



Hypogonadotropic Hypogonadism in Men With Diabetes

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One-third of men with obesity or type 2 diabetes have subnormal free testosterone concentrations. The lower free testosterone concentrations are observed in obese men at all ages, including adolescents at completion of puberty. The gonadotropin concentrations in these males are inappropriately normal; thus, these patients have hypogonadotropic hypogonadism (HH). The causative mechanism of diabetes-induced HH is yet to be defined but is likely multifactorial. Decreased insulin and leptin signaling in the central nervous system are probably significant contributors. Contrary to popular belief, estrogen concentrations are lower in men with HH. Men with diabetes and HH have more fat mass and are more insulin resistant than eugonadal men. In addition, they have a high prevalence of anemia and higher mortality rates than eugonadal men. Testosterone replacement therapy results in a loss of fat mass, gain in lean mass, and increase in insulin sensitivity in men with diabetes and HH. This is accompanied by an increase in insulin-signaling genes in adipose tissue and a reduction in inflammatory mediators that interfere with insulin signaling. There is also an improvement in sexual symptoms, anemia, LDL cholesterol, and lipoprotein (a). However, testosterone therapy does not consistently affect HbA_{1c} in men with diabetes. The effect of testosterone replacement on cardiovascular events or mortality in men with diabetes is not known and remains to be studied in prospective trials.

Approximately one-third of men with obesity, type 2 diabetes, or metabolic syndrome have subnormal free testosterone concentrations (1–3). Testosterone concentrations are inversely related to BMI and insulin resistance (3). One-third of obese young males (14–35 years of age) also have subnormal free testosterone concentrations. The gonadotropin concentrations in these males are inappropriately normal; thus, these patients have hypogonadotropic hypogonadism (HH). This review will detail the metabolic consequences of HH and the effects of testosterone replacement in men with obesity, type 2 diabetes, and metabolic syndrome. Because the pathophysiological mechanisms of all of these conditions are closely related, we have decided to refer to this group of patients as having “diabetes” in the rest of the review. Please note that this term is not limited to only those with the combination of diabetes and obesity.

MEASUREMENT OF TESTOSTERONE CONCENTRATIONS IN THE OBESE

Prior to a detailed discussion about subnormal testosterone concentrations in obesity, it is important to clarify that obesity is associated with a decrease in both total and free testosterone. Because testosterone is largely bound to sex hormone-binding globulin (SHBG) (40–80%) and albumin (20–50%), total testosterone does not reflect the bioavailability of testosterone at the cellular level. Insulin-resistant states such as obesity and type 2 diabetes are known to be associated with low SHBG concentrations, and, in fact, there are data demonstrating that low SHBG may be a marker for the development of diabetes (4). Thus, there is a physiological lowering

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of total testosterone concentrations in obese men. Hence, free or bioavailable (non-SHBG-bound) testosterone measurement is essential in obese men to assess the gonadal status. The current gold standard method of measuring free testosterone involves separation of free testosterone by equilibrium dialysis and measurement by mass spectrometry (5). Although equilibrium dialysis is a tedious, expensive, and time-consuming technique, it is readily available at many commercial laboratories in the U.S. Free testosterone measured by radioimmunoassay (an assay that is still commonly used) is unreliable (5). Bioavailable testosterone can be accurately measured by ammonium sulfate precipitation. Free and bioavailable testosterone can also be calculated from SHBG, albumin, and total testosterone concentrations. Although the calculation equation continues to be refined, this calculated free/bioavailable testosterone has been shown to correlate very well with directly measured free or bioavailable testosterone and is well suited for epidemiological and clinical studies (5). Recent data indicate that linear models used to estimate free and bioavailable testosterone are based on binding affinity assumptions that are not entirely accurate and result in a systematic bias. Multistep ensemble allosteric models of testosterone binding to SHBG provide estimates of free testosterone levels that closely match free testosterone measured by equilibrium dialysis (5).

Accuracy of calculated free/bioavailable testosterone is predicated upon the precise measurement of total testosterone. Liquid or gas chromatography/tandem mass spectrometry is the gold standard method to measure total testosterone (5). The Endocrine Society has recently concluded a project to harmonize testosterone mass spectrometry assays across the U.S. This project calculated that the harmonized reference range (2.5–97.5 percentiles) for total testosterone was 264–916 ng/dL for nonobese men aged 19–39 years (5). Further work is now needed to harmonize assays that accurately measure free or bioavailable testosterone across all laboratories and to provide validated equations for calculation of free/bioavailable testosterone. Free and bioavailable testosterone concentrations correlate strongly with each other, and measurement of only one of them is required for clinical purposes. It

is not yet clear whether free or bioavailable testosterone is a better marker of delivery of testosterone molecule to the tissue. Nor is a good test available to measure tissue androgen action. In the meantime, it is prudent to measure free testosterone by equilibrium dialysis/mass spectrometry and follow the reference ranges provided by the laboratory (5). Although these assays are more widely available in the U.S. than those for measurement of bioavailable testosterone, they usually require shipping of the sample by the local laboratory to a central laboratory. When ordering the free testosterone test, the clinician must specify that free testosterone is to be measured by the above-mentioned technique so that the sample is adequately processed and not measured by radioimmunoassay.

ASSOCIATION OF TYPE 2 DIABETES WITH LOW FREE TESTOSTERONE

It has been known for over two decades that males with type 2 diabetes frequently have low total testosterone concentrations (6). These studies did not report free testosterone or gonadotropin concentrations, nor did they place low testosterone concentrations in a clinically relevant context. Subnormal free testosterone concentrations in association with inappropriately low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations in men with type 2 diabetes were first described by us in 2004 (1,2). These patients had normal LH and FSH responses to gonadotropin-releasing hormone (GnRH) stimulation pointing to a hypothalamic defect. These abnormalities were independent of the duration and severity of diabetes (HbA_{1c}). MRI in these hypogonadal patients showed no abnormality in brain or the pituitary (2). Free testosterone concentrations were inversely related to BMI. This association of HH with type 2 diabetes has now been confirmed in several studies and is present in 25–40% of these men (7,8). We also found that younger men with type 2 diabetes between the ages of 18 and 35 years have a similarly high prevalence of HH (9).

HH is relatively rare in type 1 diabetes, unless the patients are obese. Therefore, HH is not entirely a function of diabetes or hyperglycemia per se (10). Thus, in view of the inverse relationship between BMI and testosterone concentrations in both type 1 and type 2 diabetes, HH is probably

related to insulin resistance (2,8,10). Improvement of systemic insulin resistance by rosiglitazone leads to a modest increase in testosterone concentrations in men with type 2 diabetes (11), but without the restoration of testosterone concentrations to normal.

ASSOCIATION OF OBESITY AND METABOLIC SYNDROME WITH LOW FREE TESTOSTERONE

Many studies have shown free testosterone concentrations to be low in the obese, especially in those with a BMI ≥ 40 kg/m² (12,13). Zumoff et al. (13) studied 48 healthy men with BMI ranging from 21 to 95 kg/m² and collected blood samples every 20 min for a period of 24 h. They found that 24-h mean free testosterone and non-SHBG-bound testosterone were related inversely to BMI. Vermeulen et al. (12) compared 35 obese men (mean BMI 41.1 kg/m²) with 54 lean men. The free testosterone concentrations were 26% lower in the obese. The authors also compared LH pulsatility over 12 h in eight obese and lean men and found that the mean integrated LH levels over 12 h were significantly lower in obese men. Free testosterone concentrations correlated positively with the sum of LH pulse amplitudes in each individual (12). Some recent studies have examined the prevalence of hypogonadism in obesity in a much larger number of men. A study from the Netherlands in 160 obese men (mean age 58 years) found a 36% prevalence of HH (14). The largest study in this regard found that 40% of obese men and 50% of obese men with diabetes had subnormal free testosterone concentrations (Fig. 1) (3). Thus, obesity is associated with a high prevalence of hypogonadism, and the presence of diabetes adds to that risk only minimally (1).

The inverse relation of free testosterone concentrations with obesity is not restricted to middle-aged men (9,15,16). We compared the testosterone, LH, and FSH concentrations of 25 lean and 25 obese boys in Tanner stage 4 and 5 (aged 14–20 years) (16). The free testosterone concentrations (measured by equilibrium dialysis followed by mass spectrometry) of obese boys were 40% lower than those of lean boys. In addition, 40% of obese adolescents had subnormal free testosterone concentrations (defined as <5th percentile of free testosterone concentrations of lean adolescents). The gonadotropin

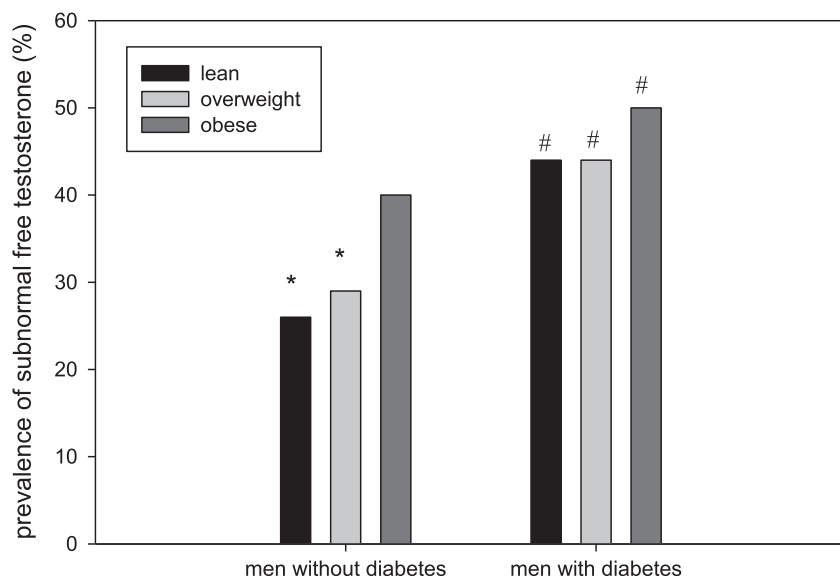


Figure 1—Prevalence of subnormal free testosterone concentrations in lean, overweight, and obese men (based on BMI) with and without diabetes. Mean age 60 years; range 45–96 years. A total of 44% of men with diabetes and 33% of age-matched men without diabetes had subnormal free testosterone concentrations, respectively. Sample size: 275 lean, 687 overweight, and 489 obese men without diabetes; 36 lean, 135 overweight, and 227 obese men with diabetes. * $P < 0.05$ vs. obese men in the same group (with diabetes or without diabetes); # $P < 0.05$ vs. men without diabetes. Adapted from data published in Dhindsa et al. (3).

concentrations of lean and obese boys were similar. The free testosterone concentrations were inversely related to BMI, HOMA of insulin resistance (HOMA-IR), and CRP concentrations. Another study has also shown lower free testosterone concentrations in obese postpubertal adolescents (17).

The association of diabetes with HH is not simply reflective of increased fat mass but also of adverse metabolic health. Some studies show that free testosterone concentrations are inversely related to HOMA-IR, triglyceride concentrations, inflammatory mediators, and subcutaneous adipocyte cell size, independently of BMI (16,18). In men with metabolic syndrome, free testosterone concentrations decrease proportionately with increasing number of components of metabolic syndrome (19).

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING HH IN DIABESITY

Estradiol

Because testosterone and androstenedione in the male can be converted to estradiol and estrone, respectively, through the action of aromatase in the mesenchymal cells and preadipocytes of adipose tissue, it has been suggested that excessive estrogen production due to aromatase

activity in the obese may potentially suppress the hypothalamic secretion of GnRH (1,20). However, we have shown that this widely believed presumption is not true (21). Total and free estradiol concentrations in men with HH are significantly lower than in those without HH (21) (Fig. 2). Population-based studies such as the European Male Ageing Study also showed that estradiol concentrations are lower in hypogonadal men as compared with eugonadal men, regardless of whether the hypogonadism is primary or secondary (22). Clomiphene (estrogen antagonist) and aromatase inhibitors (which decrease estradiol concentrations) have been shown to increase testosterone concentrations in obese men with low testosterone. This, however, cannot be taken as evidence of estradiol as the cause of low testosterone in those men. Estradiol has an inhibitory effect upon gonadotropin secretion even in a normal physiological setting (23). Clearly, the suppression of LH, FSH, and testosterone in diabetes is not induced by circulating estradiol concentrations.

Obstructive Sleep Apnea

Serum testosterone concentrations begin to increase with the onset of sleep and in young men they peak at the first rapid

eye movement sleep episode and remain at that level until waking. Testosterone production in men is related to rapid eye movement sleep, sleep duration, and sleep architecture (24). Obstructive sleep apnea is common in men with obesity and type 2 diabetes. A quarter of men with diabetes have severe sleep apnea, defined as apnea-hypopnea index of $>30/h$ (25). However, sleep apnea does not seem to be a determinant of total, free, or bioavailable testosterone concentrations independently of BMI (24). Furthermore, positive airway pressure therapy for sleep apnea does not increase testosterone concentrations (26). Thus, obstructive sleep apnea per se is not a major contributor to the lowering of free testosterone concentrations in obesity.

Neuronal Insulin Resistance

Obesity is associated with decreased insulin signaling in the central nervous system (27). This association may be bidirectional because increasing insulin delivery to the central nervous system decreases body weight in men (28). Neuronal insulin receptor knockout mice become obese and insulin resistant (29). Interestingly, these mice also have a reduction in LH concentrations by 60–90% and low testosterone concentrations. These animals respond to GnRH challenge by normal or supranormal release of LH. In addition, it is known that the incubation of hypothalamic neurons with insulin results in the facilitation of secretion of GnRH (30). However, it is unlikely that the site of action of insulin on reproductive axis in vivo is the GnRH neuron. Isolated knockout of the insulin receptor in a GnRH neuron does not lead to a decrease in LH concentrations or in fertility in either male or female mice (31). Although the site (or sites) responsible for hypogonadotropism in neuronal insulin receptor knockout mice is not known, it is clear that insulin action and insulin responsiveness in the brain are necessary for the maintenance of the functional integrity of the hypothalamo-hypophyseal-gonadal axis.

Leptin

Leptin is known to play a permissive role in the regulation of reproductive axis. Leptin appears to serve as a signal of energy reserves to regulate the hypothalamo-pituitary-gonadal axis in relation to nutritional status. Men and women with anorexia nervosa have hypogonadotropism and

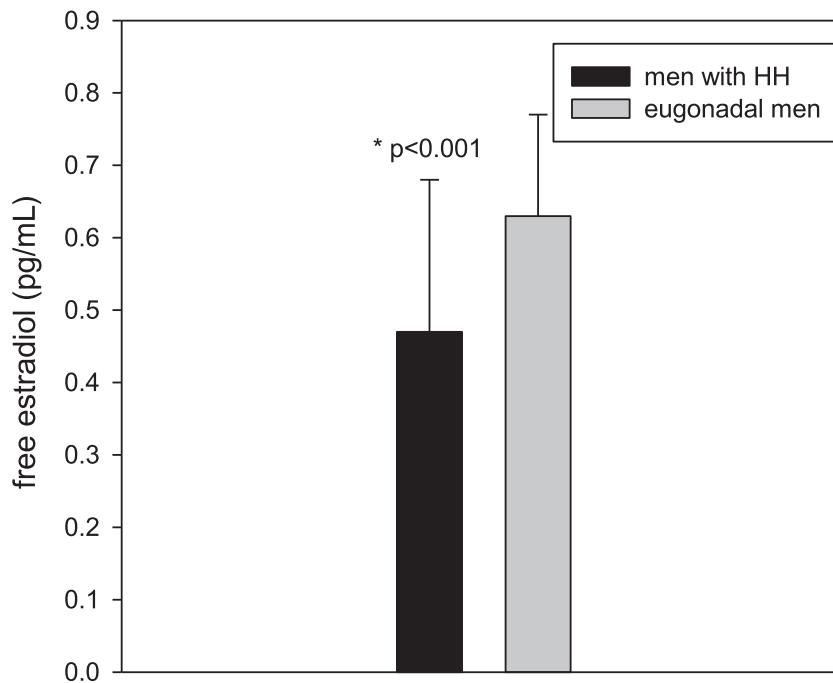


Figure 2—Men with HH have lower free estradiol concentrations than eugonadal men. Estradiol concentrations in men with and without HH were 0.47 (0.35, 0.68) and 0.63 (0.46, 0.77) pg/mL, respectively. Adapted from Dhindsa et al. (21).

low levels of leptin. Absence of the leptin gene or leptin signaling in humans results in HH (32). Although there are extremely uncommon forms of human obesity due to the lack of the leptin gene, almost all obesity in humans is associated with leptin resistance and high leptin concentrations. It is possible that leptin resistance in the hypothalamus or in some other neurons is responsible for the hypogonadotropism seen in obesity.

Kisspeptin

It is now known that kisspeptin, a hypothalamic neuropeptide encoded by the KISS1 gene, and the presence of kisspeptin receptors on the GnRH neurons (G protein-coupled receptor 54) is obligate for the release of GnRH (33). Intravenous injection of kisspeptin increases LH and testosterone concentrations in men with type 2 diabetes and HH (34). This suggests that the hypothalamic defect in men with HH and type 2 diabetes is either at kisspeptin level or proximal to it. Kisspeptin neurons express both leptin and insulin receptors, thus possibly accumulating evidence of metabolic health and translating it into reproductive health.

Inflammation

Tumor necrosis factor- α and interleukin-1 β have been shown to suppress hypothalamic

GnRH and LH secretion in experimental animals and in vitro (35). CRP concentrations are markedly increased in hypogonadal men as compared with men with normal testosterone concentrations (6.5 vs. 3.2 mg/L) (8,36). It is thus possible that inflammatory mediators may contribute to the suppression of the hypothalamo-hypophyseal axis and the syndrome of HH in type 2 diabetes. The presence of inflammation may also contribute to insulin resistance because inflammation-related mediators contribute to insulin resistance (37). These mediators are also known to be increased in obesity (38).

What Comes First: HH or Diabetes?

It is generally assumed that the association of low testosterone and obesity is bidirectional. Low testosterone predisposes to obesity and vice versa. Indeed, there are definite lines of evidence for both directions of this association in different clinical settings. Men who are rendered hypogonadal by GnRH agonist therapy for advanced prostate cancer increase their subcutaneous and visceral fat mass by 15–20%. Consistent with this, they develop insulin resistance, and their risk of incident type 2 diabetes increases by 30% (39). In the other direction, boys who are obese prepubertally do not achieve normal testosterone concentrations at the completion of puberty.

As mentioned above, obese boys have lower free testosterone concentrations than lean boys (16). Furthermore, bariatric surgery in morbidly obese patients restores testosterone concentrations to normal after marked weight loss (40).

Is Testicular Function Directly Altered in Diabetes?

Human chorionic gonadotropin-induced testosterone secretion by Leydig cells is related inversely to insulin sensitivity among men with varying degrees of glucose tolerance (41). Decreased testosterone secretion in insulin-resistant men after pharmacological stimulation by high doses of human chorionic gonadotropin suggests that the lesion resulting in HH of diabetes may occur at several levels of the hypothalamic-pituitary-gonadal axis. The absence, however, of an increase in gonadotropin concentrations indicates that the primary major defect in diabetes is at the hypothalamo-hypophyseal level (1).

The specific metabolic insult in diabetes that results in hypogonadotropism is yet to be defined. It is very likely that the cause is multifactorial (Fig. 3). Decreased insulin and leptin signaling in the central nervous system appear to be the leading candidates. Direct evidence in humans supporting or disproving this hypothesis is, however, lacking.

EFFECT OF WEIGHT LOSS ON TESTOSTERONE CONCENTRATIONS

Many studies have shown that weight loss increases total testosterone and SHBG concentrations (summarized in Grossmann [42]). On average, 5% weight loss increases total testosterone concentrations by 50 ng/dL. Bariatric surgery in morbidly obese adults has been shown to induce a reversal of the hypogonadal state and the restoration of normal testosterone concentrations (40). A meta-analysis of 29 studies of men undergoing bariatric surgery showed that 64% of the men had subnormal total testosterone concentrations prior to surgery (40). The prevalence of subnormal free testosterone concentrations was not ascertained in the analysis. After bariatric surgery, total testosterone and SHBG concentrations increased by 233 ng/dL and 22 nmol/L, respectively, in a total of 439 men across 16 studies. Eight studies calculated free testosterone concentrations in a total of 259 men: there was

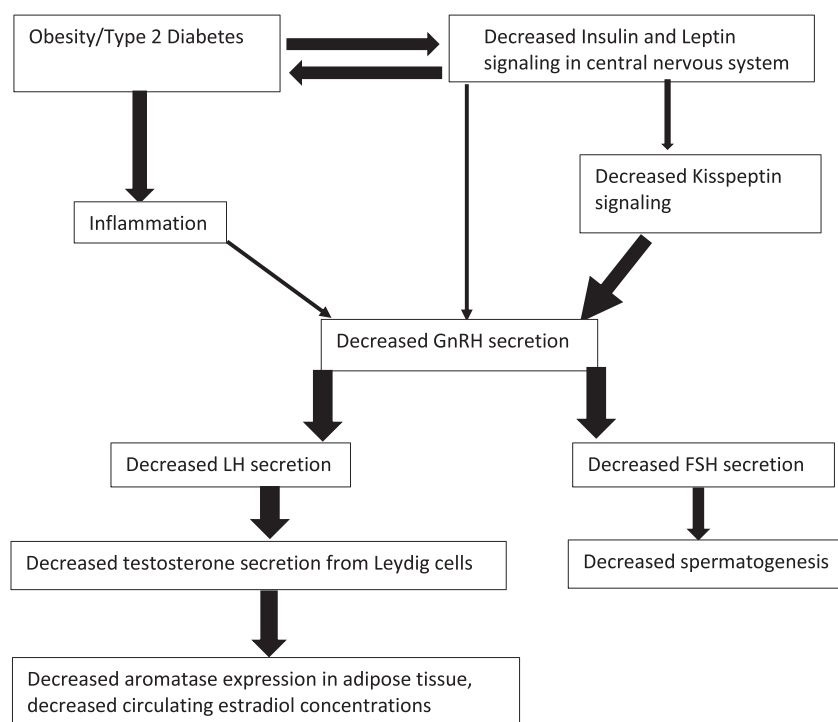


Figure 3—Interplay of different factors in obesity associated HH. The thickness of arrows is proportional to the strength of available evidence supporting the mechanism.

an increase of 2.2 ng/dL on average. LH and FSH concentrations increased by 1.0 and 1.8 IU/L, respectively.

It is tempting to speculate that the reduction in aromatase activity due to fat loss is the major mechanism underlying the increase in testosterone concentrations following weight loss. However, as we have discussed before, elevated estrogen concentrations are not the cause of obesity-associated HH. Weight loss may restore neuronal leptin sensitivity and thus increase gonadotropin release. However, exercise, even in the absence of weight loss, increases testosterone concentrations (43). It is possible that insulin sensitization at the hypothalamic level mediates the increase in free testosterone concentrations following weight loss.

CLINICAL CHARACTERISTICS OF HH IN MEN WITH DIABESITY AND THE EFFECTS OF TESTOSTERONE TREATMENT

Sexual Symptoms

It is well accepted that subnormal testosterone concentrations are associated with sexual symptoms in elderly men. Cross-sectional studies have found that approximately two-thirds of men with type 2 diabetes and HH have symptoms of low libido, erectile dysfunction, or fatigue (7). In clinical practice, it is often difficult

to determine whether the etiology of symptoms is hypogonadism or one of the other comorbidities. However, the prevalence of sexual symptoms is higher in men with HH as compared with eugonadal men (44). In a randomized trial of transdermal testosterone gel or placebo gel for 1 year in patients with type 2 diabetes and hypogonadism, there was an improvement in sexual desire, but other symptoms did not change (45). Trials of testosterone replacement in hypogonadal men with type 2 diabetes have also shown an improvement in sexual desire (44–46). In contrast to consistent effect of testosterone replacement therapy (TRT) on improving libido, its effect on erectile dysfunction is modest and inconsistent among studies (44,45). Hypogonadal men with erectile dysfunction are much more likely to have symptomatic benefit from phosphodiesterase-5 inhibitors than from TRT. Furthermore, addition of TRT to phosphodiesterase-5 inhibitors does not improve the erectile response as compared with phosphodiesterase-5 inhibitors alone (47).

Body Composition

It is well known that muscle mass is inversely related to testosterone concentrations in men and that testosterone treatment results in an increase in muscle

mass. We measured the fat mass and lean mass by DEXA scans in 138 men with type 2 diabetes. Men with HH had a higher BMI (by 3 to 4 kg/m²), 12% more subcutaneous fat mass, and higher waist-to-hip ratio (2,7,48) as compared with eugonadal men. Men with HH also have higher visceral and subcutaneous fat content as compared with eugonadal men (44). After testosterone replacement, there is a decrease in fat mass and increase in lean mass (Table 1). We randomized 44 men with type 2 diabetes and HH to intramuscular therapy with testosterone or placebo injections for 6 months (44). Men randomized to TRT lost ~3 kg of subcutaneous fat and gained ~3 kg of lean mass, without a net change in body weight. There was no change in visceral or hepatic fat mass after TRT.

Similar to the effects of TRT in men with type 2 diabetes, a decrease in subcutaneous fat and an increase in lean mass after TRT have been shown to occur in obese men without diabetes and men with metabolic syndrome (49–51). The loss of fat after testosterone therapy is attributed to aromatization of testosterone to estradiol (52). It is of interest that although caloric reduction induced weight loss is due to reduction of both fat mass and lean mass, weight loss due to TRT in combination with very low-calorie diet is exclusively due to fat loss (53). TRT also reduces circulating leptin concentrations (44).

Insulin Resistance

Many studies have shown that hypogonadism is associated with insulin resistance. Almost two decades ago, Mårin et al. (49,50,54) demonstrated an improvement in insulin sensitivity (as measured by euglycemic clamp) with oral and transdermal T treatment in obese men without diabetes. We have recently shown that men with type 2 diabetes and HH are less insulin sensitive than those without HH and that TRT increases insulin sensitivity (as measured by glucose infusion rate during hyperinsulinemic-euglycemic clamps) in men with HH (Fig. 4) (44). HOMA-IR also decreased by 40%. Jones et al. (45) showed a 16% decrease in HOMA-IR after 1 year of treatment with transdermal testosterone in 220 hypogonadal men with type 2 diabetes. However, two trials did not show a change in HOMA-IR after replacement with long-acting intramuscular

Table 1—Effect of TRT on nonsexual parameters in men with diabetes

Parameter	Change	References
Fat mass	↓	(44,49–51,53,54,56,61)
Lean mass	↑	(44,53,56)
BMI	↔	(44,45,55,56)
Insulin sensitivity	↑	(44,49,50,54)
Glycemic control	↔	(44–46,55,56,61)
Hemoglobin	↑	(44,62)
Bone density	Not studied	
Lipids	↓ in total cholesterol, LDL, and lipoprotein (a), minor decrease in HDL, ↔ in triglycerides	(44,45,56)
Cardiovascular disease	Not studied	
PSA	↔	(44,45,51,54)

We focused on randomized controlled trials in men with obesity, type 2 diabetes, or metabolic syndrome. If there was disagreement among studies on a parameter, we chose to depict it as increased (↑), decreased (↓), or no change/variable results (↔) based on the totality of evidence.

testosterone given for 30–40 weeks in hypogonadal men with type 2 diabetes (55,56). HOMA-IR may be inadequate as an index of insulin resistance, especially in patients with type 2 diabetes, because β -cell loss and inadequate insulin secretion can lead to inappropriately low insulin concentrations and HOMA-IR. In contrast, HOMA-IR is assessed under fasting conditions and therefore a different index of insulin sensitivity than hyperinsulinemic clamp, which largely measures glucose uptake by muscle. Because TRT increases muscle mass, TRT may have a more prominent effect on muscle glucose uptake rather than HOMA-IR. In our study, there was no change in glucose uptake during clamps at an early time point of 3 weeks (44). Thus, it appears that the insulin sensitization of testosterone is not an immediate effect and may be mediated by changes in body composition. The results of TRT on insulin sensitization are inconsistent in hypogonadal men who are not obese (57). In addition, TRT replacement in trials composed largely of men with low normal testosterone (instead of subnormal) concentrations fail to show a change in insulin sensitivity (58).

In parallel with an increase in glucose uptake during clamps, we found a significant increase in the expression of insulin receptor β , insulin receptor substrate-1 (IRS-1), Akt-2, and GLUT-4 in adipose tissue. These data are consistent with similar effects found after TRT in mice (59). This provides a mechanistic explanation for the increase in insulin sensitivity. Testosterone administration

also induced a reduction in free fatty acid concentrations, probably through the suppression of lipolysis. Free fatty acids are known to induce oxidative and inflammatory stress and interfere with insulin signal transduction (60). The improvement in insulin sensitivity following testosterone treatment was also associated with suppression of other inflammatory mediators that interfere with insulin signaling. These included IKK β , SOCS-3, and PTEN in mononuclear cells and TLR-4 and PTP-1B in adipose tissue. Although SOCS-3 interferes with insulin signal transduction by causing the ubiquitination and proteasomal degradation of IRS-1, IKK β induces serine phosphorylation of IRS-1 and thus prevents insulin signal transduction through IRS-1. PTP-1B dephosphorylates the insulin receptor after the autophosphorylation by tyrosine kinase and thus limits insulin signaling. The expression of PTEN, another protein that interferes with insulin signaling, was also suppressed in mononuclear cells following testosterone treatment (44). However, we cannot state whether they are the direct actions of testosterone or are indirectly mediated by changes in adiposity.

Glycemic Control

Some studies have evaluated glycemic control by measuring HbA_{1c} and fasting glucose after testosterone therapy (Table 1). Kapoor et al. (46) showed a decrease in fasting glucose (28 mg/dL) and HbA_{1c} (0.37%) as compared with placebo with 3 months of testosterone replacement in a small trial. A trial in men with new-onset

type 2 diabetes with transdermal testosterone also showed a decrease in HbA_{1c} from 7.5 to 6.3% over a period of 1 year (61). This was in conjunction with diet and exercise, but no hypoglycemic medications. However, some randomized trials did not show an effect of testosterone replacement on HbA_{1c} (44,45,55,56). Furthermore, it is possible that increased erythropoiesis after testosterone replacement may affect HbA_{1c} independently of changes in glycemia. Studies with careful collection of self-monitored glucose concentrations and measures of glycemia other than HbA_{1c} should be designed to evaluate the effect of testosterone on HbA_{1c} independently of glycemia.

Anemia

Men with HH have a higher prevalence of normocytic normochromic anemia (38%) as compared with eugonadal men (3%) (36). This anemia is associated with an increase in hepcidin and a decrease in ferroportin and transferrin receptor expression. Testosterone therapy increases erythropoiesis. We found that hemoglobin and hematocrit concentrations increased by 0.54 g/dL and 2.3%, respectively, after 6 months of testosterone therapy in men with type 2 diabetes (44). TRT in hypogonadal men with type 2 diabetes leads to a significant increase in plasma erythropoietin concentration and enhances the mobilization of iron from its stores by suppressing hepcidin and increasing the expression of ferroportin and transferrin on mononuclear cells (62).

Expression of Androgen Receptor in HH

It is intuitive to expect that the state of HH in diabetes would result in a compensatory increase in the expression of androgen receptor. However, we found a decreased expression of androgen receptor in mononuclear cells and adipose tissue in men with HH and diabetes as compared with eugonadal men (63). The expression of estrogen receptor- α and aromatase was also reduced in adipose tissue. Thus, rather than there being a compensatory increase, there is a decrease in androgen receptor, estrogen receptor, and aromatase expression. Thus, the hypogonadal state in diabetes is also associated with diminished responsiveness to testosterone and estradiol. TRT restored the expression of androgen receptor, estrogen receptor, and aromatase to normal.

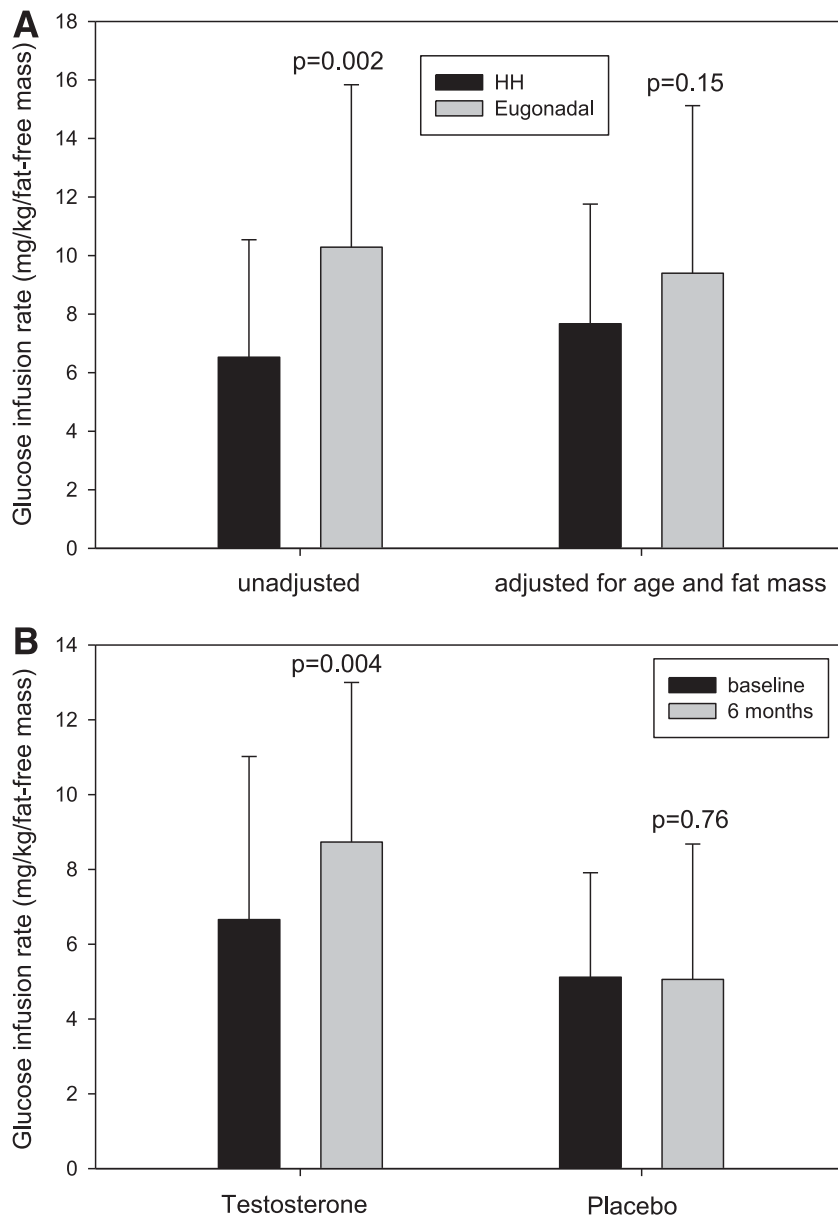


Figure 4—A: Insulin sensitivity measured by hyperinsulinemic-euglycemic insulin clamps in 94 men with type 2 diabetes (44 men had HH, and 50 were eugonadal). Men with HH had greater BMI (40 vs. 34 kg/m²; $P < 0.001$) but similar age (55 vs. 52 years; $P = 0.08$) and HbA_{1c} (7.0 vs. 7.1%; $P = 0.7$) as compared with eugonadal men. The glucose infusion rate during hyperinsulinemic-euglycemic insulin clamps was 36% lower in men with HH as compared with eugonadal men. The glucose infusion rate between men with and without HH was, however, not different once adjusted for BMI difference in the two groups. This suggests that obesity is the predominant determinant of insulin resistance in men with HH. B: A total of 44 men with HH were randomized to intramuscular testosterone or placebo injections every 2 weeks for 6 months. Insulin sensitivity (glucose uptake during clamps) increased by 32% after 6 months. Data adapted from Dhindsa et al. (44).

Bone Density

In epidemiological studies, estradiol concentrations correlate more robustly with bone mineral density than testosterone concentrations in men (64). Free testosterone concentrations are positively associated with bone density in arms, ribs, and lumbar spine in men with type 2 diabetes (48). No study has evaluated the relation between free estradiol concentrations and

bone density or fractures in men with HH and diabetes. The effect of TRT on bone density or fracture rates in men with diabetes has also not been studied.

Lipid Profile

It used to be believed that testosterone treatment adversely affects cardiovascular risk because it lowers HDL cholesterol concentration. However, that effect is

restricted to treatment that achieves supranormal concentrations of testosterone (for example, during abuse of androgens for body building). Testosterone has not been shown to cause any meaningful change in HDL concentrations in studies in which testosterone is replaced to normal levels (5). Some studies have shown a reduction in LDL or total cholesterol concentrations after TRT in men with diabetes (45,56). Most studies find no change or a small decrease in HDL cholesterol and triglycerides after TRT (44,45,56).

Cardiovascular Disease

Epidemiological studies have shown that elderly men with low testosterone are more likely to die of a major cardiovascular event (65). Inverse association of mortality with endogenous testosterone concentrations has also been observed in men with diabetes (66). However, no randomized control trials have been conducted to examine the question: “Does TRT change cardiovascular outcomes in men?” Cardiovascular outcomes have been sporadically reported in randomized trials of TRT designed for other endpoints (such as muscle strength and glucose control), but these trials were underpowered to look at cardiac events. Meta-analyses of these trials do not find a consistent effect of TRT on cardiovascular events (67). A recently concluded randomized placebo-controlled trial in elderly men (≥ 65 years of age, 790 subjects) by Snyder et al. (68) found no difference in cardiovascular events between men who received TRT or placebo for 1 year. A prospective cohort study in an endocrine clinic investigated the effect of TRT in 238 hypogonadal men with HH and type 2 diabetes on all-cause mortality (66). Sixty-four hypogonadal men received testosterone (mean duration 42 ± 20 months), and 174 men were not treated. The mortality rate in untreated hypogonadal men was 20%, whereas hypogonadal men treated with testosterone had a mortality rate of 9.4% ($P = 0.002$). Most retrospective epidemiological studies have shown a benefit on cardiovascular events from long-term testosterone use in elderly men (69–71). In one of the largest studies conducted on this issue, Sharma et al. (70) showed a 56% reduction in total mortality and 24% reduction in myocardial infarction with the use of TRT. Some reports

have shown evidence of harm with short-term testosterone use. However, these studies had a number of shortcomings (67). Large-scale prospective randomized controlled trials on testosterone therapy, focusing on cardiovascular benefits and risks, are clearly needed.

Prostate-Specific Antigen

Men with type 2 diabetes have 20% lower prostate-specific antigen (PSA) concentrations than men without diabetes. PSA concentrations are lower in hypogonadal than in eugonadal men with diabetes (0.89 vs. 1.1 ng/mL) (72). It is interesting that the incidence of prostatic carcinoma is lower in men with diabetes. This is in contrast to the increased incidence of cancer in diabetes in various organs including the colon, kidney, breast, endometrium, and pancreas. Similar to type 2 diabetes, obesity is also associated with 10–30% lower PSA concentrations and lower prostate cancer incidence (73). Obese men are half as likely to have PSA concentrations >4 mg/L. The lower PSA concentrations may not be a result of lower testosterone concentrations in obesity and type 2 diabetes, but may also be due to the larger plasma volumes and hence hemodilution (74). Prostate cancer progression and mortality, however, are increased in obese men, possibly related to later detection due to lower PSA concentrations (75).

The PSA concentrations are lower in hypogonadal men than in eugonadal men. TRT may result in a modest increase in PSA concentrations (~30%). In most studies of TRT replacement in men with diabetes, there is no change in PSA concentrations after TRT (44,45,51,54). In this context, it is important that the replacement of testosterone in hypogonadal patients in general does not lead to an increased risk of prostatic carcinoma, although the trials have been too limited in duration and number of patients (5).

Spermatogenesis

Some (but not all) studies have shown that BMI is inversely related to sperm counts, sperm morphology, and sperm motility. Data are most consistent about the impact of morbid obesity on spermatogenesis. In a meta-analysis of 21 studies, BMI >40 kg/m² was associated with a doubling of risk of oligospermia (<40 million spermatozoa per ejaculate) or azospermia (76). The high prevalence of HH in obesity and type 2 diabetes,

especially in young men, may partially explain the high prevalence of infertility or oligospermia in these men. Studies comparing sperm parameters of men who are obese or have diabetes with and without HH have not been conducted. TRT cannot be used in those who desire fertility because it decreases spermatogenesis.

PRACTICAL CONSIDERATIONS FOR A CLINICIAN

Should Every Man With Diabetes Have His Testosterone Concentration Checked?

The answer to this question is yes. The high prevalence justifies screening for HH. Limiting testing only to men who report symptoms is likely to result in false negatives. Hypogonadal patients may slide gradually into this clinical state without any overt symptoms, which may be revealed through direct questioning. Asymptomatic men may realize that they had been symptomatic only after a trial with testosterone. However, a complete discussion of risks and benefits between the patient and physician should precede a trial of TRT, and the decision about treatment should be weighed carefully by the physician.

What Test Should Be Used to Make a Biochemical Diagnosis of Testosterone Deficiency in a Man With Diabetes?

Free testosterone should be checked in the morning (fasting) by accurate methodology, preferably equilibrium dialysis/mass spectrometry. Studies have shown that testosterone has a diurnal variation, and its concentrations also decline after eating. Total testosterone should not be used to make diagnostic or therapeutic decisions.

What Workup Should Be Undertaken in a Man With Diabetes and Subnormal Free Testosterone?

Subnormal free testosterone needs to be confirmed (at least once). Men with one normal value and one low value are not hypogonadal. Studies have generally shown a lack of benefit of TRT in men with low normal testosterone concentrations. A man with confirmed hypogonadism should have LH concentrations measured. The majority have HH. MRI of the pituitary is not beneficial in the majority of these men due to low incidence of anatomical pathology. MRI of the pituitary should be done if there

are visual symptoms, headaches, or other pituitary hormone deficits. MRI is also advisable if the free testosterone is very low (<50% of the lower limit of normal).

How Should Men Receiving TRT Be Followed?

SHBG concentrations are decreased by TRT. Hence, free testosterone should be used to titrate testosterone dosing during TRT. Hemoglobin and prostate should be monitored as per guidelines (5).

These recommendations are opinions based on the authors' clinical experience.

CONCLUSIONS

HH is found in 25–33% of men with diabetes. Although the underlying mechanism is not known, neuronal insulin and leptin resistance may play a role at the hypothalamic level. Low free and bioavailable testosterone concentrations in these men are associated with an increased prevalence of sexual symptoms, obesity, high CRP concentrations, mild anemia, insulin resistance, and decreased bone mineral density. In addition, these men may have an elevated risk of cardiovascular events and death. Short-term studies of testosterone therapy have demonstrated an increase in libido, insulin sensitivity, and lean body mass and a reduction in inflammation and fat mass. Men on TRT should be monitored for the development of polycythemia or prostate complications. Trials of a longer duration are clearly required to definitively establish the benefits and risks of TRT in these men.

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