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Muscle wasting in male TNF-α blocker naïve ankylosing spondylitis patients: a comparison of gender differences in body composition

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Abstract

Objective. To assess gender differences in body composition (BC) in a cohort of AS patients naïve to TNF-α blockers.

Methods. Patients included fulfilled the Modified New York criteria for AS. Demographic information and disease activity measures (ASDAS and BASDAI) were reported. BC was measured by whole body DXA. Body fat percentage (BF%), fat mass index (FMI), fat free mass index (FFMI) and android/gynoid fat ratio were reported and compared between men and women and with the reference population (percentiles).

Results. Seventy consecutive patients were included; 60% were men. Demographic variables were similar, except for dyslipidaemia (57.1% of men; 14.3% of women). Women had significantly more fat (BF%, FMI), and less muscle (FFMI) than men, but below the median of the reference population. Male AS patients had a markedly low FFMI (31.7th percentile) compared with the reference population. In the whole group, after multivariate analysis, an ASDAS CRP >3.5 was related to lower fat free mass content. In men, a significant relationship between having a high disease activity (ASDAS, BASDAI) and lower BF% or FMI percentile was found, but in women it was the opposite.

Conclusion. Muscle wasting, measured as low FFMI compared with the reference population, was found in male TNF-α blocker naïve AS patients, especially in those with active disease. Women had higher volumes of body fat than men, but near the median of the reference population. The relationships between fat content and disease activity support the complex association between adipose tissue and inflammation.

Key words: ankylosing spondylitis, body composition, dual-energy X-ray absorptiometry, muscle wasting

CLINICAL SCIENCE

Rheumatology key messages

- Male AS patients suffer from muscle wasting before the start of TNF-α blocker treatment.
- High disease activity in AS is independently related to muscle wasting.
- Adipose tissue has different associations with disease activity in male compared with female AS patients.

Introduction

In the course of AS gender differences play an important role. Female patients have a longer delay in diagnosis and different disease characteristics compared with males [1, 2]. Several studies have demonstrated that women are less responsive to TNF-α blockers and have a shorter drug survival [3–5]. This might be explained by differences in body composition (BC), as women have a higher total body content of fat mass compared with men [6]. This fat mass could

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lead to more inflammation as adipose tissue is capable of producing inflammatory cytokines, called adipokines, including TNF-α [7, 8]. So far, only limited data are available regarding gender differences of BC in patients with AS and its influence in response to TNF-α blockers, but they suggest that being female, overweight or obese is associated with a lower rate of success [9–11]. These findings are based on the observed relationship between drug efficacy and BMI, which does not distinguish between muscle and fat mass [12]. A more accurate measurement of the BC can be obtained using the DXA scan. This method can measure the distribution of fat and lean tissue (mostly muscle) in the whole body as well as the regional localization, including the android and gynoid fat distribution. A high android to gynoid fat ratio is associated with an increased cardiovascular risk [13, 14]. This might be relevant because it could explain part of the increased cardiovascular risk reported in AS patients [15–21]. Moreover, DXA has separate reference values for men and women, stratified by age and ethnicity. The advantages of DXA compared with other methods such as CT and MRI are the very low radiation dose and the lower costs, in combination with a very strong correlation with the gold standard CT measurements [22–24].

The main objective of this study was to assess gender differences in BC measured by DXA in a cohort of AS patients naïve to TNF-α blockers. Our secondary objectives were to compare the BC variables of our patients with the values of the reference population, and to assess the relationship between BC and disease activity parameters ASDAS and BASDAI, and with the presence of dyslipidaemia and hypertension.

Methods

Patients

The Amsterdam Rheumatology and Immunology Centre initiated a prospective cohort of axial spondyloarthritis patients (the AmSpA cohort) in 1999, in which all patients who started with TNF-α blockers were included. For this study we selected from the AmSpA cohort all the consecutive patients that fulfilled the diagnosis of AS according to the 1984 New York Criteria, were $\geqslant$18 years old, and had a DXA analysis before the start of TNF-α blockers. Only patients that were naïve towards treatment with biologics and who were eligible for the start of TNF-α blockers because of high disease activity were included. Clinical assessments included age, disease duration, extra-articular manifestations, use of NSAIDs, DMARDs and/or prednisone, hypertension (systolic blood pressure $\geqslant$140 mmHg and/or a diastolic blood pressure $\geqslant$90 mmHg and/or the use of antihypertensive drugs), dyslipidaemia (total cholesterol level $\geqslant$6.5 mmol/l and/or use of cholesterol lowering drugs), lifestyle habits (tobacco and alcohol use, physical activity, by a yes/no questionnaire), ESR and CRP levels, ASDAS CRP and ESR ($<$1.3 = inactive disease; range 1.3–2 = moderate disease activity; range 2.1–3.5 = high disease activity; $>$3.5 = very high disease activity), and BASDAI (a cut-off of 4 is used to define active disease).

Outcome measures

To calculate the BMI, body weight was measured during patients' visits, without shoes and clothes, to the nearest 0.1 kg on a digital scale (Seca Deutschland, Hamburg, Germany). Height was measured without shoes, to the nearest 1 cm. BMI was calculated as weight/height^2 (kg/m^2) ratio and categorized according to sex-independent WHO categories (underweight $<$18.5; normal range 18.5–24.99; overweight range 25–29.99, obese $\geqslant$30) [25]. BC was assessed with a whole body DXA (GE Lunar iDxa, GE Corporate for Healthcare, Madison, WI, USA) and the measurements were carried out according to the protocol of the manufacturer.

The total body mass is the sum of the total fat mass (FM), total lean mass (LM) and bone mineral content. Fat mass was reported as total fat mass (sum of trunk, both arms and legs and head), and body fat % (ratio FM/total body mass). Because absolute fat mass is dependent on height, the fat mass index was calculated [FM/height^2 (kg/m^2)]. The fat free mass (FFM) was calculated as LM + bone mineral content. Likewise, the fat free mass index (FFMI) was calculated [FFM/height^2 (kg/m^2)]. The quantification of fat mass in the android and gynoid regions was carried out as previously described [26]. The caudal limit for the assessment of android fat was the top of the iliac crest and the cephalic limit was 20% of the distance from there to the base of the skull. The total height of the gynoid region was 2 times the height of the android region and its cephalic limit started 1.5 times the height of the android region below the top of the iliac crest. The android to gynoid fat ratio was calculated. The body fat %, FMI and FFMI were reported as percentiles, according to the reference population tables [27], which are stratified by ethnicity, age and gender (the 50th percentile reflects the median of the reference population).

Statistical analysis

The data were analysed using SPSS Statistics v. 22.0 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables were described as frequencies and/or percentages, and quantitative variables were described as mean and S.D. for those normally distributed or median and interquartile range (IQR) for those not normally distributed. Association between variables and differences between groups were assessed using the t-test for normally distributed continuous variables, Mann–Whitney U test for not normally distributed continuous variables, and chi-squared test or Fisher's exact test for categorical variables. Linear and logistic multivariate regression models were used to study the associations between variables. The covariates included in the models were gender, age, years since diagnosis, physical activity, alcohol, NSAIDs and DMARDs use, and other variables that had a $P < 0.05$ in the univariate analysis if appropriate. Statistical significance was defined as $P < 0.05$. In the case of missing

data, the analysis was performed only with the available data.

Ethical approval

All patients gave written informed consent prior to participation in the study, according to the Declaration of Helsinki. The study was approved by the Medical Ethical Committee of the VU University Medical Centre, Amsterdam, The Netherlands (approval number 2005-179).

Results

Patients' characteristics

Seventy consecutive patients were included; 42 (60%) were men. Age, years with symptoms, years since diagnosis, treatment, comorbidities and lifestyle variables were similar in men and women. Dyslipidaemia was significantly more frequent in men (57.1%) than women (14.3%) ($P < 0.001$) (Table 1). CRP (median 7 mg/l, IQR = 14), ESR (median 19 mm/h, IQR = 29), ASDAS CRP (mean = 3.4, S.D. = 0.9), ASDAS ESR (mean = 3.3, S.D. = 1) and BASDAI (mean = 5.7, S.D. = 2.1) did not differ significantly between men and women. Most patients had a high disease activity, with an ASDAS (CRP or ESR) $\geqslant 2.1$ (93.3%) and/or a BASDAI >4 (87.1%). None of the patients had an ASDAS (CRP or ESR) <1.3.

BC

According to the BMI-based classification there was a significantly higher proportion of obese women compared with men, and a significantly higher proportion of overweight in men compared with women. None of the patients was underweight. Women had significantly higher fat mass (kg), body fat % and FMI and lower fat free mass (kg) and FFMI as absolute values. Men had a significantly higher android to gynoid fat ratio (Table 2).

In comparison with the reference population, after adjusting for age and gender, women had similar body fat % and FMI percentiles compared with men, and a significantly higher FFMI percentile (56th percentile in women compared with 32nd percentile in men, $P < 0.001$) (Fig. 1).

After multivariate analysis in the whole group, female gender and age were significantly associated with a higher body fat content, whereas very high disease activity (ASDAS CRP >3.5) was related to a lower fat free mass. A longer disease duration (years since diagnosis) was significantly correlated with a higher FFMI and FFMI percentile (Table 3).

In men multivariate analysis revealed a significant association between a high disease activity (ASDAS CRP >3.5 or BASDAI $\geqslant 4$) and lower body fat %, fat mass or FMI percentile. In contrast, we found in women that a high disease activity (ASDAS >3.5 or BASDAI $\geqslant 4$) was significantly related to a higher body fat %, FMI or FMI percentile (Table 4) (univariate analysis results are shown in supplementary Tables S1 and S2, available at *Rheumatology* Online).

Dyslipidaemia

In the univariate analysis, male gender, psoriasis, alcohol use, NSAIDs use, overweight, the android to gynoid fat ratio, body fat % percentile and FMI percentile were significantly associated with dyslipidaemia (supplementary Table S3, available at *Rheumatology* Online).

The multivariate analysis showed that only higher values of the android to gynoid fat ratio [odds ratio (OR) = 566, 95% CI: 1.78, 180105], body fat % percentile

Table 1 Baseline characteristics of 70 TNF-α blocker naïve AS patients stratified by gender

Baseline characteristics	All, n = 70	Male, n = 42 (60%)	Female, n = 28 (40%)	P-value
Age, median (IQR), years	42 (16)	44.2 (15.2)	40.7 (17.6)	NS
Years with symptoms, median (IQR)	16 (11)	15 (13)	18.5 (16)	NS
Years since diagnosis, median (IQR)	5 (12)	5 (9)	5 (14)	NS
HLA-B27 positive (%)	82.1	82.1	82.1	NS
Comorbidities				
Psoriasis (%)	12.9	14.3	10.7	NS
IBD (%)	4.3	4.8	3.6	NS
Uveitis (%)	21.4	21.4	21.4	NS
Dyslipidaemia (%)	40	57.1	14.3	<0.001
Hypertension (%)	41.4	42.9	39.3	NS
Lifestyle[a]				
Smoker (%)	57.1	57.1	57.1	NS
Alcohol use (%)	52.9	55	50	NS
Physical activity (%)	61.4	57.1	67.9	NS
Medications				
NSAIDs (%)	85.7	81	92.9	NS
DMARDs[b] (%)	55.7	52.4	60.7	NS
Prednisone (%)	5.7	7.1	3.6	NS

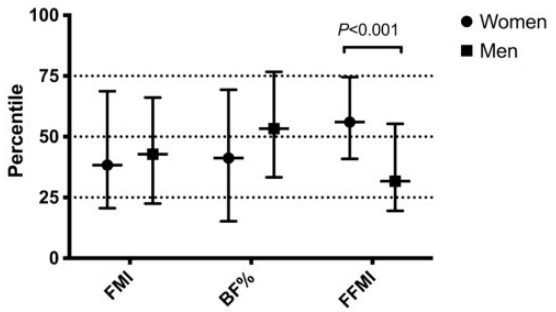
[a]Lifestyle variables were assessed by a yes/no questionnaire. [b]DMARDs used were MTX and others. NS: not significant.

Table 2 Body composition characteristics

Body composition	All, n = 70	Male, n = 42	Female, n = 28	P-value
BMI, median (IQR), kg/m^2	25.6 (5)	25.9 (4.8)	24.2 (9)	NS
Normal (18.5–24.99 kg/m^2), %	48.6	45.2	53.6	NS
Overweight (25–29.99 kg/m^2), %	35.7	47.6	17.9	0.011
Obese ($\geqslant$30 kg/m^2), %	15.7	7.1	28.6	0.021
Body fat %, mean (S.D.)	33.3 (8.9)	28.9 (7.3)	40 (6.7)	<0.001
Fat mass, mean (S.D.), kg	26 (9.3)	23.9 (8.7)	29.2 (9.6)	0.018
Fat mass index, median (IQR), kg/m^2	8.5 (3.6)	8 (4)	9.7 (6)	0.001
Fat free mass, mean (S.D.), kg	51.1 (9.9)	56.8 (7)	42.5 (7.1)	<0.001
Fat free mass index, median (IQR), kg/m^2	17 (2.5)	17.7 (1.8)	15.1 (1.8)	<0.001
Android to gynoid fat ratio, mean (S.D.)	1.04 (0.2)	1.16 (0.2)	0.88 (0.2)	<0.001

NS: not significant.

Fig. 1 Fat mass index, body fat % and fat free mass index percentiles according to the reference population



Dotted lines represent the 25th, 50th and 75th percentiles of the reference population. The FFMI percentile was remarkably low in men, and significantly lower compared with women. BF%: body fat percentage; FMI: fat mass index; FFMI: fat free mass index.

(OR = 1.1, 95% CI: 1, 1.1) and FMI percentile (OR = 1.1, 95% CI: 1, 1.1) remained significantly associated with the presence of dyslipidaemia. There were no other relevant results when women and men were analysed separately.

Hypertension

In the univariate analysis, age, years with symptoms, NSAIDs use, BMI and body fat % percentile were related to the presence of hypertension (supplementary Table S3, available at *Rheumatology* Online). In the multivariate analysis, only age remained to be associated with hypertension (OR = 1.2, 95% CI: 1.1, 1.3). In men, after multivariate analysis, BMI (OR = 1.7, 95% CI: 1.1, 2.6), body fat % percentile (OR = 1.06, 95% CI: 1.02, 1.1) and FMI percentile (OR = 1.07, 95% CI: 1.03, 1.1) were significantly related to hypertension. These associations were not significant for women.

Discussion

In our study we found that muscle wasting, measured by DXA as a low FFMI compared with the reference population, was present in male TNF-α blocker naïve AS, especially in those with active disease. In addition, women had higher volumes of body fat (fat mass, body fat % and FMI) than men, but below the median values of the reference population.

The presence of low FFMI could be a sign of cachexia. Cachexia is defined as a loss of lean tissue mass, with a weight loss >5% of body weight in 12 months (or less in the presence of a chronic illness), or as a BMI lower than 20, plus three of the following: decreased muscle strength, fatigue, anorexia, low FFMI, increase of inflammation markers such as CRP or IL-6, anaemia or low serum albumin [28]. There is a proposal to combine the concepts of muscle wasting, sarcopenia, frailty and cachexia under the term muscle wasting disease [29]. The hypothesis for cachexia in AS is that the chronic inflammation driven by TNF-α induces anorexia, increases resting energy expenditure, induces muscle loss and down-regulates anabolic hormones and growth factors [30–32]. Less appendicular (arms and legs) LM (6 kg less than controls) was reported in one study of 19 male patients with long-standing AS, and interpreted as preliminary evidence for cachexia [33]. In our study, the mean fat free mass in men was 5.5 kg lower than the reference population [34]. A recently published study reported a slightly lower fat free mass and FFMI in male AS patients compared with controls, but the percentiles were not reported, and therefore, it was not controlled by ethnicity or age. In addition, one-third of the patients were using TNF-α blockers that could affect the BC [35]. Other studies, with similar limitations, did not find differences between patients and controls [8, 36–38]. The results of our study suggest the presence of muscle wasting, especially in male patients and in those with active disease by ASDAS CRP. In order to confirm whether the patients fulfil the criteria of cachexia we should have had at least 12 months of follow-up, which we considered unethical

Table 3 Linear regression multivariate analysis for body composition variables

Outcome	Variable	β-Coefficient (95% CI)	P-value
Body fat %	Age	0.2 (0.05, 0.4)	0.014
	Male gender	−11.1 (−14.6, −7.7)	<0.001
Fat mass	Age	0.3 (0.1, 0.5)	0.002
	Male gender	−5.4 (−9.8, −1)	0.018
Fat mass index	Age	0.1 (0.03, 0.2)	0.004
	Male gender	−3.4 (−4.9, −1.8)	<0.001
Fat free mass	ASDAS CRP >3.5	−5.1 (−10.2, −0.1)	0.047
	Male gender	14.3 (10.9, 17.7)	<0.001
Fat free mass index	Years since diagnosis	0.09 (0.03, 0.1)	0.004
	Male gender	2.1 (1.2, 3)	<0.001
Fat free mass index percentile	Years since diagnosis	1 (0.3, 1.6)	0.005

Table 4 Linear regression multivariate analysis stratified by gender for body composition variables

Outcome	Variable	β-Coefficient (95% CI)	P-value
Men			
Body fat %	ASDAS CRP >3.5	−4.8 (−9.6, −0.1)	0.046
Fat mass	ASDAS CRP >3.5	−6.8 (−12.3, −1.2)	0.018
	BASDAI ⩾4	−7.8 (−15.3, −0.4)	0.04
Fat mass index percentile	ASDAS CRP >3.5	−17.1 (−33.5, −0.7)	0.042
	BASDAI ⩾4	−22.3 (−44.2, −0.5)	0.045
Women			
Body fat %	ASDAS CRP >3.5	5.6 (0.1, 11)	0.045
	ASDAS ESR >3.5	6 (0.7, 11.4)	0.029
	BASDAI ⩾4	10.9 (1.5, 20.4)	0.025
Fat mass index	ASDAS ESR >3.5	3.9 (0.9, 6.8)	0.014
Fat mass index percentile	ASDAS ESR >3.5	25.7 (4.8, 46.6)	0.018

because all these patients needed treatment with TNF-α blockers.

Interestingly, our data showed that longer disease duration was significantly associated with a higher FFMI and a higher FFMI percentile, probably due to anti-inflammatory treatment and the start of physiotherapy after the diagnosis was made, showing some muscle recovery. TNF-α blockers would be expected to improve or prevent muscle wasting in rheumatoid arthritis and AS, but the available data are not conclusive [32, 39].

The android fat distribution refers to abdominal fat that can be subclassified in subcutaneous and visceral adipose tissue (VAT). VAT is an active tissue and is capable of releasing bioactive molecules and hormones, including adipokines such as leptin, adiponectin, resistin, visfatin, TNF and IL-6. Moreover, VAT is considered to be more strongly related to various obesity-associated processes and autoimmune inflammatory conditions than other indexes such as BMI [8, 40–46]. The android to gynoid fat ratio measured by DXA has a strong correlation with VAT and cardiovascular risk [47]. In our study, we found a significant association between body fat % percentile, FMI percentile and, especially, the android to gynoid fat ratio with dyslipidaemia, supporting the relation between VAT and cardiovascular risk. We did not find an association between BMI and dyslipidaemia.

In women we found that higher body fat %, FMI and FMI percentile were associated with a higher disease activity (ASDAS), but in men we found the opposite. One hypothesis that might explain this observation is that as the fat content characteristics differ by gender, with higher android fat content in men and gynoid fat content in women, adipokines also could differ, and therefore the relationship of type of adipose tissue with inflammation. However, due to the limited number of patients in our study, more data are needed to confirm this relationship.

Another limitation is the absence of specific appendicular LM information, which some authors consider a better measurement than total LM to assess the presence of muscle wasting.

The strength of our study is the use of percentiles according to the reference population, avoiding the problems of other studies regarding the effect of age, ethnicity and gender in BC [48].

In conclusion, male AS patients and those with active disease have a lower fat free mass content compared with

the reference population, suggesting the presence of muscle wasting as a result of chronic illness and inflammation.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 van der Horst-Bruinsma IE, Zack DJ, Szumski A, Koenig AS. Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. Ann Rheum Dis 2013;72:1221–4.

2 Arends S, Maas F, Wink F *et al*. Male and female patients with axial spondyloarthritis experience disease activity, physical function and quality of life differently: results from the Groningen Leeuwarden Axial Spondyloarthritis cohort. Rheumatology 2015;54:1333–5.

3 Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. RMD Open 2015;1:e000017.

4 Glintborg B, Østergaard M, Krogh NS *et al*. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis 2013;72:1149–55.

5 Rosales-Alexander JL, Balsalobre Aznar J, Pérez-Vicente S, Magro-Checa C. Drug survival of anti-tumour necrosis factor α therapy in spondyloarthropathies: results from the Spanish emAR II Study. Rheumatology 2015;54:1459–63.

6 Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Després JP. Sex differences in the relation of visceral adipose tissue accumulation to total body fatness. Am J Clin Nutr 1993;58:463–7.

7 Tzanavari T, Giannogonas P, Karalis KP. TNF-alpha and obesity. Curr Dir Autoimmun 2010;11:145–56.

8 Toussirot E, Grandclement E, Gaugler B *et al*. Serum adipokines and adipose tissue distribution in rheumatoid arthritis and ankylosing spondylitis. A comparative study. Inflammation 2013;4:453.

9 Gremese E, Bernardi S, Bonazza S *et al*. Body weight, gender and response to TNF-α blockers in axial spondyloarthritis. Rheumatology 2014;53:875–81.

10 Ottaviani S, Allanore Y, Tubach F *et al*. Body mass index influences the response to infliximab in ankylosing spondylitis. Arthritis Res Ther 2012;14:R115.

11 Maas F, Arends S, van der Veer E *et al*. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. J Rheumatol 2016;43:383–7.

12 Konijn NPC, van Tuyl LHD, Bultink IEM, Lems WF, van Bokhorst-de van der Schueren MAE. Body mass index measurements have limited value for the assessment of body composition in rheumatoid arthritis: comment on the article by Wolfe and Michaud. Arthritis Care Res 2013;65:833–4.

13 Okosun IS, Seale JP, Lyn R. Commingling effect of gynoid and android fat patterns on cardiometabolic dysregulation in normal weight American adults. Nutr Diabetes 2015;5:e155.

14 Wiklund P, Toss F, Weinehall L *et al*. Abdominal and gynoid fat mass are associated with cardiovascular risk factors in men and women. J Clin Endocrinol Metab 2008;93:4360–6.

15 Chou C-H, Lin M-C, Peng C-L *et al*. A nationwide population-based retrospective cohort study: increased risk of acute coronary syndrome in patients with ankylosing spondylitis. Scand J Rheumatol 2014;43:132–6.

16 Nurmohamed MT, van der Horst-Bruinsma I, Maksymowych WP. Cardiovascular and cerebrovascular diseases in ankylosing spondylitis: current insights. Curr Rheumatol Rep 2012;14:415–21.

17 Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 2004;34:585–92.

18 Szabo SM, Levy AR, Rao SR *et al*. Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: A population-based study. Arthritis Rheum 2011;63:3294–304.

19 Bremander A, Petersson IF, Bergman S, Englund M. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. Arthritis Care Res 2011;63:550–6.

20 Wright KA, Crowson CS, Michet CJ, Matteson EL. Time trends in incidence, clinical features, and cardiovascular disease in ankylosing spondylitis over three decades: a population-based study. Arthritis Care Res 2015;67:836–41.

21 Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: A population-based study. Ann Intern Med 2015;163:409–16.

22 Kaul S, Rothney MP, Peters DM *et al*. Dual-Energy X-Ray absorptiometry for quantification of visceral fat. Obesity 2012;20:1313–8.

23 Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL. Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. Obesity 2012;20:1109–14.

24 Choi YJ. Dual-energy X-ray absorptiometry: beyond bone mineral density determination. Endocrinol Metab 2016;31:25.

25 WHO. Global Database on Body Mass Index. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (5 September 2016, date last accessed).

26 Petak S, Barbu CG, Yu EW *et al*. The Official Positions of the International Society for Clinical Densitometry: body composition analysis reporting. J Clin Densitom Off J Int Soc Clin Densitom 2013;16:508–19.

27 Fan B, Shepherd JA, Levine MA *et al*. National Health and Nutrition Examination Survey whole-body dual-energy X-ray absorptiometry reference data for GE Lunar systems. J Clin Densitom 2014;17:344–77.

28 Evans WJ, Morley JE, Argilés J *et al*. Cachexia: a new definition. Clin Nutr 2008;27:793–9.

29 Anker SD, Coats AJS, Morley JE *et al*. Muscle wasting disease: a proposal for a new disease classification. J Cachexia Sarcopenia Muscle 2014;5:1–3.

30 Rall LC, Rosen CJ, Dolnikowski G *et al*. Protein metabolism in rheumatoid arthritis and aging. Effects of muscle strength training and tumor necrosis factor alpha. Arthritis Rheum 1996;39:1115–24.

31 Roubenoff R, Rall LC. Humoral mediation of changing body composition during aging and chronic inflammation. Nutr Rev 1993;51:1–11.

32 Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr 2006;84:1463–72.

33 Marcora S, Casanova F, Williams E *et al*. Preliminary evidence for cachexia in patients with well-established ankylosing spondylitis. Rheumatology 2006;45:1385–8.

34 Li C, Ford ES, Zhao G, Balluz LS, Giles WH. Estimates of body composition with dual-energy X-ray absorptiometry in adults. Am J Clin Nutr 2009;90:1457–65.

35 El Maghraoui A, Ebo'o FB, Sadni S *et al*. Is there a relation between pre-sarcopenia, sarcopenia, cachexia and osteoporosis in patients with ankylosing spondylitis? BMC Musculoskelet Disord 2016;17:268.

36 Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology 2001;40:882–8.

37 Toussirot É, Streit G, Nguyen NU *et al*. Adipose tissue, serum adipokines, and ghrelin in patients with ankylosing spondylitis. Metabolism 2007;56:1383–9.

38 Plasqui G, Boonen A, Geusens P *et al*. Physical activity and body composition in patients with ankylosing spondylitis. Arthritis Care Res 2012;64:101–7.

39 Briot K, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-alpha treatment. J Rheumatol 2008;35:855–61.

40 Mathieu P, Poirier P, Pibarot P, Lemieux I, Després J-P. Visceral obesity the link among inflammation, hypertension, and cardiovascular disease. Hypertension 2009;53:577–84.

41 Bouchard C. BMI, fat mass, abdominal adiposity and visceral fat: where is the 'beef'? Int J Obes 2007;31:1552–3.

42 Kuk JL, Katzmarzyk PT, Nichaman MZ *et al*. Visceral fat is an independent predictor of all-cause mortality in men. Obesity 2006;14:336–41.

43 Després J-P. Body fat distribution and risk of cardiovascular disease an update. Circulation 2012;126:1301–13.

44 Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. Eur J Nutr 2012;51:513–28.

45 Ferraccioli G, Gremese E. Adiposity, joint and systemic inflammation: the additional risk of having a metabolic syndrome in rheumatoid arthritis. Swiss Med Wkly 2011;141:w13211.

46 Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res 2005;96:939–49.

47 Bouchi R, Nakano Y, Ohara N *et al*. Clinical relevance of dual-energy X-ray absorptiometry (DXA) as a simultaneous evaluation of fatty liver disease and atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol 2016;15:64.

48 Sheane BJ. Tumor necrosis factor inhibition and adipose tissue distribution—are reported changes relevant to cardiometabolic risk? J Rheumatol 2014;41:1035–7.