

RESEARCH

Effects of liraglutide on obesity-associated functional hypogonadism in men

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Abstract

Lifestyle measures (LSMs) should be the first-line approach offered for obesity-related functional hypogonadism (FH). When LSMs fail, the role of testosterone replacement treatment (TRT) is unclear. GLP1 receptor agonist liraglutide is linked to progressive and sustained weight loss. A potential direct impact of GLP1 on hypothalamus-pituitary-testicular (HPT) axis was reported in animal models. We aimed to compare the effects of liraglutide and TRT on FH in obese men that had been poor responders to LSM, by means of reversal of FH and weight reduction. We designed a 16-week prospective randomized open-label study with 30 men (aged 46.5 ± 10.9 years, BMI 41.2 ± 8.4 kg/m², mean \pm s.d.) that were randomized to liraglutide 3.0 mg QD (LIRA) or 50 mg of 1% transdermal gel QD (TRT). Sexual function and anthropometric measures were assessed. Fasting blood was drawn for determination of endocrine and metabolic parameters followed by OGTT. Model-derived parameters including HOMA_{IR} and calculated free testosterone (cFT) were calculated. Total testosterone significantly increased in both arms ($+5.9 \pm 7.2$ in TRT vs $+2.6 \pm 3.5$ nmol/L in LIRA) and led to improved sexual function. LIRA resulted in a significant increase of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) ($P < 0.001$ for between-treatment effect). Subjects treated with LIRA lost on average 7.9 ± 3.8 kg compared with a 0.9 ± 4.5 kg loss in TRT ($P < 0.001$). Metabolic syndrome was resolved in two patients in LIRA and in no subjects in TRT. Liraglutide was superior to TRT in improving an overall health benefit in men with obesity-associated FH after LSM failed.

Key Words

- ▶ liraglutide
- ▶ GLP1 receptor agonist
- ▶ obesity
- ▶ functional hypogonadism

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Introduction

Obesity causes functional hypogonadism (FH) due to suppression of hypothalamus-pituitary-testicular (HPT) axis that is potentially reversible (1). Recent evidence suggests that weight reduction (WR) with lifestyle measures (LSMs) should be recommended as the first-line approach (2, 3), yet in clinical practice LSM often fails. On the other hand, testosterone replacement therapy (TRT) appears to improve body composition and glycometabolic profile without clearly affecting weight lost as well as its role after a trail of unsuccessful LSM is unclear. Only few studies to date reported that combination of TRT and LSM is superior to LSM alone in increasing insulin

sensitivity, glycemic control, muscle mass and reducing liver fat (4, 5). One study in middle-aged obese men with low testosterone subjected to a rigorous weight loss program has reported that men not receiving TRT lost adipose tissue and lean body mass, whereas weight loss in testosterone-treated men was almost exclusively due to loss of body fat (6). In selected patients, TRT could be started concomitantly or in addition to LSM to augment the benefits of LSM, although the quality of evidence supporting this concept is low (2).

GLP1 receptor agonists are linked to progressive and sustained weight loss in subjects with or without

diabetes (7). Despite the fact that the prevalence of FH in obese male population is increased by 13-fold (8), the impact of liraglutide on obesity-related FH has not yet been addressed in a prospective clinical study. There was only one retrospective observational study reporting that adding long-acting GLP1 receptor agonist liraglutide to LSM, metformin and TRT boosted erectile function in obese men with type 2 diabetes and different forms of hypogonadism (9). Furthermore, some animal models have demonstrated that GLP1 might even have a direct impact on HPT that is beyond WR (10, 11, 12, 13, 14). These observations provided an additional rationale to evaluate the effect of liraglutide on male obesity-associated FH.

The aim of this pilot study was to compare the effects of short-term intervention with liraglutide in an anti-obesity dose and TRT on FH and weight loss in obese men who had been poor responders to LSM, by means of reversal of FH and WR. The primary outcome measures were changes in testosterone, sexual function and gonadotropins. The secondary outcomes were measures of obesity and metabolic profile.

Materials and methods

Subjects

Thirty middle-aged obese men with FH (aged 46.5 ± 10.9 years, BMI 41.2 ± 8.4 kg/m², mean \pm s.d.) who had been previously poor responders to LSM, by means of WR and recovery of FH, were included in the study. They were eligible for enrolment if they were 18–65 years old, obese (BMI ≥ 30 kg/m²) and had been diagnosed with FH. FH was diagnosed as consistently low serum total testosterone below 11 nmol/L on at least two separate morning measurements after an overnight fast in addition to at least two symptoms of sexual dysfunction and low or inappropriately normal gonadotropin levels. Specific pathologic etiologies suppressing the HPT axis such as hyperprolactinemia and endogenous Cushing syndrome were excluded. Evaluation of other pituitary hormones and pituitary MRI to exclude hypopituitarism and/or pituitary or hypothalamic tumor or infiltrative disease was performed when it was clinically indicated (15). Other exclusion criteria were iron overload, history of carcinoma, venous thromboembolism, thrombophilia, known preexisting cardiovascular disease or stroke, initial PSA more than 3 ng/L, severe

lower urinary tract symptoms with an International Prostate Symptom Score (IPSS) >19 , untreated sleep apnea, initial hematocrit more than 50%, significant kidney or liver disease, active desire for fertility, opioids or glucocorticoids use and personal or family history of MEN 2.

All subjects were informed of the study aims and provided written consent before entering the study, which was conducted in accordance with the Declaration of Helsinki and approved by the National Ethical Committee. The study is registered with ClinicalTrials.gov identifier: NCT03619330.

Study protocol

We conducted a 16-week prospective randomized open-label study with 30 eligible men who were randomized to liraglutide 3.0 mg QD s.c. (LIRA arm) and 50 mg of 1% transdermal gel QD (TRT arm). Liraglutide was initiated with a dose of 0.6 mg injected s.c. once per day and weekly titrated up to 3 mg. 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 glycemic 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 consumption of fibers, whole grains, cereals, fruits and vegetables along with at least 30 min of moderate-intensity physical activity daily.

Methods

All patients underwent clinical, anthropometric and biochemical assessment at baseline and at study end point.

Assessment of symptoms and signs of FH

We assessed sexual function through a self-reported evaluation of both the number of morning erections per week and the number of ejaculations per week as well as a self-reported measurement of libido. Libido was defined and scaled as 1 for very poor, 2 for poor and 3 for good. A questionnaire, aging male syndrome (AMS) scale, was collected and analyzed before and at the end of the study. Translation of Slovene version was performed in congruence with international methodological recommendations for linguistic and cultural adaptation

of HRQoL measures using the English version as source language to ensure cross-cultural equivalence among countries. Six steps of the translation process were followed as recommended (16).

Assessment of endocrine parameters

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%. Sex hormone-binding globulin (SHBG), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were determined with a chemiluminescent immunoassay (Immulite 2000 XPi Analyzer; Siemens Healthcare). Within and between assays, coefficients of variation for the applied method ranged from 1.2 to 4.0% and 1.8 to 4.3%. Calculated free testosterone (cFT) and bioavailable testosterone were derived from the calculator at <http://www.issam.ch/freetesto.htm> (accessed 7/10/2018) (17).

Assessment of anthropometric parameters

Height, weight and waist circumference were measured at the baseline and at study end point. Waist circumference was measured in a standing position midway between the lower costal margin and the iliac crest. BMI was calculated as the weight in kilograms divided by square of height in meters.

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 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, coefficients of variation for HbA1c were 1.67 and 2.27%. Lipids were determined using Adiva 1800, Siemens analyzer. Insulin resistance (IR) was calculated by the homeostasis model assessment for IR ($HOMA_{IR}$): fasting serum insulin (mU/L) \times fasting plasma glucose (mmol/L)/22.5 (18). Impaired glucose tolerance (IGT) was identified by 2h glucose levels between

7.8 and 11.0 mmol/L, as defined by the American Diabetes Association criteria (19).

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 16 weeks of study treatment. All men were instructed to report any side effects during the treatment.

Statistical analysis

The results for continuous variables are presented as means \pm s.d. Wilcoxon signed-rank test was used for comparison of related samples such as pre- and posttreatment values, while Mann-Whitney test was used for comparison of independent groups. *P* values below 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 21 (IBM Corp).

Results

Baseline characteristics of the study population are provided in Table 1. The mean age of participants was 49.3 \pm 9.8 years in TRT and 43.9 \pm 11.6 years in LIRA arm. There were no significant differences at baseline in any of the parameters between the treatment groups.

Symptoms and signs of FH

Libido and sexual functions were significantly improved in both arms. In TRT arm, libido as reported by self-measurement increased from 1.0 \pm 0.0 to 2.2 \pm 0.7 scores (*P*=0.003). In LIRA, libido increased from 1.1 \pm 0.3 to 1.8 \pm 0.6 scores (*P*=0.003). The number of morning erections per week as reported by self-evaluation increased from 1.4 \pm 1.3 to 3.8 \pm 2.6 N/week in TRT (*P*=0.012) and from 1.4 \pm 2.2 to 2.9 \pm 2.5 N/week in LIRA (*P*=0.017). Ejaculations per week increased from 0.9 \pm 1.0 to 3.3 \pm 2.2 N/week (*P*=0.008) in TRT and from 2.6 \pm 2.8 to 3.8 \pm 2.9 N/week in LIRA (*P*=0.048). There were no significant between-treatment differences for any parameters (*P*=0.762 for libido, *P*=0.550 for morning erections, *P*=0.204 for ejaculations). AMS score was significantly improved in TRT (Table 1).

Table 1 Pre- and posttreatment characteristics of patients treated with TRT (N = 15) and liraglutide (N = 15).

Characteristics	TRT			Liraglutide			Comparison of pretreatment values	
	Pretreatment	Posttreatment	P	Pretreatment	Posttreatment	P	P	
Weight (kg)	123 ± 29	122 ± 29	0.332	134 ± 18	126 ± 18	0.001	0.239	
BMI (kg/m ²)	39 ± 9	38.8 ± 9.2	0.363	43.2 ± 7.5	40.6 ± 7.5	0.001	0.185	
Total testosterone (nmol/L)	7.2 ± 3.2	13.1 ± 8.1	0.005	7.6 ± 1.5	10.2 ± 4.2	0.048	0.458	
Calculated free testosterone (nmol/L)	0.17 ± 0.07	0.30 ± 0.25	0.099	0.17 ± 0.04	0.22 ± 0.08	0.155	0.979	
Calculated bioavailable testosterone (nmol/L)	4.28 ± 1.68	7.67 ± 6.19	0.084	4.33 ± 1.03	5.15 ± 2.12	0.182	0.852	
AMS	40.6 ± 9.9	31.5 ± 5.7	0.002	43.4 ± 12.4	37.6 ± 12.3 [1]	0.157	0.616	
LH (IU/L)	3.1 ± 1.3	1.1 ± 1.3	0.004	2.7 ± 1.2	3.4 ± 1.1	0.048	0.291	
FSH (mIU/L)	5.6 ± 2.5 [1]	2.4 ± 2.1 [1]	0.002	4 ± 1.7	4.9 ± 2.1	0.031	0.089	
SHBG (nmol/L)	20.2 ± 5.4	20.8 ± 6.2	0.968	26.3 ± 13.6	29.3 ± 14.1	0.063	0.239	
Waist circumference (cm)	125 ± 23 [1]	124 ± 22	0.136	128 ± 14 [1]	124 ± 15	0.010	0.295	
BP systolic (mmHg)	150 ± 16 [1]	143 ± 18	0.023	144 ± 12 [1]	138 ± 13 [1]	0.387	0.611	
BP diastolic (mmHg)	92 ± 10 [1]	88 ± 17	0.065	88 ± 13 [1]	87 ± 10 [1]	0.074	0.470	
Glu 0 min OGTT (mmol/L)	8.1 ± 3.2	6.8 ± 2.3	0.294	6.2 ± 1.1	5.8 ± 0.7	0.102	0.202	
Glu 120 min OGTT (mmol/L)	9.2 ± 5 [3]	8.9 ± 3.9 [3]	0.944	7.4 ± 3.1	6.4 ± 2.2 [1]	0.196	0.437	
Insulin 0 min OGTT (mU/L)	24.7 ± 13.3	17.9 ± 8.4 [2]	0.016	31.6 ± 19.4 [1]	29 ± 18.9 [2]	0.556	0.287	
Insulin 120 min OGTT (mU/L)	77.7 ± 43.3 [2]	65.7 ± 31.8 [2]	0.091	131.3 ± 91.5 [1]	140.5 ± 146.2 [3]	0.477	0.093	
HOMA _{IR} score	9.1 ± 6.4	5.4 ± 3.3 [1]	0.033	9 ± 6.5 [1]	7.9 ± 6 [1]	0.754	0.880	
HbA1c (%)	6.4 ± 1.3	6.4 ± 1.1	0.937	5.9 ± 0.8	5.3 ± 0.4 [1]	0.001	0.202	
Cholesterol (mmol/L)	5.2 ± 0.9 [1]	5.3 ± 0.9	0.783	4.9 ± 0.8	4.9 ± 0.9	0.823	0.595	
HDL (mmol/L)	1.1 ± 0.2 [1]	1.1 ± 0.3 [1]	0.903	1.1 ± 0.3 [1]	1.1 ± 0.23	0.952	0.247	
LDL (mmol/L)	3.1 ± 0.8 [1]	3.4 ± 0.8 [1]	0.259	3.2 ± 0.7 [1]	3.2 ± 0.9	0.476	0.979	
TAG (mmol/L)	2.2 ± 1.3 [1]	2.7 ± 1.2 [1]	0.020	1.9 ± 1.5 [1]	2.0 ± 1.0 [1]	0.007	0.168	

Data presented as mean ± s.d., P values calculated using Wilcoxon test for related samples, comparison of pretreatment values calculated using Mann–Whitney test. Bold indicates statistical significance. [missing data].

Endocrine changes

Total testosterone significantly increased in both arms, with no significant differences between groups. SHBG tended to increase in LIRA. There was a significant differential effect on HPT axis resulting in further suppression of LH and FSH in TRT and a significant increase of LH and FSH in LIRA ($P < 0.001$) (Tables 1 and 2).

Measures of obesity

Subjects treated with liraglutide lost on average $6.0 \pm 3.2\%$ of initial weight compared with a $0.8 \pm 3.3\%$ in TRT arm. LIRA was also superior in reduction of BMI and waist circumference (Tables 1 and 2).

Metabolic parameters

Two men in LIRA and two in TRT had IGT at the beginning of the study. After 16 weeks all of them had normal glucose tolerance. Five patients in LIRA and six patients in TRT had type 2 diabetes at baseline. After 16 months, three patients in LIRA reported lowering of insulin doses.

In TRT one man progressed from normal glucose tolerance to type 2 diabetes mellitus. Ten men in the liraglutide arm and ten in testosterone arm had metabolic syndrome at baseline. It was resolved in two patients in LIRA and in no subjects in TRT.

Hb1Ac significantly decreased in LIRA. HOMA_{IR} score and fasting insulin decreased in TRT. Fasting glucose, glucose and insulin after OGTT, LDL and total cholesterol did not consistently decrease in either group. Triacylglycerol (TAG) significantly increased in both arms and systolic blood pressure (BP) significantly decreased in TRT (Table 1). The between-treatment difference was significant for HbA1c, LIRA being superior to TRT (Table 2).

Adverse events

In TRT none of the patients reported adverse events. Ht and PSA did not increase significantly in either arm. PSA did not increase for more than $1.4 \mu\text{g/L}$ in any subjects (from 0.57 ± 0.33 to $0.59 \pm 0.36 \mu\text{g/L}$ in TRT and from 0.93 ± 0.76 to $0.88 \pm 0.66 \mu\text{g/L}$ in LIRA). Ht did not rise over 52% during either intervention from 0.44 ± 0.03 to

Table 2 Change in patients' clinical characteristics during treatment.

Characteristics	TRT	Liraglutide	P
Weight (kg)	-1 ± 5	-8 ± 4	<0.001
BMI (kg/m ²)	-0.3 ± 1.4	-2.6 ± 1.3	<0.001
Total testosterone (nmol/L)	5.9 ± 7.2	2.6 ± 3.5	0.239
Calculated free testosterone (nmol/L)	0.13 ± 0.25	0.04 ± 0.07	0.551
Calculated bioavailable testosterone (nmol/L)	3.43 ± 6.06	0.90 ± 1.78	0.514
AMS	-9.1 ± 7	-4.8 ± 10.3 [1]	0.243
LH (IU/L)	-2 ± 1.3	0.7 ± 1.2	<0.001
FSH (mIU/L)	-3.2 ± 1.7	0.9 ± 1.8	<0.001
SHBG (nmol/L)	0.6 ± 4	3 ± 5.3	0.202
Waist circumference (cm)	-2 ± 4 [1]	-5 ± 5 [1]	0.035
BP systolic (mmHg)	-9 ± 11 [1]	-7 ± 17 [1]	0.514
BP diastolic (mmHg)	-7 ± 11 [1]	-4 ± 6 [1]	0.319
Glu 0 min OGTT (mmol/L)	-1.3 ± 3	-0.4 ± 0.8 [0]	0.583
Glu 120 min OGTT (mmol/L)	0 ± 2.2 [4]	-1.2 ± 2.8 [1]	0.431
Insulin 0 min OGTT (mU/L)	-5.9 ± 6.5 [2]	-2.8 ± 12.2 [2]	0.347
Insulin 120 min OGTT (mU/L)	-12 ± 18.9 [2]	-0.1 ± 142.4 [3]	0.748
HOMA _{IR} score	-2.9 ± 3.9 [1]	-1.3 ± 3.7 [1]	0.134
HbA1c (%)	0 ± 0.8	-0.5 ± 0.5 [1]	0.004
Cholesterol (mmol/L)	0.1 ± 0.6 [1]	0 ± 0.5	0.667
HDL (mmol/L)	0.01 ± 0.15 [2]	0 ± 0.17 [1]	0.865
LDL (mmol/L)	0.15 ± 0.49 [2]	-0.07 ± 0.36 [1]	0.207
TAG (mmol/L)	0.37 ± 0.44 [2]	0.3 ± 0.53 [2]	0.525

Data presented as mean ± s.d., P values calculated using Mann-Whitney test. Bold indicates statistical significance. [missing data].

0.46 ± 0.03 in TRT or from 0.46 ± 0.04 to 0.45 ± 0.03 in TRT. The most frequent adverse events in LIRA were mild to moderate, transient and gastrointestinal in nature. Nausea was reported by four, headache by one and stomach pain by two patients. None of the patients in LIRA reported hypoglycemic events.

Discussion

This is the first report demonstrating that 16-week intervention with liraglutide in obese middle-aged men who had been poor responders to LSM, by means of improvement of FH and WR, improved sexual health and overall health benefit. Treatment with liraglutide in an anti-obesity dose resulted in significant improvement of sexual symptoms, increase in total testosterone concentrations, recovery of HPT axis, reduction of anthropometric measures of obesity and improvement of glycemic control. TRT improved sexual functions, total testosterone levels and HOMA_{IR}.

In LIRA arm, 6% of weight loss was related with modest increase of total testosterone with 2.6 nmol/L. The impact of WR on testosterone level in obese men has been evaluated only in few RCT and meta-analysis that was limited to small studies with short-term follow-up and heterogeneous study designs (3, 20). Its impact

was generally related to the magnitude of WR. Five per cent of weight loss with LSM was associated with the 2 mmol/L increase of total testosterone and no increase of free testosterone (21), 10% of LSM induced weight loss with 2.9 nmol/L increase of total testosterone, weight loss of more than 15% with increase by 5.7 mmol/L (21) and 30% of weight loss after bariatric surgery with the increase of total testosterone by 8.7 nmol/L (3, 20, 22). The observed magnitude of the increase in total testosterone in our patients who had been treated with liraglutide was slightly greater than expected for the amount of WR, although they remained hypogonadal by laboratory standards. If WR rate would be maintained in LIRA arm then treatment could result in eugonadal numbers with longer follow-up.

In TRT arm, 50 mg of 1% transdermal gel QD in our study led to moderate increase of total testosterone level by 5.9 nmol/L. The testosterone increase in TRT arm was associated with significant improvement of sexual functions and mood as assessed by AMS score. The observations were in line with other studies reporting that TRT consistently improved sexual functions only in men with significantly reduced total testosterone, as observed in our cohort where mean value of total testosterone at baseline was below 8 nmol/L (23). Interestingly, in LIRA arm, sexual functions also improved, despite only a modest rise of total testosterone by 2.6 nmol/L.

We hypothesized that mechanisms other than testosterone increase, including psychosocial factors related to improved body image due to significant WR, might play a role in clinically improved sexual symptoms in LIRA arm. In line with this observation, another study reported that the degree of WR predicted improved erectile function, whereas changes in testosterone level did not (24). Since AMS did not significantly improve in LIRA arm this possibly means it has less effect on nonsexual symptoms of testosterone deficiency including mood, fatigue, sleep and well-being.

The suppression of HPT axis in FH associated with obesity is considered to be an adaptive response to the weight variation (25). Indeed, especially the severe form of obesity (BMI>38) is characterized by reduction of serum T, its free fraction and quality and quantity of LH secretion (26). Moreover, several additional causes can have a key role in bringing about this clinical condition (27). Several adipokines were proposed as negative mediators on the reproductive axis (28). IR has a distortive impact on GnRH neurons (29). It has been reported previously that LH increased with WR in magnitude-dependent manner (8). With weight loss of more than 15% LH increased for 2.2IU (8). In our study 6% of WR in LIRA was associated with an increase of LH by 0.7IU/L and FSH by 0.9mIU/L, whereas both gonadotropins were further suppressed in TRT as expected. Although the current data on GLP1-receptor analogs and reproduction are scarce, some animal studies demonstrated the potential involvement of GLP1 in the direct regulation of the hypothalamus-pituitary system. Intracerebroventricular injection of GLP1 increased the levels of LH in rats (30). Furthermore, in response to fasting, the rats' hypothalamic GLP1 content significantly decreased when there was a rapid reduction in pituitary LH. Upon refeeding period GLP1 increased, perhaps aiding the recovery of LH secretion (14).

LIRA resulted in a significant weight loss of about 6% in men who had been poor responders to LSM. In agreement with our study the data from SCALE trials reported similar but slightly pronounced weight loss ranging from 5.7% to 8% (31, 32, 33). By contrast, TRT in our study did not result in significant weight or waist circumference reduction. The contribution of TRT to WR is uncertain. While some studies and meta-analyses highlighted that TRT may reduce body weight in obese men (34, 35, 36, 37), few randomized, double-blind placebo controlled trials and a meta-analysis of RCT studies (38) have not confirmed those encouraging results (15, 39, 40).

As expected, LIRA improved glycemic control resulting in a significant decrease in HbA1c. Metabolic syndrome was resolved in two men treated with LIRA, while no such changes were observed in TRT. However, TRT led to significant improvement of IR as assessed by HOMA_{IR}. It is known that TRT might decrease IR by means of promoting the commitment of pluripotent stem cells into the myogenic lineage and inhibiting their differentiation into mature adipocyte (41). A compelling number of clinical studies demonstrated that TRT led to improvement in glycemic control and insulin sensitivity (4, 5, 37, 42), whereas some failed to confirm these observations (43).

Our study has some limitations. The conclusions are limited by a small sample size and short-term observation. Further larger studies of longer duration should be powered using these preliminary results. Libido and sexual function were not measured with validated tools, and therefore could be inaccurate. Furthermore, 11 out of 30 subjects had type 2 diabetes that could have an independent impact on HPT axis. However, the presence of type 2 diabetes was balanced between the groups and well controlled throughout the study. We assumed that a complex bidirectional relationship between dysglycemia and HPT was controlled in one direction. However, the main strength of this pilot study is the original concept of comparing TRT and liraglutide as a second-line approach in patients who had been poor responders to LSM. The design addressed a common clinical dilemma that is raised after LSM fails.

In conclusion, the pathophysiological background of FH supports a rationale for therapy, other than TRT. Body weight loss with LSM should be the first approach offered to obese men with FH. When LSM fails and bariatric surgery is not yet indicated, novel pharmacological anti-obesity strategies with liraglutide should be advised over TRT, by means of overall health improvement. We demonstrated that liraglutide had modest effect on testosterone levels, potential to improve sexual symptoms irrespective of modest increase in total testosterone, reversed the HPT axis suppression, reduced weight and waist circumference and improved glycemic control. Future studies should investigate the complex relationship between WR and FH beyond the mere impact of the magnitude of WR. Comparing different approaches for WR, including diet, exercises, GLP1 receptor agonists and bariatric surgery, might additionally enlighten the complex cross talks among gut, brain and reproductive axis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, *et al.* Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2737–2745. (<https://doi.org/10.1210/jc.2007-1972>)
- Grossmann M & Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 1067–1075. (<https://doi.org/10.1210/jc.2016-3580>)
- Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Lucchese M, Facciano E, Sforza A, Forti G, Mannucci E, *et al.* Body weight loss reverses obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *European Journal of Endocrinology* 2013 **168** 829–843. (<https://doi.org/10.1530/EJE-12-0955>)
- Heufelder AE, Saad F, Bunck MC & Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *Journal of Andrology* 2009 **30** 726–733. (<https://doi.org/10.2164/jandrol.108.007005>)
- Hoyos CM, Yee BJ, Phillips CL, Machan EA, Grunstein RR & Liu PY. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial. *European Journal of Endocrinology* 2012 **167** 531–541. (<https://doi.org/10.1530/EJE-12-0525>)
- Ng Tang Fui M, Prendergast LA, Dupuis P, Raval M, Strauss BJ, Zajac JD & Grossmann M. Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial. *BMC Medicine* 2016 **14** 153. (<https://doi.org/10.1186/s12916-016-0700-9>)
- Viltsboll T, Christensen M, Junker AE, Knop FK & Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2012 **344** d7771. (<https://doi.org/10.1136/bmj.d7771>)
- Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, Serrano V, Singh-Ospina N, Rodriguez-Gutierrez R, Salcido-Montenegro A, Benkhadra R, Prokop LJ, Bhasin S, *et al.* The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 1745–1754. (<https://doi.org/10.1210/jc.2018-00404>)
- Giagulli VA, Carbone MD, Ramunni MI, Licchelli B, De Pergola G, Sabba C, Guastamacchia E & Triggiani V. Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism. *Andrology* 2015 **3** 1094–1103. (<https://doi.org/10.1111/andr.12099>)
- MacLusky NJ, Cook S, Scrocchi L, Shin J, Kim J, Vaccarino F, Asa SL & Drucker DJ. Neuroendocrine function and response to stress in mice with complete disruption of glucagon-like peptide-1 receptor signaling. *Endocrinology* 2000 **141** 752–762. (<https://doi.org/10.1210/endo.141.2.7326>)
- Garris DR. Diabetes (db/db) mutation-induced endometrial epithelial lipoapoptosis: ultrastructural and cytochemical analysis of reproductive tract atrophy. *Reproductive Biology and Endocrinology* 2005 **3** 15. (<https://doi.org/10.1186/1477-7827-3-15>)
- Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G & Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. *Gynecological Endocrinology* 2015 **31** 196–201. (<https://doi.org/10.3109/09513590.2014.975686>)
- Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, *et al.* Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes and Endocrinology* 2018 **6** 105–113. ([https://doi.org/10.1016/S2213-8587\(17\)30412-6](https://doi.org/10.1016/S2213-8587(17)30412-6))
- Greco D. Normal pregnancy outcome after first-trimester exposure to liraglutide in a woman with type 2 diabetes. *Diabetic Medicine* 2015 **32** e29–e30. (<https://doi.org/10.1111/dme.12726>)
- Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM & Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2536–2559. (<https://doi.org/10.1210/jc.2009-2354>)
- Heinemann LA, Saad F, Zimmermann T, Novak A, Myon E, Badia X, Potthoff P, T'Sjoen G, Pollanen P, Goncharov NP, *et al.* The Aging Males' Symptoms (AMS) scale: update and compilation of international versions. *Health and Quality of Life Outcomes* 2003 **1** 15. (<https://doi.org/10.1186/1477-7525-1-15>)
- Vermeulen A, Verdonck L & Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 3666–3672. (<https://doi.org/10.1210/jcem.84.10.6079>)
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF & Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985 **28** 412–419. (<https://doi.org/10.1007/BF00280883>)
- Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, *et al.* Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003 **26** 3160–3167. (<https://doi.org/10.2337/diacare.26.11.3160>)
- Higgins JP, Thompson SG, Deeks JJ & Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003 **327** 557–560. (<https://doi.org/10.1136/bmj.327.7414.557>)
- Roy CN, Snyder PJ, Stephens-Shields AJ, Artz AS, Bhasin S, Cohen HJ, Farrar JT, Gill TM, Zeldow B, Cella D, *et al.* Association of testosterone levels with anemia in older men: a controlled clinical trial. *JAMA Internal Medicine* 2017 **177** 480–490. (<https://doi.org/10.1001/jamainternmed.2016.9540>)
- Camacho EM, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, Tajar A, Bartfai G, Boonen S, Casanueva FF, *et al.* Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *European Journal of Endocrinology* 2013 **168** 445–455. (<https://doi.org/10.1530/EJE-12-0890>)

- 23 Tsametis CP & Isidori AM. Testosterone replacement therapy: for whom, when and how? *Metabolism: Clinical and Experimental* 2018 **86** 69–78. (<https://doi.org/10.1016/j.metabol.2018.03.007>)
- 24 Seftel AD, Mack RJ, Secrest AR & Smith TM. Restorative increases in serum testosterone levels are significantly correlated to improvements in sexual functioning. *Journal of Andrology* 2004 **25** 963–972. (<https://doi.org/10.1002/j.1939-4640.2004.tb03169.x>)
- 25 Wu F, Zitzmann M, Heiselman D, Donatucci C, Knorr J, Patel AB & Kinchen K. Demographic and clinical correlates of patient-reported improvement in sex drive, erectile function, and energy with testosterone solution 2. *Journal of Sexual Medicine* 2016 **13** 1212–1219. (<https://doi.org/10.1016/j.jsxm.2016.05.010>)
- 26 Giagulli VA, Kaufman JM & Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 997–1000. (<https://doi.org/10.1210/jcem.79.4.7962311>)
- 27 Vermeulen A, Kaufman JM & Giagulli VA. Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 1821–1826. (<https://doi.org/10.1210/jcem.81.5.8626841>)
- 28 Michalakakis K, Mintziore G, Kaprara A, Tarlatzis BC & Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. *Metabolism: Clinical and Experimental* 2013 **62** 457–478. (<https://doi.org/10.1016/j.metabol.2012.08.012>)
- 29 Burcelin R, Thorens B, Glauser M, Gaillard RC & Pralong FP. Gonadotropin-releasing hormone secretion from hypothalamic neurons: stimulation by insulin and potentiation by leptin. *Endocrinology* 2003 **144** 4484–4491. (<https://doi.org/10.1210/en.2003-0457>)
- 30 Jeibmann A, Zahedi S, Simoni M, Nieschlag E & Byrne MM. Glucagon-like peptide-1 reduces the pulsatile component of testosterone secretion in healthy males. *European Journal of Clinical Investigation* 2005 **35** 565–572. (<https://doi.org/10.1111/j.1365-2362.2005.01542.x>)
- 31 Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, Le Roux CW, Violante Ortiz R, Jensen CB, *et al.* A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *New England Journal of Medicine* 2015 **373** 11–22. (<https://doi.org/10.1056/NEJMoa1411892>)
- 32 Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, Andreasen AH, Jensen CB, DeFronzo RA & NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients With Type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* 2015 **314** 687–699. (<https://doi.org/10.1001/jama.2015.9676>)
- 33 Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, Claudius B, Jensen CB & Mignot E. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *International Journal of Obesity* 2016 **40** 1310–1319. (<https://doi.org/10.1038/ijo.2016.52>)
- 34 Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, Morales AM, Volterrani M, Yellowlees A, Howell JD, *et al.* Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study) *Diabetes Care* 2011 **34** 828–837. (<https://doi.org/10.2337/dc10-1233>)
- 35 Hackett G, Cole N, Bhartia M, Kennedy D, Raju J & Wilkinson P. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *Journal of Sexual Medicine* 2013 **10** 1612–1627. (<https://doi.org/10.1111/jsm.12146>)
- 36 Corona G, Monami M, Rastrelli G, Aversa A, Sforza A, Lenzi A, Forti G, Mannucci E & Maggi M. Type 2 diabetes mellitus and testosterone: a meta-analysis study. *International Journal of Andrology* 2011 **34** 528–540. (<https://doi.org/10.1111/j.1365-2605.2010.01117.x>)
- 37 Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P & BLAST Study Group. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. *Journal of Sexual Medicine* 2014 **11** 840–856. (<https://doi.org/10.1111/jsm.12404>)
- 38 Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, Saad F, Mannucci E & Maggi M. THERAPY OF ENDOCRINE DISEASE: Testosterone supplementation and body composition: results from a meta-analysis study. *European Journal of Endocrinology* 2016 **174** R99–R116. (<https://doi.org/10.1530/EJE-15-0262>)
- 39 Wang C, Jackson G, Jones TH, Matsumoto AM, Nehra A, Perelman MA, Swerdloff RS, Traish A, Zitzmann M & Cunningham G. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care* 2011 **34** 1669–1675. (<https://doi.org/10.2337/dc10-2339>)
- 40 Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, *et al.* Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *European Journal of Endocrinology* 2008 **159** 507–514. (<https://doi.org/10.1530/EJE-08-0601>)
- 41 Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF & Bhasin S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology* 2003 **144** 5081–5088. (<https://doi.org/10.1210/en.2003-0741>)
- 42 Groti K, Zuran I, Antonic B, Forsnaric L & Pfeifer M. The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. *Aging Male* 2018 **21** 158–169. (<https://doi.org/10.1080/13685538.2018.1468429>)
- 43 Gianatti EJ, Dupuis P, Hoermann R, Zajac JD & Grossmann M. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3821–3828. (<https://doi.org/10.1210/jc.2014-1872>)

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