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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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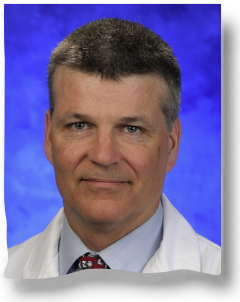

Dr Richard S. Legro is Professor at the Department of Obstetrics and Gynecology and Public Health Sciences at Penn State University College of Medicine in Hershey, PA. His research and clinical practice are primarily focused on diagnosis, treatment, and genetic and environmental causes of polycystic ovary syndrome, as well as on improving infertility diagnosis and treatment. He has been the principal investigator on a number of National Institutes of Health (NIH) grants and published over 200 peer-reviewed articles in medical journals and multiple books in the field of reproductive endocrinology.

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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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