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Inhibin-B Levels in Healthy Young Adult Men and Prepubertal Boys: Is Obesity the Cause for the Contemporary Decline in Sperm Count Because of Fewer Sertoli Cells?

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Abstract

Inhibin-B is a heterodimeric glycoprotein produced by Sertoli cells. Although inhibin-B levels are low when seminiferous tubules are damaged, studies in normal monkeys reveal that inhibin-B levels also correlate positively with Sertoli cell number. In this study, we measured inhibin-B levels in healthy young adult men aged 18–24 years and in prepubertal boys aged 5–9 years in relation to body mass index (BMI). Inhibin-B levels declined with increasing obesity in young adult men; values were 26% lower in men who were obese compared to normal-weight men. Sex hormone–binding globulin and total testosterone, but not free testosterone, were also lower with increasing BMI; serum follicle-stimulating hormone and luteinizing hormone levels were unaffected by obesity. In prepubertal boys, by contrast, inhibin-B was unaffected by obesity. We propose that reduced levels of inhibin-B indicate that obese men have fewer Sertoli cells than men of normal weight. Moreover, normal values in obese prepubertal boys suggest that the effect of obesity on inhibin-B is established during puberty. Finally, because each Sertoli cell is thought to support a finite number of germ cells, fewer Sertoli cells in obesity may predispose to a lower sperm count in adulthood. We speculate that the escalating prevalence of obesity and insulin resistance among adolescents might negatively influence male reproductive function for the next generation.

Key words: Male infertility, testis, puberty

Many studies have reported a decline in semen quality over the past 60 years (Sharpe, 1993; Jouannet et al, 2001). The explanation most offered for this trend has been the introduction into the environment of chemical disruptors with the properties of estrogens, androgens, or antiandrogens that might exert deleterious effects on pituitary testicular function (Akingbemi and Hardy, 2001). But whether the trace amounts of substances that migrate from commercial products into the environment truly influence male reproductive health remains unproven (Sharpe and Irvine, 2004).

Sertoli cells provide developing germ cells with structural and hormonal support (Mruk and Cheng, 2004). Experiments in newborn rats in which Sertoli cell proliferation was suppressed by treatment with cytosine arabinoside produced adult rats with a parallel reduction in round spermatids, whereas the number of spermatids per Sertoli cell was unaffected (Orth et al, 1988). These observations and others have led to the idea that the number of germ cells in adulthood is related directly to the number of functional Sertoli cells (Sharpe et al, 2003).

In humans, only about 10% of the adult complement of 4 billion Sertoli cells is present at birth (Cortes et al, 1987). Controlled studies in the nonhuman primate revealed that the number of Sertoli cells increases between the neonatal and the juvenile period, with a further increase during puberty (Simorangkir et al, 2003). Both the neonatal and the pubertal increase in Sertoli cell number are paralleled by a rise in circulating levels of inhibin-B (Andersson et al, 1998; Winters and Plant, 1999), and in normal adult rhesus monkeys, inhibin-B is strongly positively correlated with the number of Sertoli cells (Ramaswamy et al, 1999).

Obesity is known to suppress adult Leydig cell function (Vermeulen, 1996). In this study, we measured serum inhibin-B levels in 2 populations of normal male volunteers, prepubertal boys and young adult men, and have related inhibin-B to measures of overweight. From our findings, we propose that obesity suppresses Sertoli cell proliferation during puberty, and hypothesize that the rising prevalence of obesity has contributed to the contemporary decline in sperm production.

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Study Subjects

Blood samples were analyzed from 2 cross-sectional studies that were designed originally to examine racial differences in circulating androgens and sex hormone–binding globulin (SHBG). One study enrolled 74 African American and Caucasian young adult men ages 18–24 years who were recruited by advertisement from the undergraduate and graduate students at the University of Pittsburgh (Winters et al, 2001). Subjects with any active medical illness, history of gonadal dysfunction, daily use of alcohol, or status as elite athletes were excluded. The second study, conducted in Louisville, Ky, enrolled 48 African American and Caucasian boys between the ages of 5 and 9 years at the time of a routine school physical examination (Abdelrahaman et al, 2005). No subject had a chronic illness or was taking any regular medication. A physical examination that included height, weight, blood pressure, waist and hip circumference, and Tanner staging was performed, and a blood sample was obtained between 0830 and 1030 hours. Informed consent was obtained according to protocols approved by the Institutional Review Boards of the University of Pittsburgh and the University of Louisville.

Outcome Measures

In each study, testis size was estimated by 1 examiner using an orchidometer. Inhibin-B levels were measured with an Inhibin-B ELISA kit from DSLabs (Webster, Tex). The minimal detectable dose was 15 pg/mL, and the within- and between assay coefficients of variation were less than 7.5% and 14.8%, respectively. Serum levels of testosterone, SHBG, estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured using established immunoassays described previously (Abdelrahaman et al, 2005). Free testosterone was calculated from the levels of total testosterone and SHBG (Sodergard et al, 1982). Body mass index (BMI) was calculated as the ratio of weight (kg) to the square of height (m), and was plotted onto the BMI growth curve for boys (www.cdc.gov/growthcharts) to determine the BMI percentile. Boys were categorized as overweight if BMI percentile was greater than or equal to 85, or obese if BMI percentile was greater than or equal to 95.

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*Endocrine profiles in healthy young men in relation to body mass index**

Statistical Analysis

Data are presented as mean ± SEM. Mean hormone concentrations in normal-weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obese (BMI > 30 kg/m^2) men were compared by analysis of variance and Tukey's test. Scattergrams of inhibin-B were plotted by BMI, and subsequent Pearson correlation coefficients were computed to assess any linear relation between the variables. Inhibin-B was also regressed on BMI adjusting for age.

Results

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Of the 72 young adult men studied, 29% were overweight and 11% were obese. The Table compares the hormone levels in these men stratified according to BMI. As in many previous studies (Glass et al, 1981), SHBG levels decreased with increasing BMI. Total testosterone levels were slightly lower in obese men, but the difference did not achieve statistical significance. Inhibin-B levels declined with increasing BMI, and the levels in obese men were 26% less ($P < .05$) than those of normal-weight men. Serum free testosterone, LH, FSH, and estradiol were unaffected by BMI.

The scattergram in Figure 1 shows that a high BMI was associated with a reduced level of inhibin-B ($r = -.226$), although low levels were also found among normal-weight men. A plot of inhibin-B levels versus waist circumference produced a similar result ($r = -.23$; not shown). For the group as a whole, the level of inhibin-B decreased 4.57 pg per unit of BMI increase ($P = .075$). In whites, the BMI effect was more pronounced (inhibin-B decreased 10.00 pg per unit of BMI increase, $P = .03$) whereas in blacks the effect was not significant ($P = .63$).

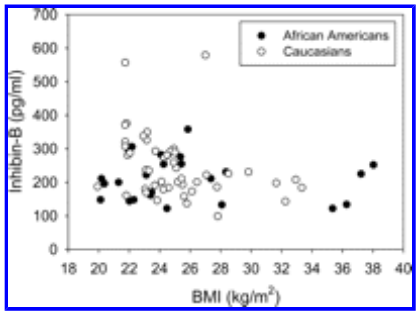

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Figure 1. Relationship between body mass index and inhibin-B in 72 healthy young adult men.

The 2000 Centers for Disease Control and Prevention BMI-for-Age Growth Chart was used to define boys as overweight or obese; according to this classification, 10 boys (21.7%) were overweight and 5 boys (10.9%) were obese. Inhibin-B levels in the 5 obese boys (74 ± 13 pg/mL) were comparable to the values in boys whose BMI was below the 95th percentile for age (79 ± 6 pg/mL). Figure 2 shows that inhibin-B levels in boys tend to rise (r = .21) with increasing BMI adjusted for age. There was no difference between African Americans and Caucasians. Furthermore, no relationship between inhibin-B and BMI (r = .09) or waist circumference (r = 2.09) was found in boys (not shown).

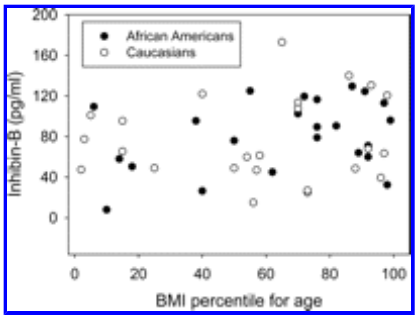

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Figure 2. Relationship between BMI and inhibin-B in 48 healthy young boys aged 5–9 years. BMI was calculated as the ratio of weight (kg) to the square of height (m), and was plotted onto the BMI growth curve for boys (www.cdc.gov/growthcharts) to determine the BMI percentile for age.

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In order to study the impact of obesity on Sertoli cells in normal children and young adults, in whom testicular biopsy cannot be performed for research purposes, we measured the levels of inhibin-B in serum. The results reveal that inhibin-B levels are lower in obese young adult men than in normal-weight men, whereas inhibin-B is unrelated to BMI among prepubertal boys. The variable relationship observed between inhibin-B and BMI among African American and Caucasian men is intriguing, and could be a consequence of racial differences in adipose tissue distribution (Hill et al, 1999), but conclusions will require confirmation in a larger study population.

Inhibin-B levels vary fourfold among fertile men (Andersson et al, 2004), but the determinants of

this between-subject variability have not been defined. There is no major moment-to-moment variation in circulating inhibin-B, although some men exhibit a diurnal variation that parallels that of testosterone (Carlsen et al, 1999). All blood samples in this study were drawn in the morning. Inhibin-B levels rise twofold to threefold during puberty to plateau by pubertal stage II–III (Andersson and Skakkebaek, 2001). Because inhibin-B levels are very low in men with congenital hypogonadotropic hypogonadism (Anawalt et al, 1996; Seminara et al, 1996), and increase as Sertoli cell number increases in juvenile monkeys administered gonadotropin-releasing hormone (GnRH), FSH, or LH (Marshall and Plant, 1996; Majumdar et al, 1997), the rise in inhibin-B during puberty is presumably attributable to Sertoli cell proliferation with increased GnRH-LH-FSH activation. From these findings, and the strong positive correlation between inhibin-B with the number of Sertoli cells (Ramaswamy et al, 1999), we propose that lower levels of inhibin-B among obese young adult men, together with unchanged values in boys, reflect suppressed Sertoli cell proliferation during puberty.

Although inhibin-B levels were reduced in obese men, FSH levels were normal. Inhibin functions to down-regulate the level of expression of the FSH-ß gene (Attardi et al, 1989). Accordingly, serum FSH levels tend to be elevated when the testes are damaged and circulating inhibin-B is reduced (Jensen et al, 1997). The finding of normal FSH levels in obese men in this study could reflect a limitation in study design, because LH and FSH are released into the circulation in pulses, and the single blood samples obtained may have provided insufficiently accurate information to identify small between-group differences. On the other hand, FSH levels are reduced in morbidly obese men (Strain et al, 2003), and the mechanisms responsible for that difference may have prevented a rise in FSH. Gonadotropin insufficiency is unlikely to have caused the low levels of inhibin-B, however, because LH and free testosterone as well as FSH were normal. Furthermore, inhibin-B levels in normal men declined only slightly during long-term gonadotropin suppression by testosterone (Matthiesson et al, 2003) or testosterone together with medroxyprogesterone acetate (McLachlan et al, 2002).

Low testosterone is an established consequence of obesity in adult men (Vermeulen, 1996), and is partly explained by a low level of SHBG (Glass et al, 1981). Free testosterone declines with extreme obesity, although the mechanisms for this decline are not well understood. SHBG and total testosterone were lower in the moderately obese subjects (BMI 31–38 kg/m^2) in this study, whereas free testosterone was normal. Mean LH levels (Strain et al, 2003) and LH pulse amplitude tend to decline in extremely obese adult men (BMI > 40 kg/m^2), whereas LH pulse frequency was reported to be normal (Giagulli et al, 1994). Decreased LH pulse amplitude could reflect less GnRH secreted per burst or reduced pituitary responsiveness to GnRH; however, reports of a normal response to administered GnRH (Glass et al, 1977) favor the former mechanism. Like free testosterone, LH levels were normal in the moderately obese subjects in our study.

Little information is so far available concerning the reproductive consequences of obesity in men. In a study from Argentina, 40% of men attending an infertility clinic were overweight (Oliva et al, 2001). In a recent study of military recruits from Denmark, men with BMI exceeding 25 kg/m^2 had a 23.9% lower total sperm count than men with a BMI of 20–25. Semen volume and the percentage of motile sperm were, on the other hand, unrelated to BMI. Serum FSH and inhibin-B levels, as well as SHBG and total testosterone, also decreased with increasing BMI in that study (Jensen et al, 2004). In a preliminary study, Pauli et al (2004) reported an inverse correlation between BMI and both FSH and inhibin-B, but no relation of BMI to the parameters of the semen analysis. In an earlier study of semen samples from 16 men who were 52%–332% above ideal body weight, the authors concluded that spermatogenesis in obese men was not different from that of historical controls (Strain et al, 1982). Globerman et al (2005) recently reported low levels of inhibin-B in some morbidly obese men that failed to rise after gastroplasty, although weight loss was associated with a rise in

testosterone. Their findings support the notion that inhibin-B levels are a surrogate marker for Sertoli cell number.

The prevalence of obesity among US adolescents has increased from 5% to 15.5% between the 1960s and 1999–2001 (Ogden et al, 2002). If our interpretation of the data is correct, the negative impact of obesity on Sertoli cell proliferation during puberty might substantially compromise male reproductive function for the next generation.

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Footnotes

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