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ORIGINAL CONTRIBUTIONS

Lack of Improvement of Sperm Characteristics in Obese Males After Obesity Surgery Despite the Beneficial Changes Observed in Reproductive Hormones

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Abstract

Background Even though obesity surgery normalizes circulating testosterone concentrations in males with obesity-associated secondary hypogonadism, its impact on spermatogenesis remains controversial. We aimed to evaluate sperm characteristics in obese men after bariatric surgery as well as changes in reproductive hormones.

Methods Twenty severely obese men (body mass index (BMI) ≥ 35 kg/m^2) were evaluated before and 2 years after bariatric surgery. The serum was assayed for insulin, leptin, kisspeptin, and inhibin B, among other hormones. Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated. We used World Health Organization reference values for sperm analysis.

Results After surgery, serum total testosterone, calculated free testosterone, inhibin B, and kisspeptin increased, whereas fasting insulin, HOMA-IR, and leptin concentrations decreased. Despite these improvements, sperm volume showed a small decrease after surgery, while the rest of sperm characteristics remained mostly unchanged. Abnormal sperm concentration persisted in 60% of the patients.

Conclusions Sperm characteristics may not improve after bariatric surgery despite the beneficial changes of reproductive hormones.

Keywords Obesity · Bariatric surgery · Kisspeptin · Leptin · Semen analysis · Male infertility

Introduction

The worldwide increase in obesity rates has not only triggered metabolic diseases, cardiovascular disorders, sleep apnea, and cancer but also gonadal dysfunction [1–3]. In men, semen abnormalities such as reduced sperm concentration and total counts, altered motility and morphology, DNA fragmentation, and abnormal acrosome reaction are associated with increased body weight [4–6].

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Obesity surgery, the most effective approach for the resolution of obesity-related comorbidities [7–9], may induce remission of gonadal dysfunction, such as polycystic ovary syndrome in women and secondary hypogonadism in men [10]. However, even though testosterone concentrations are rapidly restored after weight loss [10], the same might not apply to sperm characteristics.

Previous published case reports and small cohort studies reported no improvement or even worsening in sperm characteristics after obesity surgery [11–17]. A recent meta-analysis on the effects of obesity surgery on male sex hormones and sperm parameters has shown a significant effect on increasing androgens and decreasing estrogens, but sperm quality and function were not improved [18]. This meta-analysis concluded that long-term comparative studies or randomized controlled trials were warranted to further examine the impact of obesity surgery on male sex hormones and sperm quality.

In order to provide new insights on this important issue, we here performed a long-term follow-up in severely obese men after obesity surgery, with sperm analysis in parallel to the evaluation of many reproductive hormones.

Subjects and Methods

Subjects

Twenty male patients with moderate to severe obesity who gave written informed consent to participate in this study were included. These patients were a sample from within a wider cohort of male bariatric patients [6] who had reproductive health assessed before and after obesity surgery. The patients included here were submitted to laparoscopic sleeve gastrectomy (four cases) and to laparoscopic gastric bypass (16 patients) and completed 2 years of follow-up before analyzing changes in sperm characteristics. Inclusion criteria required a body mass index (BMI) of at least 35 kg/m^2 and the compromise to attend the scheduled visits. Exclusion criteria included previous diagnoses of hypogonadism (other non-functional causes of hypogonadism, such as Klinefelter syndrome, other primary hypogonadism, and secondary hypogonadism of organic and well-defined causes), thyroid disease, heart disease, kidney or liver failure, hyperprolactinemia, and treatment for sexual dysfunction. In the case of drugs, we excluded patients on antiandrogens and/or GnRH agonist (such as those with prostate disease or antiandrogens for treating alopecia). Those on spironolactone, antipsychotic, antidepressant, antiepileptic, or immunosuppressive drugs were also excluded as these could interfere with gonadal function.

The present study was approved by the Institutional Review Board of our Hospital, and followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Methods

Anthropometric parameters were recorded and BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured in the horizontal plane midway between the lowest ribs and the iliac crest.

Serum creatinine, alanine aminotransferase, aspartic aminotransferase, serum glucose concentrations, fasting insulin, total testosterone (TT), sex hormone-binding globulin (SHBG), ferritin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol were assayed as previously reported [6]. Free testosterone concentrations were calculated from TT and SHBG levels [19]. Insulin resistance in the fasting state was estimated by homeostasis model assessment (HOMA-IR) [20]. All these assays had coefficients of variation below 10%. Normal ranges were 300–1000 ng/dl for TT and 117–639 μg/dl for SHBG as provided by the Central Laboratory of our Hospital. The reference range of FT was set at 6.5–18.3 ng/dl, as previously reported [6].

We used commercial enzyme-linked immunosorbent assays (ELISA) to measure serum kisspeptin 1 (Kiss 1, SEC559-Hu, Cloud-Clone Corp, Houston, USA), inhibin B (Ray Bio Human/Mouse/Rat Inhibin B, beta subunit, Ray Biotech, Georgia, USA), and leptin (BMS 20391, INST, eBioscience, San Diego CA, USA) concentrations. All these assays had coefficients of variation below 10%.

Sperm samples were obtained via masturbation and ejaculation into a clean wide-mouthed container, following a standardized 4-day sexual abstinence period. Sperm concentration was determined in a Bürker hemocytometer. The number of motile sperm was analyzed using a Sperm Class Analyzer® SCA 2002 (Microptic Inc. Barcelona, Spain). For semen analysis, we used the reference values proposed by the World Health Organization in 2010, as previously reported [6, 21]. Briefly, they include the following: sperm volume ≥ 1.5 ml, sperm concentration ≥ 15 × 10^6/ml, semen pH ≥ 7.2, total motility ≥ 40% within 60 min after ejaculation and progressive motility ≥ 32%, sperm viability ≥ 58%, and normal sperm morphology ≥ 4%.

Statistics

As mentioned above, the included patients in this study were part of a larger cohort previously reported [6], so although sample size was calculated in the whole cohort for finding significant changes in testosterone, regarding sperm analysis, this sub-study should be regarded as a pilot one. Results are expressed as means ± SD unless otherwise stated. The Kolmogorov–Smirnov statistic was applied to continuous variables to check for normal distribution. Comparisons of continuous variables before and after obesity surgery were performed using paired *t* test or Wilcoxon test as needed. Analyses were performed using SPSS 17 (SPSS Inc., Chicago, Illinois). $P < 0.05$ was considered statistically significant.

Results

The included patients were 40 ± 8 years old, with a BMI of 41 ± 10. At baseline, sperm analysis showed abnormal results in 11 patients (55%): 8 (72%) presented abnormal morphology (52% corresponded to head alterations and 48% to mixed alterations), 5 (45%) abnormal sperm motility, and 4 (36%) low sperm concentration (Table 1).

In 15 patients, sperm analysis and hormone profiles were repeated 2 years after bariatric surgery. Their serum TT, SHBG, and FT concentrations increased (Table 1), whereas fasting insulin and HOMA-IR decreased (Table 1). Serum inhibin B and kisspeptin levels also increased after surgery, whereas serum leptin concentrations decreased (Table 1).

Regarding sperm analysis, all 15 patients had at least one abnormal parameter. Sixty percent of patients had abnormal sperm concentrations, 58% abnormal motility, and 62.5% abnormal morphology. At the end of the study, nine patients had oligozoospermia. Only sperm volume showed a small decrease after surgery and semen pH a small increase, whereas all other sperm characteristics remained mostly unchanged (Table 1). Of note, four of these patients were re-evaluated also 4 years after surgery showing no change in sperm parameters compared with pre-surgical values (data not shown).

When addressing fertility, one patient had a child after surgery and in another patient, in whom assisted reproductive techniques preoperatively were unsuccessful, these techniques failed again after bariatric surgery. Both patients had similar sperm parameters. The rest of patients did not express fertility desire after the bariatric procedure. Overall, taking into consideration fertility both before and after surgery, 7 of the 15 patients included in the follow-up study have had offspring: one had three children, another had two children and five had at least one child.

Discussion

Our present results show that sperm characteristics did not improve 2 years after bariatric surgery despite an increase in serum androgens and FSH and inhibin B concentrations. Regarding

Table 1 Characteristics of the obese patients evaluated at baseline and 2 years after obesity surgery

	At baseline	After surgery	*P* value
Anthropometric and analytical parameters			
Body mass index (kg/m^2)	50 ± 10	32 ± 7	< 0.001
Waist circumference (cm)	144 ± 12	106 ± 12	0.012
Fasting glucose (mg/dl)	120 ± 63	86 ± 13	0.010
Fasting insulin (μU/ml)	25 ± 13	6 ± 2	0.001
HOMA-IR	7.5 ± 5.6	1.2 ± 0.3	0.001
Leptin (ng/ml)	31.2 ± 26.8	3.0 ± 1.4	0.003
Kisspeptin (ng/ml)	0.43 ± 0.14	0.50 ± 0.14	0.016
Reproductive hormones			
Total testosterone (ng/dl)	364 ± 163	660 ± 208	0.025
SHBG (μg/dl)	224 ± 83	478 ± 144	0.001
Free testosterone (ng/dl)	8 ± 4	11 ± 3	0.005
Estradiol (pg/ml)	37 ± 12	36 ± 12	0.151
Follicle-stimulating hormone (U/l)	3.5 ± 1.1	4.0 ± 1.5	< 0.001
Luteinizing hormone (U/l)	3.5 ± 1.0	3.8 ± 1.3	0.066
Inhibin B (ng/ml)	0.56 ± 0.25	0.70 ± 0.24	0.041
Sperm analysis			
Sperm volume (ml)[a]	2.5 (1.0)	2.3 (1.8)	0.041
Sperm concentration (10^6/ml)	18 ± 69	12 ± 38	0.074
Semen pH	8.1 ± 0.2	8.3 ± 0.3	0.046
Total motility (% of sperms)	35 ± 35	35 ± 50	0.579
Progressive motility (% of sperms)	20 ± 30	25 ± 35	0.244
Sperm viability (% of sperms)	10 ± 5	10 ± 5	0.550
Normal morphology (% of sperms)	2 ± 4	2 ± 4	0.783

Data are means ± SD. Reference values for sperm analysis by the World Health Organization: sperm volume ≥ 1.5 ml, sperm concentration ≥ 15 × 10^6 /ml, semen pH ≥ 7.2, total motility ≥ 40% within 60 min after ejaculation and progressive motility ≥ 32%, sperm viability ≥ 58%, and normal morphology ≥ 4%

SHBG sex hormone-binding globulin, *HOMA-IR* homeostatic model assessment of insulin resistance

[a] Shown as medians (interquartile range)

fertility, one patient had a child after surgery, but another patient did not succeed in such aim even after being submitted to assisted reproductive techniques.

Previous data on these issues were controversial. Earlier case reports showed an important worsening in sperm parameters after bariatric surgery. Di Frega et al. [11] reported six previously fertile male patients who developed secondary infertility after gastric bypass for severe obesity. Their reproductive function was assessed with a series of spermiograms and testicular biopsies, which demonstrated secondary azoospermia with complete spermatogenic arrest [11]. Later on, Lazaros et al. [13] reported two obese men who showed marked reduction in sperm parameters when, 12 to 18 months after bariatric surgery, referred to an in vitro fertilization unit. Simultaneously, Sermondade et al. [17] reported three male patients who underwent bariatric surgery and experienced severe worsening of semen parameters including the development of extreme oligo-astheno-terato-zoospermia. Only in one case, the alterations of spermatogenesis were reversible 2 years after the surgical procedure [17]. On the other hand, the other two patients required intracytoplasmic sperm injection using fresh spermatozoa, after multiple sperm collection for cryopreservation, to achieve pregnancy [17].

In contrast, Reis et al. [15] reported ten male patients, studied before and 2 years after gastric bypass, who experienced no changes in sperm quality despite improvements in their sexual function and TT, FT, and FSH concentrations. Similarly, Legro et al. [14] reported six male subjects studied before and 1 year after gastric bypass surgery whose sperm parameters remained unchanged after the operation. In fact, their sequential semen analyses showed results that were within the normal range for most parameters despite massive weight loss [14].

A few prospective cohort studies have been published recently. One study included 46 patients undergoing sleeve gastrectomy whose semen analysis and serum hormone tests were analyzed before and 12 months after surgery [12]. Almost 70% or these patients showed abnormal sperm parameters before surgery that were followed by an increase in sperm concentrations that occurred independently of the amount of weight loss [12]. No information about fertility was, however, reported [12]. Another study reported 23 patients submitted to gastric bypass and a control group of ten non-operated obese men and showed an increase in semen volume and viability in sperm analysis in the former that was apparent as soon as 6 months after surgery [16].

One meta-analysis to establish the effects of bariatric surgery on male sex hormones, sperm parameters, and sexual function has been recently published [18]. The results showed a significant effect on increasing androgens and decreasing estrogens in male patients with obesity, but sperm quality and function were not improved after surgery. This meta-analysis concluded that long-term comparative studies or randomized controlled trials were warranted to further examine the impact of obesity surgery on male sex hormones and sperm quality. In this sense, we have tried to expand the data by performing a long-term study with the concomitant analysis of reproductive hormones.

A long period of follow-up may be needed to correctly assess the recovery of sperm after bariatric surgery: first, because the nutritional deficiencies are more likely during the initial weight loss phase after bariatric surgery (between 12 and 18 months) which may affect spermatogenesis [22, 23] and, second, because in the currently employed protocols for the treatment of hypogonadism with gonadotropin-releasing hormone (GnRH) or human chorionic gonadotropin (hCG), the average duration of therapy until the first sperm appears in the ejaculate is about 4 months [24] and sperm induction cycles may take several more months before resulting in natural pregnancy [25, 26]. Therefore, studies with less than 2 years of follow-up may not be valid for the assessment of sperm recovery after bariatric surgery. Nevertheless, our present results do not completely support the hypothesis of spontaneous sperm recovery on the long term as four of our patients, who were re-evaluated a second time 4 years after the intervention, had no improvement either.

During normal spermatogenesis, circulating FSH concentrations rise in response to low-frequency GnRH pulses and activate Sertoli cells to nourish developing sperm cells throughout the different phases of spermatogenesis [26]. Sertoli cells produce inhibin B, the most effective marker for normal spermatogenesis, which in turns inhibits FSH secretion and stimulates testosterone production by Leydig cells. Intra-testicular testosterone is 30 times higher than its serum concentrations, and these high concentrations are an absolute requisite for spermatogenesis [27]. Besides, leptin is secreted in direct proportion to the amount of energy stored in adipose tissue and has stimulatory effects on GnRH secretion through kisspeptin neurons [28, 29]. This mechanism is disrupted in obese men who are characterized by leptin resistance, contributing to male obesity-associated secondary hypogonadism [28, 29].

Although bariatric surgery was able to decrease leptin after weight loss—suggesting an increase in leptin sensitivity—and to increase inhibin B—possibly indicating the functional recovery of Sertoli cells—and to restore normal TT, FT, and FSH concentrations, sperm parameters did not improve in our patients. Therefore, other factors that might impair spermatogenesis, such as elevated testis temperature, nutritional deficiencies, or inflammatory responses of the testis and hypothalamus [30], may have not been corrected by bariatric surgery and weight loss.

Limitations of the Present Study

We are aware of several limitations of our present study, particularly its small sample size, as the calculation was

performed to achieve significant changes in circulating testosterone after surgery, but not for changes in sperm analysis. Besides, even though sperm analysis has traditionally been the cornerstone in the evaluation of the infertile male and remains the initial test of choice, a normal spermiogram does not necessarily warrants the fertility potential, because it does not accurately assess sperm function [21]. Other more reliable techniques such as DNA fragmentation were not performed in our present study.

Future Directions of Research in This Field

Taking all the previous published results together with our present findings, sperm parameters may experience either no change or only little improvement after bariatric surgery, without achieving the complete restoration of the fertility potential. As circulating reproductive hormones did actually improve after obesity surgery, the precise physiopathology of the abnormalities in sperm analysis needs further research. These results might be of relevance for obese men seeking fertility, and future studies should also address whether a longer period of time—above 2 and even 4 years after surgery—is needed to recover fertility potential or if operated men may need assisted reproductive techniques.

Conclusions

Sperm characteristics may not improve after bariatric surgery despite successful weight loss and the improvement of the circulating concentrations of reproductive hormones.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent was obtained from all the participants included in the study.

References

1. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of Obesity. N Engl J Med. 2017;376(3):254–66.
2. Mongraw-Chaffin M, Foster MC, Anderson CAM, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2018;71(17):1857–65.
3. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27.
4. Hammiche F, Laven JS, Twigt JM, et al. Body mass index and central adiposity are associated with sperm quality in men of subfertile couples. Hum Reprod. 2012;27(8):2365–72.
5. Samavat J, Natali I, Degl'Innocenti S, et al. Acrosome reaction is impaired in spermatozoa of obese men: a preliminary study. Fertil Steril. 2014;102(5):1274–81. e2
6. Calderon B, Gomez-Martin JM, Vega-Pinero B, et al. Prevalence of male secondary hypogonadism in moderate to severe obesity and its relationship with insulin resistance and excess body weight. Andrology. 2016;4(1):62–7.
7. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol. 2009;10(7):653–62.
8. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357(8):741–52.
9. Adams TD, Davidson LE, Litwin SE, et al. Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med. 2017;377(12):1143–55.
10. Escobar-Morreale HF, Santacruz E, Luque-Ramirez M, et al. Prevalence of 'obesity-associated gonadal dysfunction' in severely obese men and women and its resolution after bariatric surgery: a systematic review and meta-analysis. Hum Reprod Update. 2017;23(4):390–408.
11. di Frega AS, Dale B, Di Matteo L, et al. Secondary male factor infertility after Roux-en-Y gastric bypass for morbid obesity: case report. Hum Reprod. 2005;20(4):997–8.
12. El Bardisi H, Majzoub A, Arafa M, et al. Effect of bariatric surgery on semen parameters and sex hormone concentrations: a prospective study. Reprod BioMed Online. 2016;33(5):606–11.
13. Lazaros L, Hatzi E, Markoula S, et al. Dramatic reduction in sperm parameters following bariatric surgery: report of two cases. Andrologia. 2012;44(6):428–32.
14. Legro RS, Kunselman AR, Meadows JW, et al. Time-related increase in urinary testosterone levels and stable semen analysis parameters after bariatric surgery in men. Reprod BioMed Online. 2015;30(2):150–6.
15. Reis LO, Zani EL, Saad RD, et al. Bariatric surgery does not interfere with sperm quality—a preliminary long-term study. Reprod Sci. 2012;19(10):1057–62.
16. Samavat J, Cantini G, Lotti F, 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(1):69–76.
17. Sermondade N, Massin N, Boitrelle F, et al. Sperm parameters and male fertility after bariatric surgery: three case series. Reprod BioMed Online. 2012;24(2):206–10.

18. Lee Y, Dang JT, Switzer N, et al. Impact of bariatric surgery on male sex hormones and sperm quality: a systematic review and meta-analysis. Obes Surg. 2019;29(1):334–346.
19. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84(10):3666–72.
20. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9.
21. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231–45.
22. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring). 2013;21(Suppl 1):S1–27.
23. Calderon B, Hevia V, Vega-Pinero B, et al. Serum retinol, folic acid, and copper are associated with sperm abnormalities in men with obesity. J Am Coll Nutr. 2018;37(3):194–200.
24. Buchter D, Behre HM, Kliesch S, et al. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. Eur J Endocrinol. 1998;139(3):298–303.
25. Liu PY, Baker HW, Jayadev V, et al. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab. 2009;94(3):801–8.
26. Prior M, Stewart J, McEleny K, et al. Fertility induction in hypogonadotropic hypogonadal men. Clin Endocrinol (Oxf). 2018;89(6):712–8.
27. Davidson LM, Millar K, Jones C, et al. Deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermatogenesis and male fertility. Hum Fertil (Camb). 2015;18(3):184–93.
28. Khan SM, Hamnvik OP, Brinkoetter M, et al. Leptin as a modulator of neuroendocrine function in humans. Yonsei Med J. 2012;53(4):671–9.
29. George JT, Millar RP, Anderson RA. Hypothesis: kisspeptin mediates male hypogonadism in obesity and type 2 diabetes. Neuroendocrinology. 2010;91(4):302–7.
30. Xiang J, Bian C, Wan X, et al. Sleeve gastrectomy reversed obesity-induced hypogonadism in a rat model by regulating inflammatory responses in the hypothalamus and testis. Obes Surg. 2018;28(8):2272–80.