Original Article
Male reproductive health and infertility

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Aug 21, 2024
https://doi.org/10.5534/wjmh.240091

The World Journal of MEN's HEALTH

Weight Loss as Therapeutic Option to Restore Fertility in Obese Men: A Meta-Analytic Study

Daniele Santi[1,2], Carla Greco[1,2], Arcangelo Barbonetti[3], Manuela Simoni[1,2], Mario Maggi[4], Giovanni Corona[5]

[1]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, [2]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, [3]Andrology Unit, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, [4]Endocrinology Unit, Mario Serio Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, [5]Endocrinology Unit, Azienda AUSL, Bologna, Italy

Purpose: Weight loss has been shown to significantly elevate testosterone serum levels, though the impact on semen analysis parameters and fertility remains incompletely understood. The objective of this study was to examine the influence of body weight loss on semen parameters in obese men.

Materials and Methods: A meta-analysis was performed that included clinical trials in which a semen analysis before and after weight loss was evaluated. All strategies potentially available for weight loss were considered eligible. The primary outcome was the comparison of conventional semen analysis parameters before and after weight loss.

Results: Twelve studies were considered including 345 subjects (mean age 37.6±7.9 years; mean baseline body mass index 45.4±6.0 kg/m^2). Weight loss resulted in a significant increase of sperm concentration (effect size 0.495, standard error 0.251 [0.003, 0.986], p=0.049) and progressive motility (effect size 0.567, standard error 0.372 [0.370, 0.764], p<0.001). Moreover, a significant decrease of sperm DNA fragmentation index after weight loss (effect size -0.689, standard error 0.278 [-1.123, -0.255], p=0.002) was observed.

Conclusions: This meta-analytic analysis confirmed that body weight loss may improve qualitative and quantitative sperm characteristics providing evidence for suggesting weight loss to male partners with obesity and semen analysis alteration in couples attempting conception.

Keywords: Infertility, male; Obesity; Semen analysis; Therapy; Weight loss

INTRODUCTION

The unfavorable effect of overweight and obesity on female fertility is well documented either when spontaneous [1-3] or when assisted reproductive-derived pregnancies have been considered [4,5]. Accordingly, obesity has been reported as the most important factor related to anovulatory infertility [6]. In line with this evidence, guidelines from the European Society of Human Reproduction and Embryology strongly recommend a healthy diet and regular exercise, supported by behavioral therapy in overweight and obese women

Received: Apr 11, 2024 **Accepted:** May 17, 2024 **Published online** Aug 21, 2024
Correspondence to: Daniele Santi https://orcid.org/0000-0001-6607-7105
Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, Via Giardini 1355, Modena 41126, Italy.
Tel: +39-0590961816, **Fax:** +39-0593961322, **E-mail:** daniele.santi@unimore.it

with unexpected infertility [7]. Despite this evidence a clear body mass index (BMI) threshold to suggest in favor or against assisted reproduction still does not exist, although several programs and/or national health systems regulations suggest losing weight before starting these procedures [8].

Obesity plays a well-documented negative impact on male sexual function due to its association with vascular disease and age-related testosterone (T) declined [9-11]. Despite this evidence, the role of obesity on male reproduction has not been completely clarified. Available meta-analyses produced conflicting results [12,13]. One of the main limitations of these studies deals with the high heterogeneity derived from the use of different criteria for semen analysis [14]. In order to overcome these pitfalls and obtain a more homogenous population, we recently performed a new systematic review of the literature, including only those papers using WHO 2010 criteria for semen analysis [14]. Our data indeed show, for the first time, a negative impact of body weight excess on male fertility in terms of semen analysis [14]. In addition, in this analysis, we highlighted, for the first time, that just a slight excess of body weight is associated with worse semen parameters, at least when total sperm count and progressive sperm motility were considered.

Regardless of the aforementioned evidence, the real impact of weight loss on male fertility and semen analysis parameters is not completely clarified so far. The aim of this study was to perform a systematic review and meta-analysis of available trials on the effect of body weight loss on semen parameters in obese men, considering all potential available therapeutic approaches.

A large body of evidence has clarified that the negative consequences of obesity on male fertility seem to be potentially reversible since weight loss could restore physiological testicular function. Accordingly, several studies have documented that weight loss significantly improves sexual function [15-17], and T circulating levels [18] in men. Available guidelines on age-related T deficiency (also called late onset hypogonadism) strongly recommend weight management strategies based on lifestyle modifications including both regular physical exercise and well-balanced diet. In this context, a lifestyle change in individuals with obesity must reverse the chronic uncoupling of energy intake and energy expenditure that leads to excess weight [19]. Alongside nutritional treatment, additional options include medications that improve underlying mediators of obesity-related complications, such as treatment with glucagon-like peptide-1 receptor (GLP1R) agonists. These drugs are more recently introduced in clinical practice, with interesting evidence about their efficacy on weight loss [20].

This study was designed to evaluate the influence of body weight loss on semen parameters in obese men.

MATERIALS AND METHODS

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and a priori registered in the International prospective register of systematic reviews (PROSPERO) database (CRD42023434703).

1. Search strategy

The literature search was performed using the following search ((“weight loss”[All Fields] OR “diet”[All Fields] OR “bariatric surgery”[All Fields] OR “metabolic surgery”[All Fields]) AND “semen analysis”[All Fields]) OR “male fertility”[All Fields]. Three datasets were queried, *i.e.* Medline, Embase, and Cochrane library.

The literature search was performed until July 31st, 2023. Only English-language articles including human participants were considered.

The identification of relevant studies was performed independently by two authors (D.S., C.G.), and conflicts were resolved a third investigator (G.C.). The Endnote software (Version X9.2; Clarivate Analytics (US) LLC) was used for literature management and duplication filtration and removal.

2. Study selection

The following inclusion criteria were considered: (1) prospective and retrospective design, (2) in which men (3) underwent any strategy available for weight loss, and (4) performed a semen analysis before and after weight loss. Case reports were excluded.

All strategies potentially available for weight loss were considered eligible, such as diet, bariatric-metabolic surgery, and drugs assumption.

3. Outcome and quality assessment

The primary outcome was the comparison of semen parameters, obtained by conventional semen analysis

before and after weight loss. Secondary outcomes included effect of weight loss on sperm DNA fragmentation, when available. The therapeutic strategies used to obtain the weight loss were considered as covariates to adjust analysis. Basal BMI and T serum levels, patients' age, months of follow-up and the change of BMI during follow up were considered as covariates for secondary analyses.

Semen analysis is a complex parameter, and its accurate performance is essential for a thorough understanding of male fertility potential [21]. However, due to the constraints of our study design, we were unable to comprehensively assess the quality of semen analysis conducted in each original work. Therefore, we evaluated whether the semen analysis reported in each study adhered to the WHO manual, noting the manual edition number when available, as an indicator of compliance. Moreover, given that a thorough basic semen examination is fundamental for assessing potential male fertility, the evaluation of semen analysis quality was supplemented by considering the availability of other pertinent andrological sources of information. These may include history collection, physical examination, endocrine assessment, and any additional tests deemed necessary [22].

The quality of trials included was assessed using the Cochrane criteria [23].

4. Statistical analysis

Each study included was considered according to the follow-up duration. If a study considered different follow up after weight loss (*i.e.*, 3, 6, and 12 months), each of them were considered as separated trial.

Heterogeneity in semen parameters was assessed using I^2 statistics. When low heterogeneity was detected (*i.e.* I^2 <60%), the fixed-effect model was applied. Otherwise, the random effect model was applied, because the validity of heterogeneity tests can be limited with a small number of component studies. In addition, in order to avoid possible limitations related to the use of different criteria for semen parameter analysis, standardized means were considered [24].

We used funnel plots and the Begg adjusted rank correlation test to estimate possible publication or disclosure bias [23]. However, undetected biases may still be present because these tests have low statistical power when the number of trials is small.

Continuous data were compared considering the examination before and after weight loss. All semen analysis parameters extracted were analyzed separately.

Meta-regression analyses were performed to test the effect of different covariates on the differences between pre- and post-weight loss. The meta-regression analysis result was synthesized reporting both slope (S) and intercept (I) with appropriate lower and upper limits.

All data were calculated using Comprehensive Meta-analysis Version 2, Biostat.

RESULTS

Out of 8,176 articles only 12 studies were eventually included in the analysis [25-36]. Among the 12 studies included, each therapeutic approach to obtain weight loss was analyzed separately. Likewise, if semen analysis was assessed at various follow-up durations, each time-frame interval was treated as a distinct consideration. Consequently, several studies reported different groups, that have been analyzed separately, resulting in a total of 18 trials (Supplement Fig. 1).

The selected studies included 345 subjects with a mean age 37.6±7.9 years. The mean baseline BMI was 45.4±6.0 kg/m^2, showing a significant decrease during the study (average BMI reduction -6.4±0.1 kg/m^2, lower limit -6.8, upper limit -6.0, p<0.001). Studies characteristics are reported in Table 1.

Eleven studies reported the WHO manual edition used to perform semen analysis (Table 1), describing the methodology applied and the adherence to the guidelines. On the contrary, one study did not reported the WHO manual edition used to perform semen analysis (Table 1). However, in this study [27], the semen analysis evaluation was completed by a wide andrological work-up [21], useful to improve the accuracy of the analysis performed.

1. Sperm concentration

Fifteen trials reported data on sperm concentration before and after weight loss. Thirteen trials considered weight loss after bariatric surgery, one after diet and one after GLP1R agonist liraglutide administration. The I^2 was 87.8, p<0.001 suggesting high heterogeneity among the included studies. The funnel plot and Begg adjusted rank correlation test (Kendall's τ: 0.028; p=0.441) suggested no publication bias. Weight loss led

https://doi.org/10.5534/wjmh.240091

Table 1. Characteristics of studies included in the meta-analysis

First author	Year	Study type	Intervention	Patients number	Age (y)	Inclusion criteria	Control group	Length of follow up (mo)	WHO edition for semen analysis	BMI change after treatment (kg/m^2)
Reis [25]	2012	Interventional	Bariatric-metabolic	20	39.3±11.3	NA	Yes, 10 subjects not undergoing surgery	24	WHO 2010	-12.1±5.0
Faure [26]	2014	Observational	Diet	6	31.8±6.3	Abdominal fat >4 as measured by bioimpedance	No	4.6	WHO 2010	-1.2±6.5
Legro [27]	2015	Observational	Bariatric-metabolic	6	35.6±9.5	BMI ≥35.0 kg/m^2 and presence of comorbidities or BMI ≥40.0 kg/m^2 and aged 20–50 years	No	3, 6, and 12	NR	-5.0±7.0
El Bardisi [28]	2016	Observational	Bariatric-metabolic	46	37.0±6.0	National Institute of Health (NIH) criteria indicating weight loss surgery	No	12	WHO 2010	-22.89 (median)
Samavat [29]	2017	Observational	Bariatric-metabolic	23	45.8±7.4	BMI >40 kg/m^2	Yes, 8 subjects not undergoing surgery	6	WHO 2010	-11.1±5.1
Calderón [30]	2019	Observational	Bariatric-metabolic	15	40.0±8.0	BMI >35 kg/m^2	No	24	WHO 2010	-18.0±8.5
Carette [31]	2019	Interventional	Bariatric-metabolic	46	38.9±7.9	BMI ≥40 kg/m^2 or 35 kg/m^2 and, at least one obesity comorbidity	No	12	WHO 2010	12.7 (min, -11.6; max, -13.8)
Wood [32]	2020	Interventional	Bariatric-metabolic	18	39.0±12.9	BMI ≥35.0 kg/m^2 and presence of comorbidities or BMI ≥40.0 kg/m^2, and aged 20–50 years	Yes, 14 subjects not undergoing surgery	6	WHO 2010	11.6 (median)
Fariello [33]	2021	Interventional	Bariatric-metabolic	15	NR	BMI ≥35.0 kg/m^2 and presence of comorbidities or BMI ≥40.0 kg/m^2, and aged 20–50 years	No	3, 6, 9, and 12	WHO 2010	-7.6±1.4
Velotti [34]	2021	Observational	Bariatric-metabolic	35	36.4±5.2	Obesity and idiopathic infertility	No	6	WHO 2010	-17.7±6.0
Andersen [36]	2022	Interventional	Diet and GLP1RA	37	41.1±9.7	BMI 32–43 kg/m^2	No	2	WHO 2010	-5.0±2.8
La Vignera [35]	2023	Interventional	GLP1RA	35	26.0±6.0	BMI >30 kg/m^2	Yes, 40 subjects treated with testosterone	2	WHO 2010	-6.0±2.5

Values are presented as mean±standard deviation.
NA: not applicable, NR: not reported, BMI: body mass index.

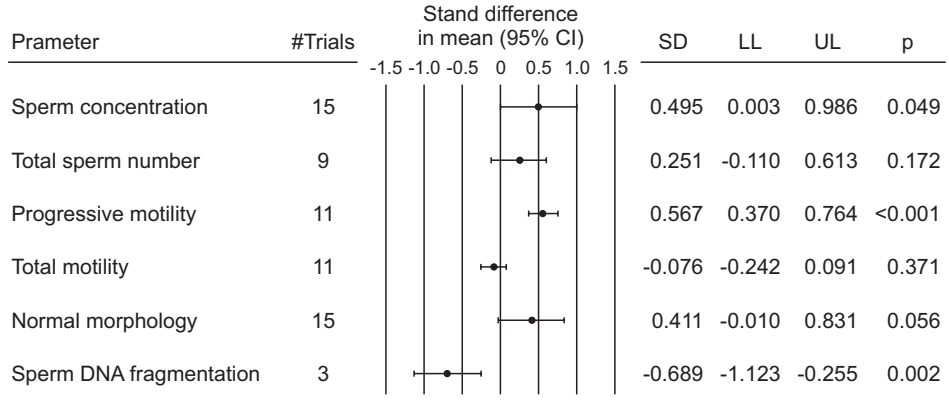

Fig. 1. Comprehensive standardized mean difference in each parameter evaluated after weight loss. CI: confidence interval, LL: lower limit, UL: upper limit.

Table 2. Meta-regression analyses results

	All studies	Studies applying bariatric-metabolic surgery
Sperm concentration		
BMI at enrollment	S=-0.015 [-0.032, 0.002] p=0.077, I=1.073 [0.207, 1.939], p=0.015	S=-0.015 [-0.032, 0.002] p=0.077, I=1.073 [0.207, 1.939], p=0.015
BMI reduction	S=0.026 [-0.001, 0.023] p=0.063, I=0.648 [0.231, 1.065], p=0.002	S=0.055 [0.019, 0.092] p=0.002, I=1.180 [0.308, 0.576], p<0.001
Testosterone serum levels at baseline	S=-0.023 [-0.736, 0.039] p=0.462, I=0.491 [-0.294, 1.276], p=0.220	S=-0.023 [-0.736, 0.039] p=0.462, I=0.491 [-0.294, 1.276], p=0.220
Follow-up length	S=-0.004 [-0.033, 0.026] p=0.794, I=0.272 [-0.111, 0.655], p=0.163	S=-0.004 [-0.033, 0.026] p=0.794, I=0.272 [-0.111, 0.655], p=0.163
Patients' age	S=0.063 [-0.010, 0.135] p=0.092, I=-2.051 [-4.877, 0.776], p=0.155	S=0.063 [-0.010, 0.135] p=0.092, I=-2.051 [-4.877, 0.776], p=0.155
Progressive sperm motility		
BMI at enrollment	S=0.023 [-0.131, 0.177] p=0.770, I=-0.685 [-7.781, 6.410], p=0.850	S=-0.018 [-0.035, 0.001] p=0.245, I=1.336 [0.427, 2.244], p=0.074
BMI reduction	S=0.038 [-0.027, 0.043] p=0.641, I=0.596 [1.164, 2.054], p=0.039	S=0.038 [0.001, 0.077] p=0.033, I=0.887 [0.253, 1.521], p<0.001
Testosterone serum levels at baseline	S=-0.049 [-0.124, 0.025] p=0.193, I=0.868 [-0.012, 1.749], p=0.053	S=-0.049 [-0.124, 0.025] p=0.193, I=0.868 [-0.012, 1.749], p=0.053
Follow-up length	S=-0.023 [-0.070, 0.022] p=0.318, I=0.721 [0.169, 1.273], p=0.010	S=-0.023 [-0.070, 0.022] p=0.318, I=0.721 [0.169, 1.273], p=0.010
Patients' age	S=-0.045 [-0.117, 0.028] p=0.227, I=2.054 [-0.782, 4.891], p=0.156	S=-0.045 [-0.117, 0.028] p=0.227, I=2.054 [-0.782, 4.891], p=0.156

Values are presented as standard error.
BMI: body mass index, S: slope, I: intercept.

to a substantial increase in sperm concentration, reflecting an overall improvement of approximately 7.6 million/mL (Fig. 1, Supplement Fig. 2A).

The subgroup analysis performed considering the treatment used confirmed the significant sperm concentration increase, when only bariatric-metabolic surgery was considered (I^2=47.6, p=0.028, effect size 0.310, standard error 0.294 [0.124, 0.496], p=0.001) (Supplement Fig. 2B).

Meta-regression analysis performed in the whole sample showed a trend towards a sperm concentration increase as a function of BMI reduction after weight loss (Table 2, Supplement Fig. 3). In order to avoid potential sources of bias, the meta-regression analysis was repeated considering only studies in which the bariatric-metabolic surgery was applied to obtain weight reduction, confirming the direct significant correlation between sperm concentration increase and BMI reduction obtained (Table 2, Supplement Fig. 3).

Other meta-regression analyses showed that the sperm concentration increase after weight reduction was independent to BMI at enrollment, basal total T

levels, follow up, and patients' age (Table 2). The same results were confirmed when only studies on bariatric-metabolic surgery were considered (data not shown).

2. Total sperm number

Nine trials reported the mean total sperm count before and after weight loss, with high heterogeneity (I^2=68.6, p=0.001). The funnel plot and Begg adjusted rank correlation test (Kendall's τ: 0.278; p=0.149) suggested no publication bias. No significant differences between pre- and post- weight loss were observed (Fig. 1, Supplement Fig. 4).

Similarly, the total sperm count did not change after weight loss, when only trials including bariatric surgery were considered (effect size 0.251, standard error 0.232 [-0.110, 0.613], p=0.172).

3. Progressive sperm motility

Eleven trials evaluated progressive sperm motility before and after weight loss. The I^2 was elevated (92.2; p<0.001). The funnel plot and Begg adjusted rank correlation test (Kendall's τ: 0.038; p=0.051) suggested no publication bias. A significant sperm progressive motility increase after weight loss was documented when the whole population was considered (Fig. 1, Supplement Fig. 5A).

Similarly to what observed for sperm concentration, sperm progressive motility increase after weight loss was confirmed when only studies related to bariatric-metabolic surgery were analyzed (Supplement Fig. 5B). In line with these data meta-regression analysis considering only trials evaluating bariatric-metabolic surgery, showed a direct relationship between progressive motility increase and BMI reduction (Supplement Fig. 6).

Conversely, the sperm progressive motility increase after weight reduction was not related to basal BMI, total T basal levels, follow up duration, and patients' age (Table 2). The same results were confirmed when only studies on bariatric-metabolic surgery were considered (data not shown).

4. Total motility

Eleven trials reported the percentage of total motility before and after weight loss, with a reduced heterogeneity (I^2=0, p=0.773). The funnel plot and Begg adjusted rank correlation test (Kendall's τ: 0.236; p=0.156) suggested no publication bias. No significant difference in total sperm motility after weight loss was detected (Fig. 1, Supplement Fig. 7).

Similar results were observed by subgroup analysis, considering only trials applying bariatric-metabolic surgery (effect size -0.073, standard error 0.093 [-0.256, 0.109], p=0.431).

5. Normal sperm morphology

Fifteen trials reported sperm morphology, with a high heterogeneity (I^2=81.8, p<0.001). The funnel plot and Begg adjusted rank correlation test (Kendall's τ: 0.305; p=0.056) suggested no publication bias. No significant changes in sperm morphology after weight loss were seen (effect size 0.411, standard error 0.215 [-0.010, 0.831], p=0.056) (Fig. 1, Supplement Fig. 8).

Similarly, the lack of sperm normal morphology improvement after weight loss was confirmed by subgroup analysis, considering only trials applying bariatric-metabolic surgery (effect size 0.391, standard error 0.223 [-0.046, 0.828], p=0.079).

6. Sperm DNA fragmentation index

Three trials evaluated sperm DNA fragmentation index before and after weight loss with low heterogeneity (I^2=29.1, p=0.244). The funnel plot and Begg adjusted rank correlation test (Kendall's τ: -0.333; p=0.301) suggested no publication bias. Available data showed a significant decrease of DNA fragmentation after weight loss (Fig. 1, Supplement Fig. 9).

DISCUSSION

Here, we report the first comprehensive evidence supporting a putative role of weight loss among therapeutic strategies for male infertility management. Indeed, whether the impaired spermatogenesis is a common finding among obese men, weight reduction improves some of the most relevant semen parameters, such as sperm concentration, progressive motility and sperm DNA fragmentation. Thus, the weight loss improves semen characteristics, both quantitatively and qualitatively, and it should be considered as the first step in the clinical management of obese male patients with infertility.

Studies evaluating the relationship between weight loss and semen analysis mainly consider bariatric-metabolic surgery. Indeed, among 12 studies included in this meta-analysis, only three studies (25.0%) applied

a different approach, such as diet (2 studies) or GLP1R agonist (1 study) administration. However, irrespective of the therapeutic approach applied, we report an overall sperm concentration improvement of about 7.6 million/mL. This effect was not statistically significant when only studies applying diet were evaluated, but it is confirmed when either bariatric-metabolic surgery or GLP1R agonists were used. Moreover, this improvement is related to the extent of BMI reduction obtained, while no relationships are detected considering the baseline BMI or the duration of follow up. This result suggests that the greater the weight loss achieved is, the greater is the increase in sperm concentration. On the other side, our results suggest that the beneficial effect of weight loss on semen analysis does not depend to initial impairment of spermatogenesis, as we do not find any correlations with either baseline BMI or pre-treatment T levels which can reflect baseline hypothalamic-pituitary-gonadal axis impairment. Thus, we could speculate that the correlation between weight loss and semen analysis improvement depends mainly on the reduction of body weight. This effect should be carefully considered, as the patients included in the analysis exhibited a variable degree of obesity. Undoubtedly, the excess body weight at baseline could potentially influence the final results observed after intervention. However, which the pathophysiological mechanisms underlie this association is still not completely clarified. A large body of evidence documented that weight loss is associated with an improvement of circulating T levels with both central and peripheral mechanisms [37]. In particular, data derived from animal models have shown that decreasing visceral adiposity through physical exercise can ameliorate meta-inflammation at hypothalamus and testis level resulting in T production increase [38-40]. A quantitatively and qualitatively normal spermatogenesis requires high T concentration within the testis [41]. Thus, we could speculate that the sperm concentration improvement after weight loss could be related to the increased hormonal stimulation on spermatogenesis. To better understand this mechanism, we should consider the potential reasons behind the obesity-infertility connection. Indeed, the first mechanism is the expansion of adipose tissue, which could disrupt the hormonal balance, impairing normal testicular function. Second, an increased estrogen serum levels in men with obesity has been suggested, leading to a decrease in T production [42]. In an animal model, increased visceral adiposity was associated with a greater expression of estrogen receptors in the median hypothalamus [39,40]. Although this effect is still debated [43], the negative consequence on testicular function seems to be mediated by negative feedback, inhibiting the pulsatile gonadotropin-releasing hormone release [44]. Accordingly, limited evidence supports the role of SERM in improving T levels and sperm parameters in obese subjects [45-47]. Third, insulin resistance and hyperinsulinemia typical of obesity could lead to a reduction in sex-hormone-binding globulin (SHBG) serum levels which are needed for T transportation. In the presence of low SHBG levels, the increase of T bioavailable for aromatization in adipose tissue could occur [48]. Fourth, increased leptin secretion in obesity may also inhibit T production by the Leydig cells [49]. Fifth, adipose tissue produces inflammatory cytokines, which could disrupt normal testicular function, impairing both T production and sperm production and maturation [37,50]. Thus, while weight loss is known to restore normal T production, we cannot rule out other mechanisms behind the increase sperm quantity and quality here comprehensively detected. In particular, weight loss could be related to a reduction in both leptin and pro-inflammatory cytokines, which are known to be abundant in obese men. Evidence available so far are not sufficient to clearly discriminate among potential mechanisms relating weight loss and sperm quantity improvement.

Alongside sperm concentration, we highlight a significant improvement in sperm progressive motility following weight loss. The observed increase in progressive motility exhibits similar characteristics to those detected for sperm concentration. Consequently, we can speculate that weight loss directly influences both sperm quantity and quality. This is further supported by the significant decrease in the sperm DNA fragmentation index after weight loss. However, both total sperm count and total motility remain unaffected by weight loss, suggesting that these parameters may not be accurate variables for measuring the impact of weight loss on male fertility. The degree of improvement in sperm quality appears to be somewhat weaker than that observed in sperm concentration, at least from a statistical standpoint. This discrepancy could be attributed to the relatively low number of studies reporting on these parameters. Given these consider-

ations, future studies should thoroughly investigate the actual extent of sperm quality improvement after weight loss, particularly considering the wealth of evidence suggesting that these parameters significantly impact pregnancy outcomes, especially in the context of assisted reproduction [51,52].

The strict bi-directional correlation between excess body weight and hypogonadism is widely demonstrated [53-55], and in this context the weight loss is expected to be efficient in T serum levels raise [56,57]. However, whether the same effect should be expected on the spermatogenetic compartment is largely unclear. Indeed, the literature is still scanty on the topic for several reasons. First, weight loss could be obtained by different approaches, from diet to bariatric-metabolic surgery or GLP1R agonists. These approaches could influence sperm production either directly or indirectly through weight loss. Considering diet, several studies evaluated the positive impact of healthy dietary patterns on the sperm quality, using different healthy eating indexes [58]. A recent systematic review of the literature highlighted that diet modifications may be useful in modulating male fertility [58]. Many hypotheses have been made to explain the association between diet and male fertility, such as the prevention of chronic diseases [59,60], the reduction of inflammatory factors and endothelial dysfunction [61]. Thus, the diet itself could be linked to sperm function and fertility, although the mechanisms are still largely unknown.

It is not possible to determine which is the main effector on semen analysis parameters, *e.g.* the therapeutic approach itself or the weight loss. Trials evaluating semen analysis parameters after weight loss considered different follow-up duration. Andersen et al [62] demonstrated that the semen parameters improvement after an 8-week-diet was preserved after 52 weeks, suggesting that the beneficial effect of weight loss on male fertility could remain until the weight reduction was maintained. The causes of male infertility are largely unknown, and about 30% of infertile men are still included in the large category of male idiopathic infertility. Thus, whether the sperm alteration in obese men is really related to body weight excess or to still unknown causes could be not defined. With this in mind, obese men with infertility are heterogeneous and the effect of weight loss could lead to different results, depending on the underlying causes of sperm alteration. Besides these limitations several other problems should be taken in account. No information on other parameters which could negatively impact spermatogenesis, such as the loss of mitochondrial membrane potential and high concentrations of reactive oxygen species within the testes was available. Similarly, the impact of weight loss in primary and secondary infertility as well as on pregnancy or live birth rate was not possible due to the lack of information. The vast majority of the data were derived from studies based on bariatric surgery whereas the impact of dieting or use of GLP1 analogs was limited [62].

Several limitations should be recognized. First, no sufficient information related to pregnancy rate or live birth rate was available. Second, the methodologies employed for weight loss and the specific procedures used for semen analysis differed among studies. Indeed, the variability of semen analysis *per se* should be carefully considered, in particular since these parameters were not controlled in the original study for influential factors, such as age and abstinence time [21]. Moreover, the obesity condition is clearly different among studies included in the meta-analysis, potentially influencing the effect of weight loss on semen analysis. In particular, outcomes related to overweight subjects cannot be evaluated. The observed effects could be driven by the small number of studies detected and included, impeding to analyze whether the semen analysis improvement could be related to other factors other than weight loss, such as alterations in hormones (*i.e.* like GLP1 or leptin) when drugs were used. Third, the majority of our data derived from bariatric surgery in severely obese patients, and this might not be translatable to non-surgical weight loss in moderately obese men. Thus, our study suggests the necessity for additional investigation on the effects of diet and pharmacological interventions on semen analysis, especially considering that bariatric-metabolic surgery is not a universally accessible, quick, cost-effective, or recommended solution for every obese and infertile man. Finally, the quality of semen analysis conducted in each included study could be deemed a confounding factor. Our meta-analytic approach lacks the ability to assess the impact of semen analysis quality on the final outcome. Nonetheless, all studies included in the analysis have reported the methodology employed for semen analysis, thereby mitigating its potential confounding influence.

CONCLUSIONS

In conclusion, despite all potential challenges in the evaluation of weight loss-related semen analysis improvement, our findings suggest that body weight loss may improve qualitatively and quantitatively semen parameters. Thus, weight loss should be suggested in all male partners suffering by obesity with semen analysis impairment who are attempting conception. Moreover, further studies are also needed to understand specific mechanisms and the effect on fertility outcome induced by weight treatment.

Conflict of Interest

The authors have nothing to disclose.

Funding

None.

Acknowledgements

None.

Author Contribution

Conceptualization: DS, GC. Data curation: DS, GC, CG, AB. Writing – original draft: DS, GC. Writing – review & editing: AB, MS, MM. All authors evaluated the final draft of the manuscript.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.240091.

REFERENCES

1. Haase CL, Varbo A, Laursen PN, Schnecke V, Balen AH. Association between body mass index, weight loss and the chance of pregnancy in women with polycystic ovary syndrome and overweight or obesity: a retrospective cohort study in the UK. Hum Reprod 2023;38:471-81.
2. Hoek A, Wang Z, van Oers AM, Groen H, Cantineau AEP. Effects of preconception weight loss after lifestyle intervention on fertility outcomes and pregnancy complications. Fertil Steril 2022;118:456-62.
3. Hiller RAF, Griesinger G. How effective are lifestyle interventions for overweight women trying to conceive? Curr Opin Obstet Gynecol 2023;35:230-7.
4. Lintsen AM, Pasker-de Jong PC, de Boer EJ, Burger CW, Jansen CA, Braat DD, et al. Effects of subfertility cause, smoking and body weight on the success rate of IVF. Hum Reprod 2005;20:1867-75.
5. Yu S, Lian R, Chen C, Chen X, Xu J, Zeng Y, et al. Impact of body mass index on peripheral and uterine immune status in the window of implantation in patients with recurrent reproductive failure. Hum Fertil (Camb) 2023;26:1322-33.
6. Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, et al. Physical activity, body mass index, and ovulatory disorder infertility. Epidemiology 2002;13:184-90.
7. Romualdi D, Ata B, Bhattacharya S, Bosch E, Costello M, Gersak K, et al. Evidence-based guideline: unexplained infertility. European Society of Human Reproduction and Embryology; 2023.
8. Legro RS. Effects of obesity treatment on female reproduction: results do not match expectations. Fertil Steril 2017;107:860-7.
9. Rastrelli G, Lotti F, Reisman Y, Sforza A, Maggi M, Corona G. Metabolically healthy and unhealthy obesity in erectile dysfunction and male infertility. Expert Rev Endocrinol Metab 2019;14:321-34.
10. Corona G, Rastrelli G, Morgentaler A, Sforza A, Mannucci E, Maggi M. Meta-analysis of results of testosterone therapy on sexual function based on International Index of Erectile Function scores. Eur Urol 2017;72:1000-11.
11. Corona G, Rastrelli G, Morelli A, Vignozzi L, Mannucci E, Maggi M. Hypogonadism and metabolic syndrome. J Endocrinol Invest 2011;34:557-67.
12. Campbell JM, Lane M, Owens JA, Bakos HW. Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis. Reprod Biomed Online 2015;31:593-604.
13. Zhou J, Zhang F, Qin X, Li P, Teng Y, Zhang S, et al. Age at adiposity rebound and the relevance for obesity: a systematic review and meta-analysis. Int J Obes (Lond) 2022;46:1413-24.
14. Santi D, Lotti F, Sparano C, Rastrelli G, Isidori AM, Pivonello R, et al. Does an increase in adipose tissue 'weight' affect male fertility? A systematic review and meta-analysis based on semen analysis performed using the WHO 2010 criteria. Andrology 2024;12:123-36.
15. Corona G, Vena W, Pizzocaro A, Vignozzi L, Sforza A, Maggi M. Testosterone therapy in diabetes and pre-diabetes. Andrology 2023;11:204-14.

16. Fahmy A, Abdeldaiem H, Abdelsattar M, Aboyoussif T, Assem A, Zahran A, et al. Impact of bariatric surgery on sexual dysfunction in obese men. Sex Med 2021;9:100322.
17. Bates JN, Pastuszak AW, Khera M. Effect of body weight on sexual function in men and women. Curr Sex Health Rep 2019;11:52-9.
18. Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Lucchese M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol 2013;168:829-43.
19. Basolo A, Magno S, Santini F, Ceccarini G. Ketogenic diet and weight loss: is there an effect on energy expenditure? Nutrients 2022;14:1814.
20. Liu Y, Ruan B, Jiang H, Le S, Liu Y, Ao X, et al. The weight-loss effect of GLP-1RAs glucagon-like peptide-1 receptor agonists in non-diabetic individuals with overweight or obesity: a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. Am J Clin Nutr 2023;118:614-26.
21. Björndahl L, Esteves SC, Ferlin A, Jørgensen N, O'Flaherty C. Improving standard practices in studies using results from basic human semen examination. Andrology 2023;11:1225-31.
22. Esteves SC. Evolution of the World Health Organization semen analysis manual: where are we? Nat Rev Urol 2022;19:439-46.
23. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
24. Andrade C. Mean difference, standardized mean difference (SMD), and their use in meta-analysis: as simple as it gets. J Clin Psychiatry 2020;81:20f13681.
25. Reis LO, Zani EL, Saad RD, Chaim EA, de Oliveira LC, Fregonesi A. Bariatric surgery does not interfere with sperm quality: a preliminary long-term study. Reprod Sci 2012;19:1057-62.
26. Faure C, Dupont C, Baraibar MA, Ladouce R, Cedrin-Durnerin I, Wolf JP, et al. In subfertile couple, abdominal fat loss in men is associated with improvement of sperm quality and pregnancy: a case-series. PLoS One 2014;9:e86300.
27. Legro RS, Kunselman AR, Meadows JW, Kesner JS, Krieg EF, Rogers AM, et al. Time-related increase in urinary testosterone levels and stable semen analysis parameters after bariatric surgery in men. Reprod Biomed Online 2015;30:150-6.
28. El Bardisi H, Majzoub A, Arafa M, AlMalki A, Al Said S, Khalafalla K, et al. Effect of bariatric surgery on semen parameters and sex hormone concentrations: a prospective study. Reprod Biomed Online 2016;33:606-11.
29. Samavat J, Cantini G, Lotti F, Di Franco A, Tamburrino L, Degl'Innocenti S, et al. Massive weight loss obtained by bariatric surgery affects semen quality in morbid male obesity: a preliminary prospective double-armed study. Obes Surg 2018;28:69-76.
30. Calderón B, Huerta L, Galindo J, González Casbas JM, Escobar-Morreale HF, Martín-Hidalgo A, et al. Lack of improvement of sperm characteristics in obese males after obesity surgery despite the beneficial changes observed in reproductive hormones. Obes Surg 2019;29:2045-50.
31. Carette C, Levy R, Eustache F, Baron G, Coupaye M, Msika S, et al. Changes in total sperm count after gastric bypass and sleeve gastrectomy: the BARIASPERM prospective study. Surg Obes Relat Dis 2019;15:1271-9.
32. Wood GJA, Tiseo BC, Paluello DV, de Martin H, Santo MA, Nahas W, et al. Bariatric surgery impact on reproductive hormones, semen analysis, and sperm DNA fragmentation in men with severe obesity: prospective study. Obes Surg 2020;30:4840-51.
33. Fariello RM, de Carvalho RC, Spaine DM, Andretta RR, Caetano EM Jr, Sá GPD, et al. Analysis of the functional aspects of sperm and testicular oxidative stress in individuals undergoing metabolic surgery. Obes Surg 2021;31:2887-95.
34. Velotti N, Elisa De Palma FD, Sosa Fernandez LM, Manigrasso M, Galloro G, Vitiello A, et al. Effect of bariatric surgery on in vitro fertilization in infertile men with obesity. Surg Obes Relat Dis 2021;17:1752-9.
35. La Vignera S, Condorelli RA, Calogero AE, Cannarella R, Aversa A. Sexual and reproductive outcomes in obese fertile men with functional hypogonadism after treatment with liraglutide: preliminary results. J Clin Med 2023;12:672.
36. Andersen AG, Ziebe S, Jørgensen N, Petersen JH, Skakkebaek NE, Andersen AN. Time to pregnancy in relation to semen quality assessed by CASA before and after sperm separation. Hum Reprod 2002;17:173-7.
37. Corona G, Rastrelli G, Morelli A, Sarchielli E, Cipriani S, Vignozzi L, et al. Treatment of functional hypogonadism besides pharmacological substitution. World J Mens Health 2020;38:256-70.
38. Sarchielli E, Comeglio P, Filippi S, Cellai I, Guarnieri G, Marzoppi A, et al. Neuroprotective effects of testosterone in the hypothalamus of an animal model of metabolic syndrome. Int J Mol Sci 2021;22:1589.
39. Morelli A, Filippi S, Comeglio P, Sarchielli E, Cellai I, Pallecchi M, et al. Physical activity counteracts metabolic syndrome-induced hypogonadotropic hypogonadism and erectile dysfunction in the rabbit. Am J Physiol Endocrinol Metab 2019;316:E519-35.
40. Morelli A, Sarchielli E, Comeglio P, Filippi S, Vignozzi L, Marini M, et al. Metabolic syndrome induces inflammation

and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits. Mol Cell Endocrinol 2014;382:107-19.
41. Oduwole OO, Huhtaniemi IT, Misrahi M. The roles of luteinizing hormone, follicle-stimulating hormone and testosterone in spermatogenesis and folliculogenesis revisited. Int J Mol Sci 2021;22:12735.
42. Yuxin L, Chen L, Xiaoxia L, Yue L, Junjie L, Youzhu L, et al. Research progress on the relationship between obesity-inflammation-aromatase axis and male infertility. Oxid Med Cell Longev 2021;2021:6612796.
43. Li J, Sun H, Wang Y, Liu J, Wang G. Apolipoprotein C3 is negatively associated with estrogen and mediates the protective effect of estrogen on hypertriglyceridemia in obese adults. Lipids Health Dis 2023;22:29.
44. Chimento A, Sirianni R, Casaburi I, Pezzi V. Role of estrogen receptors and g protein-coupled estrogen receptor in regulation of hypothalamus-pituitary-testis axis and spermatogenesis. Front Endocrinol (Lausanne) 2014;5:1.
45. Tienforti D, Castellini C, Di Giulio F, Totaro M, Dalmazio G, Spagnolo L, et al. Selective modulation of estrogen receptor in obese men with androgen deficiency: a systematic review and meta-analysis. Andrology 2023;11:1067-76.
46. Huijben M, Huijsmans RLN, Lock MTWT, de Kemp VF, de Kort LMO, van Breda JHMK. Clomiphene citrate for male infertility: a systematic review and meta-analysis. Andrology 2023;11:987-96.
47. de Silva NL, Dissanayake H, Suarez C, Wickramarachchi RE, Ramasamy R, Dhillo WS, et al. Effect of oestrogen modulation on semen parameters in men with secondary hypogonadism: systematic review and meta-analysis. Andrology 2024;12:259-76.
48. van Hulsteijn LT, Pasquali R, Casanueva F, Haluzik M, Ledoux S, Monteiro MP, et al. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. Eur J Endocrinol 2020;182:11-21.
49. Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 1999;84:3673-80.
50. Corona G, Rastrelli G, Vignozzi L, Barbonetti A, Sforza A, Mannucci E, et al. The role of testosterone treatment in patients with metabolic disorders. Expert Rev Clin Pharmacol 2021;14:1091-103.
51. Villani MT, Morini D, Spaggiari G, Falbo AI, Melli B, La Sala GB, et al. Are sperm parameters able to predict the success of assisted reproductive technology? A retrospective analysis of over 22,000 assisted reproductive technology cycles. Andrology 2022;10:310-21.
52. Muthigi A, Jahandideh S, Bishop LA, Naeemi FK, Shipley SK, O'Brien JE, et al. Clarifying the relationship between total motile sperm counts and intrauterine insemination pregnancy rates. Fertil Steril 2021;115:1454-60.
53. Dandona P, Dhindsa S, Chaudhuri A, Bhatia V, Topiwala S, Mohanty P. Hypogonadotrophic hypogonadism in type 2 diabetes, obesity and the metabolic syndrome. Curr Mol Med 2008;8:816-28.
54. Dhindsa S, Miller MG, McWhirter CL, Mager DE, Ghanim H, Chaudhuri A, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010;33:1186-92.
55. Corona G, Monami M, Rastrelli G, Aversa A, Tishova Y, Saad F, et al. Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med 2011;8:272-83.
56. Cignarelli A, Santi D, Genchi VA, Conte E, Giordano F, Di Leo S, et al. Very low-calorie ketogenic diet rapidly augments testosterone levels in non-diabetic obese subjects. Andrology 2023;11:234-44.
57. Furini C, Spaggiari G, Simoni M, Greco C, Santi D. Ketogenic state improves testosterone serum levels-results from a systematic review and meta-analysis. Endocrine 2023;79:273-82.
58. Salas-Huetos A, Bulló M, Salas-Salvadó J. Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies. Hum Reprod Update 2017;23:371-89.
59. Jacobs S, Harmon BE, Boushey CJ, Morimoto Y, Wilkens LR, Le Marchand L, et al. A priori-defined diet quality indexes and risk of type 2 diabetes: the Multiethnic Cohort. Diabetologia 2015;58:98-112.
60. Mattei J, Sotos-Prieto M, Bigornia SJ, Noel SE, Tucker KL. The Mediterranean diet score is more strongly associated with favorable cardiometabolic risk factors over 2 years than other diet quality indexes in Puerto Rican adults. J Nutr 2017;147:661-9.
61. van Bussel BC, Henry RM, Ferreira I, van Greevenbroek MM, van der Kallen CJ, Twisk JW, et al. A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period in adults at risk of cardiovascular disease. J Nutr 2015;145:532-40.
62. Andersen E, Juhl CR, Kjøller ET, Lundgren JR, Janus C, Dehestani Y, et al. Sperm count is increased by diet-induced weight loss and maintained by exercise or GLP-1 analogue treatment: a randomized controlled trial. Hum Reprod 2022;37:1414-22.