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## Time Related Increase in Urinary Testosterone Levels and Stable Semen Analysis Parameters after Bariatric Surgery in Men

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### Abstract

We sought to determine the time-course in androgen and semen parameters in men after weight loss associated with bariatric surgery with a prospective cohort study of 6 male subjects, age 18-40 years, meeting NIH bariatric surgery guidelines, conducted in 2005-2008, with study visits at baseline, then 1, 3, 6 and 12 months after surgery. All men had a Roux-en-y-Gastric-Bypass (RYGB) performed at Penn State Milton S. Hershey Medical Center. We collected at each visit biometric, questionnaire, serum, and urinary specimens as well as a semen analysis. Urinary integrated total testosterone levels increased significantly 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 to baseline. Serum SHBG levels were significantly elevated at all time points post-operatively. After RYGB surgery, there were no significant changes in urinary estrogen metabolites (estrone 3-glucuronide) or serum estradiol levels, serial semen parameters, or male sexual function by questionnaire. This study supports the idea that a threshold of weight loss is necessary to improve male reproductive function by reversing male hypogonadism, manifested as increased testosterone levels. Further serial semen analysis results showed normal ranges for most parameters despite massive weight loss.

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### AUTHORS' ROLES

RSL, ARK, AMR and RNC contributed to the conception and design, acquisition of data, and analysis and interpretation of data. JWM, JSK, and EFK contributed to the acquisition of data, and analyses and interpretation of data. All authors contributed to the drafting and revision of the manuscript and approved the final submitted version.

## Keywords

hypogonadism; sexual dysfunction; obesity; androgens; semen; weight loss

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## 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, Gibson, Hunt, Adams, Carrell, Kolotkin and Meikle, 2009). Increased peripheral conversion of androgens into weak bioactive estrogens by excess adipose tissue may further exacerbate these symptoms (Schneider, Kirschner, Berkowitz and Ertel, 1979). This, in turn, analogous to polycystic ovary syndrome (PCOS) 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, Gibson, Hunt, Adams, Carrell, Kolotkin and Meikle, 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. Further, there is a higher compliance with caloric restriction after bariatric surgery as compared with lifestyle studies due to restrictive effects of most bariatric surgery on ingestive behavior.

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

## MATERIALS AND METHODS

### Subjects

The protocol was reviewed and approved by the Institutional Review Board at Penn State College of Medicine. Men were recruited between 2005 and 2008 and studied for up to two years afterwards. All subjects gave written informed consent. Due to close-out of the grant, the study was terminated on January 1, 2010 and planned visits beyond this date could not be completed.

Inclusion ages were 18-40 years. The 1991 NIH Guidelines for bariatric surgery were followed (1991): body mass index (BMI) above 40 kg/m<sup>2</sup> or a BMI between 35 and 39.9 kg/m<sup>2</sup> 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. Subjects with obesity caused by hypothyroidism, Cushing's syndrome, or genetic predisposition were excluded. We limited our study to subjects who had undergone RYGB surgery.

## Visits

There were six visits planned during the study. A preoperative study visit was performed one month prior to gastric bypass surgery, then visits at 1, 3, 6, and 12 months after surgery. An additional visit was also planned at 24 months, but due to funding issues and closeout of the grant we were unable to obtain this visit in most participants and therefore do not report any data from this visit (Legro, et al., 2012). At each visit, a history and physical exam was performed, 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. Subjects were instructed to collect first void daily urine samples from the preoperative visit until one month after, then for a month prior to each subsequent visit. Visits were scheduled to correspond with regular bariatric surgery follow-ups.

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

**Semen Analysis**—Semen was collected at each visit after a period of abstinence ranging from 2 to 7 days. After liquefaction, volume was determined with a 5 mL pipette, concentration was determined. Concentration was determined by microscopic counting of sperm in a hemacytometer 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, 1998).

**Assays**—Fasting serum collected in the a.m. from each visit was assayed for estradiol, total testosterone, and sex hormone binding globulin (SHBG) as previously reported (Legro, Dodson, Gnatuk, Estes, Kunselman, Meadows, Kesner, Krieg, Rogers, Haluck and Cooney, 2012, Legro, et al., 2008). Every third daily urine sample collected was assayed. Urinary estrone 3-glucuronide (E<sub>1</sub>3G) was measured in triplicate using a competitive double-antibody time-resolved fluoroimmunoassay (Kesner, et al., 1994, Legro, Dodson, Gnatuk, Estes, Kunselman, Meadows, Kesner, Krieg, Rogers, Haluck and Cooney, 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 T and SHBG, using the following equation: (FAI = Total testosterone in nmol/L / SHBG in nmol/L) X 100. Urinary E<sub>1</sub>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 the monthly serum and mean urinary total testosterone concentrations and semen analyses parameters at the various time points before and after surgery. We performed an *a priori* power analysis and arrived at a sample size of 20 men, 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 estrogen levels, and erectile function. Due to limited funding we had to cease enrollment after we had enrolled 6 subjects into this study.

Mixed-effects models were used to test for changes in the primary and secondary endpoints after surgery (Laird and Ware, 1982). A separate model was fit for each endpoint. Data were analyzed at 5 time points: before and 1, 3, 6, and 12 months after surgery. Contrasts were constructed to compare each post-surgery time point to the pre-surgical time point. Residual diagnostics from the mixed-effects models were examined to ensure the parametric modeling assumptions were met. All calculations were done with SAS<sup>®</sup> (Version 9.2, SAS Institute, Inc., Cary, North Carolina).

## RESULTS

We screened 9 men and enrolled 6 subjects in the study. The median [minimum, maximum] age of the enrolled subjects was 37.5 [30, 40] years. Biometric, serum endocrine, and semen measurements before and after surgery are presented in **Table I**.

Urinary total testosterone levels, normalized to creatinine, increased significantly by 3 months after RYGB surgery, compared to baseline, and remained elevated at subsequent visits through 12 months after surgery ( $P < 0.01$ ) (**Figure 1**). Serum total testosterone levels were also higher at 1 month ( $P < 0.01$ ), 3 months ( $P=0.08$ ), and 6 months ( $P < 0.01$ ) after surgery compared to baseline (**Table 2**). Serum SHBG levels significantly increased by 1 month post operatively, and remained elevated through 12 months after surgery (**Table 2**).

Neither urinary E<sub>1</sub>3G nor circulating estradiol levels significantly changed after surgery. Urinary creatinine concentrations increased for 3 months after surgery ( $P < 0.01$ ), and then declined over time to baseline. Sperm concentrations tended to decrease 1 month after surgery ( $P=0.11$ ), but then returned to pre-operative levels by 12 months. Relative to pre-surgical assessment, male erectile function, as captured by the SHIM, tended to improve by 12 months ( $13.5 \pm 8.9$  vs  $18.0 \pm 8.4$ ,  $P = 0.13$ ).

## 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 post-operatively. We noted no changes in semen parameters or estrogen concentrations in serum or urine. Although our sample size is small, our repeated measures of semen analysis from pre-operative to 12 months post operatively are novel. As such they are reassuring about the persistence of normal semen parameters during massive weight loss. There was a nonsignificant trend towards enhanced male erectile function 12 months after surgery. And, 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. We expanded the endocrine assessment to include urinary measurements, which are valuable in epidemiological studies and even clinically. The weaknesses include the small sample size, which did not meet our statistically powered target sample size. Our inability to detect changes in additional biological endpoints after RYGB surgery is likely primarily due to limited power. Larger studies have supported an improvement in circulating sex steroid levels, increased SHBG levels and improved erectile function after bypass surgery (Hammond et al., 2009). The primary reason for the low male enrollment is that, compared to women, relatively few men elect RYGB surgery. But, a similar proportion of men (6 of 9 = 67%) and women (29 of 41 = 71%) who we screened for the study, 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 also have noted primarily 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 due to increased gonadal production of testosterone, not to increased clearance of testosterone from the blood or reduced peripheral conversion of testosterone to estrogens. Increased testosterone levels are probably responsible for the trend towards improved male erectile function noted in our study and other larger studies of men after bariatric surgery (Hammoud, Gibson, Hunt, Adams, Carrell, Kolotkin and Meikle, 2009), despite the increase in SHBG that is likely related to decreased weight and insulin resistance. Improved mood and body image with weight loss may also be a factor as we have noted in women (Legro et al, 2012), but we did not track these in men.

These endocrine changes may, independent of estrogen levels, alter hypothalamic-pituitary-gonadal function. Weight loss after bariatric surgery is associated with increased circulating levels of FSH (Facchiano, et al., 2013, Pellitero, et al., 2012, Reis, Favaro, Barreiro, de Oliveira, Chaim, Fregonesi and Ferreira, 2010, Strain, Zumoff, Miller, Rosner, Levit, Kalin, Hershcopf and Rosenfeld, 1988) and occasionally LH (Facchiano, Scaringi, Veltri, Samavat, Maggi, Forti, Luconi and Lucchese, 2013). Some have reported that serum estradiol levels decrease with BMI in men (Facchiano, Scaringi, Veltri, Samavat, Maggi, Forti, Luconi and Lucchese, 2013, Hammoud, Gibson, Hunt, Adams, Carrell, Kolotkin and Meikle, 2009, Pellitero, Olaizola, Alastrue, Martinez, Granada, Balibrea, Moreno, Serra, Navarro-Diaz, Romero and Puig-Domingo, 2012).

Although other studies of semen quality after bariatric surgery have had larger samples sizes (up to 20 subjects) (Reis, Favaro, Barreiro, de Oliveira, Chaim, Fregonesi and Ferreira, 2010), most studies have assessed 10 subjects or less and lack multiple time points of observation beginning prior to surgery. Thus there is a tendency to publication bias with smaller case series showing dramatic reductions in sperm parameters after surgery (Lazaros, Hatz, Markoula, Takenaka, Sofikitis, Zikopoulos and Georgiou, 2012, Sermondade, Massin, Boitrelle, Pfeffer, Eustache, Sifer, Czernichow and Levy, 2012). While 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, Favaro, Barreiro, de Oliveira, Chaim, Fregonesi and Ferreira, 2010). Larger studies are needed to more reliably assess the effects of weight loss on this outcome.

Our study, though small, supports an improvement in male reproductive function after RYGB surgery as evidenced by increased serum and urinary testosterone levels. Further study of reproductive changes and especially effects on male fertility are needed.

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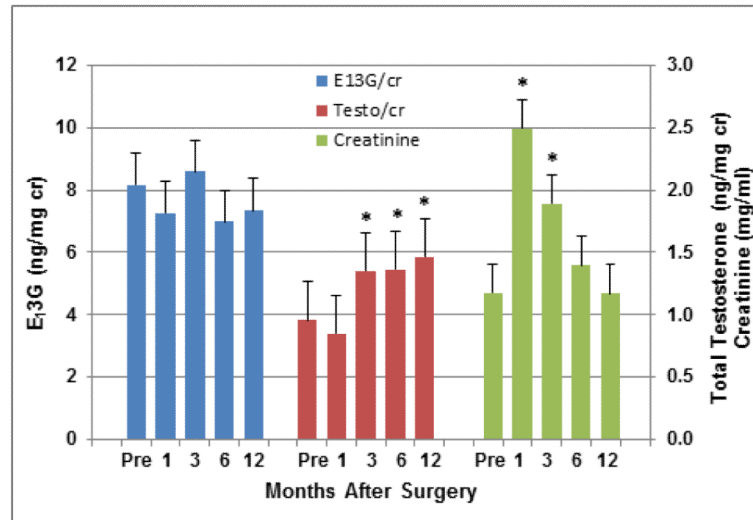
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**Figure 1.**

Urinary concentrations (means + SE) of E<sub>13</sub>G, total testosterone and creatinine in men before and 1, 3, 6 and 12 months after RYGB surgery. E<sub>13</sub>G 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.



**Table 1**

Baseline and post-surgery changes in biometric, serum endocrine and semen parameters.

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

**Table 2**

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

Parameters	1-month post-surgery change from baseline		3-month post-surgery change from baseline		6-month post-surgery change from baseline		12-month post-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
<b>Biometric</b>	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 <sup>2</sup> )	-6 (-9,-3)	<0.01	-9 (-13,-5)	<0.01	-12 (-17,-6)	<0.01	-14 (-21,-7)	<0.01
Fat %	-1 (-6,3)	0.53	-11 (-17,-4)	<0.01	-16 (-24,-8)	<0.01	-17 (-27,-7)	<0.01
<b>Endocrine</b>	n=6		n=6		n=6		n=5	
Serum Estradiol (pmol/L)	19 (-15,53)	0.25	22 (-22,66)	0.31	18 (-33,69)	0.46	-26 (-85,34)	0.38
Serum Testosterone (nmol/L)	5 (2,8)	<0.01	4 (0,8)	0.08	6 (2,11)	0.01	4 (-1,10)	0.12
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)	0.14	-3 (-19,14)	0.74	-2 (-24,20)	0.83
<b>Semen</b>	n=4		n=4		n=4		n=3	
Vol. (mL)	0.6 (-1.7,2.9)	0.52	0.9 (-1.4,3.2)	0.40	0.3 (-1.9,2.5)	0.77	0.0 (-2.2,2.2)	0.99
Concentration (Million/mL)	-42 (-92,8)	0.09	-35 (-104,34)	0.29	-15 (-103,73)	0.71	33 (-88,154)	0.57
Motility %	-2 (-27,22)	0.84	8 (-22,39)	0.56	2 (-33,37)	0.90	10 (-31,51)	0.60
Normal Morphology %	3 (-15,22)	0.71	3 (-14,20)	0.69	-2 (-21,16)	0.79	-3 (-22,15)	0.70