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IS BODY FAT PERCENTAGE A GOOD PREDICTOR OF MENSTRUAL RECOVERY IN FEMALES WITH ANOREXIA NERVOSA AFTER WEIGHT RESTORATION? A SYSTEMATIC REVIEW AND EXPLORATORY AND SELECTIVE META-ANALYSIS

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ABSTRACT

The resumption of menses (ROM) is an important outcome in anorexia nervosa treatment and is considered as a sign of recovery. Identification of relevant factors in its prediction is important in clinical practice. Therefore we aimed to conduct a systematic review and exploratory meta-analysis of the association between total body fat percentage (%BF) and ROM after weight restoration in adolescents and young adults with anorexia nervosa. The study was conducted by adhering to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Data were collated using meta-analysis and a narrative approach. Of the 604 articles retrieved, only seven studies comprising a total of 366 adolescent and young adult females with anorexia nervosa met the inclusion criteria and were reviewed, and preliminary results revealed three main findings. Firstly, patients who resumed their menstrual cycle had a significantly higher mean %BF when compared to those who did not, an overall effect confirmed by the meta-analysis (SMD: 3.74, 95% CI: 2.26–5.22). Secondly, %BF was found to be an independent predictor of the ROM in this population and an increase of only one unit of %BF can increase the odds of menstruation by ≈15–20%. Thirdly, despite the paucity of data, a cut-off point of %BF≈21was suggested as the minimum needed for ROM. In conclusion, a higher %BF seems to be

associated with the ROM in weight-restored adolescent and young adult females with anorexia nervosa. Its assessment is important in a clinical setting, especially after complete weight restoration.
The PROSPERO Registry – A systematic review and meta-analysis of the factors associated with the resumption of the menstrual cycle in females with anorexia nervosa after weight restoration (CRD42019111841).

Keywords: *Anorexia nervosa; Body fat percentage; Dual-energy X-ray absorptiometry; Weight restoration; Menstrual resumption*

INTRODUCTION

Secondary amenorrhoea is a common medical complication in females with anorexia nervosa (1–3), mainly due to weight loss (4) and usually associated with infertility (5, 6), reduction in bone mineral density and a higher risk of bone fractures (7–9). Resumption of menses (ROM) during anorexia nervosa treatment is an important outcome and is considered as a reliable biological indicator of healthy status (i.e. more than body weight) and a sign of recovery (10). Restoration of normal body weight seems to be the main determinant (11). However, in a subgroup of patients, amenorrhoea persists even after achievement of the former (12). This implies that other factors may play a role in the ROM in this population, despite complete body weight restoration (13).

In this direction, many clinicians frequently prescribe oestrogens under the form of hormone medication and oral contraceptives with the aim to induce ROM in order to cope for bone loss in this population (14); however strong evidence showed that the administration of oestrogens in patients with anorexia nervosa has no benefits in terms of prevention and treatment of low bone mineral density (7). For this reason, a recent position statement indicated that females with anorexia nervosa should not be treated with oestrogen or birth control pills (i.e. in underweight or during treatment), because this may create a false impression that their skeleton is protected against osteopenia and osteoporosis (15), and the induced ROM may create a false sense of health, and therefore, motivation to regain and restore weight and adherence to treatment of the eating disorder may be negatively affected (15).

A considerable amount of data has been derived from research on body composition in anorexia nervosa (16–25) and in terms of treatment outcomes (i.e., relapse, cardio-metabolic consequences and psychological distress) (26–32). In particular, it has been suggested that total body fat percentage (%BF) may play a potential role in the ROM after restoration of body weight. However, the available data are discordant in their findings (33). In fact some studies have found an association between body fat and the ROM in patients with anorexia nervosa (34); however, others did not (35). Moreover, to the best of our knowledge, no systematic review posing this issue as important outcome has yet been conducted in order to provide a more valid interpretation of the evidence published to date. In light of these considerations, we set out to systematically review published literature on this topic in accordance with the PICO process (36), as detailed below:

P – Population: Female adolescents or young adults who met the diagnosis criteria for anorexia nervosa and had amenorrhoea (37)

I – Intervention: Weight restoration

C – Comparison: Two groups with anorexia nervosa group before and after weight restoration; one resumed menses and the other did not

O – Outcome: (i) %BF however assessed, that is, skinfold thickness, bioimpedance analyser (BIA) and dual-energy X-ray absorptiometry

(DXA), before and after weight restoration; (ii) ROM was defined as three or more menstrual periods over the preceding 6 months with at least one menstrual period in the preceding 3 months (38).

METHODS

This article has been completed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (39) and registered in the PROSPERO Registry: no. CRD42019111841 (40).

Inclusion and exclusion criteria

All studies evaluating %BF and ROM in adolescent (41) and young adult females of fertile age with anorexia nervosa after weight gain/restoration were included, provided that they met the following criteria: (i) they were written in English; (ii) they were original articles on studies with a longitudinal design; and (iii) they were related to prospective or retrospective observational (analytical or descriptive), experimental or quasi-experimental controlled or non-controlled studies, documenting significant weight gain or weight restoration in patients. No reviews, cross-sectional studies or non-original articles (i.e. case reports, editorials, 'Letters to the Editor' or book chapters) were included.

Information source and search strategy

The literature search was designed and performed independently in duplicate by two authors, namely the principal (ST) and the senior investigator (ME). The PubMed and Scopus databases were systematically screened using the following MeSH terms: #1 anorexia nervosa, #2 weight gain, #3 weight restoration, #4 weight normalisation, #5 amenorrhoea, #6 resumption of menses, #7 resumption of menses cycle, #8 body composition, #9 body fat and #10 body fat percentage. The following combinations were also applied as search parameters: (#1 AND #2 OR #3 OR #4) AND (#5 OR #6 OR #7) AND (#8 OR #9 OR #10), and a manual search was carried out to retrieve other articles that had not been identified via the initial search strategy. Publication date was not considered an exclusion criterion for the purposes of this review.

Study selection

Two authors independently screened the resulting articles for their methodology and appropriateness for inclusion. Non-controlled studies were selected for quality appraisal according to the National Institute for Health and Care Excellence (NICE) guidelines checklist, in which a total score of 0–3 indicates poor quality; between 4 and 6, fair quality; and ≥7, good quality (42). In controlled studies, quality appraisal was conducted according to the Newcastle-Ottawa Scale (NOS), which relies on a 9-star system whereby scores of 0–3, 4–6 and 7–9 are considered poor, moderate and good quality, respectively (43). Consensus discussion was used to resolve disagreements between reviewers.

Data collection process and data items

The title and abstract of each paper were firstly assessed by two independent authors for language suitability and subject matter relevance, and the studies thereby selected were assessed in terms of their appropriateness for inclusion and the quality of the method (Figure 1). The first author, year of publication, sample size and age, mean body mass index (BMI) at baseline and discharge, duration of follow-up, percentage of patients who achieved ROM from the entire sample, body composition assessment method, mean duration to achieve ROM, and mean %BF at baseline and discharge of those studies passing both rounds of screening are shown in Table 1.

Data synthesis

All the studies that met the inclusion criteria have been presented as a narrative synthesis (44). Moreover, a meta-analysis was conducted where possible using Review Manager 5 software (RevMan 5.3), developed by and for the Cochrane collaboration (45).

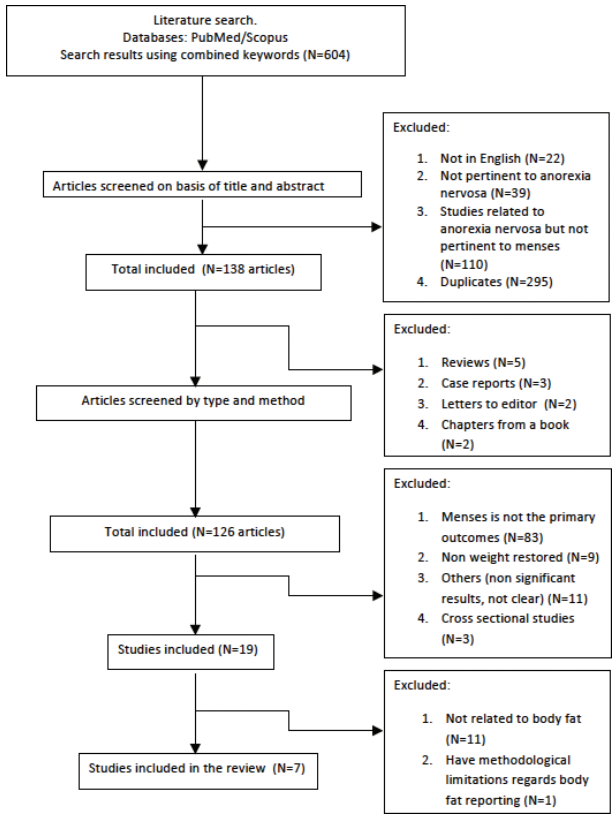

FIG 1. Flow chart summarising the study selection procedure.

RESULTS

The initial search retrieved 604 papers. After the first round of screening (titles and abstracts), 466 papers were excluded on the following grounds: 22 were not in English; 39 had no bearing on anorexia nervosa; 110 dealt with anorexia nervosa but did not consider menstrual status; and 295 were considered duplicates. The second round of screening excluded review articles (n = 5), clinical case reports (n = 3), chapters from books (n = 2) and Letters to the Editor (n = 2). Of the remaining 126 articles dealing with anorexia nervosa and menstrual cycle status, a further 106 papers were excluded on the following grounds: ROM was not the primary outcome (n = 83); cross-sectional designs (n = 3); incomplete weight restoration in patients (n = 9); or other factors (i.e. results were non-significant, not clear or not accessible) (n = 11). Finally, 12 studies were excluded on the grounds that they related to anorexia nervosa and ROM but were not related to body fat, or because the information regarding the latter was not clearly reported. Thus, at the end of the screening process, only seven articles were available for systematic review, narrative and meta-analysis (Figure 1).

According to the NICE checklist, the non-controlled studies (n = 5) were of good quality (mean score 6 points) (Table 2), while the NOS checklist indicated that controlled studies (n = 2) were of high quality (mean score 7 points) (Table 3).

In 1997, Golden et al. (35) conducted a cohort study of a 2-year follow-up and assessed %BF by means of skinfold measurements in a sample of 100 patients with anorexia nervosa aged between 12 and 24 years. Sixty-nine patients remained in the study, and 47 of these had resumed their menstrual cycle in the first year (68%); 56 out of 59 remained menstrual after 2 years (95%). The BMI changed over a mean of 9.4 ± 8.2 months from 16.9 ± 1.6 kg/m^2 to 19.2 ± 1.8 kg/m^2, and %BF increased from 17.2 ± 3.8% to 20.6 ± 3.6% in the patients who resumed their menstrual cycle. In this study, the authors found no significant difference in mean %BF between patients who resumed their menstrual cycle when compared to those who did not (20.6 ± 3.6% vs. 19.5 + 5.1%; p = 0.43).

In 2006, Misra et al. (46) assessed %BF by means of DXA in 33 patients with anorexia nervosa and 33 controls aged between 12 and 18 years. Fifty-eight patients remained in the study (29 patients; 29 controls) and 19 out of the 29 patients resumed their menstrual cycle after recovery within a time window of 6 months (65.5%). BMI changed over 1 year from 16.8 ± 1.2 kg/m^2 to 20.0 ± 2.1 kg/m^2, and %BF increased from 19.2 ± 5.4% to 25.5 ± 4.8% in patients who resumed their menstrual cycle. The authors found a significant difference in mean

TABLE 1. Studies included in the systematic review.

Study	Sample		Age (years)		BMI (kg/m²)		Follow-up	Percentage ROM	Body composition method	Duration to ROM	ROM and %BF	%BF	
	Baseline	Completers	Mean	Range	Admission	Discharge						Admission	Discharge
Golden et al. 1997 (Cohort)	100	59	16.9 ± 2.8	12–24	16.9 ± 1.6	19.2 ± 1.8	2 years	At year 1: 68% ROM (47/69) At year 2: 95% remained menstruating (56/59)	Skinfold thickness	Mean 9.4 ± 8.2 months	No	17.2 ± 3.8	20.6 ± 3.6
Misra et al. 2006 (Prospective)	66 (33 AN, 33 Controls)	58 (29 AN, 29 Controls) and8 no available data	16.1 ± 1.5	12–18	16.8 ± 1.2	20.0 ± 2.1	1 year	19/29 (33–4 no data = 29) yielding 65.5% ROM	DXA	6 months	Yes	19.2 ± 5.4	25.5 ± 4.8
Arimura et al. 2010 (Prospective)	32 (20 AN, 12 Controls)	32	19.2 ± 6.2		13.1 ± 1.4	17.8 ± 0.9	40–225 days	9/20 ROM yielding 45%	DXA	50 ± 33 days after reaching 85% of SBW	Unclear	9.9 ± 1.1	24.4 ± 4.2
Pitts et al. 2013 (Prospective)	37	29	18 ± 3.1	13–27	17.7 ± 1.4	20	18 months	22/29 ROM yielding 76%	DXA	Range 3–18 months	Yes	18.0 ± 5.0	23
El Ghoch et al. 2016 (Cohort)	54	54	25.7 ± 8.0	18–45	15.6 ± 1.7	19.9 ± 0.8	1 year	19/54 ROM yielding 35%	DXA	1 year	Yes	Not available	27.7 ± 5.7
Karountzos et al. 2017 (Prospective)	60	60	16.83 ± 0.75	15–18	16.95 ± 0.64	19.58 ± 0.62	8–26 months	35/60 ROM yielding 58%	DXA	Mean 13.34 ± 2.87Range 8–24	Yes	17.65 ± 0.82	22.57 ± 2.39
Latzer et al. 2018 (Prospective)	62	62	15.8 ± 1.4	10–18	17.3 ± 1.6	20.2 ± 1.1	2012–2017	42/62 ROM yielding 68%	BIA	1.9 ± 0.9 months after reaching the target weight (7.2 ± 3.2 months hospital stay)	Yes	19.8 ± 5.3	24.6 ± 3.5

BMI: body mass index; ROM: resumption of menses; %BF: body fat percentage; AN: anorexia nervosa; SBW: standard body weight; DXA: dual-energy X-ray absorptiometry; BIA: bioimpedance analyser.

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TABLE 2. Quality assessment of non-controlled studies.

	Golden 1997	Karountzos 2017	Pitts 2013	El Ghoch 2016	Latzer 2018
Case series collected in more than one centre, i.e., multi-centre study	0	0	0	0	0
Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1
Are the inclusion and exclusion criteria (case definition) clearly reported?	1	1	1	1	1
Is there a clear definition of the outcomes reported?	1	0	0	1	1
Were data collected prospectively?	1	1	1	1	1
Is there an explicit statement that patients were recruited consecutively?	1	0	0	1	0
Are the main findings of the study clearly described?	1	1	1	1	1
Are outcomes stratified? (e.g. by disease stage, abnormal test results and patient characteristics)	1	1	1	1	1
Total score	7	5	5	7	6

NICE guidelines checklist: Yes = 1, No (not reported, not available) = 0; Total score, 8; ≤3, poor quality; 4–6, fair quality; ≥7, good quality.

TABLE 3. Quality assessment of controlled studies.

Authors	Arimura 2010	Misra 2006
Selection		
Represents cases with independent validation	1	1
Cases are consecutive or obviously representative	0	1
Controls are from community	1	1
Controls have no history of anorexia nervosa	1	1
Comparability		
Controls are comparable for the most important factors.	1	1
Control for any additional factor	0	0
Ascertainment of exposure		
Secured record or structured interview where blind to case/control status	1	1
Same method of ascertainment for cases and controls	1	1
Cases and controls have completed follow-up	1	0
Total score	7	7

Newcastle-Ottawa Scale (NOS) for longitudinal case control studies. Yes = 1, No (not reported, not available) = 0; Studies with scores of 0–3, 4–6, 7–9 were considered as low, moderate and high quality, respectively.

%BF between patients who resumed their menstrual cycle when compared to those who did not (25.5 ± 4.8% vs. 18.1 ± 3.7%; $p < 0.0001$) and identified %BF after weight restoration as an independent predictor of resumption of the menstrual cycle. Specifically, they found that an odds ratio of

resuming menses for %BF above 24.4%, compared with %BF below 18.1%, was 15.5 (p = 0.003).

In 2010, Arimura et al. (47) assessed %BF by means of DXA in 20 patients with anorexia nervosa and 12 controls aged 19.2 ± 6.2 years. Nine out of the 20 patients (45%) resumed their menstrual cycle after recovery within a time window of 50 ± 33 days after reaching 85% of the standard body weight. BMI changed over 1 year from 13.1 ± 1.4 kg/m^2 to 17.8 ± 0.9 kg/m^2, and %BF increased from 9.9 ± 1.1% to 24.4 ± 4.2% in subjects who resumed their menstrual cycle. The authors concluded that %BF was not different between patients who resumed menstruation after recovery of body weight and those who did not (24.4 ± 4.2% vs. 22.2 ± 3.0%; p > 0.05).

In 2013, Pitts et al. (48) assessed %BF by means of DXA in 37 patients with anorexia nervosa aged between 13 and 27 years. Twenty-nine patients remained in the study and 22 out of the 29 patients (76%) resumed their menstrual cycle after recovery within a time window of 3–18 months. BMI changed over 1 year from 17.7 kg/m^2 to 20 kg/m^2, and %BF increased from 18.0 ± 5.0% to 23.1% in patients who resumed their menstrual cycle. The authors found a difference in mean %BF between patients who resumed menstrual cycle when compared to those who did not (23.1% vs. 18.1%; p < 0.05), and that a higher %BF was associated with ROM (odds ratio = 1.19, 95% CI = 1.06–1.33, p < 0.01), indicating that one unit of change in the %BF increases the odds of menstruation resuming by 19%.

In a 2016 cohort study, El Ghoch et al. (49) assessed %BF using DXA in patients with anorexia nervosa aged 18–45 years over a 1-year follow-up after inpatient discharge. The study included 54 patients, 19 of whom had resumed menstruation at the 1-year follow-up (35%). BMI changed over 1 year from 15.6 ± 1.7 kg/m^2 to 19.9 ± 0.8 kg/m^2, and %BF increased to 27.7 ± 5.7% in subjects who resumed their menstrual cycle. The authors found a difference in mean %BF between patients who resumed their menstrual cycle when compared to those who did not (27.7 ± 5.7% vs. 23.7 ± 5.8%; p = 0.019) and an association between %BF and ROM (odds ratio = 1.14, 95% CI = 1.001–1.303, p = 0.049), indicating that a change in the total body fat percentage of one unit increases the odds of menstruation resuming by 14%.

In 2017, Karountzos et al. (50) assessed %BF by means of DXA in 60 patients with anorexia nervosa aged 15–18 years. Thirty-five out of the 60 patients (58%) resumed their menstrual cycle after recovery within a time range of 8–26 months. BMI changed over a mean of 13.34 ± 2.87 months from 16.95 ± 0.64 kg/m^2 to 19.58 ± 0.62 kg/m^2 and %BF increased from 17.65 ± 0.82% to 22.57 ± 2.39% in patients who resumed their menstrual cycle. The authors found a difference in mean %BF between patients who resumed their menstrual cycle when compared to those who did not (22.57 ± 2.39% vs. 18.96 ± 0.8%; p < 0.05).

In 2018 longitudinal study over a period of 15.8 ± 1.4 months, Latzer et al. (51) enrolled 62 adolescent patients with anorexia nervosa aged between 10 and 18 years, 42 of whom resumed their menstrual cycles (68%). BMI changed from 17.3 kg/m^2 to 20.2 kg/m^2 and %BF increased from 19.8 ± 5.3% to 24.6 ± 3.5% in patients who resumed their menstrual cycle. The authors found an association between %BF and resumption of the menstrual cycle, establishing a cut-off point of 21.2% of total body fat.

Meta-analysis

The variable of interest for the meta-analysis was the mean difference in %BF after weight restoration in patients who had a ROM, compared to those that did not. Figure 2 shows the effect sizes and 95% CI of the six studies included in the meta-analysis. The random effect model standardised mean difference in %BF between the two (resumed vs. non-resumed menses) groups was statistically significant (SMD: 3.74, 95%

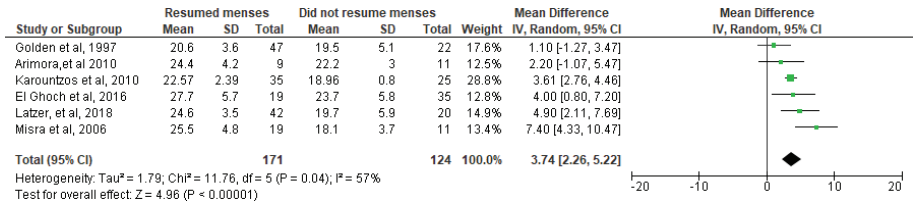

FIG 2. Forest plot of the meta-analysis for difference in mean %BF between resumed and non-resumed menstruation groups.

CI: 2.26–5.22). Thus, the hypothesis that the mean of the true effect is different from zero was confirmed ($p < 0.05$). Heterogeneity analysis on the six included studies revealed $I^2 = 57\%$. According to Cochrane handbook, heterogeneity is inevitable, and the chi-squared test might be of low power with small number of studies with small sample size (52). However, the confidence intervals in the Forest plot (Figure 2) are quite overlapping which indicate acceptable variability, and hence, this allows for considering $I^2 = 57\%$ as moderate heterogeneity (52). Each study is indicated by first author and year, and the individual effect sizes are indicated as mean difference with 95% CI. The overall summary effect size of the meta-analysis is identified as standardised mean difference with 95% CI and noted as a diamond to the right of the line of null effect.

DISCUSSION

The aim of this systematic review was to provide benchmark data on the association between ROM and %BF in weight-restored patients with anorexia nervosa after treatment. Only seven studies, comprising a total of 366 adolescent and young adult females with anorexia nervosa and age range between 12 and 45 years, were reviewed. These studies were objectively judged to be of good and high quality and are summarised to answer the following clinical questions:

Is a higher %BF associated with ROM in patients with anorexia nervosa?

Five studies found a higher mean %BF in patients who had resumed their menses when compared to those who had not (46, 48–51) and this was confirmed by the meta-analysis. The first of the two studies that did not find a significant difference in the mean %BF between the group who resumed menstruation and the group who did not is that conducted by Arimura et al. (47) who assessed the ROM immediately after weight recovery, rather than after a follow-up period. The second study was conducted by Golden et al. (35) and also reported no significant difference in %BF after weight restoration between patients who resumed menstruation and those who continued to have amenorrhoea at follow-up. However, the protocol used relied on skinfold thickness measurements to estimate %BF, which is a procedure not currently considered to be a valid alternative to DXA in patients with anorexia nervosa (53). All in all, stronger evidence is available, indicating that patients with anorexia nervosa after weight restoration who experience a ROM have a higher mean %BF than those who continue to have amenorrhoea.

Is %BF an independent predictor of the ROM in patients with anorexia nervosa?

Three studies confirm that %BF is an independent predictor of ROM: El Ghoch et al. (46) and Pitts et al. (45) separately showed that even a very small increase in total %BF (approximately 1%) dramatically (and independently) increases the probability of ROM by approximately 14% and 19%, respectively, during the 1–1.5 years after weight restoration, thereby highlighting the importance of this variable (48, 49). Similarly, Misra et al. showed the probability of ROM to

increase by 15 times after weight restoration, in patients with %BF ≥ 24.2% when compared to those with %BF ≤ 18.1% (46). However, we are not in the position to exclude the role of other factors as low dietary intake, stress, excessive exercising and seasonality that were found to predict ROM in this population as such, since body composition assessment has not been conducted in these studies (38, 54).

Is there a cut-off for %BF associated with the ROM in patients with anorexia nervosa?

In the seven studies included in our systematic review, all subgroups resuming menses after weight restoration had a mean %BF > 20.5%. Even if it is incorrect to consider this as a cut-off, we nonetheless saw that the minimum mean %BF of the subgroup that resumed menses among the seven included studies was that in the study conducted by Golden et al. and was 20.6 ± 3.6% (35). Only recently, Latzer et al., through receiver operating characteristic (ROC) analysis, identified a cut-off point of ≈21% as the %BF identified by BIA as being necessary for the ROM in adolescents with anorexia nervosa (51). To underline that this cut-off (%BF ≈21%) is close to that suggested by earlier study conducted in the general population on maintenance of a regular menses and reproductive ability at %BF around 22% (55).

Clinical implications

Our findings have two main clinical implications. Firstly, it is important to discuss the association between %BF and the ROM with patients suffering from anorexia nervosa and to emphasise that restoring an adequate amount of body fat is vital to facilitate the ROM. Secondly, clinicians should be aware of several strategies regarding %BF, that is, aiming to achieve a small increase in total body fat percentage (≈1%), or consideration of cut-offs for %BF (>20%), which can help in the ROM before considering other strategies (i.e., menstrual induction medication). Indeed, this accords with the recommendations of experts who underline the importance of nutritional intervention and weight gain as the cornerstone strategy for ROM in patients with anorexia nervosa; such recommendations also clearly indicate that hormone and oral contraceptive therapy should not be prescribed for young women with amenorrhoea and concurrent eating disorders (15). However, this recommendation needs to be discussed with caution, since patients with anorexia nervosa are characterised by intense fear of gaining weight or becoming fat, undue influence of body weight or shape on medical consequences (i.e. amenorrhoea and osteoporosis).

Strengths and limitations

Although (to the best of our knowledge) this systematic review and meta-analysis is the first to assess the association between %BF and ROM – an important outcome in the treatment of anorexia nervosa – because of certain limitations, our findings should be interpreted with caution. Foremost, the small number of studies included in the systematic review and meta-analysis and, in particular, a small sample size was a common feature of most of the studies reviewed and even fewer participants completed the follow-up assessment. Secondly, some studies assessed body composition by means of non-gold-standard measures in patients with anorexia nervosa (i.e. skinfold thickness), so the estimation of %BF is highly arguable (53). Thirdly, %BF is not the only factor associated with ROM in patients with anorexia nervosa. For instance, it has been suggested that low dietary intake, psychological distress and excessive exercising play a role in the maintenance of amenorrhoea despite weight restoration and should be taken into consideration (56). Fourthly, the time frame in which a patient with anorexia nervosa is expected to resume menstruation is unclear and needs to be understood more fully. Finally, the fact that only studies published in English were

included presents a limitation too, in particular considering the small number of studies retrieved for meta-analysis.

CONCLUSIONS

A higher %BF is associated with the ROM in weight-restored adolescent and young adult females with anorexia nervosa. Therefore, its assessment is useful in a clinical setting, especially after complete weight restoration, to predict ROM. However, clinicians should keep in mind the existence of other factors (i.e., dietary intake, excessive physical activity, time and psychological distress) whose roles need to be better clarified.

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CONFLICT-OF-INTEREST STATEMENT

The authors have no conflict of interest to declare.

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