Review

TNF inhibitors increase fat mass in inflammatory rheumatic disease: a systematic review with meta-analysis

S. Marouen[1], T. Barnetche[2], B. Combe[1,3], J. Morel[1,3], C.I. Daïen[1,3]

[1]*Rheumatology Department, Lapeyronie Hospital and Montpellier University, France;*
[2]*Rheumatology Department, Pellegrin Hospital and Bordeaux 2 University, France;*
[3]*Institute of Molecular Genetics, UMR5535, CNRS, Montpellier, France.*

Sarah Marouen, MD
Thomas Barnetche, PhD
Bernard Combe, MD, PhD
Jacques Morel, MD, PhD
Claire I. Daïen, MD, PhD

Please address correspondence and reprint requests to:
Dr Claire Daien,
Rheumatology Department,
Hôpital Lapeyronie,
371 Avenue du Doyen Gaston Giraud,
34295 Montpellier Cedex 5, France.
E-mail: c-daien@chu-montpellier.fr

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ABSTRACT

Objective. *To assess body composition of patients with inflammatory rheumatic disease and the effect of TNF inhibitors on it.*

Methods. *This was systematic review with meta-analysis of studies consulted on PubMed, Cochrane Library and EMBASE and assessing body composition in patients with rheumatoid arthritis or spondyloarthritis. We compared i) patients with healthy controls and ii) body components before and after TNF inhibitors.*

Results. *Among the 703 articles reviewed, 19 met the inclusion criteria. In patients with rheumatoid arthritis, a significant increase in fat mass (+1.85 kg, p=0.02), adiposity (+3.53%, p<0.00001) and android mass (+1.7 kg, p<0.00001) and a significant decrease in lean mass (-3.03 kg, p=0.01), were observed. In patients with spondyloarthritis, a significant but modest increase in fat mass (+0.69 kg, p=0.03) and a significant decrease in lean mass (-3.74 kg, p=0.03) were observed. Nine studies assessed impact of TNF inhibitors on body composition, with an increase of fat mass in the short and long term in all studies. Data on lean mass were controversial. Two studies found an increase in visceral or android mass under TNF inhibitors.*

Conclusion. *Patients with inflammatory rheumatic disease have a significant decrease in lean mass and increase in fat mass. The use of TNF inhibitors is associated with a further increase in fat mass including android fat, which could potentially have cardiovascular consequences.*

Introduction

Patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) suffer from chronic inflammation that may impact body composition (1). RA patients were described to suffer from "rheumatoid cachexia" (2) but more recently obesity has also been associated with RA (3). Modification in body composition influences health. A decrease in lean mass may be responsible of physical disability, weakness, infections and premature death (4, 5). An excess of fat mass may predispose to metabolic syndrome with hypertension and diabetes. Moreover, an increase in android fat mass is recognised as a cardiovascular risk factor (6). RA and SpA are associated with increased cardiovascular morbidity and mortality (7). Body composition may be evaluated by dual-energy x-ray absorptiometry (DEXA). DEXA, developed to measure bone mineral density, is a reliable tool to measure fat mass, lean mass and regional body composition in global population (8, 9) and in RA patients (10), conversely to other methods such as bio impedance and anthropometric measures.

Some studies have evaluated body composition including regional distribution of lean mass and fat mass in rheumatic disease. In SpA patients, data on body composition are conflicting and it remains unclear whether patients are at risk of cachexia (11–13). In RA patients with active disease, body mass decrease might be improved by long-term therapy with TNF-α inhibitors (TNFi) (14). Body weight gain is often reported by SpA patients treated by TNFi (15). However, effects on body composition remain unclear. We performed a systematic review of the literature and a meta-analysis to assess changes in body composition in RA and SpA and to evaluate the impact of TNFi on this body composition.

Methods

Literature search

We searched Medline via PubMed,

Cochrane Library and EMBASE for articles published up to February 2015 and abstracts of 2013 and 2014 EULAR and ACR congresses, without any limits. Following terms used for research were ("body fat distribution" OR "fat mass" OR "lean mass" OR "body mass component" OR "body composition") AND ("rheumatoid arthritis" OR "spondylarthritis" OR "psoriatic arthritis" OR "spondylitis" OR "ankylosing spondylitis"). Manual search was performed using references of the selected studies.

Study selection

To be selected, studies had to include adults with RA meeting the 1987 revised ACR criteria (16) or 2010 ACR EULAR criteria (17) and adults with SpA meeting modified New York or ASAS criteria (18). Body composition should be evaluated by DEXA. To evaluate body composition in RA and SpA, only studies with healthy subjects as control group were included. For the evaluation of TNFi impact on body composition, data on body composition before and after TNFi was required. Studies were initially selected on their titles and abstracts, then on their full text; duplicates were removed. We excluded reviews, case reports, studies not written in English and animal studies.

Data extraction

Two investigators (SM and CD) collected the data between December 2014 and February 2015. Demographic characteristics, type of rheumatic disease, treatments, values of fat mass, lean mass, android mass and adiposity were collected. Concerning the impact of TNFi on body composition, available data about BMI, fat mass, lean mass, adiposity, visceral fat mass were collected at 6, 12 and 24 months after the beginning of treatment. Data were transcribed in an Excel table.

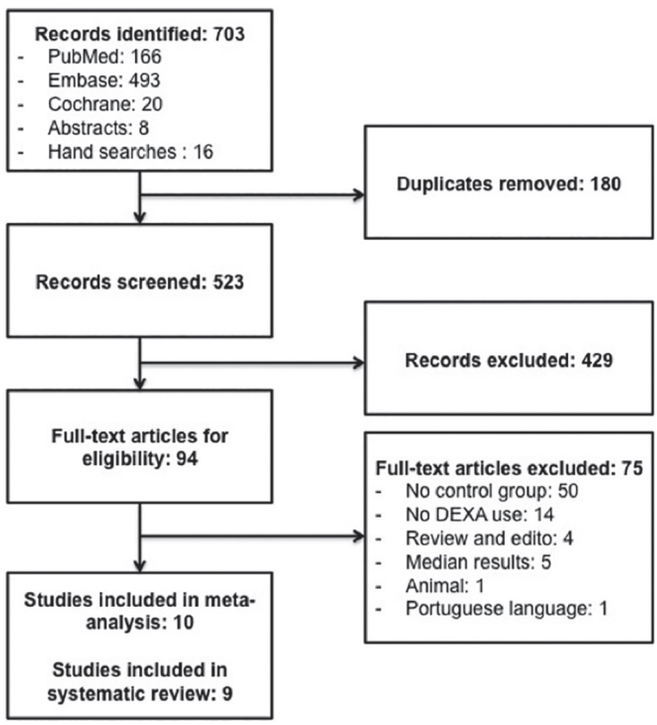
Risk of bias assessment

We used a Quality Assessment tool for observational and cross sectional studies to evaluate the quality of studies in the meta-analysis (19).

Statistical analysis

A meta-analysis comparing DEXA body composition in patients with RA or SpA *versus* healthy controls was performed. The results of each selected study were presented as mean differences with their 95% confidence interval. Meta-analyses were carried out using the inverse variance method, pooling estimates of each study using fixed or random effect model according to the level and significance of heterogeneity. Heterogeneity was tested with Cochrane's Q-test and evaluated by the I^2 statistic with the following and considerable heterogeneity for values above 75%. For the Q-test, a *p*-value <0.10 was considered significant and a random-effect model was used. Standardised means were used to analyse radiographic joint damage because of varied radiographic scores used among studies. The analysis was performed using RevMan 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). *P*-values less than 0.05 were considered statistically significant.

Fig. 1. Flowchart.



Results

The literature search retrieved 703 articles. Ten of these were included in the meta-analysis. Concerning the effect of TNFi on body composition, 9 articles were included in the systematic review (Fig. 1).

Characteristics of the studies

Table I shows the characteristics of the included studies. Studies were mainly prospective, conducted in various centers and countries. Body composition was evaluated by DEXA in 367 patients with RA and in 143 patients with SpA. RA patients were most frequently women and older than SpA patients. body mass index (BMI) was similar between both rheumatic diseases: most of them were overweight (>25 kg/m^2). Patients with RA used often glucocorticoids with doses below 10 mg/day. Only one study about SpA patients (12) and one study which evaluated the effect of TNFi on body composition (20) notified glucocorticoid intake.

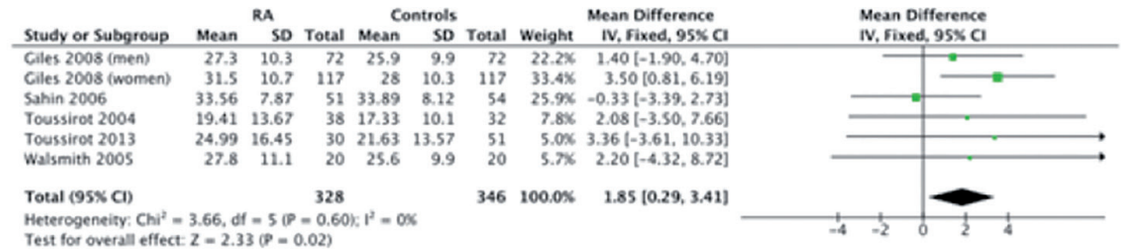
Risk of bias assessment

Articles were rated as low bias with regards to the studied population, except for two articles where data on controls or on place and date inclusion were missing (21, 22). Studies were rated as moderate bias with regards to statistical analysis since only two studies reported sample size calculation (22, 23). All studies correctly explained the outcome measure, except for one where the DEXA measures differered between patients (24). Four studies did not account for the confounding variables (21-23, 25).

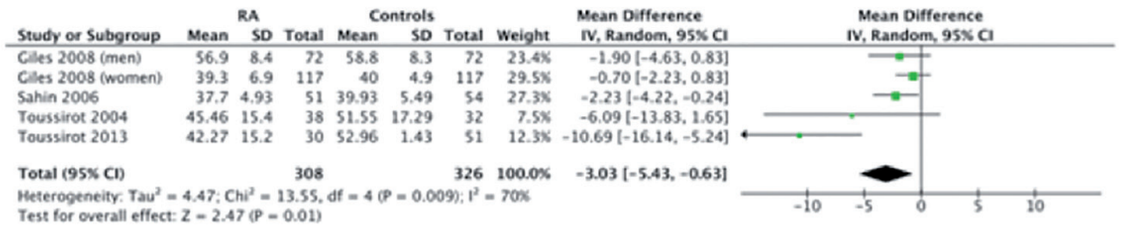
Table I. Characteristics of studies on body composition in inflammatory rheumatic diseases and on impact of TNF inhibitors.

Ref.	Disease	Cases (n)	Age (years) Female (n) BMI (kg/m^2)	Controls (n)	Age Female BMI	GC, mean (mg/day)	Treatment (n)	Disease duration (years)
(13)	RA	30	56.9 (37-73) 19 25.5±0.8	51	46.6±1.5 22 24.9±0.7	<10	MTX (23) LEF (4) SSZ (2), GC (26)	11.7±1.6
(23)	RA	23	60.0±2.0 16 27.6±0.9	23	60.0±3.0 16 26.4±0.9	<10	MTX (18) IFX (2) ADA (1) SSZ (3) NSAI (9), GC (6)	12.9±1.8
(24)	RA	189	59.0±8.4 117 NA	189	60.7±8.8 117 NA	NA	cDMARD (158) bDMARD (85) GC (83)	9 (5-17)
(21)	RA	51	55.4±9.5 51 27.7±3.5	54	55.2±7.6 51 28.4±4.2	NA	NA	9.2±7.3
(1)	RA	20	47.0±14.0 20 25±4.5	20	48.0±14.0 20 24.2±3.3	5.1±1.7	NA	7.5±6.5
(27)	RA	38	47.6±2.1 18 25.6±0.9	32	44.3±1.7 6 25.7±0.8	7.5±0.6	MTX (23) SSZ (7) HCQ (4) Tiopronine (1) Ciclosporine (1)	8.0±7.0
(26)	RA	16	45.4±13.2 16 24.7±4.2	17	47.1±14.6 16 23.7±1.3	2.4±2.7	GC (8) MTX (6)	9.7±10.2
(12)	SpA	53	44.1±0.6 9 26.2±0.6	35	44.6±1,6 8 26.1±0.8	NA	NSAI (47) MTX (4) SSZ (7), CTC (3)	10.3±1.3
(22)	SpA	19	53.0±12.0 0 26±4.1	19	54.0±10.0 0 27.1±3	NA	NSAI (NA) SSZ (NA)	19.0±13.0
(25)	SpA	71	39.1±9.5 22 23.8±3.8	71	37.3±10.5 22 23±3.7	NA	NA	10.6±8.3
(20)	SpA	85	39.3 ± 11.4 12	-	-	NA	IFX (56) ETN (29) GC (12)	13.1±9.5
(31)	RA + SpA	20 8 RA 12 SpA	48,6±3,7 6 23.7±0.9	-	-	0	IFX (3) ETN (7) ADA (12)	9.6±2.1
(32)	RA	28	57 (46.5-62) 28 NA	-	-	0	ADA (12)	NA
(28)	RA	16	NA 16 26.6±1,23	-	-	0	IFX (16)	7.1±1.0
(33)	PsA	20	42.2±8,9 NA 27.11±3.93	-	-	0	NA	14.1±11.2
(29)	RA	18	56 (42-73) 13 24.7±3.7	-	-	0	IFX (18)	4.9±4.3 months
(30)	RA	19	54.0±18.0 19 26.11±4.98	-	-	0	IFX (12) ADA (7)	9.0±7.0
(15)	SpA	106	38.0±11.0 80 26.2±5.0	-	-	0	TNFi (NA)	16.5±8.5
(11)	RA	12	54.0±7.0 9 28.0±7.0	-	-	0	ETN (12)	<6 months

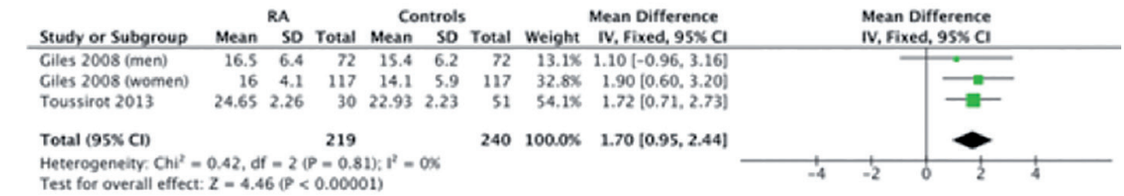
Ref.: reference; BMI: body mass index (kg/m^2); M: Mean; CD: cumulative dose; MTX: Methotrexate; LEF: Leflunomide; SSZ: Sulfasalazine; GC: Glucosteroid; cDMARD: conventional disease-modifying anti-rheumatic drug; bDMARD: biological DMARD; NSAI: Non-steroidal anti-inflammatory; RA: rheumatoid arthritis; SpA: spondyloarthritis; PsA: psoriatic arthritis; IFX: Infliximab; ETN: Etanercept; ADA: Adalimumab; NA: not available; -: non applicable.



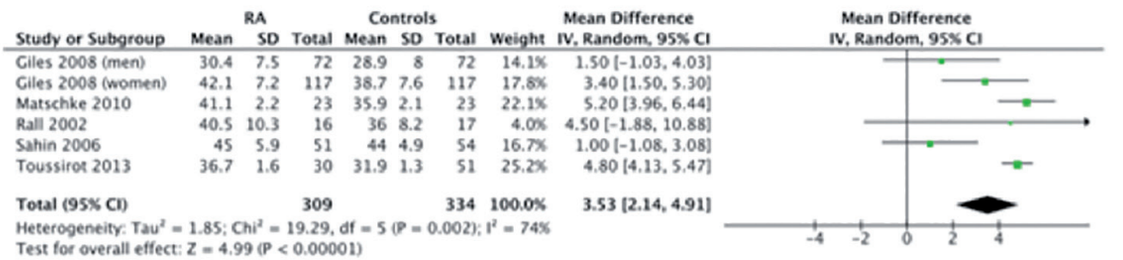
A. Forest plot of fat mass in RA patients (kg)



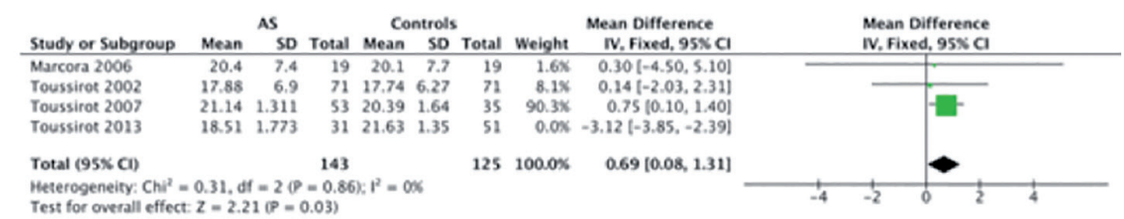
B. Forest plot of lean mass in RA patients (kg)



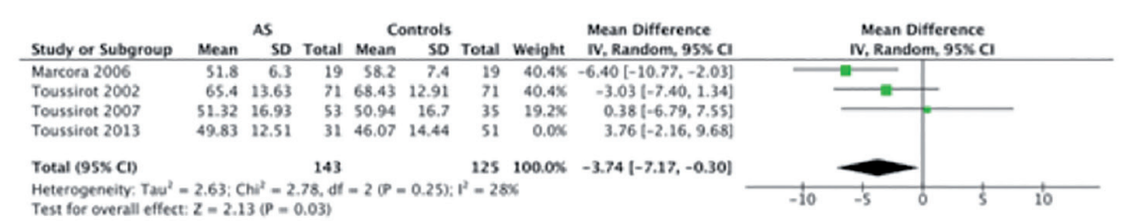
C. Forest plot of android mass in RA patients (kg)



D. Forest plot of adiposity in RA patients (%)



E. Forest plot of fat mass in SpA patients (kg)



F. Forest plot of lean mass in SpA patients (kg)

Fig. 2. Forest plot.

Table II. Effect of TNF inhibitors on body composition.

Ref	Disease	Timepoint (months)	Fat mass	Lean mass	Adiposity	Android fat mass (%)	Visceral adipose tissue
(11)	RA	6	M0: 31.7±8.2 kg M6: 32.3±8.5 kg	M0: 41.3±9.7 kg M6: 41.9±10.5 kg	M0: 42.0±6.8 kg M6: 38.7±12.5 kg	NA	NA
(32)	RA	6	M0: 31.1 (20.6-42.6) kg M6: 32.3 (23.9–44.9) kg*	M0: 44.4(38.5– 54.1) kg M6: 45.4 (40.253.4) kg*	NA	NA	NA
(20)	SpA	6	0.3±0.6 kg*	0.4±0.8 kg*	NA	NA	13.7±20.6 cm^{2**}
(33)	PsA	6	+8.9%*	+2.9**	M0: 31.1±6.6 M6: 31.3±5.3 kg	NA	NA
(28)	RA	12	M0: 26.6±2.9 M12: 28.0±2.6 kg*	M0: 40.2±1.4 M12: 40.5±1.0 kg	NA	NA	NA
(29)	RA	12	3.77 (1.63-5.9) kg*	0.52 (-0.81-1.86) kg**	2.8 (0.67-4.9) kg	NA	NA
(30)	RA	12	M0: 28.4±10.1 M12: 28.5±10.2	M0: 39.7±7.4 M12: 39.8±7.3	NA	NA	NA
(15)	SpA	12	+12.1±22.4%***	1.9%±5.2%***	NA	NA	NA
(20)	SpA	12	0.6±0.8 kg**	0.2±0.8 kg	NA	NA	21.0±26.6 cm^{2**}
(20)	SpA	24	0.7±1.0 kg**	0.2±0.8 kg	NA	NA	29.1±33.4 cm^{2**}
(15)	SpA	24	14.5%±26.8%***	2.0%±5.6%***	NA	NA	NA
(31)	RA + SpA	24	+ 11.1%**	+ 1.5%	+ 7.2%	+ 18.3*	+ 24.3%

*p=0.05; **p<0.001; ***p<0.0001; Ref.: reference; RA: rheumatoid arthritis; SpA: spondyloarthritis; PsA: psoriatic arthritis; kg: kilograms; NA: not available.

Study outcomes

• *Patients with RA*

The first analysis evaluating body composition in patients with RA and healthy controls involved 7 studies (1, 13, 21, 23, 24, 26, 27). A significant increase in fat mass (+1.85 kg, p=0.02; n=328; I^2=0%), adiposity (+3.53%, p<0.00001, n=219, I^2= 0%) and android mass (+1.7 kg, p<0.00001, n=309, I^2=74%)and a significant decrease in lean mass (-3.03 kg, p=0.01, n=308, I^2=70%) were found (Figs. 2A-D).

• *Patients with SpA*

The second analysis comparing body composition between patients with SpA and healthy controls involved 4 articles (12, 13, 22, 25). Significant decreases in fat mass (-0.62 kg, p=0.00001, n=174, I^2 =95%) and in lean mass (-1.77 kg, p=0.05, n=174, I^2=63%) were found but heterogeneity was high. Toussirot's study is the only one that shows a decrease in fat mass and an increase in lean mass in SpA patients (13). This could be due to a higher percentage of males in SpA patients than in controls. In other studies, patients and controls were comparable on age and gender. Therefore, we decided to exclude Toussirot's study from the meta-analysis. We then observed homogeneous results with a significant increase in fat mass (+ 0.69 kg, p=0.03, n=143, I^2= 0%) and a significant decrease in lean mass (-3.74 kg, p=0.03, n=143, I^2=28%) (Figs. 2E-F). No study was available on android mass in SpA patients.

• *Effect of TNF inhibitors*

The influence of TNFi on body composition at 6, 12 and 24 months, was assessed in 6 articles on RA (101 patients) (11, 28–32), 3 articles on SpA (203 patients) (15, 20, 31) and 1 on psoriatic arthritis (20 patients) (33). Four of these articles evaluated the impact of TNFi at 6 months, 5 at 12 months and 3 articles at 24 months. The results are summarised in Table II.

At 6 months, 3 studies showed a significant increase in fat and lean mass whereas the fourth one found a non-significant increase. Visceral adiposity, assessed in only one study, was also increased.

At 12 months, 4 out of 5 studies showed a significant increase in fat mass and 2 out of 5 a significant increase in lean mass. Visceral adiposity, assessed in only one study, was also increased.

At 24 months, all 3 studies showed a significant increase in fat mass and 1 out of 3 a significant increase in lean mass. Android fat mass, assessed in one study, was increased as well as visceral adiposity, assessed in 2 studies.

Discussion

Our systematic review and meta-analysis showed a significant increase in fat mass and a significant decrease in lean mass in patients with RA and to a less extent in patients with SpA.. Patients with RA have a significant increase of android mass and adiposity. TNFi significantly increased fat mass at 6, 12 and 24 months of treatment. Android and visceral fat mass were increased by TNFi. Most studies found an increase in lean mass at 6 months of TNFi, whereas long-term data are controversial,

In inflammatory arthritis, a decrease in lean mass may induce physical disability and weakness. In RA patients, this concept is known under the name of rheumatoid cachexia. Book *et al*., studying body composition in patients with early RA with a mean disease du-

ration of 7 months, showed that loss of lean mass occurs early in disease course (34). This loss of lean mass was associated with disease activity and inflammatory cytokines production, that induce hyper metabolism (2, 35). Our results show that short-term TNFi increases lean mass. This can be explained by the control of inflammation, the decrease of pro-inflammatory cytokines and an increase of physical activity secondarily to disease activity control. Growing evidence reveals that gut hormones including acyl ghrelin, des-acyl ghrelin, glucose-dependent insulinotropic polypeptide actively participate to the regulation of inflammation, appetite and energy homeostasis (36). Variations of plasma acyl ghrelin during TNFi have been reported with conflicting results (14, 36). Modulation of gut hormones by TNFi could thus be involved in the variations of appetite and body composition observed.

Fat mass increase was significant in both forms of rheumatism. However, in SpA patients, fat mass gain was weak. The difference between RA and SpA patients may be explained by gender, age and glucocorticoid use. RA patients are older and more often women. We know that, in the general population, fat mass is higher in females and increases with age. Moreover, glucocorticoids are rarely used in patients with SpA (12). The data in the literature are conflicting: one study showed that patients treated by prednisone had a significantly higher fat mass than patients without prednisone, independently of current inflammation (37), whereas others showed that body composition in RA patients is abnormal regardless of steroid treatment, suggesting that low doses did not affect body composition (38). Low-dose oral glucocorticoids, such as those received by the patients in the reported studies, may in fact protect against loss of lean body mass by reducing inflammation that causes catabolism (2).

TNFi induced a further increase in fat mass suggesting that fat mass increase observed in inflammatory arthritis is not directly explained by inflammation. In one study, TNFi were compared with conventional DMARDs: despite a similar reduction in disease activity, patients with TNFi experienced a more important gain in fat mass, which suggests a specific drug effect (29).

BMI values are very similar in RA and SpA patients. Median BMI of patients was around 25 kg/m^2. Many prospective studies have reported a strong relation between BMI and mortality/morbidity with either a correlation, a J-shape or a U-shaped curve depending on the event studied (39, 40). However, recent studies showed that more than BMI, visceral fat tissue was predictive of an increased risk of dyslipidaemia, hypertension, cardiovascular disease and diabetes mellitus (41). It seems that low dose glucocorticoids in RA patients have no significant impact on trunk/peripheral fat ratio (37). In RA patients, android mass was significantly increased which may participate in the predisposition for cardiovascular events. The increase in visceral and android fat mass with TNFi may have pejorative cardiovascular consequences. However, several studies, but not all, reported reinsuring data with a protective effect of TNFi on cardiovascular diseases (42).

This meta-analysis has some limitations, notably due to the number of studies. We could not perform a meta-analysis on the impact of TNFi due to the absence of *p*-values that are mandatory to perform paired data before/after meta-analysis. Moreover, the data were heterogeneous. The most important confounding effect was glucocorticoid use. In the included studies, the majority of patients with RA received prednisone, but doses were below 10 mg/day. Conversely, few SpA patients used glucocorticoids.

To conclude, patients with RA and to a lesser extent patients with SpA have a significant gain in fat mass, and particularly in android mass, which may partly explain the increase in cardiovascular risk. This difference between RA patients and SpA patients may be explained by a more frequent glucocorticoid use in RA than in SpA. TNFi further increase fat and android mass.

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