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Semaglutide improved sperm morphology in obese men with type 2 diabetes mellitus and functional hypogonadism

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Abstract

Aims: To compare the effects of semaglutide and testosterone replacement therapy (TRT) on semen quality and parameters of functional hypogonadism (FH) in men with type 2 diabetes mellitus and obesity.

Materials and Methods: We designed a randomised open-label trial in 25 men with type 2 diabetes (aged 50 [46–60] years, BMI 35.9 [32.8–38.7] kg/m^2) and FH randomised to semaglutide (SEMA) 1 mg/week or intramuscular testosterone undecanoate (TRT) 1000 mg/10–12 weeks for 24 weeks. Semen analysis and parameters of FH were measured at baseline and after 24 weeks of treatment. Participants completed questionnaires of the International Index of Erectile Function-15 (IIEF-15) and the Aging Symptoms in Men (AMS).

Results: The quality of baseline sperm parameters of our study cohort was poor, below the 5th percentile of reference values. In the SEMA group, there was a significant increase in morphologically normal sperm from baseline to the end of the study (2% [2; 3.5] vs. 4% [2; 5.5]; $p = 0.012$), whereas sperm concentration and total number decreased significantly in the TRT group. Compared to TRT, the SEMA group had a significantly higher number of morphologically normal sperm, sperm concentration and total number. Both groups experienced an increase in total testosterone and improvement in the AMS score, whereas the IIEF-15 score significantly improved only in the TRT group.

Conclusion: Semaglutide markedly improved sperm morphology, total testosterone levels and symptoms of hypogonadism. These findings highlight semaglutide's potential as a therapeutic approach for men with obesity-related FH who desire fertility.

Clinical trial registration number: NCT06489457, www.clinicaltrials.gov.

KEYWORDS
functional hypogonadism, obesity, semaglutide, sperm, type 2 diabetes

1 | INTRODUCTION

More than one-third of men with type 2 diabetes with obesity have functional hypogonadism (FH).[1–3] This form of hypogonadotropic hypogonadism is characterised by low levels of testosterone and low or inappropriately normal levels of gonadotropins without any apparent organic cause. It is believed to be multifactorial, with increased body mass index (BMI) and insulin resistance being the most significant contributing factors. Decreased insulin and leptin signalling disrupt the hypothalamic–pituitary–gonadal (HPG) axis and result in low testosterone production and impaired spermatogenesis. Physical and psychological symptoms along with impaired sexual function are the most prominent features of male hypogonadism. Another key aspect of hypogonadism is the deterioration of sperm quality, which significantly impacts male fertility. Moreover, men with diabetes are at risk of having reduced sperm quality, even when their testosterone levels are still within normal limits.[4,5]

Lifestyle measures (LSM), particularly weight reduction, is the recommended approach for obese men with FH. The evidence of beneficial effects of testosterone replacement therapy (TRT) is limited to the improvement in sexual function.[6] Despite potential positive impacts on body composition and metabolism, the role of TRT remains uncertain.[7–11] Furthermore, in men of reproductive age, the negative effects of TRT on the HPG axis and sperm production are a significant concern.

GLP-1 and its agonists play an important role in regulating the HPG axis. Studies with various GLP-1 receptor agonists (GLP-1 RA) have shown elevated testosterone levels and enhanced sexual function.[12,13] These positive effects appear to be primarily driven by weight loss, yet the distribution of GLP-1 receptors along the HPG axis also indicates a potential direct impact of GLP-1 agonism on reproductive system, predominantly mediated via anti-inflammatory action.[14] Moreover, direct stimulation with a GLP-1 RA has demonstrated several metabolic effects on sperm.[15]

The impact of GLP-1 RA on sperm quality and parameters of FH is insufficiently studied in patients with type 2 diabetes mellitus and obesity. Therefore, we aimed to compare the effects of semaglutide and TRT on parameters of FH and semen quality in this population.

2 | MATERIALS AND METHODS

A 24-week, randomized, controlled open-label trial was conducted at the University Medical Centre Ljubljana, Slovenia, from November 2020 to May 2023. The study was listed in ClinicalTrials.gov (Identifier: NCT06489457) and approved by the local Ethics Committee.

All patients gave written informed consent at the screening visit.

2.1 | Study population

Men aged 18–65 years, with type 2 diabetes on oral antidiabetic treatment, BMI above 30 kg/m^2 and FH were eligible for inclusion in the trial. The criteria for FH were total testosterone less than 11 nmol/L measured on at least two separate morning measurements at least 4 weeks apart after an overnight fast, along with at least two symptoms of sexual dysfunction and low or inappropriately normal gonadotropin levels. Specific pathologic aetiologies suppressing the HPG axis such as hyperprolactinaemia and endogenous Cushing syndrome were excluded. Other pituitary hormones were evaluated to rule out hypopituitarism. Pituitary MRI was performed in men with serum total testosterone level below 5.2 nmol/L or symptoms of tumour mass effect (e.g. visual impairment, visual field defect or new-onset headache) to rule out pituitary or hypothalamic tumours, or infiltrative disease. The exclusion criteria also included primary or secondary hypogonadism, hemochromatosis, active malignant disease, thrombophilia, venous thrombosis within 6 months, recent acute myocardial infarction or stroke, prostate-specific antigen (PSA) higher than 3 ng/L, severe lower urinary tract symptoms (LUTS) with an International Prostate Symptom Score (IPSS) above 19, severe sleep apnoea syndrome, haematocrit greater than 0.5, significant kidney or liver disease, ongoing treatment with opioid analgesics, antipsychotics or glucocorticoids, alcohol abuse, severe ongoing mental illness, personal history of pancreatitis or medullary thyroid carcinoma and personal or family history of multiple endocrine neoplasia type 2 (MEN 2). Patients were recruited at our clinic and by general practitioners in the local area.

2.2 | Screening and study protocol

At the screening visit, 54 patients were asked about symptoms and signs suggestive of hypogonadism in accordance with clinical practice guideline. Seventy-two per cent (39/54) of patients with at least two positive symptoms and/or signs were further evaluated for total testosterone; of these, 64% (25/39) had low total testosterone levels and were eligible for inclusion.

Finally, 25 eligible participants were randomized using a computer program from www.random.org. Thirteen patients were randomized to semaglutide 1 mg QW s.c. (SEMA group) and 12 to testosterone undecanoate 1000 mg once 10–12 weeks i.m. (TRT group). Semaglutide was initiated and titrated in concordance with SMPC, with a dose of 0.25 mg injected QW over the first month, 0.5 mg QW over the second month and 1 mg QW from the third month onwards. At the beginning of the study, LSM was again actively promoted in both groups. A reduced intake of 500–800 kcal/day and a diet consisting of up to 50% of carbohydrates preferably with low glycaemic index, 20% of proteins and 30% of fat, mostly mono- and polyunsaturated, with the amount of saturated fat less than 10%, was advised. The participants were encouraged to increase their consumption of fibre, whole grains, cereals, fruits and vegetables, and to engage in at least 30 min of moderate-intensity physical activity daily.

2.3 | Antihyperglycaemic medication

All the patients were on equal dose of metformin, 1000 mg BID. Other oral antihyperglycaemic treatments included sulfonylurea (SU) and/or dipeptidyl peptidase-4 (DPP-4) inhibitors. Patients

randomized to semaglutide who were previously taking DPP4-inhibitors were switched to SU 3 months prior to the trial to ensure stable glycaemic control during the run-in period. Also, patients who were previously taking sodium-glucose cotransporter-2 (SGLT-2) inhibitors were switched to either SU or DPP-4 inhibitors, depending on the randomisation. No other medication was introduced during the study except for treatment of an acute illness.

2.4 | Methods

All patients underwent clinical, anthropometric and biochemical assessment at the beginning and at the end of the trial. Primary outcomes were change in sperm parameters (semen volume, concentration, total number, total motility, morphologically normal sperm). Secondary outcomes were change in total testosterone concentration, LH, FSH, IIEF-15 and AMS score, HbA1c, body mass, BMI, percentage of body fat, estimated visceral adipose tissue and fasting lipids within and between the groups.

2.5 | Assessment of symptoms and signs of FH

We assessed sexual function using the International Index of Erectile Function (IIEF-15) questionnaire and the Aging Male Syndrome (AMS) scale. The assessment was taken and analysed before and at the end of the trial. The questionnaires were translated into Slovene following international methodological recommendations for adapting HRQoL measures linguistically and culturally. The English version was used as the source language to ensure cross-cultural equivalence among countries. Six steps of the translation process were followed as recommended.

2.6 | Assessment of endocrine parameters

Blood samples were collected in the morning between 7 and 8 AM after fasting. Total testosterone levels were measured by coated tube RIA (DiaSorin S. p. A., Salluggia, Italy and Diagnostic Products Corporation, Los Angeles, CA, USA, respectively). Within and between assays, coefficients of variation for testosterone were 1.05% and 5.75%. The levels of sex hormone-binding globulin (SHBG), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured using a chemiluminescent immunoassay (Immulite 2000 XPi Analyzer; Siemens Healthcare). Within and between assays, the coefficients of variation for the applied method ranged from 1.2% to 4.0% and 1.8% to 4.3%. The calculated free testosterone (cFT) and bioavailable testosterone were obtained from the calculator at http://www.issam.ch/freetesto.htm (23 October 2023).

2.7 | Assessment of anthropometric parameters and body composition

Height and weight were measured at the baseline and at the trial end point. BMI was calculated as the weight in kilograms divided by square of height in metres. Assessment of body composition was done by dual energy X-ray absorptiometry (DXA) (Discovery A; Hologic, Waltham, MA, USA) with the software provided by the manufacturer (QDR for Windows Version 12.5). The instrument generates values for whole-body fat mass, lean body mass and bone mineral content.

2.8 | Assessment of semen

Semen collection, handling and examination was performed in accordance with WHO recommendations.[16] The patients were required to abstain from sexual activity for at least two but not more than 7 days. Single ejaculate semen samples were collected in a private room close to the laboratory at the Department of Human Reproduction, Division of Obstetrics and Gynecology, University Medical Centre Ljubljana. All assessments were performed at room temperature immediately after receiving the sample. The volume was determined using a graduated disposable pipette. Sperm concentration was assessed using 20 µm 10 × 10 grid disposable counting slides (CellVision, Heerhugowaard, The Netherlands) following the instructions provided by the manufacturer. Five microlitres of semen was added to a slide and left for 5–10 min to stabilise. Where possible, at least 200 spermatozoa were counted per slide using a phase contrast microscope, 400× magnification. Sperm motility was evaluated from the same sample as sperm counting; spermatozoa were classified only as motile or immotile. To assess morphology, semen smears were stained using a Papanicolaou method and Tygerberg strict criteria were used for the evaluation. Where possible, at least 200 spermatozoa were assessed under 1000× magnification.

2.9 | Assessment of metabolic parameters

Glucose levels were determined using the standard glucose oxidase method (Beckman Coulter Glucose Analyzer; Beckman Coulter Inc., CA, USA). Insulin was determined by an immunoradiometric assay (Biosource Europe S.A., Nivelles, Belgium). Within and between assays, coefficients of variation for insulin were 3.6% and 3.8%. HbA1c was assessed by high-performance liquid chromatography (D-100; Bio-Rad Laboratories). Within and between assays, the coefficients of variation for HbA1c were 1.67% and 2.27%. Lipids were determined using Adiva 1800, Siemens analyser. Homeostasis model assessment for IR ($HOMA_{IR}$) was used to assess insulin resistance (IR). $HOMA_{IR}$ was calculated as fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. Seventy-five grams oral glucose tolerance test (OGTT) was performed in concordance to the guidelines. Comorbid conditions included self-reported heart condition, diabetes, cancer, liver conditions, kidney conditions, prostate disease and thyroid disorders. The self-reported history was checked and completed by available medical records. Safety parameters (complete blood count, PSA, markers of hepatic and renal functions and serum electrolytes) were assessed before and after 12 weeks and at the end of the trial. All participants were instructed to report any side effects during the treatment.

TABLE 1 Anthropometric and biochemical characteristics.

	Semaglutide ($n = 13$)				Testosterone ($n = 12$)				
	Baseline	24 weeks	Difference	*p* value	Baseline	24 weeks	Difference	*p* value	*p* value*
Body mass (kg)	115 (102; 120)	99 (96; 118)	−6 (−15; −2)	**0.004**	111.5 (101.7; 125.2)	111 (102; 125.2)	0.5 (−2; 2.3)	0.92	***0.007***
BMI (kg/m^2)	35.9 (32.8; 38.7)	33.5 (30; 37.8)	−2.1 (−4.6; −0.6)	**0.005**	35.8 (32.7; 39.9)	34.8 (31.9; 40.1)	0.1 (−0.6; 0.7)	0.79	***0.005***
HbA1c (%)	7.1 (6.7; 8)	6.1 (5.6; 6.8)	−1.2 (−1.5; −0.6)	**0.009**	7.2 (6.8; 8.0)	7.6 (6.1; 8.5)	0.1 (−0.3; 0,8)	0.51	***0.019***
Glucose 0 min OGTT (mmol/L)	8.8 (7.7; 11.4)	7.4 (6.5; 8.1)	−3.4 (−5.9; −1.5)	**0.046**	8.3 (7.6; 10.0)	10.5 (9.3; 11.5)	0.3 (−1.4; 1.9)	0.08	***0.007***
Glucose 120 min OGTT (mmol/L)	13.4 (10.4; 15.1)	8.4 (6.9; 10.6)	−4.6 (−6.0; −2.7)	**0.003**	11.4 (10.2; 14.2)	12.6 (11.4; 13.9)	−0.3 (−2.6; 1.7)	0.48	***0.003***
Insulin 0 min OGTT (mU/L)	13.9 (9.0; 20.7) [1]	19.1 (13.2; 31.8) [1]	1.9 (−0.1; 15.0) [1]	0.14	18.3 (14.1; 22.7)	20.4 (17.1; 27.8)	0.3 (−3.1; 3.5)	0.70	*0.51*
Insulin 120 min OGTT (mU/L)	34.7 (23.1; 49.6) [1]	37.1 (23.2; 83.3) [1]	15.4 (−5.2; 37.0) [1]	0.21	42.9 (24,5; 61,3)	28.9 (24.5; 47.2)	−5.7 (−13.8; 2.1)	0.18	*0.09*
C-peptide 0 min (nmol/L)	1.1 (0.7; 1.4)	1.0 (0.7; 1.2)	−0.0 (−0.2; 0.1)	0.68	0.9 (0,8; 1,5)	10.0 (0.8; 1.4)	−0.0 (−0.2; 0.2)	0.88	*0.89*
C-peptide 120 min (nmol/L)	1.9 (1.4; 2.6)	1.7 (1.2; 2.7)	−0.2 (−0.4; 0.6)	0.92	1.7 (1.2; 2.5)	1.7 (1.2; 1.9)	−0.1 (−0.4; 0.1)	0.46	*0.69*
HOMA IR score	6.5 (3.5; 12.2)	5.7 (3.2; 10.9)	−0.9 (−4.5; −0.3) [1]	0.18	8.2 (5.3; 12.5) [1]	9.0 (7.4; 13.3) [1]	0.2 (−1.5; 4.4)	0.42	*0.22*
Haematocrit (%)	43 (42; 45)	44 (43; 45)	1 (−2; 1)	0.94	45 (43; 45)	46 (43; 47)	1 (0; 2)	0.18	*0.32*
Total cholesterol (mmol/L)	4.6 (4.0; 5.2)	4.3 (4.0; 4.7)	−0.1 (−1; 0.2)	0.17	4.7 (4.0; 5.4)	4.5 (3.6; 5.4)	−0.3 (−0.5; −0.1)	0.27	*0.65*
HDL cholesterol (mmol/L)	0.9 (0.8; 0.9)	0.8 (0.8; 0.9)	0.0 (−0.1; 0.0)	0.43	1.0 (0,7; 1,1)	0.9 (0.8; 0.9)	−0.1 (−0.1; 0.0)	0.86	*0.94*
LDL cholesterol (mmol/L)	3.1 (2.8; 3.3)	2.6 (2.5; 3.1)	−0.2 (−0.7; 0.0)	**0.045**	2.8 (2.2; 2.9)	2.3 (1.9; 2.9)	−0.2 (−0.5; 0.1)	0.15	*0.54*
Triglycerides (mmol/L)	2.0 (1.4; 25)	1.6 (1.1; 1.9)	−0.6 (−0.7; 0.3)	**0.036**	2.3 (1.8; 3.8)	2.0 (1.3; 3.6)	−0.4 (−0.6; 1.0)	0.91	*0.27*
PSA (µg/L)	0.6 (0.4; 0.9)	0.7 (0.6; 1.0)	0.1 (0.0; 0.2)	0.09	0.7 (0.5; 0.8)	0.7 (0.6; 0.8)	−0.1 (−0.0; 0.3)	0.21	*1.00*
LH (IU/L)	3.2 (2.9; 4.0)	3.1 (2.3; 4.4)	0.2 (−0.6; 1.0)	0.55	4.2 (1.5; 7.0)	1.2 (1.4; 8.0)	−1.7 (−4.1; −1.3)	**0.003**	***0.001***
FSH (IU/L)	5.5 (4.6; 8.0)	6.5 (4.0; 9.2)	−0.3 (−0.9; 0.6)	0.38	8.5 (3.2; 15.2)	2.6 (0.5; 7.2)	−4.9 (−6.3; −2.7)	**0.002**	***0.002***
Total testosterone (nmol/L)	6.1 (5.1; 8.6)	7.8 (6.1; 9.5)	1.6 (0.7; 1.8)	**0.023**	6.7 (3.9; 9.0)	12.3 (11.4; 15.3)	6.9 (2.3; 12.1)	**0.002**	***0.002***
Free testosterone (pmol/L)	19.5 (16.7; 28.6)	22.1 (16.1; 40.8)	2.9 (−1.0; 8.2)	0.10	26.3 (18.7; 36.3)	48.1 (38.3; 59.8)	26.5 (9.1; 38.6)	**0.008**	***0.01***
SHBG (nmol/L)	19 (16; 27)	21 (19; 25)	0 (−2; 3)	0.72	23.5 (13.3; 33.3)	21.5 (11.5; 29.5)	−0.5 (−2.5; 0.5)	0.37	*0.19*
Body fat (%)	34.5 (32.7; 36.0) [1]	33.3 (31.4; 34.6) [1]	0.7 (−1.7; 0.1) [1]	**0.038**	37.4 (29.2; 42.4)	35.2 (30.2; 39.3)	−0.8 (−1.8; 0.8) [1]	0.31	*0.538*
Visceral adipose tissue (g)	1259 (1014; 1451) [1]	1019 (884; 1173) [1]	−212 (−301; −80) [1]	**0.003**	1105 (827; 1574)	1092 (849; 1375)	−41 (−190; 81) [1]	0.35	*0.1*

Note: Data presented as median (interquartile range). *p* values were calculated using Wilcoxon test (for paired samples) and Mann–Whitney test (for independent samples). Bold indicates statistical significance. Value in square brackets show the number of missing samples.

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OGTT, oral glucose tolerance test; PSA, prostate-specific antigen; SHBG, sex hormone-binding globulin.

**p* value—treatment difference between the groups.

2.10 | Sample size calculation

The sample size was calculated taking into account the clinically significant changes in sperm parameters as our primary outcome (semen volume, concentration, total number, total motility, number of morphologically normal sperm) between groups after treatment. We assumed an alpha error of 0.05, beta error of 0.8, semen concentration mean difference of 0.3 million/mL and standard deviation of 0.6 million/mL, which resulted in 12 patients in each group.

2.11 | Statistical analysis

The Shapiro–Wilk test was used to assess the normality of data distributions. The variables following normal distribution are presented as mean with standard deviation (SD). The *t* test was used to compare the differences within and between the groups. The variables that did not follow normal distribution are presented as median with interquartile range (25%–75%). For the latter, the Wilcoxon signed-rank test was used to compare the differences within the group, while the Mann–Whitney test was used to compare independent groups. To assess the correlation between treatment changes, we used Pearson correlation. *p* values below 0.05 were considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics, version 21 (IBM Corporation, Armonk, NY, USA).

3 | RESULTS

Twenty-five participants, 13 patients in the SEMA group and 12 patients in the TRT group, were included in the study. All patients concluded the study. The median age of the patients was 50 (46.1; 59.7) years. The mean duration of diabetes was 4 years (2; 8). Of concomitant diseases, 68% patients had arterial hypertension and 52% had hypercholesterolaemia. Of antihyperglycaemic agents, all the patients had metformin and 60% had sulfonylureas. Of patients who were on TRT, 42% had DPP-4 inhibitors. A large proportion of the participants (76%) were able to father a child. The baseline and final characteristics of the study population are outlined in Table 1. At baseline, there were no statistically significant differences between the groups, in any of the parameters ($p > 0.05$).

3.1 | Semen analysis

In the SEMA group, there was a significant increase in morphologically normal sperm (relative change 0.37 (21; 88), $p = 0.012$) (Table 2). In the TRT group, there was a significant decrease in sperm concentration (relative change −0.67 (−88; −54), $p = 0.028$) and total number (relative change −0.59 (−87; 50), $p = 0.018$). There was no significant change in semen volume and total motility in either of the groups (both $p > 0.05$). SEMA, compared to TRT, had a significantly higher number of morphologically normal sperm ($p = 0.001$), sperm concentration ($p = 0.002$) and total number ($p = 0.026$).

3.2 | Symptoms and signs of FH

Ageing male symptoms as evaluated by AMS improved overall in both groups. In the SEMA group, psychological (−2 (−7; −2), $p = 0.009$) and physical (−5 (−5; 0), $p = 0.01$) symptoms improved significantly, whereas sexual symptoms remained unchanged ($p = 0.3$). TRT improved psychological (−1 (−4.2; −0.2), $p = 0.02$) and sexual (−2 (−6; −0.7), $p = 0.022$) symptoms but not physical ($p = 0.13$) ones. There was no difference in any of the AMS symptom subsets between the two groups.

TRT significantly improved sexual function as evaluated by IIEF-15. There were improvements in erectile function (4 (0; 8.7), $p = 0.019$), sexual desire (2 (0; 4), $p = 0.035$), sexual intercourse (1 (0; 6.2), $p = 0.034$) and overall satisfaction (2 (0; 3.2), $p = 0.028$). The orgasmic function also improved but failed to reach statistical significance ($p = 0.11$). SEMA improved only sexual desire (2 (0; 2), $p = 0.009$). There were no significant differences between the groups (Table 3).

3.3 | Endocrine parameters

Total testosterone increased significantly from baseline in both groups; however, patients receiving TRT had a significantly greater increase than those receiving SEMA (1.6 nmol/L (0.7; 8.2) vs. 6.9 nmol/L (2.3; 12.1), $p = 0.002$). As expected, the effect of TRT on LH (−1.7 IU/L (−4.1; 1.3), $p = 0.003$) and FSH (−4.9 IU/L (−6.3; 2.65), $p = 0.002$) was suppressive while in SEMA, it remained unchanged (Table 1). The difference between the groups was statistically significant ($p = 0.001$ and $p = 0.002$, for LH and FSH, respectively).

3.4 | Body weight and body composition

Body weight (−6 kg (−15; −2) vs. 0.5 kg (−2; 2,2), $p = 0.007$) and BMI (−2.1 kg/m^2 (−4.6; −0.6) vs. 0.2 kg/m^2 (−0.6; 0.7), $p = 0.005$) decreased significantly in SEMA compared to TRT. Body fat percentage (−0.7% (−1.7; 0.1), $p = 0.038$) and estimated visceral adipose tissue (VAT) (−212 g (−301; −80), $p = 0.003$) decreased significantly from the baseline to the end of the study in SEMA. However, the differences in the latter two anthropometric parameters failed to reach statistical significance between the groups (Table 1).

3.5 | Glucose and lipid metabolism

HbA1c (−2.1% (−1.5; −0.6) vs. 0.1% (−0.3; 0.8), $p = 0.019$), fasting glucose (−3.4 mmol/L (−5.9; −1.5) vs. 0.35 mmol/L (−1.4; 1.9),

TABLE 2 Semen analysis.

	Semaglutide ($n = 13$)				Testosterone ($n = 12$)				
	Baseline	24 weeks	Difference (%)	*p* value	Baseline	24 weeks	Difference (%)	*p* value	*p* value*
Volume (mL)	1.3 (0.8; 1.5)	1.3 (0.5; 2.1)	−19 (−45; 57)	0.98	1.7 (0.7; 3.5)	1.7 (1.1; 2.5)	16 (−27; 113)	0.86	*0.44*
Concentration (10^6/mL)	25 (15; 125.5)	37 (16.5; 60.5)	17 (−2; 71)	0.58	25 (9; 76)	10 (5.6; 18.5)	−67 (−88; −54)	**0.028**	***0.002***
Total number (10^6/ejaculate)	34.5 (19.6; 64.8)	41 (15.3; 70)	−5 (−59; 167)	0.79	31.5 (10; 53.2)	19 (8.9; 60.0)	−59 (−87; 50)	**0.018**	***0.026***
Total motility (%)	30 (21.3; 43.8)	30 (22.5; 35)	−17 (−41; 15)	0.09	20 (8.8; 21.3)	7.5 (5; 16;3)	−16 (−56; 0)	0.078	*0.69*
Normal morphology (%)	2 (2; 3.5)	4 (2; 5.5)	37 (21; 88)	**0.012**	2 (1; 2)	1 (1; 1)	−50 (−90; 41)	0.157	***0.001***

Note: Data presented as median (interquartile range). *p* values were calculated using Wilcoxon test (for paired samples) and Mann–Whitney test (for independent samples). Bold indicates statistical significance.
**p* value—treatment difference between the groups.

TABLE 3 Ageing male symptoms (AMS) and International Index of Erectile Function (IIEF-15).

	Semaglutide ($n = 13$)				Testosterone ($n = 12$)				
	Baseline	24 weeks	Difference	*p* value	Baseline	24 weeks	Difference	*p* value	*p* value*
AMS									
Psychological	12 (6; 16)	7 (6; 10)	−2 (−7; −2)	**0.009**	11 (9.5; 15)	9.5 (6.5; 13.5)	−1 (−4.2; 0.0)	**0.02**	*0.38*
Somatic	19 (17;23)	15 (12; 16)	−5 (−5; 0)	**0.01**	18.5 (12.5; 23)	18 (10.8; 20)	−1.5 (−1.2; 0.0)	0.13	*0.12*
Sexual	11 (9; 13)	11 (9;14)	−1 (−2; 0)	0.3	11 (9,8; 15,3)	10 (7; 11)	−2 (−6; −0.7)	**0.022**	*0.19*
Total score	46 (32; 51)	33 (28; 41)	−7 (−13; −3)	**0.011**	45.5 (31,5; 47,8)	36 (27; 44)	−6 (−12.2; −2.2)	**0.011**	*0.61*
IIEF-15									
Erectile function	12 (6; 14)	18 (3; 25)	0 (0; 6)	0.15	6.5 (1; 13.3)	13 (9.5; 27.5)	4 (0; 8.7)	**0.019**	*0.32*
Orgasm	8 (4; 9)	6 (3; 10)	0 (−2; 0)	0.2	4 (1; 7.5)	8 (2.8; 10)	1.5 (0; 4)	0.11	*0.052*
Sexual desire	4 (2; 6)	6 (4; 7)	2 (0; 2)	**0.009**	2.5 (2; 6)	7.5 (3.8; 8.3)	2 (0; 3)	**0.035**	*0.98*
Intercourse satisfaction	5 (3; 6)	8 (0; 9)	1 (0; 3)	0.37	3.5 (0; 5,8)	6.5 (1.5; 14)	1 (0; 6,2)	**0.034**	*0.44*
Overall satisfaction	5 (3; 6)	4 (2; 8)	0 (−1; 0)	1.0	3.5 (2; 5.3)	6 (4.8; 8)	2 (0; 3,2)	**0.028**	*0.052*
Total score	31 (19; 38)	44 (10; 55)	3 (0; 10)	0.17	20 (10; 35)	39 (26.5; 67.5)	13 (0,7; 22,5)	**0.013**	*0.22*

Note: Data presented as median (interquartile range). *p* values were calculated using Wilcoxon test (for paired samples) and Mann–Whitney test (for independent samples). Bold indicates statistical significance.
**p* value—treatment difference between the groups.

$p = 0.007$) and glucose after 120 min of OGTT (−4.6 mmol/L (−6.0; −2.7), $p = 0.003$) decreased significantly in SEMA compared to TRT. Insulin and C-peptide (fasting and after 120 min), the $HOMA_{IR}$ score remained unchanged (Table 1).

LDL cholesterol (−0.2 mmol/L (−0.7; 0), $p = 0.045$) and triglycerides (−0.6 mmol/L (−0.7; 0.3), $p = 0.036$) decreased significantly in SEMA from the baseline to the end of the study, but the changes were not significant compared to TRT (Table 1). Total and HDL cholesterol remained unchanged in both groups (Table 1).

3.6 | Correlations

The correlations between changes in sperm parameters and changes in anthropometric parameters (body weight, BMI, body fat percentage) as well as metabolic parameters (HbA1c, $HOMA_{IR}$ score) and endocrine parameters (LH and FSH) were non-significant (all p values below 0.05).

4 | DISCUSSION

A 24-week treatment with semaglutide resulted in improvement in sperm morphology, total testosterone levels and symptoms of FH related to obesity and type 2 diabetes mellitus. As expected, TRT improved total testosterone levels and symptoms of hypogonadism, but had an adverse effect on sperm concentration and total sperm number. Compared to TRT, semaglutide significantly reduced body weight.

The current recommended approach for managing FH includes LSM and weight reduction. The impact of weight reduction on testosterone levels in obese and diabetic men has been evaluated in several RCTs and meta-analyses.[17–19] The effect is closely related to the extent of weight loss. In the present study, the SEMA group, which experienced a 6.5% weight loss, achieved a 1.6 nmol/L increase in total testosterone, somewhat lower than anticipated according to prior meta-analysis[18] and our previous study with a similar design and duration where treatment with liraglutide led to a weight reduction of 5.9% and a 2.6 nmol/L improvement in total testosterone.[12] The cohort in that study was younger, with an average age of 46 years, had a higher baseline BMI of 41.2 kg/m^2 and most patients did not have type 2 diabetes. This aligns with previous trials demonstrating that older and diabetic patients achieve smaller improvements in testosterone levels despite similar weight reduction.[18] Additionally, despite significant reduction of HbA1c by 1.2%, glycaemic control seems to have a lesser impact on testosterone levels than weight loss.[19]

In the TRT arm, intramuscular administration of testosterone undecanoate every 10–12 weeks resulted in a moderate increase in total testosterone by 6.9 nmol/L, reaching a median concentration of 12.3 nmol/L. In our TRT group, there was no improvement in glycaemic control and weight reduction. The metabolic effects of TRT remain debated due to the lack of high-quality RCTs and the heterogeneity of the available data. However, a recent meta-analysis of 18 studies on patients with type 2 diabetes or metabolic syndrome with decreased levels of testosterone concluded that TRT had favourable effect on weight loss (−3.94 kg) and HbA1c (−0.67%).[20] The lack of metabolic improvement in our study may be attributed to factors such as small sample size, short study duration and low baseline HbA1c.

In the SEMA arm, patients reported significant improvements in physical and psychological symptoms, leading to a significant improvement in the overall AMS score. Furthermore, there was a significant improvement in sexual desire, a subset of IIEF-15, but the overall improvement in the IIEF-15 score was not statistically significant. The data from other trials on GLP-1 RA are inconclusive. While our previous randomized study with liraglutide failed to show an improvement in symptoms as evaluated by AMS,[12] two observational studies with liraglutide or dulaglutide, respectively, demonstrated a significant improvement in sexual function (IIEF-15).[13,19] In one of the latter studies, the improvement in sexual function was consistent with an increase in total testosterone and weight loss.[13] It is worth noting that the studies differed in design, study population and duration. In the present study, with only modest elevation in total testosterone levels of 1.6 nmol/L, we hypothesised that the improvement in physical and psychological symptoms and sexual desire may also be driven by factors other than testosterone, such as HbA1c reduction and enhanced self-image resulting from weight loss. In the TRT arm, where the increase in total testosterone levels was more pronounced, sexual function improved significantly in most subsets and in the overall scores of AMS and IIEF-15. This is consistent with the data from testosterone clinical trials, where sexual function consistently improved in patients with lower testosterone baseline levels.[21]

The quality of baseline sperm parameters of our study population is poor. Compared to WHO reference values for fertile men, most parameters fall below the 5th percentile, except for semen volume and sperm concentration, which are between the 5th and 10th percentile.[22] To date, no study has performed semen analysis on such a diseased population. However, a meta-analysis of 13 077 men has shown a J-shaped association between BMI and abnormal sperm count, with an odds ratio of 1.28 for obese men (BMI 30–39 kg/m^2).[23] Another meta-analysis on diabetic men examined for infertility has reported that diabetes mellitus decreases the semen volume and the percentage of motile spermatozoa.[24] In men with FH, spermatogenesis is impaired not only due to the lack of the hypothalamo-pituitary stimuli but also from low intratesticular testosterone concentration.[25] Despite poor sperm quality, 76% of men in our study were able to father a child, indicating that they were fertile earlier in life.

In the SEMA arm, there was a significant increase in morphologically normal sperm. Thus far, only a few clinical trials have examined the effects of GLP-1 agonism on sperm parameters in animal models and humans. In obese mice, 8-week treatment with GLP-1 RA exenatide improved sperm motility, DNA integrity and mitochondrial function.[26] To date, a single clinical study has investigated the effect of GLP-1 RA on human sperm parameters. In this RCT, the authors

examined the impact of different means of weight loss on sperm parameters.[27] After initial low-calorie diet weight reduction, men with obesity but without diabetes were randomized to four groups: placebo, exercise, liraglutide treatment and exercise combined with liraglutide treatment for 52 weeks. Total sperm number and sperm concentration improved after the initial weight loss, but after randomisation, only patients who were able to sustain the reduced weight by more than 11.7 kg, regardless of intervention, had a significant increase in sperm concentration and sperm count. There was no further improvement in semen parameters in men treated with liraglutide; therefore, the authors concluded the positive effect is achieved only through weight loss.[27] This is supported by another study that examined the effect of diet and exercise-induced weight loss on sperm parameters and demonstrated that obese individuals who lost more than 12% of body weight had improvement in semen volume and total sperm number.[28] However, contrary to previous results, in bariatric surgery where weight reduction is the greatest and favourable effects on HPG axis are well documented, the results are conflicting[29–32] and a recent meta-analysis showed no improvements in semen quality.[33] In the present study, we also observed no correlation between weight reduction and improvement in sperm parameters.

None of the participants in our study had detectable glucosuria before or after treatment. Therefore, the potential effects of varying glucose concentrations in the urogenital tract on sperm characteristics could not be significant.

The presence of GLP-1 receptor on human Sertoli[34] and Leydig cells[35] as well as on human sperm[15] indicates a direct and indirect involvement of GLP-1 in sperm biology. In vitro, GLP-1 increased glucose uptake and lactate production in human Sertoli cells providing nutrients to sperm.[34] Rago et al. demonstrated direct metabolic effects of GLP-1 RA, exendin-4, on sperm. In vitro stimulation of GLP-1 receptor leads to several metabolic insulin-mediated effects that enable energy stores to be more readily available.[15] These metabolic changes are consistent with the functional maturation of the capacitation process that enables sperm to survive in a biochemically different environment—that is, the female genital tract. Moreover, a recent study on diabetic mouse models has demonstrated a mitigating effect of semaglutide by improving glucose/lipid metabolism and inhibiting ferroptosis.[36]

Whether GLP-1 agonism could, to some extent, improve sperm function and enhance its reproductive capability beyond weight reduction remains to be determined. Transport of molecules through the blood–testis barrier is tightly regulated,[37] and it is unknown whether semaglutide reaches seminiferous tubules to provide the direct effect. In line with the reported anti-inflammatory effects on other organs, semaglutide could provide some beneficial effects on spermatogenesis through its anti-inflammatory actions by the mechanisms of a newly discovered gut-brain GLP-1 axis for centrally regulated suppression of peripheral inflammation.[38] Further research is needed on the mechanisms of potential direct and indirect effects of semaglutide on spermatogenesis and sperm quality.

Opposite to SEMA, patients on TRT had a significant decrease in total sperm number and sperm concentration. The results underline the negative effect of exogenous testosterone on HPG.[39,40]

Our study has a few limitations. A single sample may not be the best representation of sperm quality due to natural fluctuations. Moreover, the 24-week study duration may not be long enough to fully determine the treatment effects of semaglutide and testosterone on anthropometric and metabolic parameters. However, the main strength of our study is that it examined the wide ranging effects of GLP-1RA on FH, especially on reproductive health, where clinical data are lacking. Our results well complement the findings from preclinical research.[15,34,36]

In conclusion, semaglutide provided beneficial effects on body weight and metabolism, general symptoms of FH, and sperm morphology, while TRT had a greater impact on sexual function in men with diabetes and obesity-related FH. Considering the favourable impact on reproductive health, semaglutide may present a good therapeutic option for men with obesity and diabetes-related FH who desire fertility. Combining both treatments could provide greater overall health benefits in some subsets of patients with obesity and diabetes-related FH, which should be a subject for further research.

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CONFLICT OF INTEREST STATEMENT

NG has received lecture honoraria from Novo Nordisk, Eli Lilly, BioMarin, Genesis Pharm and Boehringer Ingelheim. AJ has served as a consultant and is on speaker bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Abbott, Novo Nordisk, Medtronic and Sanofi. MJ has received lecture honoraria from Novo Nordisk, Eli Lilly, Pfizer, Amgen, Novartis and Sanofi, and is an advisory board member of Novo Nordisk, Eli Lilly, Amgen and Pfizer. JS declares no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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