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ARTICLE

Time-related increase in urinary testosterone levels and stable semen analysis parameters after bariatric surgery in men

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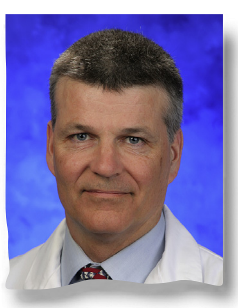

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Abstract The aim of this prospective cohort study was to determine the time-course in androgen and semen parameters in men after weight loss associated with bariatric surgery. Six men aged 18–40 years, meeting National Institutes of Health bariatric surgery guidelines, were followed between 2005 and 2008. Study visits took place at baseline, then 1, 3, 6 and 12 months after surgery. All men underwent Roux-en-y gastric bypass (RYGB). At each visit, biometric, questionnaire, serum, and urinary specimens and seman analysis were collected. Urinary integrated total testosterone levels increased significantly ($P < 0.0001$) by 3 months after surgery, and remained elevated throughout the study. Circulating testosterone levels were also higher at 1 and 6 months after surgery, compared with baseline. Serum sex hormone-binding globulin levels were significantly elevated at all time points after surgery ($P < 0.01$ to $P = 0.02$). After RYGB surgery, no significant changes occurred in urinary oestrogen metabolites (oestrone 3-glucuronide), serum oestradiol levels, serial semen parameters or male sexual function by questionnaire. A threshold of weight loss is necessary to improve male reproductive function by reversing male hypogonadism, manifested as increased testosterone levels. Further serial semen analyses showed normal ranges for most parameters despite massive weight loss.

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KEYWORDS: androgens, hypogonadism, obesity, semen, sexual dysfunction, weight loss

Introduction

Obesity in men is associated with various reproductive abnormalities, including hypogonadism (Schneider et al., 1979), abnormalities in semen quality (Reis and Dias, 2012), erectile dysfunction and diminished sexual desire (Hammoud et al., 2009), and lower rates of paternity (Pauli et al., 2008). These abnormalities are interrelated and may primarily stem from diminished androgen production and circulating levels (Hammoud et al., 2009). Increased peripheral conversion of androgens into weak bioactive oestrogens by excess adipose tissue may further exacerbate these symptoms (Schneider et al., 1979). This, in turn, analogous to polycystic ovary syndrome in women, can lead to a vicious circle of inappropriate sex steroid feedback upon the hypothalamic-pituitary-gonadal axis (Rebar et al., 1976) and, in men, to a persistent hypogonadal state (George et al., 2010).

Weight loss, both by diet and lifestyle, or more profoundly after bariatric surgery, is associated with an improvement in male reproduction function. Studies have documented an increase and normalization of circulating testosterone levels, improved sexual function but marked reduction in semen quality (Hammoud et al., 2009; Lazaros et al., 2012; Sermondade et al., 2012). Most of these studies have been limited by a two-time point analysis, before and after intervention. Bariatric surgery provides a useful model to look at the effects of progressive weight loss over many time points and to better quantitate the relationship between weight loss and improvement in reproductive function. Also, after bariatric surgery compliance with caloric restriction is higher compared with lifestyle studies owing to the restrictive effects of most bariatric surgery on ingestive behaviour.

We recently reported on this model in a cohort of women undergoing Roux-en-Y gastric bypass (RYGB) surgery (Legro et al., 2012). A similar pilot study was subsequently conducted in a group of men, which is reported here. As in the female study, a daily collection of urine was instituted to better understand changes in the excretion of sex steroid hormones (testosterone and oestradiol metabolites) and to better define the effects of time and weight loss on reproductive function in men.

Materials and methods

Participants

The protocol was reviewed and approved by the Institutional Review Board at Penn State College of Medicine (IRB Study Number: PRAMS019366A, Initial Approval: 1 September, 2005). Men were recruited between 2005 and 2008 and studied for up to 2 years afterwards. All participants gave written informed consent. The study was terminated on1 January, 2010, owing to close-out of the grant, and planned visits beyond this date could not be completed.

Inclusion ages were 18–40 years. The 1991 National Institutes of Health guidelines for bariatric surgery were followed (Anonymous, 1991): body mass index (BMI) above 40 kg/m^2 or a BMI between 35 and 39.9 kg/m^2, with a weight-related health problem such as diabetes or high blood pressure, and failed medical weight loss. Exclusion criteria included smoking or a history of alcohol or substance abuse. Patients with obesity caused by hypothyroidism, Cushing's syndrome, or genetic predisposition were excluded. Our study was limited to men who had undergone RYGB surgery.

Visits

Six visits were planned during the study. A preoperative study visit was carried out 1 month before gastric bypass surgery, then visits at 1, 3, 6, and 12 months after surgery. An additional visit was also planned at 24 months, but owing to funding issues and closeout of the grant, this visit could not be undertaken in most participants and, therefore, do not report any data from this visit (Legro et al., 2012). At each visit, a history was taken and physical examination carried out. Fasting blood was obtained in the morning, body composition was obtained via electroimpedance using a Tanita Model 310 Body Composition Analyzer and daily urine collections were delivered. Participants were instructed to collect first void daily urine samples from the preoperative visit until 1 month after, then for a month before each subsequent visit. Visits were scheduled to correspond to regular bariatric surgery follow-ups.

Before and 12 months after bariatric surgery, participants filled out the Sexual Health Inventory for Men (SHIM), a brief multidimensional scale for assessing erectile dysfunction in men (Cappelleri and Rosen, 2005). The scores can range from 1 to 25, where 1–7 is severe erectile dysfunction, 8–11is moderate, 12–16 is mild to moderate, 17–21 is mild, and 22–25 is non-existent erectile dysfunction.

Semen analysis

Semen was collected at each visit after a period of abstinence ranging from 2–7 days. After liquefacation, volume was determined with a 5 ml pipette. Concentration was determined by microscopic counting of sperm in a haemacytometer and motility by microscopic counting of motile sperm (at least 100) with a microcell chamber. Morphology was determined using Spermac staining and strict Kruger criteria (Kruger et al., 1988).

Assays

Fasting serum collected in the morning from each visit was assayed for oestradiol, total testosterone, and sex hormone binding globulin (SHBG) as previously reported (Legro et al., 2008, 2012). Every third daily urine sample collected was assayed. Urinary estrone 3-glucuronide ($E_1$3G) was measured in triplicate using a competitive double-antibody time-resolved fluoroimmunoassay (Kesner et al., 1994; Legro et al., 2012). Total testosterone was measured in duplicate in hydrolyzed urine samples using a radioimmunoassay (Siemens Coat-A-Count; cat no. TKTT5). The free androgen index (FAI) is calculated from measurable values for total testosterone and SHBG, using the following equation: (FAI = total testosterone in nmol/L/SHBG in nmol/L) × 100. Urinary $E_1$3G and total testosterone values were divided by urinary creatinine concentrations to standardize for urine flow rate. All assays had a coefficient of variation less than or equal to 10%.

Statistical analysis

Primary outcome

The primary outcomes were changes in monthly serum and mean urinary total testosterone concentrations and semen analyses parameters at the various time points before and after surgery. An a-priori power analysis was conducted, and a sample size of 20 men was reached, which would provide at least 86% power to detect an effect size, $|\mu_d|/\sigma$, of 0.9 ng testosterone/mg Cr between any two visits using a two-sided, paired t-test with a family wise type I error of 0.05. Secondary outcomes included changes in body weight and body composition, other circulating hormones, urinary oestrogen levels and erectile function. Enrolment was ceased after six particpants were enrolled owing to limited funding.

Mixed-effects models were used to test for changes in the primary and secondary end-points after surgery (Laird and Ware, 1982). A separate model was fit for each end-point. Data were analysed at five time points: before and 1, 3, 6, and 12 months after surgery. Contrasts were constructed to compare each post-surgical time point to the pre-surgical time point. Residual diagnostics from the mixed-effects models were examined to ensure the parametric modelling assumptions were met. All calculations were done with SAS® (Version 9.2, SAS Institute, Inc., Cary, North Carolina). $P < 0.05$ was considered to be statistically significant.

Results

Nine men were screened and six were enrolled into the study. The median (minimum, maximum) age of the enrolled participants was 37.5 (30, 40) years. Biometric, serum endocrine, and semen measurements before and after surgery are presented in **Table 1**.

Urinary total testosterone levels, normalized to creatinine, increased significantly by 3 months after RYGB surgery, compared with baseline, and remained elevated at subsequent visits to 12 months after surgery ($P < 0.0001$) (**Figure 1**). Serum total testosterone levels were also higher at 1 month ($P < 0.01$) and 6 months ($P = 0.01$) after surgery compared with baseline (**Table 2**). Serum SHBG levels significantly increased by 1 month after surgery, and remained elevated up to 12 months after surgery ($P < 0.01$ to $P = 0.02$) (**Table 2**).

Neither urinary $E_1$3G (**Figure 1**) nor circulating oestradiol levels (**Table 2**) significantly changed after surgery. Urinary creatinine concentrations increased for 3 months after surgery ($P < 0.0001$), and then declined over time to baseline (**Figure 1**). Sperm concentrations tended to decrease 1 month after surgery, but then returned to pre-operative levels by 12 months (**Table 2**). Relative to pre-surgical assessment, male erectile function, as captured by the SHIM, tended to improve by 12 months (13.5 ± 8.9 versus 18.0 ± 8.4).

Discussion

Our study showed a significant improvement in urinary total testosterone levels within 3 months after RYGB surgery, which plateaued for the next 9 months despite continued weight loss. This suggests a threshold effect of weight loss rather than a dose-response change in testosterone excretion with increasing weight loss. This was associated with a similarly sustained increase in serum levels of total testosterone and SHBG after surgery. No changes were found in semen parameters or oestrogen concentrations in serum or urine. Although the sample size is small, the repeated measures of semen analysis from before surgery to 12 months after surgery is novel. As such, the persistence of normal semen parameters during massive weight loss are reassuring. A non-significant trend was observed towards enhanced male erectile function 12 months after surgery. As in our previous study of women (Legro et al., 2012), urinary creatinine levels increased for 3 months after surgery, which we attribute primarily to muscle loss during this period.

The strengths of our study include the detailed time-course for endocrine along with semen parameters in men after RYGB surgery. Endocrine assessment was expanded to include urinary measurements, which are valuable in epidemiological studies and even clinically. The weaknesses includes the small sample size, which did not meet our statistically powered target sample size. Limited power is likely to be the main cause of our inability to detect changes in additional biological end-points after RYGB surgery. Larger studies have supported an improvement in circulating sex steroid levels, increased SHBG levels and improved erectile function after bypass surgery (Hammoud et al., 2009). The primary reason for the low male enrolment is that, compared with women, relatively few men elect RYGB surgery. A similar proportion of men (6/9 [67%]) and women (29/41 [71%]) who we screened for the study, however, were qualified and agreed to participate in our detailed studies of reproductive function before and after surgery (Legro et al., 2008).

Our findings are consistent with other detailed studies of significant weight loss in obese men, which have also reported an improvement in androgen levels as well as increases in SHBG levels (Reis et al., 2010; Strain et al., 1988). The elevated urinary circulating testosterone levels are most likely caused by increased gonadal production of testosterone, not by increased clearance of testosterone from the blood or reduced peripheral conversion of testosterone to oestrogens. Increased testosterone levels may be responsible for the trend towards improved male erectile function noted in our study and other larger studies of men after bariatric surgery (Hammoud et al., 2009), despite the increase in SHBG that is most likely to be related to decreased weight and insulin resistance. Improved mood and body image with weight loss may also be a factor as observed in women (Legro et al., 2012), but we did not track these in men.

These endocrine changes may, independent of oestrogen levels, alter hypothalamic-pituitary-gonadal function. Weight

Table 1 Baseline and post-surgery biometric, serum endocrine and semen parameters.

Parameters	*Baseline*	*1 month after surgery*	*3 months after surgery*	*6 months after surgery*	*12 months after surgery*
	Mean (SD) median (minimum, maximum)	*Mean (SD) median (minimum, maximum)*	*Mean (SD) median (minimum, maximum)*	*Mean (SD) median (minimum, maximum)*	*Mean (SD) median (minimum, maximum)*
Biometric	*n* = 6	*n* = 6	*n* = 6	*n* = 6	*n* = 5
Weight (kg)	166 (36)	146 (35)	134 (36)	120 (33)	111 (30)
	156 (139, 238)	136 (124, 216)	121 (112, 207)	112 (95, 183)	103 (85, 162)
BMI (kg/m^2)	48 (7)	43 (7)	39 (8)	35 (7)	32 (7)
	47 (41, 62)	41 (36, 57)	37 (33, 54)	34 (28, 48)	31 (26, 43)
Fat (%)	46 (4)	45 (9)	36 (6)	31 (10)	29 (13)
	47 (39, 51)	44 (32, 57)	37 (25, 42)	32 (19, 46)	31 (15, 47)
Endocrine	*n* = 6	*n* = 6	*n* = 6	*n* = 6	*n* = 5
Serum oestradiol (pmol/L)	105 (31)	124 (33)	127 (62)	123 (45)	81 (55)
	106 (55, 136)	132 (81, 165)	125 (37, 228)	103 (88, 198)	62 (37, 176)
Serum testosterone (nmol/L)	15 (6)	20 (5)	18 (6)	21 (4)	20 (3)
	15 (8, 23)	22 (12, 27)	20 (9, 26)	22 (15, 27)	20 (15, 23)
Serum SHBG (nmol/L)	30 (15)	54 (21)	47 (25)	51 (28)	59 (29)
	25 (14, 56)	54 (24, 79)	44 (18, 90)	48 (21, 98)	64 (19, 90)
Free androgen index	53 (11)	41 (10)	43 (10)	50 (19)	47 (37)
	50 (41, 69)	44 (28, 50)	44 (28, 56)	51 (24, 71)	33 (17, 106)
Semen	*n* = 4	*n* = 4	*n* = 4	*n* = 4	*n* = 3
Volume (ml)	2.1 (1.1)	2.7 (1.3)	3.0 (1.2)	2.4 (0.9)	2.0 (2.0)
	2.0 (0.7, 3.5)	2.6 (1.2, 4.3)	2.7 (2.0, 4.5)	2.6 (1.0, 3.2)	1.0 (0.8, 4.3)
Concentration (million/ml)	65 (73)	23 (28)	30 (28)	50 (63)	99 (148)
	44 (3, 170)	13 (3, 63)	22 (6, 68)	29 (1, 140)	25 (3, 270)
Motility (%)	46 (25)	44 (9)	55 (16)	48 (23)	55 (28)
	57 (9, 62)	46 (32, 53)	57 (35, 69)	56 (15, 67)	59 (25, 80)
Normal morphology (%)	10 (8)	13 (15)	13 (11)	8 (9)	7 (11)
	10 (0, 20)	9 (2, 34)	10 (5, 29)	4 (1, 18)	1 (0, 19)

BMI = body mass index.

Table 2 Post-surgery change from baseline in biometric, serum endocrine and semen parameters.

Parameters	*1 month after surgery change from baseline*		*3 months after surgery change from baseline*		*6 months after surgery change from baseline*		*12 months after surgery change from baseline*	
	Estimated mean change (95% CI)	*P-value*	*Estimated mean change (95% CI)*	*P-value*	*Estimated mean change (95% CI)*	*P-value*	*Estimated mean change (95% CI)*	*P-value*
Biometric	$n = 6$		$n = 6$		$n = 6$		$n = 5$	
Weight (kg)	−19 (−25, −14)	<0.01	−32 (−39, −24)	<0.01	−46 (−56, −37)	<0.01	−55 (−69, −41)	<0.01
BMI (kg/m^2)	−6 (−9, −3)	<0.01	−9 (−13, −5)	<0.01	−12 (−17, −6)	<0.01	−14 (−21, −7)	<0.01
Fat (%)	−1 (−6, 3)	NS	−11 (−17, −4)	<0.01	−16 (−24, −8)	<0.01	−17 (−27, −7)	<0.01
Endocrine	$n = 6$		$n = 6$		$n = 6$		$n = 5$	
Serum oestradiol (pmol/l)	19 (−15, 53)	NS	22 (−22, 66)	NS	18 (−33, 69)	NS	−26 (−85, 34)	NS
Serum testosterone (nmol/l)	5 (2, 8)	<0.01	4 (0, 8)	NS	6 (2, 11)	0.01	4 (−1, 10)	NS
Serum SHBG (nmol/l)	24 (15, 32)	<0.01	17 (5, 29)	0.01	21 (6, 37)	0.01	25 (5, 46)	0.02
Free androgen index	−12 (−21, −2)	0.02	−9 (−22, 3)	NS	−3 (−19, 14)	NS	−2 (−24, 20)	NS
Semen	$n = 4$		$n = 4$		$n = 4$		$n = 3$	
Volume (ml)	0.6 (−1.7, 2.9)	NS	0.9 (−1.4, 3.2)	NS	0.3 (−1.9, 2.5)	NS	0.0 (−2.2, 2.2)	NS
Concentration (million/ml)	−42 (−92, 8)	NS	−35 (−104, 34)	NS	−15 (−103, 73)	NS	33 (−88, 154)	NS
Motility (%)	−2 (−27, 22)	NS	8 (−22, 39)	NS	2 (−33, 37)	NS	10 (−31, 51)	NS
Normal morphology (%)	3 (−15, 22)	NS	3 (−14, 20)	NS	−2 (−21, 16)	NS	−3 (−22, 15)	NS

BMI = body mass index; CI = confidence interval; NS = not statistically significant.

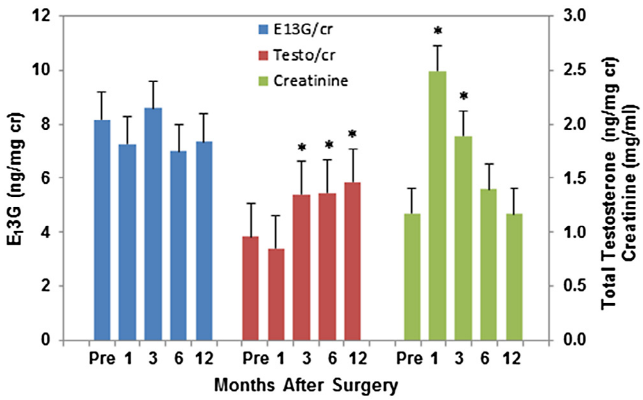

Figure 1 Urinary concentrations (means + SE) of $E_1$3G, total testosterone and creatinine in men before and 1, 3, 6 and 12 months after Roux-en-y gastric bypass surgery. $E_1$3G and testosterone levels are corrected for creatinine. Asterisks indicate differences ($P < 0.0001$) between post-surgical and pre-surgical measurements. $n = 6$ at all times except $n = 5$ at 12 months.

loss after bariatric surgery is associated with increased circulating levels of FSH (Facchiano et al., 2013; Pellitero et al., 2012; Reis et al., 2010; Strain et al., 1988) and occasionally LH (Facchiano et al., 2013). Some have reported that serum oestradiol levels decrease with BMI in men (Facchiano et al., 2013; Hammoud et al., 2009; Pellitero et al., 2012).

Although other studies of semen quality after bariatric surgery have had larger samples sizes (up to 20 participants) (Reis et al., 2010), most studies have assessed 10 participants or fewer and lack multiple time points of observation beginning before surgery. Therefore, publication bias tends to occur with smaller case studies showing dramatic reductions in sperm parameters after surgery (Lazaros et al., 2012; Sermondade et al., 2012). Although our study, with more frequent sampling of semen parameters, initially detected a numerical reduction in sperm concentration after surgery, this trend was neither statistically significant nor sustained. Another recent larger study also failed to detect reduced sperm concentrations after 4 and 24 months (Reis et al., 2010). Larger studies are needed to more reliably assess the effects of weight loss on this outcome.

Although the present study is small, it supports an improvement in male reproductive function after RYGB surgery as shown by increased serum and urinary testosterone levels. Further study of reproductive changes and especially effects on male fertility are needed.

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