

RESEARCH

Open Access



# High BMI is associated with lower TNF- $\alpha$ inhibitor serum trough levels and higher disease activity in patients with axial spondyloarthritis

Liseth de Wolff<sup>1\*</sup>, Suzanne Arends<sup>1</sup>, Elisabeth Brouwer<sup>1</sup>, Hendrika Bootsma<sup>1</sup> and Anneke Spoorenberg<sup>1</sup>

## Abstract

**Background** TNF- $\alpha$  inhibitor (TNFi) serum trough levels have previously been found to be related to disease activity in axial spondyloarthritis (axSpA). However, most research regarding serum trough levels has been conducted in patients who only recently started TNFi therapy. Therefore, our objective was to explore TNFi serum trough level measurements in relation to disease activity and BMI in the total axSpA population in daily clinical practice, also including patients on long-term TNFi therapy.

**Methods** Consecutive patients from the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort were approached for a TNFi serum trough level measurement during their regular outpatient visit at the UMCG. Spearman's correlation coefficient was used to analyse the relation of serum trough levels with disease activity and BMI. Logistic regression was performed to analyse the relation between therapeutic drug levels and disease activity, corrected for potential confounders, including BMI.

**Results** Thirty-four patients on adalimumab and 21 patients on etanercept were included. Mean age was  $45 \pm 12$  years, 47% were male, median BMI was 26.4 (IQR 23.9–32.5) and median treatment duration was 41 months (range 2–126). According to definitions of Sanquin, 47% of patients had therapeutic serum trough levels. No significant correlations were found between TNFi levels and disease activity (ASDAS-CRP: adalimumab:  $\rho = -0.16$ ,  $p = 0.39$ ; etanercept:  $\rho = -0.29$ ,  $p = 0.20$ ). TNFi levels were moderately correlated with BMI (adalimumab:  $\rho = -0.48$ ,  $p = 0.004$ ; etanercept:  $\rho = -0.50$ ,  $p = 0.021$ ). Patients with active disease ( $ASDAS \geq 2.1$ ) showed higher BMI than patients with inactive disease (median 29.7 vs. 24.6,  $p = 0.015$ ). In multivariable regression analyses, BMI was identified as the only confounder for the relationship between therapeutic drug levels and ASDAS.

**Conclusion** In this cross-sectional, observational study of axSpA patients mainly on long-term treatment with TNFi, higher BMI was significantly associated with lower adalimumab and etanercept serum trough levels and higher disease activity.

**Keywords** Axial spondyloarthritis, TNF- $\alpha$  inhibitors, BMI, Serum trough levels, Disease activity

\*Correspondence:

Liseth de Wolff  
l.de.wolff01@umcg.nl

<sup>1</sup> Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

## Introduction

Axial spondyloarthritis (axSpA) is a chronic, inflammatory rheumatic disease which mainly affects the spine and sacroiliac joints. The treatment of axSpA usually consists of non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. If this first treatment fails to control disease activity, the next step is to start with biological treatment, e.g. tumour necrosis factor



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

alpha inhibitor (TNFi) therapy [1]. However, TNFi treatment may fail, and is discontinued in approximately half of the patients, which can be related to persistently high disease activity, loss of treatment response or side effects [2, 3]. Previous studies have shown that lower TNFi serum trough levels are associated with an impaired initial therapeutic response in axSpA patients [4, 5]. Presence of anti-drug antibodies has been found to be one of the reasons for low drug levels and high disease activity [6, 7]. Furthermore, high body mass index (BMI) has been suggested as another explanation for low drug levels as some studies in axSpA patients found associations of high BMI with an impaired response to TNFi and lower TNFi serum trough levels [8, 9].

Most of the studies on therapeutic response and serum trough levels primarily involved patients on short-term treatment, often within 1 year [4, 7]. Only few studies have examined patients undergoing treatment for a longer duration. One study in 94 SpA patients showed an association between serum trough levels of infliximab and levels of disease activity, as measured with Ankylosing Spondylitis Disease Activity Score (ASDAS), at 6 months, 1 year and 4 years of treatment [6]. On the other hand, a retrospective study involving 81 SpA patients treated with adalimumab, etanercept or infliximab for a median treatment duration of 6, 30 and 54 months respectively, found no significant associations of serum trough levels with therapeutic response, defined as ASDAS < 2.1 [10].

Additionally, studies have been performed to determine cut-off values for therapeutic TNFi serum levels with mixed results. A study in 221 patients with rheumatoid arthritis (RA) showed that the optimal cut-off point for adalimumab trough levels was 5 µg/ml, based on the distinction between good responders and non or moderate responders based on the European Alliance of Associations for Rheumatology (EULAR) response criteria, showing a sensitivity of 91% and specificity of 43% [11]. A similar study in 102 AS patients was not able to show an association between adalimumab trough levels and therapeutic response, when evaluating change in disease activity ( $\Delta$ ASDAS and  $\Delta$ Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) [12]. In a separate study of 292 RA patients on etanercept, it was observed that 40% of non-responding patients had etanercept trough levels below 2.1 mg/l. This study suggested that it might be useful to assess the effect of dosage increase in such cases [13]. Similarly, a study in 162 AS patients receiving etanercept yielded comparable results: 35% of patients with ongoing active disease according to ASDAS ( $\geq 2.1$ ) exhibited low etanercept trough levels of < 1.8 mg/l. This study could not identify a clear therapeutic drug level window for etanercept [5]. Sanquin, a

Dutch national laboratory for diagnostic services, defined a below therapeutic adalimumab trough level as < 5 µg/ml and, until 2019, a below therapeutic etanercept trough level as < 2 µg/ml [14].

Since most research regarding serum trough levels has been conducted in patients who only recently started TNFi therapy, our objective was to explore TNFi serum trough level measurements in relation to disease activity and BMI in the total axSpA population in daily clinical practice, also including patients on long-term TNFi therapy.

## Methods

### Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort

The Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort is an ongoing prospective longitudinal observational cohort study [15]. This cohort includes axSpA patients, fulfilling the modified New York (NY) criteria and/or the Assessment of SpondyloArthritis international Society (ASAS) classification criteria [15–17]. The local ethics committees of the Medical Centre Leeuwarden (MCL) and University Medical Centre Groningen (UMCG) approved the GLAS cohort, and all patients provided written informed consent according to the Declaration of Helsinki.

### Study patients

All consecutive patients from the UMCG on TNFi with a regular outpatient GLAS visit between June 2015 and June 2016 were asked to perform a single TNFi serum trough level measurement. This measurement was not performed because of a clinical indication, such as an increase in disease activity. Clinical data from GLAS visits closest to the serum trough level measurements were used. TNFi serum trough level was defined as a TNFi serum level measurement shortly before (on the same day or the day prior) the next drug administration. Patients were excluded from the analyses if their serum TNFi level did not fulfil the definition of a trough level measurement and/or if clinical data collection exceeded a period of more than two months from the serum trough level measurement date.

### Treatment with TNFi

Treatment with TNFi was initiated because of active disease according to the ASAS consensus statement [18]. The selection of the specific TNFi was determined by the rheumatologist's clinical judgement and/or the specific preference of the patients. The following TNFi were used: infliximab, etanercept, adalimumab, golimumab and certolizumab. The standard regimens of the different TNFi were: for adalimumab (40 mg) subcutaneous injections

once per two weeks; for etanercept (50 mg) subcutaneous injections once a week; for infliximab 5 mg/kg intravenously at 0, 2 and 6 weeks when starting treatment and then every 8 weeks; for golimumab (50 mg) subcutaneous injections once a month; for certolizumab (200 mg) subcutaneous injections once per two weeks. The dosing regimen could be adjusted in response to disease activity, side effects or co-morbidity. Patients were allowed to receive concomitant medication as usual.

#### TNFi serum trough levels and cut-off values

The methods of measurement of TNFi trough serum levels have been described previously [19]. In short, TNFi trough serum levels were measured by enzyme-linked immunosorbent assay (ELISA: Sanquin, Amsterdam [20]). Based on reference values of Sanquin, serum trough levels were split into a therapeutic and below therapeutic range [14]. Sanquin published until 2019 the following definitions of below therapeutic cut-off trough levels for TNFi: adalimumab < 5 µg/ml, etanercept < 2 µg/ml and infliximab < 1 µg/ml. For golimumab and certolizumab, there are no clear therapeutic cut-off levels. If serum trough levels were in the below therapeutic range, anti-drug antibodies were assessed. For etanercept, anti-drug antibodies cannot be measured. High avidity IgG anti-drug antibodies to TNFi were detected by radioimmunoassay (RIA: Sanquin, Amsterdam) [14].

#### Clinical data including disease activity

Clinical data were collected during the GLAS visit according to the GLAS protocol [15] and included patient characteristics including, among other characteristics, BMI and the following disease activity assessments: ASDAS, BASDAI and C-reactive protein (CRP). Cut-off values for active disease were  $\geq 2.1$  for ASDAS,  $\geq 4.0$  for BASDAI and  $\geq 5.0$  mg/L for CRP [18, 21].

#### Statistical analyses

The statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 23.0. Group differences in patient characteristics and disease activity were assessed using Independent Samples T-test for normally distributed data and Mann–Whitney U test for non-normally distributed data. For dichotomous variables, Chi-Square test or Fisher's exact test was used. Within subgroups of specific TNFi, Spearman's correlation coefficient was used to analyse correlations of serum trough levels with disease activity as well as BMI. To further explore this association, logistic regression was used with therapeutic and below therapeutic drug levels as dependent variable. Multivariable logistic regression was performed to correct the relation between therapeutic drug levels and disease activity for potential confounders.

Each potential confounder was individually added to the multivariable model. The threshold for statistical significance was set at  $p < 0.05$  with a confidence interval of 95%.

## Results

### Patient characteristics

One hundred eight axSpA patients were approached for a TNFi serum trough level measurement, of which 67 (62%) had a serum trough level measurement taken within two months from their GLAS visit. Of the 67 patients with a serum trough level measurement, 34 (51%) were treated with adalimumab, 21 (31%) with etanercept, 6 (9%) with infliximab, 4 (6%) with golimumab and 2 (3%) with certolizumab. Further analyses were only performed for patients on adalimumab and etanercept, since number of patients on infliximab, golimumab and certolizumab were too small.

Characteristics of the 55 patients on adalimumab or etanercept with a serum trough level measurement within two months from their GLAS visit (median time 5 days, IQR 0–12) were compared with 36 patients on adalimumab or etanercept without this measurement. The percentage of male patients was significantly higher in the group without a measurement. Furthermore, patients without a measurement had a significantly longer TNFi treatment duration and significantly more often a lower dosage of the TNFi. No differences were seen in disease activity or in diagnosis of AS or non-radiographic axSpA (Supplementary Table 1).

Mean age of the 55 included patients on adalimumab or etanercept was 45 years (SD  $\pm 12$ ), 26 (47%) patients were male, mean symptom duration was 21 years (SD  $\pm 12$ ), and 45 (82%) patients were human leucocyte antigen (HLA)-B27 positive. 46 (84%) patients had a diagnosis of AS and 9 (16%) of non-radiographic axSpA. Median treatment duration of their current TNFi was 41 months (range 2–126, 41 (75%) patients with treatment duration of  $\geq 1$  year). Median BMI was 26.4 (IQR 23.9–32.5) and median ASDAS was 2.0 (IQR 1.5–3.0) (Table 1).

Patients on adalimumab showed significantly higher BMI and disease activity, measured with ASDAS and BASDAI compared to etanercept. Furthermore, patients on adalimumab had more often a diagnosis of non-radiographic axSpA, had a shorter treatment duration with their current TNFi and were treated more often with a previous TNFi.

### Adalimumab and etanercept serum trough levels in relation to patient characteristics

Of the 34 patients on adalimumab, median serum trough level was 5.2 (IQR 3.7–8.0) µg/ml. Of the 21 patients on etanercept, median serum trough level was

**Table 1** Combined and separate characteristics of 55 axSpA patients on adalimumab ( $n = 34$ ) or etanercept ( $n = 21$ ) with TNFi serum trough level measurements

	<i>Adalimumab and etanercept (n = 55)</i>	<i>Adalimumab (n = 34)</i>	<i>Etanercept (n = 21)</i>
<i>Demographics</i>			
Age (years)	45 ± 12	45 ± 13	46 ± 12
Sex (male)	26 (47)	14 (41)	12 (57)
BMI (kg/m <sup>2</sup> )	26.4 (23.9–32.5)	27.7 (24.6–33.7)	24.3 (22.2–29.7)*
BMI (kg/m <sup>2</sup> )			
< 25	21 (38)	9 (27)	12 (57)*
25–30	15 (27)	10 (29)	5 (24)
≥ 30	19 (35)	15 (44)	4 (19)
<i>Disease status</i>			
Diagnosis of AS	46 (84)	25 (74)	21 (100)**
Duration of symptoms (years)	21 ± 12	21 ± 14	20 ± 8
HLA-B27 positive	45 (82)	27 (79)	18 (86)
<i>History of EAM</i>			
IBD	5 (9)	5 (15)	0 (0)
Psoriasis	7 (13)	5 (15)	2 (10)
Uveitis	12 (22)	8 (24)	4 (19)
ASDAS CRP	2.0 (1.5–3.0)	2.3 (1.7–3.1)	1.6 (1.3–2.0)**
ASDAS ≥ 2.1	25 (46)	21 (64)	4 (19)**
BASDAI (0–10)	3.2 (2.0–5.5)	4.4 (2.8–6.2)	2.6 (1.3–3.5)*
BASDAI ≥ 4.0	21 (39)	17 (52)	4 (19)*
CRP (mg/L)	3.0 (2.0–6.5)	3.9 (2.0–6.1)	2.0 (2.0–6.6)
CRP ≥ 5.0	23 (42)	15 (44)	8 (38)
<i>Therapy</i>			
Current NSAID use	18 (33)	12 (36)	6 (29)
Current DMARD use	4 (7)	2 (6)	2 (10)
Previous TNFi	12 (22)	11 (32)	1 (5)*
Treatment duration current TNFi (months)	41 (10–68)	27 (7–57)	60 (18–80)*
Treatment duration since first TNFi (months)	49 (14–87)	41 (14–91)	60 (18–90)
<i>TNFi dosage</i>			
Standard dosage	46 (84)	29 (85)	17 (81)
Higher dosage	2 (4)	2 (6)	0 (0)
Lower dosage	7 (13)	3 (9)	4 (19)
Serum trough level (µg/ml)	NA	5.2 (3.7–8.0)	1.6 (1.1–2.4)

Values are mean ± SD, median (IQR) or n (%)

**Abbreviations:** axSpA axial spondyloarthritis, TNFi Tumour necrosis factor (TNF)-α inhibitor, BMI Body mass index, AS Ankylosing spondylitis, HLA Human leukocyte antigen, EAM Extra-articular manifestations, IBD Inflammatory bowel disease, ASDAS AS Disease Activity Score, CRP C-reactive protein, BASDAI Bath AS Disease Activity Index, NSAID Non-steroidal anti-inflammatory drug, DMARD Disease-modifying anti-rheumatic drug

\* Significant difference ( $p < 0.05$ ) compared to patients on adalimumab

\*\* Significant difference ( $p < 0.01$ ) compared to patients on adalimumab

1.6 (IQR 1.1–2.4) µg/ml (Table 1). Using the definitions of Sanquin, 26 of 55 (47%) patients had a therapeutic serum trough level: 56% of patients on adalimumab and only 33% of patients on etanercept. Of all 29 patients on adalimumab or etanercept with below therapeutic serum trough levels, 7 (24%) patients had a lower dosage than standard, compared to none of the patients with therapeutic serum trough levels ( $p = 0.01$ ). 4 of 15 (27%) patients on adalimumab with below therapeutic

levels had presence of anti-drug antibodies, with intermediate titers ranging from 13–22 AU/ml, of which all patients had a standard dosage of their TNFi. 21 (72%) of the patients with below therapeutic serum trough levels had a BMI of  $\geq 25$  kg/m<sup>2</sup>. In comparison, 13 (50%) of the patients with therapeutic serum trough levels had a BMI of  $\geq 25$  kg/m<sup>2</sup> ( $p = 0.09$ ). Of the 21 patients with high BMI there were 5 patients who also had a lower dosage than standard.

Median BMI was higher, although not statistically significant, in the 29 patients with below therapeutic adalimumab or etanercept serum trough levels compared to the 26 patients with therapeutic serum trough levels (28.1, IQR 24.6–34.1 vs. 25.1, 22.8–31.8,  $p=0.07$ ). Furthermore, BMI had a significant moderate, negative correlation with adalimumab and etanercept serum trough levels (adalimumab:  $\rho=-0.48$ ,  $p=0.004$ , etanercept:  $\rho=-0.50$ ,  $p=0.021$ ) (Fig. 1).

**Adalimumab and etanercept serum trough levels and disease activity**

No significant differences in disease activity were found between patients with therapeutic or below therapeutic drug levels: median ASDAS was 2.2 (1.6–3.0) vs. 1.9 (1.5–3.1),  $p=0.53$ , median BASDAI 3.2 (2.8–5.6) vs. 2.8 (1.9–5.4),  $p=0.43$ , median CRP 3.9 (IQR 2.0–6.8) vs. 2.7 (IQR 2.0–6.0),  $p=0.39$ .

Furthermore, serum trough levels of adalimumab and etanercept also showed no significant correlation with ASDAS, BASDAI and CRP (Table 2). Similarly, stratifying ASDAS, BASDAI and CRP for ‘active’ and ‘inactive’ disease cut-off values, no significant differences were found in serum trough levels of adalimumab and etanercept (Table 3).

**Adalimumab and etanercept serum trough levels, disease activity and BMI**

Univariable logistic regression showed no significant associations between therapeutic drug levels (yes/no) and disease activity according to ASDAS (OR: 1.19, 95% CI 0.68–2.10), BASDAI (OR: 1.05, 0.83–1.32) or CRP (OR 1.02, 0.97–1.08). Also after correcting for sex, age, BMI, HLA-B27 status, symptom duration, diagnosis of AS or non-radiographic axSpA, current NSAID use, current duration of TNFi therapy or dosage of TNFi, there was

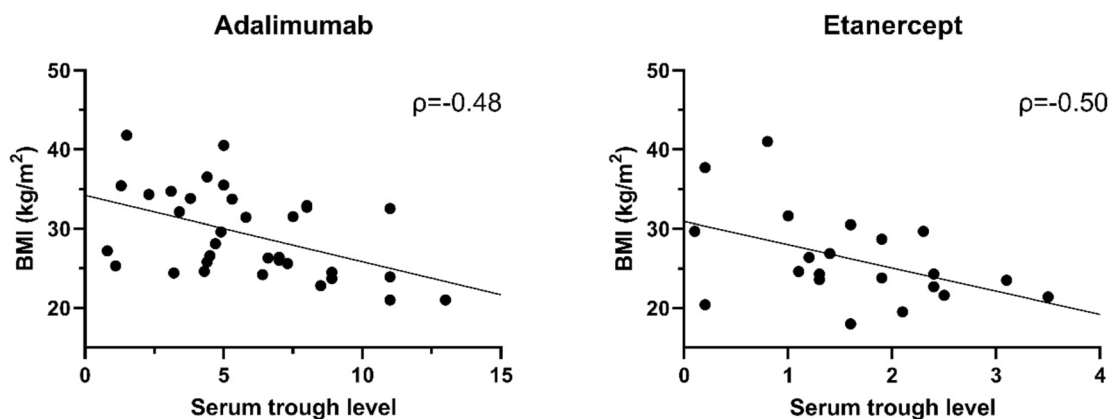
no association found (data not shown). However, BMI was identified as confounder on the relationship between therapeutic drug levels and ASDAS (with BMI in model: OR ASDAS 1.44, 95% CI 0.77–2.69).

BMI was significantly correlated with ASDAS ( $\rho=0.30$ ,  $p=0.027$ ) and BASDAI ( $\rho=0.31$ ,  $p=0.022$ ), but not with CRP ( $\rho=0.18$ ,  $p=0.19$ ). Patients with active disease according to ASDAS ( $\geq 2.1$ ) had higher BMI than patients with inactive disease (median BMI 29.7 vs. 24.6,  $p=0.015$ ). Similar results were found for high disease activity according to BASDAI (data not shown). Patients with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) had higher disease activity than patients with a BMI  $< 30$  kg/m<sup>2</sup>, although not significant (ASDAS: 2.4 vs. 1.8,  $p=0.07$ , BASDAI: 4.6 vs. 3.1,  $p=0.053$ ).

**Discussion**

In this cross-sectional observational study of axSpA patients, mainly on long-term treatment with TNFi (median treatment duration of 41 months), BMI was found to be significantly correlated with adalimumab and etanercept serum trough levels. In addition, BMI was significantly higher in patients with active disease. Furthermore, BMI was identified as confounder on the relationship between therapeutic drug levels and disease activity.

We found that 47% of patients had therapeutic serum trough levels, based on Sanquin definitions [14]. Furthermore, 24% of these patients with below therapeutic levels had a lower TNFi dosage than the standard regimen, whereas all patients with therapeutic serum trough levels had normal or higher dosages. Among patients receiving adalimumab with below therapeutic levels, 27% had anti-drug antibodies present, a known factor linked to lower drug levels [22]. For etanercept, it is not possible to measure anti-drug antibodies. Furthermore,



**Fig. 1** Scatterplot of BMI and serum trough level of adalimumab (A) and etanercept (B)

**Table 2** Correlations of disease activity assessments with serum trough level of adalimumab and etanercept

Adalimumab	Correlation coefficient ( $\rho$ )	P-value
ASDAS CRP	-0.16	0.39
BASDAI	-0.14	0.43
CRP	0.002	0.99
Etanercept	Correlation coefficient ( $\rho$ )	P-value
ASDAS CRP	-0.29	0.20
BASDAI	-0.17	0.47
CRP	-0.23	0.31

Abbreviations: see Table 1

higher BMI was significantly associated with below therapeutic serum trough levels, both for adalimumab and etanercept. There were more patients with a BMI of  $\geq 25$  kg/m<sup>2</sup> in the group with below therapeutic drug levels compared to those with therapeutic levels, with a trend towards significance.

Given the higher prevalence of obesity in axSpA patients compared to the general population [23], it is important to address the relationship of BMI with low TNFi serum trough levels. Several factors may contribute to low TNFi levels in patients with high BMI. A study in inflammatory bowel disease (IBD) patients aimed at developing a population pharmacokinetic model of adalimumab, demonstrated that higher BMI was associated with increased clearance of adalimumab [24]. Furthermore, obesity may impact the volume of distribution for TNFi [25]. Two cross-sectional studies, one in 273 SpA patients treated with TNFi and one in 57 AS patients treated with adalimumab, also found that high BMI was associated with low serum trough levels [8, 26]. Moreover, a study in 180 axSpA patients on infliximab or adalimumab found that patients with a BMI  $< 25$  kg/m<sup>2</sup> had

more often therapeutic TNFi serum trough levels. Furthermore, they found that use of concomitant conventional synthetic (cs) disease modifying anti-rheumatic drugs (DMARDs) was associated with clinical response in patients with BMI  $\geq 25$  kg/m<sup>2</sup> [9]. In our study, concomitant csDMARD use could not be analysed since only 4 patients used this. In axSpA patients it is not common practice to combine TNFi therapy with csDMARDs, unlike patients with peripheral SpA or RA [23, 24].

We not only found that BMI was correlated with serum trough levels, but BMI was also the only confounding factor amongst other clinical variables on the relationship between serum trough levels and ASDAS. Furthermore, BMI was significantly correlated with disease activity measured with ASDAS and BASDAI and patients with active disease according to ASDAS and BASDAI showed higher BMI compared to patients with inactive disease. These results are confirmed by other studies in axSpA patients. Previous studies showed that obesity was associated with higher ASDAS and BASDAI scores, which was most prominent for BASDAI [27]. A study in 624 axSpA patients who recently started with TNFi, showed that obese patients achieved ASAS40 response less frequently compared to patients with a BMI  $< 25$  kg/m<sup>2</sup> [28]. Similar findings have been reported in other auto-immune conditions such as RA, psoriasis or IBD, where higher BMI has been associated with worse response to TNFi therapy [29, 30]. It could be hypothesized that low drug levels in patients with high BMI may contribute to reduced TNFi response and higher disease activity scores. However, it is worth noting that adipose tissue in obese patients is recognized to be immunologically active, by, for example, secreting pro-inflammatory proteins like TNF [31], which offers an additional potential explanation for the decreased response to TNFi. Because BMI is associated

**Table 3** Median serum trough level of adalimumab and etanercept in groups divided by inactive and active disease or normal BMI and overweight/obesity

	Serum trough level ( $\mu\text{g/ml}$ )		P-value
	ASDAS inactive disease ( $< 2.1$ )	ASDAS active disease ( $\geq 2.1$ )	
Adalimumab	6.7 (4.0–10.5)	5.0 (3.3–7.8)	0.43
Etanercept	1.4 (1.1–2.4)	1.9 (0.5–2.3)	0.96
	BASDAI inactive disease ( $< 4.0$ )	BASDAI active disease ( $\geq 4.0$ )	
Adalimumab	7.0 (4.0–8.9)	4.9 (3.3–7.1)	0.23
Etanercept	1.6 (1.2–2.4)	0.9 (0.1–2.1)	0.24
	CRP $< 5$ mg/L	CRP $\geq 5$ mg/L	
Adalimumab	5.3 (4.3–8.0)	5.0 (1.5–8.0)	0.56
Etanercept	1.6 (1.2–2.5)	1.4 (0.4–2.3)	0.37
	Normal BMI ( $< 25$ kg/m <sup>2</sup> )	Overweight/obesity ( $\geq 25$ kg/m <sup>2</sup> )	
Adalimumab	8.9 (5.4–11.0)	4.9 (3.3–7.0)	0.012
Etanercept	2.0 (1.3–2.5)	1.2 (0.5–1.8)	0.042

Values are median (IQR)

Abbreviations: see Table 1

with lower TNFi serum trough levels and higher disease activity, it may be considered to increase the TNFi dosage in this patient group. Another approach might be weight management, as a randomised controlled trial showed that a successful hypocaloric diet in psoriatic arthritis patients resulted in reaching response to TNFi more often compared to patients without weight loss interventions [32]. Another reason to address weight in these patients is that a higher BMI has been associated with more structural damage (e.g. the presence of syndesmophytes) and worse quality of life in axSpA patients [23, 33].

We did not find significant associations between disease activity and TNFi serum trough levels, despite associations of BMI with both disease activity and TNFi levels. Possibly, the group of patients was too small to find an association between disease activity and TNFi levels. The lack of this association may also be related to many patients having a low TNFi serum trough level, especially in the etanercept group, leading to little variation in these drug levels. This is in contrast to other studies, which demonstrated that low TNFi serum trough levels were associated with a lower treatment response and higher disease activity. However, these studies were mostly performed in patients who recently started TNFi therapy [4, 5, 7, 11]. On the other hand, there are also some studies showing no associations between disease activity and TNFi serum trough levels [10, 12].

In our study, relatively more women were included in the group with the TNFi serum trough level measurement, than in the group that did not have this measurement. A possible explanation could be that women have a higher likelihood of responding to research invitations [34]. Furthermore, patients without the serum trough level measurement had a longer treatment duration. Possibly, these patients were more satisfied with their TNFi and therefore less inclined to respond to the invitation for a TNFi serum trough level measurement. However, despite these differences, disease activity and other clinical characteristics were similar across the two groups.

Patients on etanercept experienced lower disease activity according to ASDAS and BASDAI, had a longer treatment duration, lower BMI, and etanercept was more often the first TNFi compared to adalimumab. In our centre it is common practice to start TNFi treatment with etanercept, since etanercept has been registered earlier than adalimumab for AS. If etanercept is not effective or if there are side effects, patients are switched to a different TNFi, which is most often adalimumab. However, the association between BMI, serum trough levels and disease activity occurred both in patients on etanercept and adalimumab.

The main limitation of this study was that the number of patients was too small to perform robust subgroup analyses. Another limitation of this study was that we did not have data on medication compliance. However, all patients receive instructions on the administration of TNFi and at each visit patients are asked for the last date of TNFi administration. Furthermore, the cutoff values for a therapeutic and below-therapeutic range of adalimumab and etanercept were based on reference values of Sanquin, which was mainly based on research in RA and not in axSpA, and especially for etanercept it was difficult to obtain a clear therapeutic window. Because conclusive data regarding cutoff values and specificity and sensitivity is lacking, we mainly focused on TNFi serum trough levels as continuous data in this study [5, 11–13]. A strength of our study is that we studied patients from daily clinical practice of which most patients were on long-term TNFi treatment, whereas previous research regarding TNFi serum trough levels mainly focused on patients who recently started with TNFi therapy.

## Conclusions

To conclude, higher BMI was significantly associated with lower adalimumab and etanercept serum trough levels and higher disease activity assessed with ASDAS and BASDAI. Although adalimumab and etanercept serum trough levels were not associated with disease activity in axSpA patients on long-term treatment, it may be worthwhile to consider increasing the TNFi dosage before switching biological treatment in overweight or obese axSpA patients with low TNFi serum trough levels and high disease activity.

## Abbreviations

AS	Ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body mass index
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
ELISA	Enzyme-linked immunosorbent assay
EULAR	European Alliance of Associations for Rheumatology
GLAS	Groningen Leeuwarden Axial Spondyloarthritis
HLA	Human leucocyte antigen
IBD	Inflammatory bowel disease
IQR	Interquartile range
MCL	Medical Centre Leeuwarden
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
RA	Rheumatoid arthritis
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TNFi	Tumour necrosis factor alpha inhibitor
UMCG	University Medical Centre Groningen

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13075-023-03187-4>.

**Additional file 1: Supplementary Table 1.** Baseline characteristics of 55 axSpA patients with a random adalimumab or etanercept serum trough level measurement compared to 36 patients on adalimumab or etanercept without measurement.

### Acknowledgements

The authors wish to acknowledge Dr R. Bos, Mrs W. Gerlofs, Mrs S. Katerberg, Mrs A. Krol, Mrs R. Rumph and Mrs. B. Burmania for their contribution to the clinical data collection.

### Authors' contributions

LW, SA, EB and AS contributed to the study design. LW wrote the first draft of the manuscript. Statistical analyses were done by LW. All authors interpreted the data, contributed to writing, and critically revised the manuscript.

### Funding

The GLAS cohort was supported by an unrestricted grant from Pfizer pharmaceuticals. Pfizer had no role in the design, conduct, interpretation, or publication of this study.

### Availability of data and materials

Currently, we have no plans to share additional data beyond what is shared in the article.

### Declarations

#### Ethics approval and consent to participate

All data were obtained within the GLAS cohort, which was approved by the local ethics committees of the MCL and UMCG. All patients provided written informed consent according to the Declaration of Helsinki.

#### Consent for publication

Not applicable.

#### Competing interests

L. de Wolff: no financial disclosures.  
S. Arends: research grant from Pfizer.  
E. Brouwer: no financial disclosures.  
H. Bootsma: no financial disclosures.  
A. Spoorenberg: grant/research support from Abbvie, Pfizer, UCB, Novartis, consultant for Abbvie, Pfizer, MSD, UCB and Novartis.

Received: 16 June 2023 Accepted: 7 October 2023

Published online: 17 October 2023

### References

- Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. 2022;82(1):19–34.
- Arends S, Brouwer E, Efde M, Van der V, Bootsma H, Wink F, et al. Long-term drug survival and clinical effectiveness of etanercept treatment in patients with ankylosing spondylitis in daily clinical practice. *Clin Exp Rheumatol*. 2017;35(1):61–8.
- García-Lagunar MH, Gutiérrez-Cívicos MR, García-Simón MS, Conesa-Zamora P, Jimenez-Santos E, Cano-Vivar P, et al. Reasons for discontinuation and adverse effects of TNF $\alpha$  inhibitors in a cohort of patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Pharmacother*. 2017;51(5):388–93.
- Chen DY, Chen YM, Hung WT, Chen HH, Hsieh CW, Chen YH, et al. Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment. *Ann Rheum Dis*. 2015;74(12):2261–4.
- Kneepkens EL, Krieckaert CLM, Van Der Kleij D, Nurmohamed MT, Van Der Horst-Bruinsma IE, Rispen T, et al. Lower etanercept levels are associated with high disease activity in ankylosing spondylitis patients at 24 weeks of follow-up. *Ann Rheum Dis*. 2015;74(10):1825–9.
- Plasencia C, Pascual-Salcedo D, Nuño L, Bonilla G, Villalba A, Peiteado D, et al. Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. *Ann Rheum Dis*. 2012;71(12):1955–60.
- Kneepkens EL, Wei JCC, Nurmohamed MT, Yeo KJ, Chen CY, van der Horst-Bruinsma IE, et al. Immunogenicity, adalimumab levels and clinical response in ankylosing spondylitis patients during 24 weeks of follow-up. *Ann Rheum Dis*. 2015;74(2):396–401.
- Rosas J, Linares-Tello F, Senabre-Gallego JM, Barber-Vallés X, Santos-Soler G, Salas-Heredia E, et al. Obesity decreases clinical efficacy and levels of adalimumab in patients with ankylosing spondylitis. *Clin Exp Rheumatol*. 2017;35(1):145–8.
- Hernández-Breijo B, Plasencia-Rodríguez C, Navarro-Compán V, Martínez-Feito A, Jochems A, Kneepkens EL, et al. Association between concomitant csDMARDs and clinical response to TNF inhibitors in overweight patients with axial spondyloarthritis. *Arthritis Res Ther*. 2019;21(1):1–7.
- Arstikyte I, Kapleryte G, Butrimiene I, Venalis A, Shi G. Influence of immunogenicity on the efficacy of long-term treatment with TNF  $\alpha$  blockers in rheumatoid arthritis and spondyloarthritis patients. *Biomed Res Int*. 2015;2015:604872.
- Pouw MF, Krieckaert CL, Nurmohamed MT, Van Der Kleij D, Aarden L, Rispen T, et al. Key findings towards optimising adalimumab treatment: The concentration-effect curve. *Ann Rheum Dis*. 2015;74(3):513–8.
- Marsman AF, Kneepkens EL, Ruwaard J, Wei JC, Nurmohamed MT, van Denderen C, et al. Search for a concentration-effect curve of adalimumab in ankylosing spondylitis patients. *Scand J Rheumatol*. 2016;45(4):331–4.
- Jamnitski A, Krieckaert CL, Nurmohamed MT, Hart MH, Dijkmans BA, Aarden L, et al. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. *Ann Rheum Dis*. 2012;71(1):88–91.
- Diagnostic tests. Sanquin, Amsterdam. [cited 2018 May 7]. Available from: <https://www.sanquin.org/nl/producten-en-diensten/diagnostiek/diagnostische-testen/index>.
- Arends S, Brouwer E, van der Veer E, Groen H, Leijnsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor- $\alpha$  blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther*. 2011;13(3):R94.
- Zeidler H, Amor B. The Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress. *Ann Rheum Dis*. 2011;70(1):2010–2.
- van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27(4):361–8.
- van der Heijde D, Ramiro S, Landewé R, Baraliakos X, van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76(6):978–91.
- De Wolff L, Wink FR, Bootsma H, Arends S, Spoorenberg A. Change in disease activity is associated with TNF- $\alpha$  inhibitor serum levels in patients with axial spondyloarthritis in daily clinical practice TNF- $\alpha$  inhibitors in axial spondyloarthritis. *Clin Exp Rheumatol*. 2022;40(3):489–94.
- Arends S, Lebbink H. The formation of autoantibodies and antibodies to TNF- $\alpha$  blocking agents in relation to clinical response in patients with ankylosing spondylitis. *Clin Exp Rheumatol*. 2010;28:661–8.
- Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis*. 2011;70(1):47–53.
- Balsa A, Sanmarti R, Rosas J, Martin V, Cabeza A, Gómez S, et al. Drug immunogenicity in patients with inflammatory arthritis and secondary failure to tumour necrosis factor inhibitor therapies: The REASON study. *Rheumatology (United Kingdom)*. 2018;57(4):688–93.



23. Maas F, Arends S, van der Veer E, Wink F, Efde M, Bootsma H, et al. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. *J Rheumatol*. 2016;43(2):383–7.
24. Sánchez-Hernández JG, Pérez-Blanco JS, Rebollo N, Muñoz F, Prieto V, Calvo MV. Biomarkers of disease activity and other factors as predictors of adalimumab pharmacokinetics in inflammatory bowel disease. *Eur J Pharm Sci*. 2020;150:105369.
25. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet*. 2010;49(2):71–87.
26. Hiltunen J, Parmanne P, Sokka T, Lamberg T, Isomäki P, Kaipainen-Sepänen O, et al. Immunogenicity of subcutaneous TNF inhibitors and its clinical significance in real-life setting in patients with spondyloarthritis. *Rheumatol Int*. 2022;42(6):1015–25.
27. Ortolan A, Lorenzin M, Felicetti M, Ramonda R. Do obesity and overweight influence disease activity measures in axial spondyloarthritis? A systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2020;73(12):1815–25.
28. Micheroli R, Hebeisen M, Wildi LM, Exer P, Tamborrini G, Bernhard J, et al. Impact of obesity on the response to tumor necrosis factor inhibitors in axial spondyloarthritis. *Arthritis Res Ther*. 2017;19(1):1–8.
29. Singh S, Facciorusso A, Singh AG, Castele NV, Zarrinpar A, Prokop LJ, et al. Obesity and response to anti-tumor necrosis factor- $\alpha$  agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. *PLoS One*. 2018;13(5):1–26.
30. Shan J, Zhang J. Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: a systematic review and meta-analysis. *Joint Bone Spine*. 2019;86(2):173–83.
31. Grant RW, Dixit VD. Adipose tissue as an immunological organ. *Obesity*. 2015;23(3):512–8.
32. Di Minno MND, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor  $\alpha$  blockers. *Ann Rheum Dis*. 2014;73(6):1157–62.
33. Bakirci S, Dabague J, Eder L, McGonagle D, Aydin SZ. The role of obesity on inflammation and damage in spondyloarthritis: a systematic literature review on body mass index and imaging. *Clin Exp Rheumatol*. 2020;38(1):144–8.
34. Callhoff J, Jacobs H, Albrecht K, Saam J, Zink A, Hoffmann F. Factors associated with survey non-response in a cross-sectional survey of persons with an axial spondyloarthritis or osteoarthritis claims diagnosis. *Int J Environ Res Public Health*. 2020;17(24):1–13.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

