2.02)	1.42 (0.98;2.06)
Fail in year 1 (all)	1.13 (0.89;1.43)	1.15 (0.92;1.43)
Fail in year 1 (groups 1+2)	1.04 (0.82;1.31)	1.05 (0.84;1.30)
Fail in year 1 (group 3)	1.37 (0.68;2.75)	1.46 (0.75;2.83)
Fail in year 1 (group 4)	2.12 (0.93;4.83)	2.20 (0.99;4.92)

First dose: MTX monotherapy in groups 1 and 2, MTX+sulfasalazine+prednisolone in group 3, MTX+infliximab in group 4
Year 1: failing on treatment step 1 and 2: methotrexate monotherapy (15 or 25 mg/week) in groups 1 and 2, on combination therapy with prednisolone (methotrexate 7.5 or 25 mg/week) in group 3, and on treatment steps 1, 2 or 3 (methotrexate 25 mg/week plus infliximab increased from 3, 6 to 7.5mg/kg/2 months) in group 4
Reference: patients with a BMI <25
*adjusted for gender, age, smoking habits, rheumatoid factor (RF) and baseline DAS
** p-value <0.05
Data are presented as RR (95% CI)

Table 3: risk of not achieving a DAS ≤2.4 (on the first dose and during year 1) in patients with a high BMI (BMI as continuous variable)

	Crude RR	Adjusted RR*
Fail on initial treatment step (all)	1.03 (1.01;1.04)**	1.02 (1.01;1.04)**
Fail on first dose MTX monotherapy	1.02 (1.002;1.03)**	1.02 (1.003;1.03)**
Fail on initial dose MTX+SSA+prednisolone	1.05 (1.01;1.09)**	1.05 (1.01;1.09)**
Fail on initial dose MTX+infliximab	1.03 (0.99;1.07)	1.03 (0.99;1.07)
Fail in year 1 (all)	1.03 (1.008;1.06)**	1.03 (1.005;1.06)**
Fail in year 1 (groups 1+2)	1.02 (1.002;1.04)**	1.02 (0.998;1.04)**
Fail in year 1 (group 3)	1.06 (0.97;1.17)	0.99 (0.99;1.16)
Fail in year 1 (group 4)	1.04 (0.97;1.11)	1.04 (0.98;1.11)

Legend of table 2 also applies to this table

Treatment groups

In groups 3 and 4, a higher risk of impaired response to therapy for patients with a high BMI was found with RRs of 1.55 (95% CI 1.06;2.28) and 1.42 (95% CI 0.98;2.06) for response to the first dose. For group 3, the RR for response to the first 2 treatment steps in year 1 was 1.46 (95% CI 0.75;2.83). The effect of impaired response in patients with a high BMI was stronger in group 4: RR 2.20 (95% CI 0.99;4.92). In groups 1 and 2, no significant association between treatment response and BMI was observed.

Delayed infliximab

For patients initially treated with MTX+IFX in group 4 (n=120), demographic or disease characteristics between patients with a high and low BMI were similar at baseline (data not shown). In contrast, patients with a BMI≥25 who received MTX+IFX in groups 1-3 were less often positive for ACPA and RF, 57 vs 83% and 66 vs 90% respectively, p=0.004 and p=0.002. (*table S1*) They were older than patients with a BMI<25: mean age 51 vs 46, p 0.02. There were 32 patients with a BMI>30. Of these only 9 patients (28%) responded well to medication after 1 year. Of the patients in groups 1-3 with a BMI<30, 89 of 193 responded well (46%).

However, in crude analyses no association was seen between BMI and response to treatment in patients from groups 1-3 who received delayed MTX+IFX: RR 1.11 (95% CI 0.71;1.73) for response to first dose, and a trend was seen for response after 1 year: RR 1.56 (95% CI 0.80;3.04). After adjusting for the misbalance in the baseline characteristics using propensity weighing the RR of failure to the first dose changed to 1.37 (95% CI 0.81;2.31), the RR of failure after 1 year to 2.09 (95% CI 0.97;4.49).

Disease activity components

In year 1, adjusted for baseline differences, patients with high BMI had higher disease activity (difference in DAS 0.30 (95% CI 0.15;0.45)), a higher HAQ score (difference 0.14

(95% CI 0.05;0.23)) and a higher VAS pain (difference 6.2 mm (95% CI 3.0;9.4)). For DAS components, a difference was found in tender joints (difference 1.4 (95% CI 0.6;2.2)) and patient's assessment of global health (difference 4.9 mm (95% CI 1.9;7.8)), but not for swollen joints (difference 0.6, 95% CI -0.02;1.2).(*table 4, figure 1*) Radiological damage progression in year 1 and over 8 years follow up was similar in patients with high or low/normal BMI: median progression.(*figure 2*)

Table 4: differences in disease activity and its components for patients with a BMI≥25 compared to patients with a BMI<25 over the first year (analyzed using linear mixed models)

	Unadjusted difference	Adjusted difference*
DAS	0.25 (0.10;0.40)	0.30 (0.15;0.45)
HAQ	0.13 (0.04;0.21)	0.14 (0.05;0.23)
VAS global	4.4 (1.5;7.3)	4.9 (1.9;7.8)
ESR	0.9 (-1.3;3.1)	1.3 (-0.9;3.5)
CRP	0.1 (-2.2;2.3)	0.7 (-1.5;2.9)
TJC	1.1 (0.4;1.9)	1.4 (0.6;2.2)
SJC	0.5 (-0.1;1.1)	0.6 (-0.02;1.2)
VAS pain	5.4 (2.3;8.6)	6.2 (3.0;9.4)

DAS Disease Activity Score, *HAQ* Health Assessment Questionnaire score, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC* tender joint count, *SJC* swollen joint count
*Adjusted for rheumatoid factor, age, gender and smoking habits
Data are presented as β-estimate (95% CI)

DISCUSSION

In this DAS-targeted treated cohort with early RA patients, high BMI was associated with failure to achieve a low DAS (≤2.4) on anti-rheumatic therapy, also after adjustment for confounders. This was most noticeable in patients who were treated with initial combination therapy with methotrexate, either combined with prednisolone and sulfasalazine, or with infliximab. The association between high BMI and failure on treatment remained if the dose of methotrexate or infliximab was increased. After stratification for initial therapy (initial monotherapy with MTX in groups 1-2, initial combination therapy with MTX, sulfasalazine and prednisolone in group 3 or MTX and infliximab in group 4), patients with a high BMI who were treated with initial combination therapy were more likely to show a decreased response to treatment than patients with a normal BMI. This association was still seen after 1 year, after failure on the initial treatment had led to dose increases (of methotrexate in group 3 and of infliximab in group 4), but less so in group 3 than in group 4. High BMI was also associated with failure to achieve a low DAS on delayed treatment with infliximab, in patients who had failed on at least 3 conventional

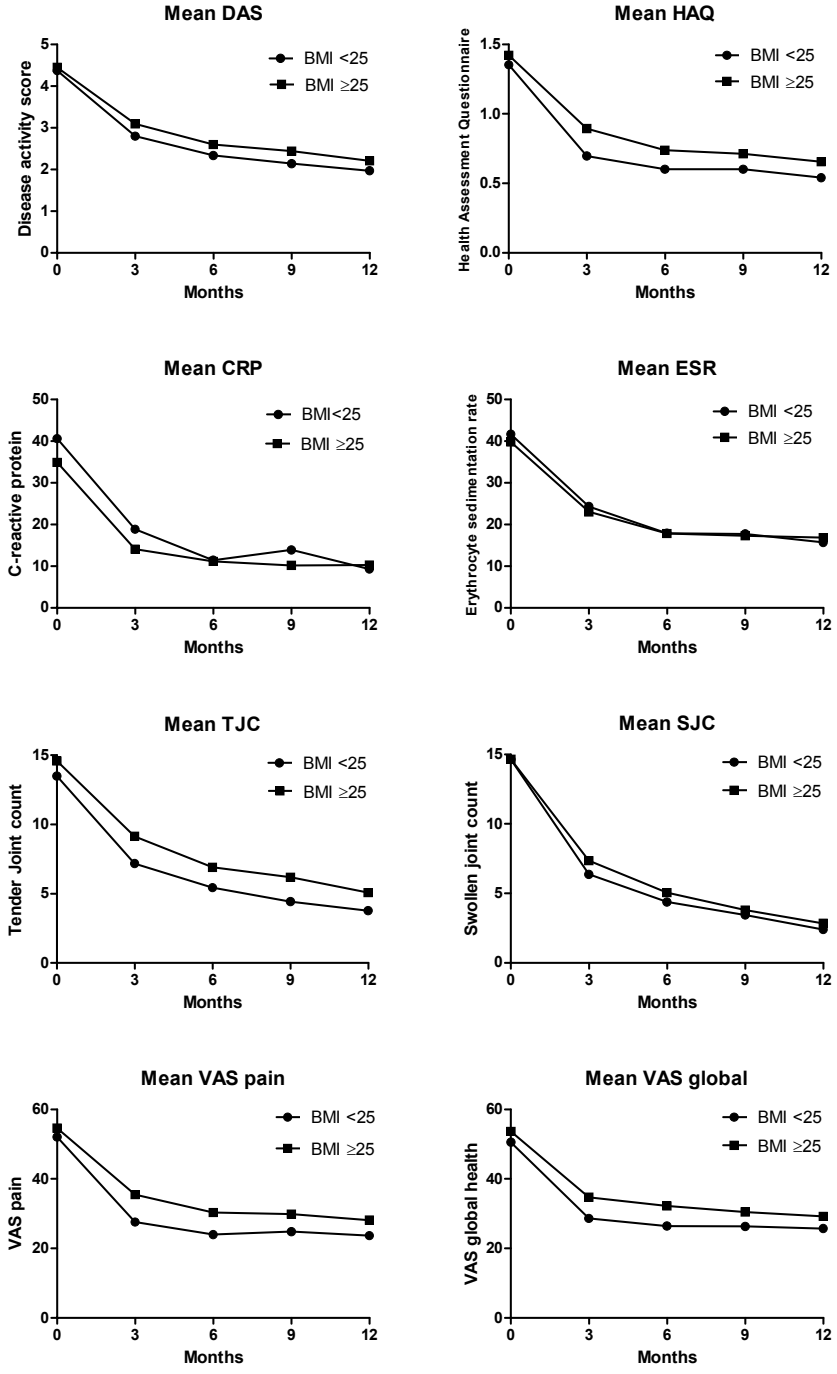

Figure 1: Disease Activity Score, Health Assessment Questionnaire, VAS global health, Erythrocyte sedimentation rate, Tender joint count, Swollen joint count, patient's assessment of pain (on a visual analogue scale) and physician's assessment of disease activity in year 1 for patients with a BMI<25 and ≥25

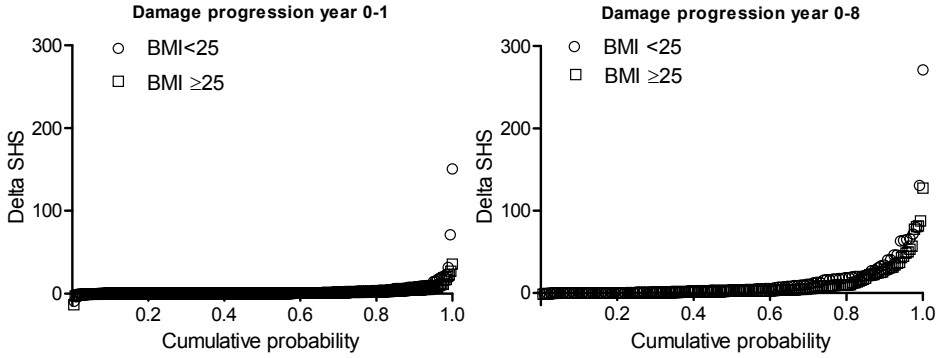

Figure 2: Cumulative probability plot of joint damage progression in year 0-1 and in years 0-8 for patients with a BMI<25 and ≥25

DMARD. Due to more failure to achieve a low DAS on treatment, patients with high BMI went through significantly more treatment steps over 8 years of DAS-targeted treatment than patients with low/normal BMI. Failure to achieve a low DAS depended mainly on the pain and joint tenderness scores, which were higher in the patients with a high BMI, whereas joint swelling and laboratory parameters of inflammation were similar in patients with high or low/normal BMI.

Recently, Klaassen *et al.* reported that patients with a high BMI responded less well to delayed treatment with fixed dose infliximab, after failure on a median of 2 DMARD.[1] It has been suggested that this may be due to high levels of proinflammatory cytokines produced by adipocytes.[3,4] Our results confirm that patients with a high BMI fail more often on infliximab, also as initial treatment, and also if the dosages are increased up to 10 mg/kg/8 weeks. Thus, a failure to respond on infliximab in patients with higher BMI is not due to underdosing, which is also theoretically unlikely, since infliximab is dosed per kilogram and the drug remains mainly in the intravascular space,[11] the volume of which can increase with higher BMI.[12] However, our data also show patients with a high BMI fail more often on treatment with a combination of methotrexate, sulfasalazine and prednisolone, and on subsequent treatment steps during 8 years of DAS≤2.4 targeted treatment. Only in patients treated with initial methotrexate monotherapy, patients with higher BMI did not fail to achieve a low DAS more often than patients with low/normal BMI. This might be related to the fact that in general, failure on initial methotrexate monotherapy was more common than on initial combination therapy, which makes it harder to analyze the role of individual risk factors.

Rather than being the result of high ESR or swollen joint counts, the higher DASs scored in patients with higher BMI appear to depend on pain. Higher pain scores and worse global health were also reported in patients with a high BMI in a large Swedish cohort.[13] There, patients with a BMI≥30 also had a higher ESR and CRP at follow up. We found no

association between a high BMI and higher parameters of inflammation or more joint swelling, but there were very few patients with a BMI≥30.

It is possible that we underestimated joint swelling in patients with a high BMI.[14] The higher tender joint counts in patients with a high BMI might still reflect more local inflammation. We previously reported that local joint tenderness is a predictor of local joint damage after 1 year, independent of swelling.[14] This in fact supports the practice of using a composite score such as the DAS as treatment target, not merely joint swelling. We found no differences in joint damage progression after 8 years of DAS-targeted treatment in patients with high or low/normal BMI. This may be due to more treatment adjustments (because of higher DAS) in patients with high BMI, or there may be another reason why patients with high BMI appear to be protected against joint damage progression.[15,16] It may also be that the pain experienced by patients with high BMI does not reflect inflammation. We did not do routine assessments of fibromyalgia features, but we cannot exclude that a fibromyalgia component was present in part of these patients. Self-reported pain, especially musculoskeletal pain, is higher in patients with a high BMI, in particular with a BMI≥30, and they are more likely to report pain in multiple locations.[5,6] The mechanism of the relationship between obesity and pain is unclear but it is suggested that disturbances in neurotransmitters and hormones might be, at least partially, responsible.[7] This relation between BMI and pain may also influence the association between high BMI and functional disability, which was found in this cohort. Pain and body size itself may both interfere with the daily activities that are listed in the Health Assessment Questionnaire.[17]

In conclusion, in the DAS≤2.4 targeted BeSt study we found that RA patients with a higher BMI fail more often than patients with low/normal BMI to achieve a low DAS on anti-rheumatic treatment. This resulted in more treatment adjustments over time. The higher DASs were mainly dependent on joint tenderness and self reported pain and wellbeing, and were associated with less functional ability, but not with more damage progression over time.

In treat to target strategies, finding a high DAS based on inflammation or on non-inflammatory pain may have different therapeutic consequences. Additional research including advanced imaging techniques and biomarker studies may further elucidate the relation between BMI and failure to treatment, thus helping us to decide how we can best treat our individual patients.

Table S1: baseline characteristics of patients in groups 1-3 who received delayed treatment with methotrexate+infliximab for patients with a BMI<25 and patients with a BMI ≥25

BMI*, delayed MTX+infliximab in groups 1-3	BMI<25 n=40	BMI≥25 n=67	p-value
Female, n (%)	30 (75)	50 (75)	0.97
Age, mean ± SD	46 ± 13	51 ± 12	0.02
BMI, mean ± SD	22.1 ±2.2	29.3 ±3.3	<0.001
Group 1 Group 2 Group 3	21 (53) 7 (18) 12 (30)	34 (51) 13 (19) 20 (30)	0.97
Symptom duration, wks	27 (15-67)	28 (17-56)	0.8
ACPA-positive, n (%)	33 (83)	36 (57)	0.004
RF positive, n (%)	36 (90)	44 (66)	0.005
DAS, mean ± SD	4.6 ± 0.8	4.6 ± 0.9	0.96
HAQ, mean ± SD	1.4 ± 0.6	1.4 ± 0.7	0.8
SHS, median (IQR)	2.5 (0.5-10.5)	2.5 (1.0-8.0)	0.8
ESR, median (IQR)	37 (24-62)	33 (21-55)	0.5
CRP, median (IQR)	23 (9-84)	20 (8-59)	0.2
TJC, median (IQR)	14 (9-20)	15 (11-21)	0.3
SJC, median (IQR)	15 (11-20)	13 (10-18)	0.3
VAS global, mean ± SD	50 ± 23	54 ±19	0.8
VAS physician, mean ± SD	58 ± 17	56 ±18	0.5
VAS pain, mean ± SD	56 ± 24	59 ±21	0.5
VAS morning stiffness, mean ± SD	64 ± 22	61 ±21	0.3
Smokers, n (%)	17 (43)	25 (37)	0.6
Alcohol users, n (%)	14 (35)	30 (45)	0.3

SD standard deviation, *BMI* body mass index, *ACPA* anti-citrullinated protein antibodies, *RF* rheumatoid factor, *DAS* disease activity score, *HAQ* health assessment questionnaire score, *SHS* Sharp-van der Heijde Score, *IQR* interquartile range, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC* tender joint count, *SJC* swollen joint count, *VAS* visual analogue scale

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