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Review

Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: A systematic review and meta-analysis

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ABSTRACT

Objective: Obesity is a worldwide epidemic and a growing body of evidence suggests that it may affect the body's response to biologic agents. We investigated the influence of obesity on the efficacy of different biologic agents used to treat inflammatory diseases.
Methods: Medline, EMBASE and the Cochrane Database were searched using relevant MeSH and keyword terms for obesity and bDMARDs. Articles were selected if they reported a clinical response in obese subjects relative to other BMI categories. Response and remission outcomes were assessed using meta-analysis and all other reported outcomes were summarized.
Results: Among the 3850 records retrieved, 24 articles met the inclusion criteria, including 10 on rheumatoid arthritis (RA), 4 on axial spondyloarthritis (axSpA), 4 on Crohn's disease (CD), 4 on psoriasis (Ps) and 2 on psoriasic arthritis (PsA). Four biological disease-modifying anti-rheumatic drugs (bDMARDs) – anti-TNF agents, T cell co-stimulation inhibitor (abatacept), IL-6 inhibitor (tocilizumab), and B-cell depletion therapy (rituximab) – were involved. The meta-analysis showed that the odds to reach a good response or achieve remission were lower in obese (BMI > 30 kg/m^2) than non-obese (BMI $\leq$ 30 kg/m^2) patients who were treated with anti-TNF agents (good responder % in RA: *OR* 0.34, 95% CI 0.18–0.64; remission% in RA: *OR* 0.36, 95% CI 0.21–0.59; BASDAI50% in axSpA: *OR* 0.41, 95% CI 0.21–0.83), but no significant difference between obese and non-obese was found in patients treated with abatacept (good responder % in RA: *OR* 0.75, 95% CI 0.42–1.36; remission% in RA: *OR* 0.84, 95% CI 0.65–1.09) and tocilizumab (good responder % in RA: *OR* 1.08, 95% CI 0.44–2.63; remission% in RA: *OR* 0.91, 95% CI 0.50–1.66).
Conclusion: Obesity hampered the effect of anti-TNF agents, but not those of abatacept and tocilizumab, suggesting that a personalized treatment strategy should be considered for obese patients with inflammatory diseases.

1. Introduction

Obesity is a global health problem that affects about one-third of the world's population [1]. It causes many health consequences and exerts biological stress on multiple systems, including the immune system. A link between obesity and autoimmunity has been strongly suggested, showing that obese subjects are at higher risk of developing inflammatory diseases, including rheumatoid arthritis [2,3], Crohn's disease [4,5], multiple sclerosis [6,7], axial spondyloarthritis [8], psoriasis and psoriatic arthritis [9–11]. This may relate to the increased pro-inflammatory cytokines and over-expressed adipokines derived from adipose tissue [12]. These inflammatory molecules are believed to be involved in modulating the immune course of the diseases, thus affecting not only the onset but also disease activity, clinical outcome and treatment efficacy in obese patients [13–15].

Recently, biological disease-modifying anti-rheumatic drugs (bDMARDs), which target tumor necrosis factor (TNF)α, IL-6 receptor, co-stimulation signals, and B cells, have become widely used for inflammatory diseases. Whether their efficacy is affected by obesity has attracted much attention. Some studies have shown that the effect of TNF blocking is impaired in obese patients [16–19], but other studies have shown that T cell co-stimulation inhibition and IL-6 receptor blocking are not influenced by obesity [20–25]. It seems that obesity differentially affects the efficacy of these bDMARDs. If so, clarifying the impact of obesity on each bDMARD could help to better treat individual patients. Thus, we performed a systematic review and meta-analysis to assess the

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impact of obesity on the clinical response to different bDMARDs in patients with inflammatory diseases.

2. Methods

2.1. Search strategy

We searched Medline, EMABSE and the Cochrane Central Register of Clinical Trials (database dates to November 2017) to identify relevant trials, using MeSH terms and keywords for obesity and bDMARDs (search strategy available in Appendix A, Supplemental Files S1-S2, see the supplementary material associated with this article online). All reports identified were independently screened by two reviewers (J.S. and J.B.Z.) to identify those satisfying the inclusion criteria; any disagreement was resolved by discussion.

2.2. Study selection

We included any original article that met the following specifications:

- patients: patients with inflammatory diseases;
- therapy: bDMARDs;
- comparison: obese category vs. non-obese, overweight, or normal weight categories;
- outcomes: clinical response in each category was assessed.

In addition, we excluded duplicated articles, meeting abstracts, reviews that lacked specific data and articles not in English or Chinese.

2.3. Data extraction

Data were extracted independently and cross-checked by two reviewers (J.S. and J.B.Z.). We extracted data on patient population, drug administration, grouping method, outcomes reported, study design and follow-up period according to a pre-designed data extraction form.

2.4. Data analysis

As the pathogenesis of each disease is different, the effect of obesity on bDMARDs may vary according to the disease. In addition, the outcome measure is different in studies of different diseases. Thus, we analyzed the results of each disease separately. The effect of obesity on achieving good response or remission was our primary outcome. For studies reporting the frequency of response or remission in each BMI category, meta-analysis was performed to estimate the odds ratio (OR) of the association between obesity and these primary outcomes using the inverse-variance approach (RevMan version 5.3) and to be as conservative as possible, the random-effect method was used to take into account the variability among included studies. Heterogeneity among trials was estimated with the Cochran Q-test and I^2 statistic. Studies that could not be pooled for meta-analysis were analyzed descriptively. The correlation between BMI and other disease activity measures were our secondary outcomes, like DAS28, tender or swollen joint counts, ESR or CRP level, patient reported outcomes, etc. We carried out a qualitative synthesis for these secondary outcomes.

2.5. Role of the funding source

A Natural Science Foundation of China (NSFC) grant No. 81401359 was received to carry out this study. The foundation provided all costs needed for literature searches and article publication.

3. Results

3.1. Literature search

The literature search yielded 24 trails for the systematic review. Among them, 10 were rheumatoid arthritis (RA), 4 were ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA), 4 were Crohn's disease (CD), 4 were psoriasis (Ps) and 2 were psoriasic arthritis (PsA) (Fig. 1).

3.2. Study characteristics

The impact of obesity on the clinical efficacy of bDMARDs was evaluated in different inflammatory diseases.

3.2.1. Patients with RA

Ten studies were included [16–25] and the clinical efficacies of 4 bDMARDs were examined, including anti-TNF agents, T cell co-stimulation inhibitor (abatacept), IL-6 inhibitor (tocilizumab) and B-cell depletion therapy (rituximab). Studies were mainly conducted prospectively [16,17,19,20,23], except for 2 pooled analyses [21,22] and 3 retrospective studies [18,24,25]. The period of study duration varied from 4 to 12 months. The proportion of obese subjects ranged from 10.3 to 45.4%. Patients were mostly women, representing 72.2 to 91.2% of patients. Frequency of response, remission, drug discontinuance and other disease activity measures (DAS28, HAQ, CRP, ESR, TJR, SJC, and VAS) were reported outcomes used to evaluate the clinical response to different bDMARDs. The definition of response and remission in each study is mentioned in Appendix A, Table S1.

3.2.2. Patients with AS or axSpA

Four studies were included [26–29] and only anti-TNF agents were examined. Studies were mainly retrospective. The duration varied from 6 to 12 months. The proportion of obese subjects ranged from 13.5 to 26.3% and women represented 30.6 to 37.8%. The BASDAI20/50/70 and ASAS40 response rate, BASDAI index and the ASDAS ESR index were the reported outcomes to evaluate the clinical response. Details are presented in Table 1.

3.2.3. Patients with CD

Four studies were included [30–33] and only anti-TNF agents were examined. Most studies were retrospective [34–36], except one prospective cohort [33]. The study duration varied from 10.5 to 36 months. The proportion of obese subjects ranged from 11.9 to 18.4% and women represented 51 to 66.7% of subjects. The risks of developing a clinical flare-up or loss of response were the reported outcomes to evaluate the clinical response. Details are presented in Table 2.

3.2.4. Patients with Ps

Four studies were included [34,35,37,38], and only anti-TNF agents were examined. Studies were retrospective, with the duration varying from 4 to 20.8 months. The proportion of obese subjects ranged from 18.2 to 45.8% and women represented 32.3 to 56.7% of subjects. Mean PASI and PASI100/PASI90/PASI75 response rate were the reported outcomes to evaluate the clinical response. Details are presented in Table 3.

3.2.5. Patients with PsA

Two studies were included [34,39] and only anti-TNF agents were examined. One study was prospective and another was retrospective, with the duration varying from 6 to 36 months. The proportion of obese subjects ranged from 32 to 33.3% and women represented 49.6 to 54.6% of subjects. The frequency of response

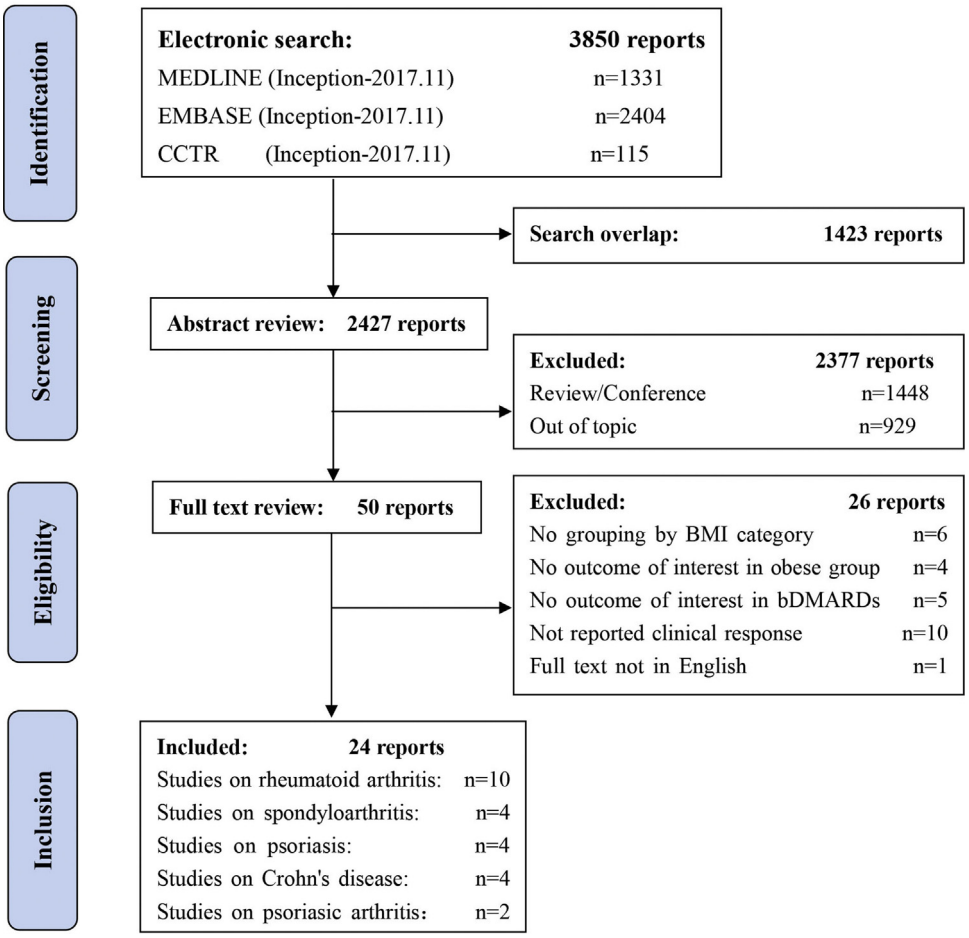

Fig. 1. Flowchart of article identification and selection.

and remission were the reported outcomes to evaluate the clinical response.

BMI categories were divided in accordance with the WHO definition in most studies, classified as normal (< 25 kg/m^2), overweight (25 to < 30 kg/m^2) and obese (BMI > 30 kg/m^2), except for 2 studies. One study had a lower boundary of 20 kg/m^2 for the normal group [16] and 1 defined obesity as BMI > 25 kg/m^2 because the population was Asian [20], in which BMI was classified as normal (BMI < 23.0 kg/m^2), overweight (23.0 to < 25.0 kg/m^2) and obese (BMI ≥ 25.0 kg/m^2).

3.3. Outcomes

3.3.1. Obesity and response to different bDMARDs in patients with RA

Studies that examined the impact of BMI on the clinical efficacy of different bDMARDs in RA patients are summarized in Appendix A, Table S1. Among the 10 included studies, 4 examined anti-TNF agents (n = 1557), 5 were abatacept (n = 4272), 3 were tocilizumab (n = 361) and one was rituximab (n = 58) (multiple bDMARDs were reported in some studies). The frequencies of response/remission were the primary reported outcomes and the results of 9 studies were included in the meta-analysis.

3.3.1.1. Frequency of remission. The association between obesity and remission was assessed in 8 studies [17–20,23–25]. Remission was determined as DAS28 < 2.6 in all included studies. Seven studies [17,18,20,23–25] involving 2782 patients were included in the meta-analysis. The percentage of remission was lower in obese than non-obese categories of patients treated with anti-TNF agents (*OR* 0.36, 95% CI 0.21–0.59; $P_{heterogeneity}$ = 0.80, I^2 = 0%). But no significant difference between obese and non-obese categories was found in patients treated with abatacept (*OR* 0.84, 95% CI 0.65–1.09; $P_{heterogeneity}$ = 0.43, I^2 = 0%), tocilizumab (*OR* 0.91, 95% CI 0.50–1.66; $P_{heterogeneity}$ = 0.69, I^2 = 0%), or rituximab (*OR* 0.14, 95% CI 0.02–1.29; only one study) (Fig. 2a). The identified study by Kim et al. [19] was not included in the meta-analysis since the data to calculate the estimate was not available. This study supported the result that obesity did not affect the remission rate in patients treated with abatacept and tocilizumab, but they did not find a significant difference between obese and overweight or normal categories in patients treated with anti-TNF agents (P = 0.957). This discrepancy may be due to the small sample size (n = 27) or the different BMI categories (defined obesity as BMI > 25 kg/m^2) used in this study.

3.3.1.2. Frequency of responders. The frequency of response by BMI category was reported in 9 studies [16,18–22,24,25], and responses were determined as:

- ΔDAS28 ≥ 1.2;
- good EULAR response;
- moderate/good EULAR response in different studies (Appendix A, Table S1).

Among them, 6 studies [18–20,22,25] reported the association between BMI and good EULAR response, and 5 of them involving 1210 patients were included in the meta-analysis. The frequency of good responses was lower in obese than non-obese patients treated with anti-TNF agents (*OR* 0.34, 95% CI 0.18–0.64; only one

Table 1
Characteristics and main findings of included studies: obesity and clinical response to anti-TNF agents in AS or axSpA patients.

Refs	Patients			BMI timing	Therapy: anti-TNF agent (*n*)	Groups (*n*)			Reported outcomes				Clinical response was assessed by	Study design	
	Rheumatic disease (*n*)	Obese %	Female %			Obese	Over weight	Normal weight	Clinical response			Other		Type of study	Duration (months)
Ottaviani et al. 2012 [26]	AS (155)	24.5	36.7	Baseline	IFX	38	54	63		BASDAI50 %[a]	BASDAI20 %[a]	BASDAI70 %[a]	BASDAI50 response rate (%) and BASDAI20%; BASDAI70%[a]	Retrospective cohort	6
									Obese[a]	26.5 [a]	41.2 %[a]	5.9 %[a]			
									Overweight[a]	48.9%[a]	71.2%[a]	29.8%[a]			
									Normal weight[a]	77.6%[a]	84.5%[a]	48.3%[a]			
										P < 0.001[a]	*P* < 0.001[a]	*P* < 0.001[a]			
Rosas et al., 2017 [27]	AS (57)	26.3	35	At treatment	ADA (57)	15	25	17	Obese ↓ Achieving BASDAI ≤ 4 (*P* = 0.05) Achieving ASDAS ≤ 2.1 (*P* = 0.02)[a]			Blood ADL levels↓ *P* = 0.032 Anti-ADL Abp = 0.13[a]	BASDAI index and the ASDAS ESR index[a]	Cross-sectional study	–
Gremese et al. 2014 [28]	Axial SpA (170)	13.5	30.6	Baseline	IFX (104) ETA (31) ADA (35)	23	55	92	BASDAI50% Obese: 30.4%; Overweight: 54.5%; Normal weight: 72.8% *P* < 0.001[a]				BASDAI50 response rate (%)[a]	Retrospective cohort	12
Micheroli et al., 2017 [29]	Axial SpA (624)	14.1	37.8	Baseline	IFX (137) ADA (215) ETA (167) GOL (105)	88	204	332		ASAS40%[a]	BASDAI50%[a]	ASDAS < 2.1%[a]	BASDAI50 response rate (%) ASAS40 response rate (%) ASDAS ESR index[a]	Retrospective cohort	12
									Obese[a]	29%[a]	33%[a]	25%			
									Overweight[a]	34%[a]	40%[a]	41%			
									Normal weight[a]	44%[a]	48%[a]	56%			
										P = 0.02[a]	*P* = 0.06[a]	*P* < 0.001[a]			

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; ASAS: Assessment in SpondyloArthritis International Society; ASAS40: 40% improvement according to ASAS; BASDAI; Bath ankylosing spondylitis disease activity index; BASDAI50: 50% improvement according to BASDAI; anti-TNF agents include infliximab (IFX), adalimumab (ADA), etanercept (ETA), certolizumab (CTZ) and golimumab (GOL).

[a] Significant difference between groups.

Table 2
Characteristics and main findings of included studies: obesity and clinical response to anti-TNF agents in CD patients.

Refs	Patients			BMI timing	Therapy: anti-TNF agent (*n*)	Groups (*n*)			Reported outcomes		Clinical response was assessed by	Study Design	
	Rheumatic disease (*n*)	Obese %	Female %			Obese	Over weight	Normal weight	Clinical response	Other		Type of study	Duration (months)
Harper et al., 2013 [30]	CD (99)	–	52.5	Baseline	IFX (99)	–	–	–	Time to LOR: Earlier in obese group $P<0.001$[a]	–[a]	A clinical flare or loss of response (LOR)[a]	Retrospective cohort	36
Bhalme et al., 2013 [31]	CD (130)	14.8	66.7	Baseline	ADA (54)	8	46		Time to LOR: Earlier in obese group $P=0.013$[a]	–[a]	Loss of response (LOR)[a]	Retrospective cohort	10.5
		18.4	55.3	Baseline	IFX (76)	14	62		Time to LOR: Two groups are close $P=0.164$[a]	–[a]			13.0
Brown et al., 2016 [32]	CD (388)	11.9	54	Baseline	IFX (388)	46	91	218	Risk of LOR (%): Obese: 45.7%: Overweight: 41.8%; Normal weight: 39.1%[a]	Any CD-related surgery or CD-related intestinal resectional surgery[a]	A clinical flare or loss of response (LOR)[a]	Retrospective cohort	12
Guerbau et al., 2017 [33]	CD (140)	16.4	51	Baseline	IFX (140)	23	21	96	IFX dose optimization (%) Obese: 56%: Overweight: 52%; Normal weight: 20% $P=0.0002$[a]	Introduction of surgery, CT or IS; IFX discontinuation[a]	IFX dose optimization[b]	Prospective cohort	12

CD: Crohn's disease; LOR: loss of response. A clinical flare or LOR in ref [30,32]was defined as the first occurrence of any of the following: (1) dose escalation of IFX from 5 mg/kg every 8 weeks to either 10 mg/kg per dose and/or a shortening of the dosing interval; (2) loss of response to IFX as manifested by switching to an alternative biologic agent; (3) hospitalization for IBD; (4) need for a course of corticosteroids for disease activity; or (5) need for IBD-related surgery. But the detail definition of LOR was not elaborated in ref [31]. IFX dose optimization was defined as increasing the dosage to more than 5 mg/kg (without limit of IFX dose in patients with a weight excess 100 kg) and/or shortening the interval between infusions to less than 8 weeks.

[a] Significant difference between groups.

Table 3
Characteristics and main findings of included studies: obesity and clinical response to anti-TNF agents in psoriasis patients.

Refs	Patients			BMI timing	Therapy: anti-TNF agent (*n*)	Groups (*n*)			Reported outcomes				Other	Clinical response was assessed by:	Study design	
	Rheumatic disease (*n*)	Obese %	Female %			Obese	Over weight	Normal weight	Clinical response						Type of study	Duration (months)
Bardazzi et al., 2010 [37]	Ps (24)	45.8	–	Baseline	ETA, ADA and IFX	11	13		Mean PASI:[a] Obese: 15.55 ± 3.195;[a] Non-obese: 5.538 ± 1.228[a] *P* = 0.0051[a]				–[a]	Mean PASI at month 4 and 8[a]	Retrospective cohort	8
Lafuente-Urrez and Pérez-Pelegay 2014 [38]	Ps (30)	33.3	56.7	Baseline	ADA	10	7	13		Non-obese[a]	Obese[a]		Drug discontinue%[a]	Percentage of patients achieve PASI100/90/75 at different visit time[a]	Retrospective cohort	20.8
									PASI75 %[a] PASI90%[a] PASI100%[a]	80 %[a] 80% 70%[a]	80 %[a] 50%[a] 40%[a]	*P* = 1[a] *P* = 0.116[a] *P* = 0.139[a]		Percentage of patients achieve PASI90/75[a]	Prospective cohort	4
Prussick et al., 2015 [34]	Ps (99)	31.3	32.3	Baseline	ADA	31	28	40		Non-obese[a]	Obese[a]		–[a]			
									PASI90 %[a] PASI75 %[a] *P* < 0.05[a]	63.2 %[a] 85.3 %[a]	35.5 %[a] 61.3 %[a]					
Giunta et al., 2016 [35]	Ps (66)	18.2	42.4	Baseline	ETA	12	21	33	Mean PASI:[a] Obese: 2.94 ± 2.81; *P* < 0.001[a] Overweight: 1.86 ± 2.88;[a] Normal weight: 1.72 ± 3.02[a]				–[a]	Mean PASI at month 12[a]	Retrospective cohort	12

Ps: psoriasis; Anti-TNF agents include adalimumab (ADA); infliximab (IFX) and etanercept (ETA); PASI: psoriasis area and severity index.
[a] Significant difference between groups.

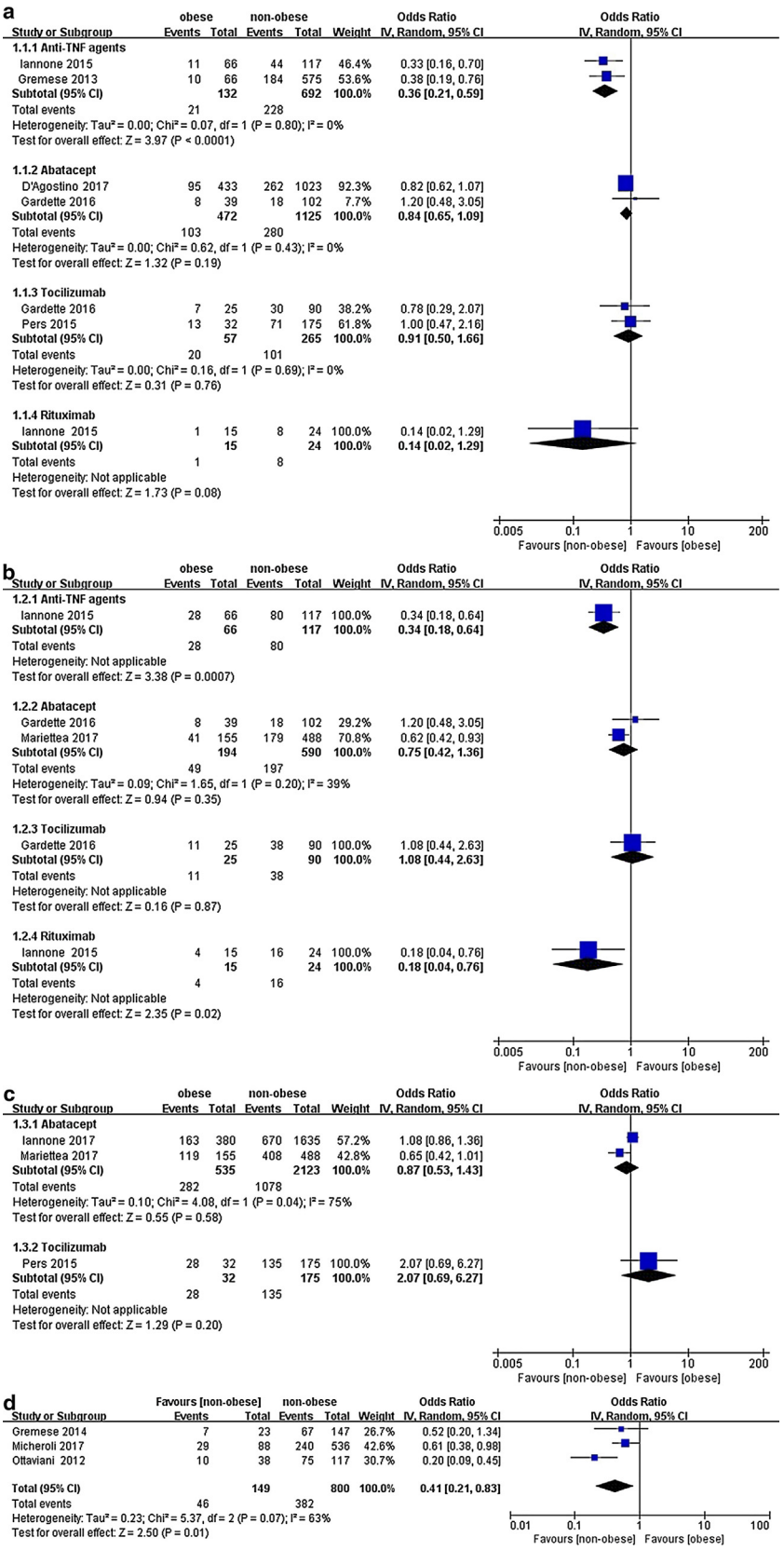

Fig. 2. Forest plot of the effect of obesity (obese $\geq 30\,kg/m^2$ vs. non-obese 18.5–30 kg/m^2). a: on the percentage of RA patients achieving EULAR remission (DAS28 < 2.6); b: on the percentage of RA patients reaching good EULAR response (ΔDAS28 $\geq$ 1.2 and DAS28 $\leq$ 3.2); c: on the percentage of RA patients reaching moderate or good EULAR response; d: on the percentage of AS or axSpA patients achieving BASDAI50.

study) and rituximab (*OR* 0.18, 95% CI 0.04–0.76; only one study), but no significant difference between obese and non-obese categories was found in patients treated with abatacept (*OR* 0.75, 95% CI 0.42–1.36; $P_{heterogeneity} = 0.20$, $I^2 = 39\%$) and tocilizumab (*OR* 1.08, 95% CI 0.44–2.63; only one study) (Fig. 2b). Another study identified but not included in the meta-analysis by Kim et al. [19] supported the result that obesity did not affect the response to abatacept and tocilizumab in RA, but they did not find a significant difference between obese and non-obese categories in patients treated with anti-TNF agents ($P = 0.54$).

Response was determined as moderate/good EULAR response in 3 studies [21,22,24] and their results indicated that obesity did not affect the response to abatacept and tocilizumab. No significant difference between obese and non-obese categories was found in patients treated with abatacept (*OR* 0.87, 95% CI 0.53–1.43; $P_{heterogeneity} = 0.04$, $I^2 = 75\%$) and tocilizumab (*OR* 2.07, 95% CI 0.69–6.27; only one study) (Fig. 2c).

3.3.1.3. Disease activity measures and other reported outcomes. Studies have also reported DAS28 change, tender or swollen joint counts, VAS pain, ESR or CRP levels, and drug discontinuance rates (Appendix A, Table S1) and they found that obesity negatively influences improvements of most disease activity measures in anti-TNF agent-treated patients, but has no effect in abatacept- or tocilizumab-treated patients (details are summarized in supplemental files).

3.3.2. Obesity and response to anti-TNF agents in patients with AS or axSpA

Four studies [26–29] (involving 1006 patients) evaluated the effect of BMI on the clinical response to anti-TNF agents in AS or axial SpA patients. Clinical response was assessed using different parameters like BASDAI50 response rate, ASAS40 response rate, BASDAI index, and the ASDAS ESR index, and they all found that higher BMI was associated with a lower rate of response to anti-TNF agents in AS [26,27] or axial SpA patients [28,29] (Table 1). Among them, 3 studies involving 949 patients reported the BASDAI50 response rate by BMI category. And their data were included in the meta-analysis, showing that the BASDAI50 response rate was lower in obese than non-obese patients treated with anti-TNF agents (*OR* 0.41, 95% CI 0.21–0.83; $P_{heterogeneity} = 0.07$, $I^2 = 63\%$) (Fig. 2d).

3.3.3. Obesity and response to anti-TNF agents in patients with Crohn's disease

In CD patients, the clinical response to anti-TNF agents was assessed in 4 studies [30–33] (involving 518 patients) by time or risk of developing a clinical flare or loss of response (LOR). Three of these studies showed that patients with high BMI present more rapid and frequent LOR to the anti-TNF agent IFX [30,32,33]. But in the study by Bhalme, 2 different anti-TNF agents, ADA and IFX, were examined. For patients on ADA, increased BMI was associated with an increased hazard of LOR ($P = 0.045$), but no significant effect of BMI upon LOR was found in patients on IFX ($P = 0.36$) [31] (Table 2).

3.3.4. Obesity and response to anti-TNF agents in patients with psoriasis

The effect of BMI on anti-TNF agent response in Ps patients was examined by 4 studies [34,35,37,38] involving 219 patients. The clinical response was assessed by mean psoriasis area severity index (PASI) or PASI100/90/75 response rate. Three of these studies showed that obese patients had higher mean PASI and lower PASI90/75 response rate than normal or overweight patients [34,35,37]. But differences in PASI100/90/75 response rate according to weight subgroups were not observed in the study by Lafuente-Urrez; this discrepancy may due to the small sample size ($n = 30$) of this study [38].

3.3.5. Obesity and response to anti-TNF agents in patients with PsA

Two studies [36,39] (involving 1406 patients) evaluated the effect of BMI on the clinical response to anti-TNF agents in PsA patients. The remission and good EULAR response rate do not seem to be affected by BMI [36]. But moderate/good EULAR response rate and adherence to anti-TNF agents were diminished by obesity [39] Table 4.

4. Discussion

In the present systematic review, we evaluated the impact of obesity on the therapeutic responses to different bDMARDs in inflammatory diseases, including RA, AS/axial SpA, CD, Ps and PsA.

In RA and axial SpA patients, our meta-analysis showed that the odds of reaching a good response and achieving remission were lower in obese patients who were treated with anti-TNF agents, but no significant difference was found between obese and non-obese patients treated with abatacept and tocilizumab. In CD, Ps and PsA patients, although meta-analysis was not feasible, most studies indicated that a higher BMI was associated with a lower response to anti-TNF agents. These data suggested that the effect of TNF-blocking was impaired by obesity, but the T cell co-stimulation inhibitor abatacept and IL-6 inhibitor tocilizumab seemed to work effectively in obese patients. Biologic agents that target TNFα, T cell co-stimulation, and IL-6 receptors are widely used in treating inflammatory diseases, but not all patients respond well to the specific agents. The finding that obesity hampers the effects of anti-TNF agents, but not those of abatacept and tocilizumab, suggests that a personalized treatment strategy should be considered for obese patients. In addition, weight loss induced by a low-calorie diet has been shown to improve the response to anti-TNF agents in overweight/obese patients with PsA [40] and Ps [41], suggesting that weight management might improve therapeutic response in obese patients, especially for those using anti-TNF agents.

Only one included study reported data on patients using B-cell depletion therapy, an anti-CD20 Ab named rituximab. A total of 58 RA patients were involved and the results showed that the percentage of responders was significantly lower in obese than in normal-weight patients ($P = 0.01$), but the difference in percentage of remission was not significant ($P = 0.04$). Another excluded case–control study ($n = 114$) supported the view that BMI does not affect the response to rituximab in RA. It showed that the median BMI was similar among responders and non-responders ($P = 0.78$) [42]. These controversial results may be influenced by bias due to the small sample size and retrospective study design. Thus, the impact of obesity on the response to rituximab still needs to be investigated in more prospective cohort studies.

The reason why the effect of TNF inhibitors was impaired, but a T cell co-stimulation inhibitor and IL-6 inhibitor continued to work in obese patients, is still unclear and currently a matter of speculation. Different pharmacokinetic properties of these drugs could be involved. Indeed, it has been showed that the median C_{min} abatacept concentration of $\geq 10\,\mu g/mL$ (efficacy threshold) can be achieved in > 90% of patients across all BMI groups with both subcutaneous (SC) and intravenous (IV) administration routes [23] and trough levels of abatacept are similar across patient weight ranges [43]. However, pharmacokinetic data for anti-TNF agents and tocilizumab in obese patients are lacking. Possible differences in the volume of distribution based on the drugs' lipophilic properties may explain why obesity seems to impact the response to a non-lipophilic drug like infliximab but not a lipophilic drug like

Table 4
Characteristics and main findings of included studies: obesity and clinical response to anti-TNF agents in PsA patients.

Refs	Patients			BMI timing	Therapy: (*n*)	Groups (*n*)			Reported outcomes			Response or remission definition[a]	Study design	
	Rheumatic disease (*n*)	Obese%	Female%			Obese	Over weight	Normal weight	Responders %[a]	Remission %[a]	Other[a]		Type of study	Duration (months)
Iannone et al., 2013 [36]	Active peripheral PsA (135)	33.3	49.6	Baseline	IFX (45) ADA (42) ETA (48)	45	47	43	Obese: 62.8%; Overweight: 63.8%; Normal weight: 61.5% $P > 0.05$[a]	Obese: 37%; Overweight: 46%; Normal weight: 44% $P = 0.31$[a]	Drug discontinuing ($P = 0.36$); DAS28 ($P = 0.42$); SDAI ($P = 0.44$); HAQ ($P = 0.06$)[a]	Response: ① good EULAR response Remission: DAS28 < 2.6[a]	Retrospective cohort	36 (6–79)
Haggard et al., 2016 [39]	PsA (1271)	32	54.6	Baseline	IFX (352) ADA (520) ETA (287) GOL (85) CTZ (27)	408	863		Obese: 55 % non-obese: 65 % $P = 0.02$[a]	–[a]	TNFI duration: Obese: 2.5 year; non-obese: 5.9 year $P < 0.01$[a]	Response ② moderate + good EULAR response[a]	Prospective cohort	6

PsA: psoriasic arthritis; DAS28: disease activity scoreuses 28 joint counts; Anti-TNF agents include infliximab (IFX), adalimumab (ADA), etanercept (ETA), certolizumab (CTZ) and Golimumab (GOL).
[a] Significant difference between groups.

tocilizumab [44], but this is mere speculation and cannot explain why lipophilic anti-TNF agents like etanercept and adalimumab were affected by obesity.

The increased pro-inflammatory cytokines and over-expressed adipokines derived from adipose tissue may be an explanation. Studies have suggested that elevated circulating levels of Th17 cells and IL-17 might be a predictor of poor therapeutic response to TNF blockers [45] and obesity has been shown to promote Th17 differentiation and IL-17 production in a collagen-induced arthritis model [46], suggesting that inflammatory cytokines and adipokines overproduced in visceral adipose milieu could counteract the effects of TNF inhibitors, but they may not affect T cell activation inhibition by abatacept and IL-6 inhibition by tocilizumab.

This review presents a full picture of current studies on the correlation between obesity and response to bDMARDs in patients with inflammatory diseases. However, several potential limitations need to be discussed. First, many retrospective studies relying on recorded medical information were included in our meta-analysis; their data may be impacted by record keeping errors and the interpretation has potential recall bias by study subjects. A second limitation is the small sample size for studies on the drugs tocilizumab and rituximab, whose results need further confirmation. Third, many studies could not be pooled for the meta-analysis because different parameters were used to evaluate the clinical outcomes, and some data were reported incompletely, so we can only summarize their results descriptively. Fourth, when comparing clinical responses to different bDMARDs in RA, the definition of response was determined differently, so we can only analyze these results separately. Also, the duration time for studies on TNF inhibitors was typically 4, 6 and 12 months, but for studies on abatacept and tocilizumab, it was mostly 6 months. So, our conclusions need further confirmation by additional studies with the same evaluation criteria and duration times.

Additional studies, including more powerful prospective cohort studies with larger sample sizes and in-depth studies on the underlying mechanism, are still needed to further elucidate the relationship between obesity and response to treatment, which could help to better treat individual patients.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (S1-S2, Table S1) associated with this article can be found, in the online version, at http://www.sciencedirect.com and https://doi.org/10.1016/j.jbspin.2018.03.007.

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