Clinical and Biochemical Assessment of Hypogonadism in Men With Type 2 Diabetes

Correlations with bioavailable testosterone and visceral adiposity

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OBJECTIVE — The aim of our study was to assess the prevalence of clinical hypogonadism, based on both symptoms and biochemical available measures of testosterone deficiency, in men with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a cross-sectional study of 355 type 2 diabetic men aged >30 years, total and bioavailable testosterone, sex hormone–binding globulin, BMI, and waist circumference were measured and free testosterone was calculated. Overt hypogonadism was defined as the presence of clinical symptoms of hypogonadism and low testosterone level (total testosterone <8 nmol/l and/or bioavailable testosterone <2.5 nmol/l). Borderline hypogonadism was defined as the presence of symptoms and total testosterone of 8–12 nmol/l or bioavailable testosterone of 2.5–4 nmol/l.

RESULTS — A low blood testosterone level was common in diabetic men, and a significant proportion of these men had symptoms of hypogonadism. Overt hypogonadism was seen in 17% of men with total testosterone <8 nmol/l and 14% with bioavailable testosterone <2.5 nmol/l. Borderline hypogonadism was found in 25% of men with total testosterone 8–12 nmol/l and bioavailable testosterone between 2.5 and 4 nmol/l; 42% of the men had free testosterone <0.255 nmol/l. BMI and waist circumference were both significantly negatively correlated with testosterone levels in men, with the association being stronger for waist circumference.

CONCLUSIONS — Testosterone levels are frequently low in men with type 2 diabetes, and the majority of these men have symptoms of hypogonadism. Obesity is associated with low testosterone levels in diabetic men.

Diabetes Care 30:911–917, 2007

Insulin resistance is an important feature of type 2 diabetes. It is being increasingly recognized that low testosterone levels in men are associated with reduced insulin sensitivity and type 2 diabetes (1). An inverse relationship exists between testosterone levels and insulin concentrations in healthy men (2). Low testosterone levels have also been found to predict insulin resistance and the future development of type 2 diabetes (3–5). Furthermore, it has been reported that testosterone levels are lower in diabetic men compared with nondiabetic subjects (6–9). Importantly, Dhindsa et al. (9) demonstrated that 33% of men with type 2 diabetes had significantly lower levels of free testosterone measured by equilibrium dialysis, which is the widely accepted most clinically relevant assay for free testosterone.

The question arising from these studies is, Which subjects should be considered for testosterone replacement therapy? Hypogonadism is a clinical condition comprising both symptoms and biochemical evidence of testosterone deficiency (10). Most of the studies in diabetic men have defined hypogonadism solely on the basis of testosterone levels (9). In no study have symptoms of hypogonadism been compared with biochemical testosterone deficiency. It is generally accepted by endocrinologists that if biochemical testosterone deficiency is associated with symptoms of hypogonadism, then testosterone substitution should be considered unless contraindicated. Currently, few diabetic men with testosterone deficiency are diagnosed and treated worldwide. The reason for this is the presumption that testosterone levels are low because the level of sex hormone–binding globulin (SHBG), the major carrier protein of testosterone in circulation, is low as a consequence of insulin resistance (8).

Testosterone is present in three major fractions: free (2–3%), albumin-bound (20–40%), and SHBG-bound (60–80%). Non–SHBG-bound testosterone is called bioavailable testosterone because both the free and albumin-bound fractions comprise the biologically active component that is readily available to the tissues, whereas SHBG-bound testosterone is tightly bound and thus considered inactive. A recent study has demonstrated that free testosterone levels, which are independent of SHBG, are low in one-third of diabetic men (9). A confounding factor is that SHBG rises with age, and thus free testosterone decreases more rapidly than

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Received for publication 7 July 2006 and accepted in revised form 27 December 2006.

K.S.C. has been a member of an advisory panel for and has received honoraria/consulting fees from Schering and Prostraken. T.H.J. has been a member of an advisory panel for and has received honoraria/consulting fees from Ipsen, Schering, Ardana Bioscience, and Prostraken.

Abbreviations: ADAM, Androgen Deficiency in the Aging Male; ED, erectile dysfunction; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-1426

total testosterone in older men (11). Thus, it is important to measure bioavailable or free testosterone in men with diabetes.

There is no clear consensus for an accepted lower limit of normal testosterone. Various guidelines for the diagnosis of hypogonadism are available, for example, from Bhasin et al. (12). Recently, published recommendations for the diagnosis of late-onset hypogonadism from a panel of European and American testosterone experts recommended that patients with total testosterone <8 nmol/l should be treated with testosterone therapy, those with total testosterone of 8–12 nmol/l and hypogonadal symptoms should be given a trial of testosterone replacement therapy, and those with total testosterone >12 nmol/l are not hypogonadal and should not be treated (13).

The major symptoms of hypogonadism are reduced or loss of libido, reduced strength of erections, fatigue, reduced physical strength, and mood changes. Questionnaires have been developed to assess androgen deficiency (14). These questionnaires, however, lack specificity but have reasonable sensitivity in the presence of a low testosterone level.

Erectile dysfunction (ED) is common in diabetic men (15,16), and the etiology may be vascular disease, autonomic neuropathy, hypogonadism, or a combination of these. Men with ED who fail to respond to phosphodiesterase inhibitors have been shown to have low testosterone levels (17). Testosterone replacement therapy in two studies was found to convert sildenafil nonresponders to responders (18,19).

Visceral obesity is an important cause of insulin resistance. Studies have shown that free testosterone levels are low in obese men and inversely correlate with the degree of obesity (20,21). There is increased deposition of abdominal adipose tissue in hypogonadal subjects, which in turn leads to a further decrease in testosterone concentrations, through conversion to estradiol by aromatase. This leads to further abdominal fat deposition and a greater degree of testosterone deficiency (1).

Interventional studies have shown a beneficial effect of testosterone replacement therapy on insulin resistance. A study in healthy men with low total testosterone reported an improvement in insulin sensitivity with testosterone or dihydrotestosterone treatment (22). Testosterone treatment has also been shown to reduce insulin resistance in obese men (23,24), men with heart failure (25), and type 2 diabetic subjects (26). Two studies in type 2 diabetic men have shown an improvement in glycemic control (26,27) with testosterone replacement therapy, although in a small study of 10 men, Corrales et al. (28) reported a neutral effect using intramuscular testosterone treatment.

These findings demonstrate the importance of investigating men with diabetes for androgen status. The aim of our study was to assess the prevalence of hypogonadism, based on both positive symptoms and low testosterone level, in men with type 2 diabetes. We measured total testosterone and bioavailable testosterone and also calculated free testosterone levels and compared each with symptoms of hypogonadism and visceral adiposity.

Table 1—*Baseline characteristics of subjects*

Parameter	Value	Sample range
Age (years)	58.05 ± 0.54	32–83
A1C (%)	7.22 ± 0.07	4.1–13.3
Total testosterone (nmol/l) (NR 8.3–41.6 nmol/l)	12.72 ± 0.29	2.6–39
SHBG (nmol/l) (NR 15–100 nmol/l)	32.48 ± 1.06	5.14–129
Bioavailable testosterone (nmol/l) (NR 2.5–11.9 nmol/l)	4.03 ± 0.08	0.89–11.49
Calculated free testosterone (nmol/l) (NR 0.26–0.71 nmol/l)	0.274 ± 0.01	0.05–1.02
FSH (units/l) (NR 1–12 units/l)	9.39 ± 0.87	2.3–58.1
LH (units/l) (NR 2–12 units/l)	5.92 ± 0.46	1.1–24.7
BMI (kg/m^2)	32.32 ± 0.31	21.05–63.05
Waist circumference (cm)	109.7 ± 0.77	81–173
Systolic blood pressure (mmHg)	143.3 ± 1.01	94–200
Diastolic blood pressure (mmHg)	82.06 ± 0.57	55–180
Medications (*n*)		
Diet	70	
Insulin	95	
Oral hypoglycemics	190	
ACE inhibitors/angiotensin receptor antagonist	198	
Statins	170	
Fibrates	6	

Data are means ± SE unless indicated otherwise. NR, normal range.

RESEARCH DESIGN AND METHODS

— This was a cross-sectional study of 355 type 2 diabetic men, aged >30 years, who were registered with the Centre for Diabetes and Endocrinology, Barnsley Hospital NHS Foundation Trust, Barnsley, U.K. Subjects were recruited from the diabetic clinic and district retinal screening program. Seventy patients were treated with diet alone, 95 with insulin, and 160 with oral hypoglycemic agents.

All patients gave written informed consent, and the local research ethics committee approved the protocol. Patients were excluded if they had any inflammatory disease or infection with a elevation of C-reactive protein >10 mg/l or were already receiving hormone replacement therapy.

Assessment

Assessments were always made between 8:00 and 10:00 A.M. Patients were screened initially with a questionnaire detailing their medical history, smoking status, and concomitant medications. Height and weight were measured, and BMI was calculated. Waist circumference was measured; waist was defined as the point midway between the iliac crest and the costal margin (lower rib). Blood pressure was recorded.

Patients were asked to complete an Androgen Deficiency in the Aging Male (ADAM) questionnaire (14). This is a 10-item screening questionnaire used to evaluate androgen deficiency in aging males. A positive response is based on decreases in libido or strength of erections or any

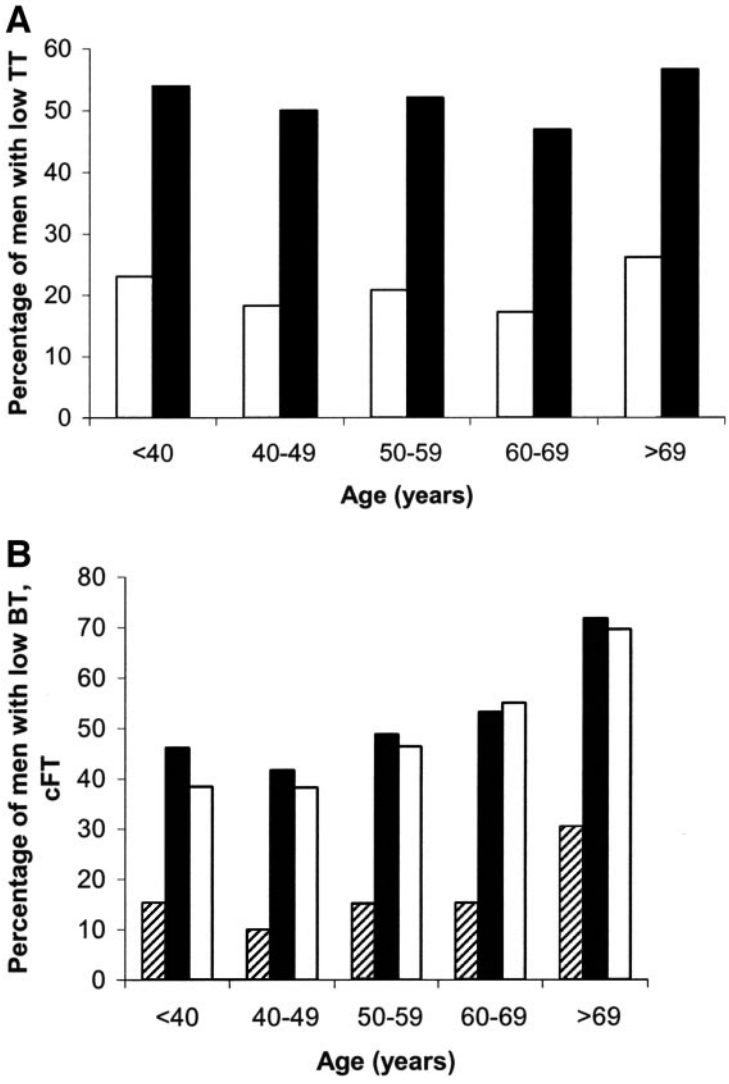

Figure 1—*Percentage of diabetic men with low and borderline low testosterone levels per decade. A: Total testosterone (TT). □, TT <8 nmol/l; ■, TT <12 nmol/l. B: Bioavailable testosterone (BT) and calculated free testosterone (cFT). ▨, BT <2.5 nmol/l; ■, BT <4 nmol/l; □, cFT <0.255 nmol/l.*

three nonspecific questions that include fatigability, decreases in muscle strength, mood changes, and loss of height. This questionnaire has 88% sensitivity and 60% specificity and should only be used in the presence of a low testosterone level. A venous blood sample (20 ml) was taken; serum samples were obtained by centrifugation and immediately frozen at −20°C pending further analysis. Total testosterone and SHBG were measured by the enzyme-linked immunosorbent assay technique (DRG Diagnostics, Germany). A total testosterone level <8 nmol/l was considered to be low, and a level between 8 and 12 nmol/l was considered to be borderline low. Bioavailable testosterone was determined by a modification of the ammonium sulfate precipitation method described by Tremblay and Dube (29). In our laboratory, bioavailable testosterone below the normal range (<2.5 nmol/l) is consistent with overt hypogonadism in young healthy men, whereas a significant proportion of patients with bioavailable testosterone between 2.5 and 4 nmol/l are also hypogonadal as shown in the study by Leifke et al. (11). Free testosterone was calculated from total testosterone, and SHBG was calculated according to the Vermeulens equation (30). A free testosterone level <0.255 nmol/l was taken as low (31). In patients with a low testosterone level (total testosterone <12 nmol/l), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by a chemiluminescent microparticle immunoassay (Abbott Laboratories).

Statistical analysis

Data were analyzed using the SPSS package. Values are expressed as a percentage of each group or as mean ± SE unless otherwise stated. The impact of clinical variables on testosterone and SHBG levels was determined by linear regression and correlation. Comparisons between groups were made using a χ^2 test. The Mann-Whitney *U* test was used to compare testosterone levels in men with and without ED. Results were considered statistically significant at $P < 0.05$.

RESULTS — Of the 359 patients screened, 4 patients were excluded because of an elevated baseline C-reactive protein level (>10 mg/l). The baseline data are presented in Table 1. Mean age was 58.05 ± 0.54 years (range 32–83). The age distribution and mean testosterone levels (total, free, and bioavailable, respectively) were <40 years (13 men; 4%): 11.1, 4.05, and 0.32 nmol/l; 40–49 years (60 men; 17%): 12.3, 4.34, and 0.30 nmol/l; 50–59 years (124 men; 35%): 12.4, 4.05, and 0.28 nmol/l; 60–69 years (112 men; 32%): 13.5, 4.03, and 0.27 nmol/l; and >69 years (46 men; 12%): 12.45, 3.51, and 0.21 nmol/l. There was a strong association between bioavailable and free testosterone ($r = 0.821$; $P < 0.001$).

Prevalence of low testosterone levels

Of the subjects, 20% (71 men) had total testosterone <8 nmol/l and 31% (109 men) had total testosterone between 8 and 12 nmol/l, 16% (58 men) had bioavailable testosterone <2.5 nmol/l and 36% (126 patients) had bioavailable testosterone between 2.5 and 4 nmol/l, and 50% (179 men) had free testosterone <0.255 nmol/l. The age distribution of low testosterone levels by decade is shown in Fig. 1.

Prevalence of symptoms and low testosterone levels (hypogonadism)

Using the definition of hypogonadism as the combination of symptoms (positive ADAM score) in addition to a low testosterone level, 17% (61 subjects) had overt hypogonadism with total testosterone <8 nmol/l and 25% (89 men) had possible hypogonadism with total testosterone between 8 and 12 nmol/l. Similarly, using bioavailable levels, 14% (51 men) had overt hypogonadism with bioavailable testosterone <2.5 nmol/l and 29% (104 men) had possible hypogonadism with bioavailable testosterone between 2.5 and

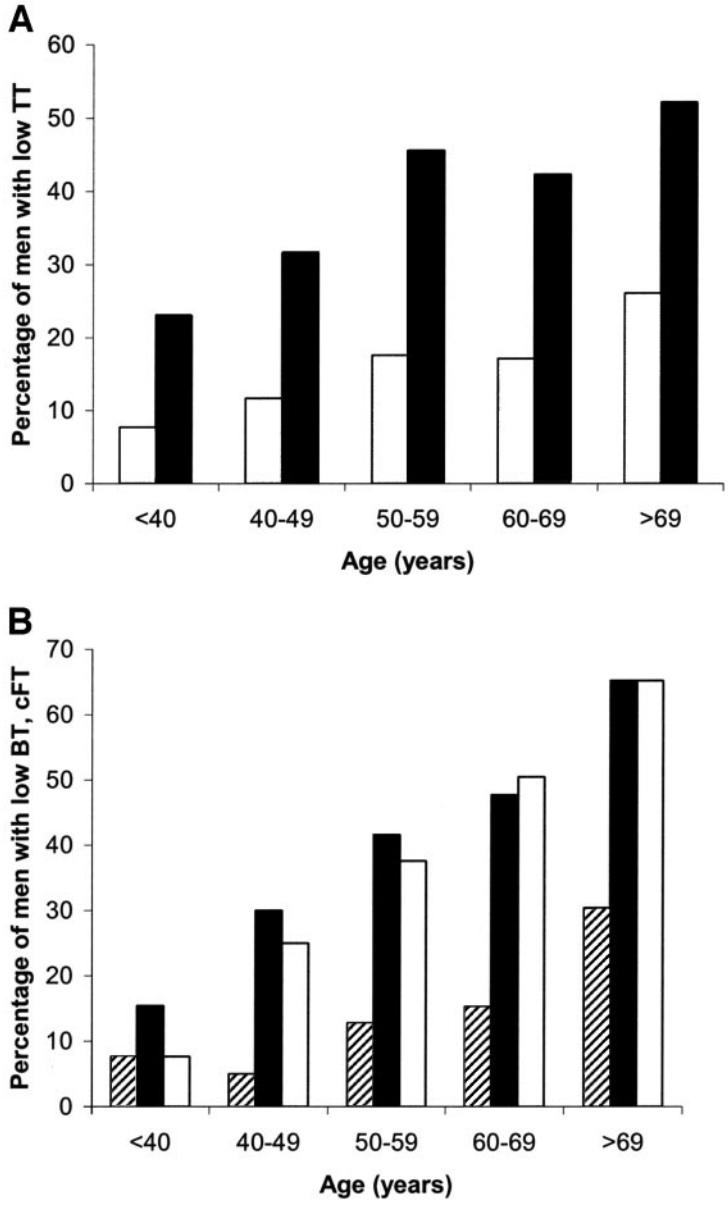

Figure 2—*Incidence of positive symptom score in men with low testosterone by decades of age.* A: *Total testosterone (TT).* □, *TT <8 nmol/l;* ■, *TT <12 nmol/l.* B: *Bioavailable testosterone (BT) and calculated free testosterone (cFT).* ▨, *BT <2.5 nmol/l;* ■, *BT <4 nmol/l;* □, *cFT <0.255 nmol/l.*

4 nmol/l; 42% (149 patients) had free testosterone <0.255 nmol/l. The prevalence of hypogonadism stratified by decade is shown in Fig. 2.

ED was the most common symptom occurring in >70% of the diabetic men with low testosterone levels (Table 2). Of the men with ED and hypogonadism (total testosterone <12 nmol/l or bioavailable testosterone <4 nmol/l or free testosterone <0.255 nmol/l), 63% had reduced libido and 23% had other symptoms of hypogonadism. Only 14% of the hypogonadal men had ED without any other associated symptom. Furthermore, men with ED had significantly lower bioavailable and free testosterone levels than those without ED (bioavailable testosterone 3.92 ± 0.09 vs. 4.25 ± 0.13 nmol/l, $P = 0.04$; free testosterone 0.265 ± 0.01 vs. 0.295 ± 0.01 nmol/l, $P = 0.006$). There were no significant differences in total testosterone levels in men with and without ED (total testosterone 12.5 ± 0.09 vs. 12.7 ± 0.08 nmol/l, $P = 0.1$). Primary hypogonadism (FSH or LH >10 IU/l) was seen in 26%, and 7% had secondary hypogonadism (FSH or LH <2 IU/l, who were further investigated and found to have no other abnormality in pituitary hormones and MRI pituitary); 67% had hypogonadism with normal levels of gonadotrophins.

Sex hormones and body composition

Total testosterone significantly and negatively correlated with both BMI ($r = -0.247$; $P < 0.001$) and waist circumference ($r = -0.275$; $P < 0.001$). SHBG also significantly correlated with both BMI ($r = -0.309$; $P < 0.001$) and waist circumference ($r = -0.277$; $P < 0.001$). Bioavailable testosterone correlated more strongly with waist circumference ($r = -0.210$; $P < 0.001$) than with BMI ($r = -0.148$; $P = 0.006$). Total and bioavailable testosterone levels were significantly lower in men with BMI >30 kg/m^2 or waist circumference >94 cm (Table 3).

A1C, blood pressure, smoking, and testosterone levels

Total testosterone was significantly associated with A1C ($r = -0.16$; $P = 0.04$). However, when both A1C and BMI were adjusted for in regression analysis, BMI ($P < 0.001$) and not A1C ($P = 0.153$) was a significant predictor of total testosterone. Similarly, only waist circumference was a significant predictor of total testosterone ($P < 0.001$) when both waist circumference and A1C were compared against total testosterone. Total testosterone was significantly lower in men with A1C >6.5% (Table 3). There was no significant correlation between A1C and bioavailable or free testosterone ($P = 0.13$) or between A1C and SHBG ($P = 0.16$). A1C was also associated with waist circumference ($r = 0.053$; $P = 0.007$) and BMI ($r = 0.126$; $P = 0.018$).

Sixty-four percent of the patients had a history of hypertension. There was no significant association between testosterone levels and history of hypertension (Table 3). Of the patients, 46% were ex-smokers and 19% were current smokers. There was no significant association between history of smoking and bioavailable or total testosterone levels (Table 3).

CONCLUSIONS — This study has demonstrated that there is a high prevalence of symptomatic hypogonadism in men with type 2 diabetes. Previous studies (9) showed that about one-third of type 2 diabetic men have low serum testosterone levels, but these studies had not correlated this value with symptoms. Furthermore, we have also demonstrated, in line with the study of Dhindsa et al. (9), that low testosterone levels cannot be ex-

Table 2—*Association of low testosterone levels with symptoms and frequency of symptoms across various decades of age in the entire population*

	Symptoms				
Parameter	Reduced libido	ED	Fatigability	Decreased muscle strength	Mood changes
Hormones					
TT <8 nmol/l	58	72	68	49	42
TT 8–12 nmol/l	50	71	64	49	60
TT >12 nmol/l (control)	48	68	54	43	49
BT <2.5 nmol/l	62	78	64	50	50
BT 2.5–4 nmol/l	49	72	63	48	50
BT >4 nmol/l (control)	47	65	57	43	52
cFT <0.255 nmol/l	64	74	63	45	50
cFT >0.255 nmol/l (control)	48	65	57	47	53
Age					
<40 years	30	30	53	15	38
40–49 years	40	55	48	27	45
50–59 years	56	67	68	48	60
60–69 years	47	81	61	54	54
>69 years	63	80	52	54	33

Data are %. BT, bioavailable testosterone; cFT, calculated free testosterone; TT, total testosterone.

plained solely by the lower levels of SHBG associated with insulin resistance. In our study, we found that a high proportion of diabetic men have low levels of bioavailable and free testosterone. Our data also showed that obesity and visceral adiposity, as assessed by both BMI and waist circumference, were negatively associated with low levels of testosterone.

Clearly, guidance on the diagnosis of hypogonadism in diabetes is important. There is no widely accepted consensus as to what constitutes the level of testosterone below which treatment is to be considered. There are various guidelines as described before. On the basis of normal ranges and international recommendations, our data show that 17% of the diabetic men had overt hypogonadism with total testosterone <8 nmol/l, and a further 25% had symptoms of hypogonadism associated with total testosterone between 8 and 12 nmol/l. The confounding factor of low SHBG with insulin resistance may have resulted in lower total testosterone levels in this population. However, the finding of a similar prevalence of hypogonadism using bioavailable testosterone and the wide range of SHBG levels (5.14–129 nmol/l) suggests that this is not the case. It may be that individual patients need to be assessed separately, but the importance of assessing bioavailable testosterone is also demonstrated.

Aging is associated with a decline in testosterone levels in men (10). In the Baltimore longitudinal study on aging, 8, 12, 19, and 28% of men aged >40, 50, 60, and 70 years, respectively, had serum total testosterone levels below the normal range (<11.3 nmol/l) (32). Using the criteria in that study, we found a higher prevalence of hypogonadism across all age-groups (42, 44, 39, and 56% in the age-groups 40–49, 50–59, 60–69, and 70–79 years, respectively). The mean total and bioavailable testosterone levels in our diabetic men were also lower in all age-groups compared with data reported by Leifke et al. (11) in healthy nonobese males and by Muller et al. (33) in independently living men. Dhindsa et al. (9) have similarly shown low total and free testosterone levels in type 2 diabetic men.

The frequencies of hypogonadal symptoms were similar in all defined groups of low testosterone. It is important to note that the ADAM questionnaire lacks specificity and is useful only in the presence of a low testosterone level. An interesting finding was that men with ED had lower bioavailable and free testosterone levels. This further underlines the importance of measuring testosterone levels in diabetic men.

The question thus arises as to why diabetic men have lower testosterone levels. Klinefelter's syndrome, the most frequent form of primary hypogonadism, is associated with insulin resistance and diabetes (34). In our study, approximately one-third of the hypogonadal men had either primary or secondary hypogonadism. The rest of the hypogonadal group had low testosterone levels with normal gonadotrophin levels. It is possible that these men have either secondary hypogonadism, as was defined in the study by Dhindsa et al. (9) wherein men with low testosterone levels and normal or low gonadotrophins were thought to have hypogonadotrophic hypogonadism, or a combination of primary and secondary hypogonadism as seen with aging (10). Moreover, it is not known whether certain men in the borderline group are hypogonadal or not.

We found that testosterone levels in-

Table 3—*Association of low testosterone levels with clinical variables*

	Patients		Control subjects		Patients		Control subjects	
	TT ≤8 nmol/l	TT 8–12 nmol/l	TT >12 nmol/l	*P*	BT ≤2.5 nmol/l	BT 2.5–4 nmol/l	BT >4 nmol/l	*P*
n	71	109	175		53	131	171	
BMI >30 kg/m^2	57 (80)	74 (68)	90 (51)	0.0001	39 (74)	90 (69)	92 (54)	0.006
WC >94 cm	65 (92)	104 (95)	147 (84)	0.009	49 (92)	123 (94)	144 (84)	0.005
A1C >6.5%	51 (72)	80 (73)	100 (57)	0.008	40 (75)	87 (66)	104 (61)	0.14
Hypertension	49 (69)	69 (63)	110 (63)	0.64	33 (62)	89 (68)	106 (62)	0.54
Smoking	49 (69)	71 (65)	109 (62)	0.59	40 (75)	80 (61)	109 (64)	0.17

Data are *n* (%). BT, bioavailable testosterone; TT, total testosterone; WC, waist circumference.

versely correlated with waist circumference and BMI. A plausible explanation for this is the hypogonadal obesity cycle, which we have recently extended (1). The cycle was first described by Cohen (35). Essentially, visceral adipocytes have a high activity of the enzyme aromatase, which converts testosterone to estrogen. Testosterone inhibits the enzyme lipoprotein lipase, which takes up free fatty acids into adipocytes (36). Lower levels of testosterone result in increased triglyceride levels in adipocytes, which promotes further adipocyte proliferation and hence higher aromatase activity. Testosterone levels are further lowered as a result of leptin resistance at the hypothalamic-pituitary and testicular levels, causing reduced LH release and testosterone secretion (1,37). It is known that a reduction in the degree of obesity results in an elevation of testosterone levels.

Visceral obesity is an important cause of insulin resistance. We have shown that glycemic control was significantly associated with both BMI and waist circumference. This is in agreement with other studies in men (38). Iso et al. (39) also showed that A1C was significantly associated with waist-to-hip ratio in urban Japanese men.

Serum testosterone levels have been reported to be lower in men with hypertension (40). Our results did not show a significant association between testosterone levels and history of hypertension. Similarly, our study found no significant association between testosterone levels and smoking. Various studies have shown significantly increased, decreased, and unchanged levels of total testosterone in male smokers (41). However, no significant differences have been reported in bioavailable testosterone levels between smokers and nonsmokers (42).

Testosterone status is becoming increasingly recognized as essential in the assessment and treatment of men with ED. It has been established that men with ED who do not respond to sildenafil frequently have hypogonadal levels of testosterone (17), and testosterone replacement therapy converts 60% of sildenafil nonresponders into responders (18,19). Furthermore, there is recent evidence that testosterone replacement therapy improves insulin resistance, glycemic control, cholesterol levels, and waist circumference in diabetic men with low testosterone levels (26). These findings and the fact that testosterone improves cardiac ischemia in men with chronic stable angina (43) and symptoms in men with heart failure (44) suggest that the diagnosis of hypogonadism in men with type 2 diabetes has important clinical consequences besides the benefits on libido and well-being associated with normalization of testosterone status.

In summary, this study demonstrates that a significant number of men with type 2 diabetes have testosterone insufficiency and symptoms of hypogonadism. It also illustrates that the diagnosis of hypogonadism is difficult in that the symptoms are nonspecific, especially in diabetic men. The data presented here also show that bioavailable testosterone measurement is an important adjunct to the assessment of borderline hypogonadism in diabetes, removing the confounding effect of variable SHBG levels. Larger studies are required to establish the benefit of testosterone replacement therapy on quality of life and the diabetic state in men.

Acknowledgments— This study was funded by Barnsley Hospital Charitable Funds for Endocrinology.

We thank Tracey Young, Statistician, from Sheffield University for her help with the statistical analysis.

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