Low Testosterone Levels Are Common and Associated with Insulin Resistance in Men with Diabetes

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Context: Low testosterone levels are common in men with type 2 diabetes and may be associated with insulin resistance.

Objective: We investigated prevalence of testosterone deficiency and the relationship between testosterone and insulin resistance in a large cohort of men with type 2 and type 1 diabetes.

Design: The study was a cross-sectional survey of 580 men with type 2 diabetes and 69 men with type 1 diabetes. A subgroup of 262 men with type 2 diabetes was then reassessed after a median of 6 months.

Results: Forty-three percent of men with type 2 diabetes had a reduced total testosterone, and 57% had a reduced calculated free testosterone. Only 7% of men with type 1 diabetes had low total testosterone. By contrast, 20.3% of men with type 1 diabetes had low calculated free testosterone, similar to that observed in type 2 diabetes (age-body mass index adjusted odds ratio = 1.4; 95% confidence interval = 0.7–2.9). Low testosterone levels were independently associated with insulin resistance in men with type 1 diabetes as well as type 2 diabetes. Serial measurements also revealed an inverse relationship between changes in testosterone levels and insulin resistance.

Conclusions: Testosterone deficiency is common in men with diabetes, regardless of the type. Testosterone levels are partly influenced by insulin resistance, which may represent an important avenue for intervention, whereas the utility of testosterone replacement remains to be established in prospective trials. **(*J Clin Endocrinol Metab* 93: 1834–1840, 2008)**

Testosterone deficiency is common in men with type 2 diabetes (1) in whom it may contribute to impaired performance, mood, and libido (2). Although a direct relationship between testosterone deficiency and cardiovascular risk remains controversial (3, 4), there is evidence that testosterone levels are inversely associated with insulin resistance (5), a potent risk factor for both micro- and macrovascular complications of diabetes (6). In particular, reduced total testosterone (TT) levels have been associated with insulin resistance and subsequent risk for developing type 2 diabetes (2, 7–10). Moreover, short-term studies in men have shown that testosterone supplementation may improve insulin sensitivity (11–15).

In contrast to studies in men with type 2 diabetes, relatively little is known about testosterone status in type 1 diabetes. A recent small study suggested that testosterone levels were lower in men with type 2 diabetes than in type 1 diabetes, concluding that low testosterone levels may be specific to type 2 diabetes (16). However, low levels of SHBG, the main carrier protein of TT in the circulation, may be independently associated with the risk of type 2 diabetes (17, 18), potentially confounding this relationship. Moreover, insulin resistance is common in treated individuals with type 1 diabetes and strongly associated with adverse outcomes (19).

In the present study, we examine the prevalence and predic-

0021-972X//$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2007-2177 Received September 27, 2007. Accepted February 22, 2008.

First Published Online March 4, 2008

Abbreviations: BMI, Body mass index; cFT, calculated free testosterone; CI, confidence interval; eGDR, effective glucose disposal rate; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; TT, total testosterone.

tors of testosterone deficiency, as estimated by both TT and SHBG-adjusted calculated free testosterone (cFT) levels (20), in a large, unselected cohort of men with type 1 or type 2 diabetes presenting at a single center. In addition, we explore the potential determinants of testosterone levels in both populations, including insulin resistance and systemic inflammation (5, 8).

Patients and Methods

Cross-sectional survey

This study was initially designed as a cross-sectional survey of adult males with diabetes but without established hypogonadism and/or testosterone replacement therapy (type 2 diabetes n = 574; type 1 diabetes n = 69) in long-term follow-up in a single clinic at Austin Health, Melbourne, Australia. The Austin Health Diabetes Clinic serves a population of 700,000. The majority of referrals to the clinic are from general practitioners requiring assistance with surveillance and management of the long-term complications of diabetes. Approximately 20% of the patients are referred from other sources, including specialty units within the medical center. The diagnosis of type 1 diabetes was designated by a history of insulin dependence within 1 yr of diagnosis, the absence of circulating C-peptide, and an age on onset of less than 35 yr. All men gave written informed consent, and the study was approved by the Human Research Ethics Committee, Research Ethics Unit, Austin Health.

Quantification of testosterone levels

Blood samples were drawn between 0800 and 1000 h after an overnight fast. Serum was obtained after centrifugation at 4 C and stored in aliquots at −80 C until analysis. Serum TT was measured using the Access testosterone assay (Beckman Coulter, Inc., Fullerton, CA) with a minimum detection limit of 0.35 nmol/liter. In our hands, the intra- and interassay coefficients of variation assessed for two different concentrations (4.7 and 26 nmol/liter) were 3.9 and 4.8% and 5.7 and 5.0%, respectively. Reference range for this TT assay was 10–27.6 nmol/liter, based on gas chromatography/mass spectrometry measurements obtained from a reference panel of 124 healthy, reproductively normal young men (21). Low TT levels were therefore designated in individuals with a TT level less than 10 nmol/liter.

SHBG levels were determined with the Immulite 2000 analyzer (Diagnostics Products Corp., Los Angeles, CA). Reference range for SHBG was 13–71 nmol/liter, and minimum detection limit was 0.02 nmol/liter. Intra- and interassay coefficients of variation for two different concentrations (5.0 and 75.9 nmol/liter) were 4.2 and 5.2% and 4.6 and 5.4%, respectively. Free testosterone values were calculated from TT, SHBG, and serum albumin based on mass action laws with Vermeulen's formula (20). The cFT levels (20) correlate well with measurements of free testosterone as determined by the gold standard of equilibrium dialysis (22). Reference range for the Access-Testosterone/Immulite SHBG combination for cFT was 0.23–0.61 nmol/liter, based on the same reference panel of 124 healthy, reproductively normal young men (21). Low cFT levels were designated in individuals with a cFT level less than 0.23 nmol/liter.

Follow-up estimation of testosterone levels

In a randomly selected subgroup of 262 men with type 2 diabetes, TT and cFT determinations were repeated at their next routine clinic appointment (median of 6 months; range 1–15 months). The clinical characteristics of this subgroup were not significantly different from those of the total cohort of men with type 2 diabetes (Table 1).

Measurement of additional parameters

On the same fasting blood samples obtained for the cross-sectional and follow-up studies, glycosylated hemoglobin (HbA_{1c}), high-sensitivity C-reactive protein (hs-CRP), triglycerides, and total and high-density lipoprotein (HDL) cholesterol were measured using standard methodologies at the Biochemistry Department, Austin Health. In individuals with type 2 diabetes, insulin resistance was estimated from fasting plasma glucose and C-peptide concentrations using the homeostatic model assessment of insulin resistance (HOMA-IR) (23). In individuals with type 1 diabetes, insulin sensitivity was estimated from the effective glucose disposal rate (eGDR) (24).

Statistical analysis

Data were analyzed using simple (Pearson) calculation, multiple regression (with results reported as partial correlations), one-way ANOVA, analysis of covariance, and Mann Whitney *U* (nonparametric) tests, as appropriate. To evaluate the independent predictors of reduced TT and cFT levels, we used logistic regression analysis, and the final model variables were determined by sequential penalized likelihood

TABLE 1. Baseline characteristics of the men with diabetes

	Type 1 diabetes (n = 69)	All type 2 diabetes (n = 574)	Type 2 diabetes follow-up (n = 262)
Median TT (nmol/liter)	15.8 (7.6–30)	10.5 (0.3–28)	10.5 (0.8–25)
Low TT (<10 nmol/liter) (%)	7%	43%	42%
Median cFT (nmol/liter)	0.31 (0.13–0.59)	0.22 (0.0–0.53)	0.22 (0.0–0.47)
Low cFT (<0.23 nmol/liter) (%)	20%	57%	60%
Age (yr)	45 ± 1	65 ± 1	65 ± 1
Duration of diabetes (yr)	19 (1–55)	10 (0.1–44)	9.5 (1–33)
BMI (kg/m^2)	27 ± 1	30 ± 1	30 ± 1
HbA_{1c} (%)	8.0 ± 0.1	7.5 ± 0.1	7.6 ± 0.1
Fasting glucose (mmol/liter)	10.5 (2.6–20)	8.1 (2.3–24)	8.6 (2.6–22)
Antihypertensive therapy (%)	36%	80%	78%
RAS blockade (%)	33%	70%	68%
Blood pressure (mm Hg)	136/78	143/78	142/79
hs-CRP (IU/ml)	1.5 (0.2–11.5)	3.0 (0.2–192)	2.9 (0.2–58)
Lipid-lowering therapy (%)	28%	62%	60%
Triglycerides (mmol/liter)	1.1 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Total cholesterol (mmol/liter)	4.8 ± 0.1	4.3 ± 0.1	4.5 ± 0.1
HDL cholesterol (mmol/liter)	1.7 ± 0.1	1.3 ± 0.1	1.4 ± 0.1
Chronic kidney disease (%)	43%	44%	45%
Macrovascular disease (%)	16%	42%	40%

Values are provided as mean ± SEM or median (range). Values for BMI and/or duration of diabetes were missing in 37 subjects of the men with type 2 diabetes. RAS, Renin-angiotensin system.

(Akaike information criterion). All variables known to be associated with TT were included in the final model, along with any variables associated with TT in univariate analyses with a P value of <0.01. To adjust for repeated measures in examining the determinants of the change in testosterone levels, linear regression (analysis of covariance) was adjusted for baseline parameters.

Results

Cohort characteristics

The initial cross-sectional survey included 580 men with type 2 diabetes and 69 men with type 1 diabetes. Six men with type 2 diabetes who produced a standardized residual greater than four were excluded from the statistical analysis. Clinical characteristics of these individuals are described in Table 1. Notably, most participants had longstanding diabetes, and the prevalence of diabetic complications was high. One third of men with type 2 diabetes had documented macrovascular disease, and two thirds (66%) had microvascular complications. Of the patients with type 2 diabetes, 24% received metformin, 12% received a sulfonylurea, 31% were on both metformin and a sulfonylurea, and 10% received a thiazolidinedione. Forty percent of men also received insulin in combination with oral hypoglycemic therapy.

Prevalence of testosterone deficiency in men with type 2 diabetes

Forty-three percent of all men (n = 249) with type 2 diabetes in our clinic had low TT levels (<10 nmol/liter) (Fig. 1). In this cohort, TT levels were inversely related to age (Fig. 2A). In men with type 2 diabetes younger than 40 yr, the prevalence of low TT levels was 20%, 29% in men aged 40–49 yr, 37% in men 50–59 yr old, 43% in men 60–69 yr old, 46% in men 70–79 yr old, and 61% in men aged 80 yr or older.

Fifty-seven percent (n = 326) of all men with type 2 diabetes in our clinic had low cFT levels (<0.23 nmol/liter), most of

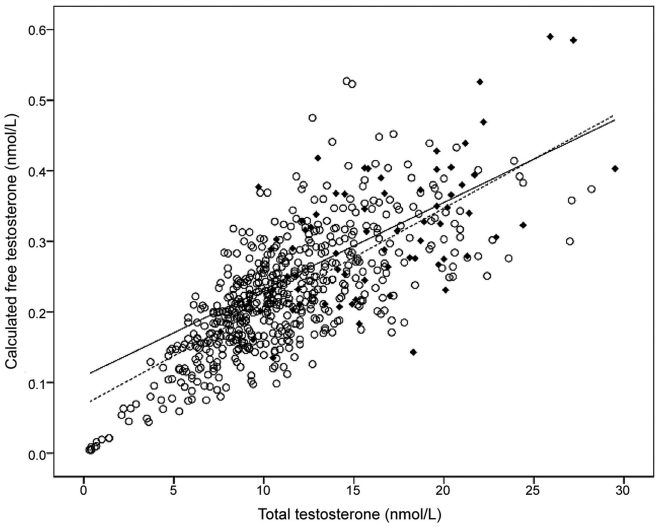

FIG. 1. TT and cFT levels in patients with diabetes. *Filled symbols* denote individuals with type 1 diabetes, and *open symbols* denote men with type 2 diabetes. The *dotted line* denotes the correlation for men with type 1 diabetes, and the *solid line* denotes the correlation for men with type 2 diabetes.

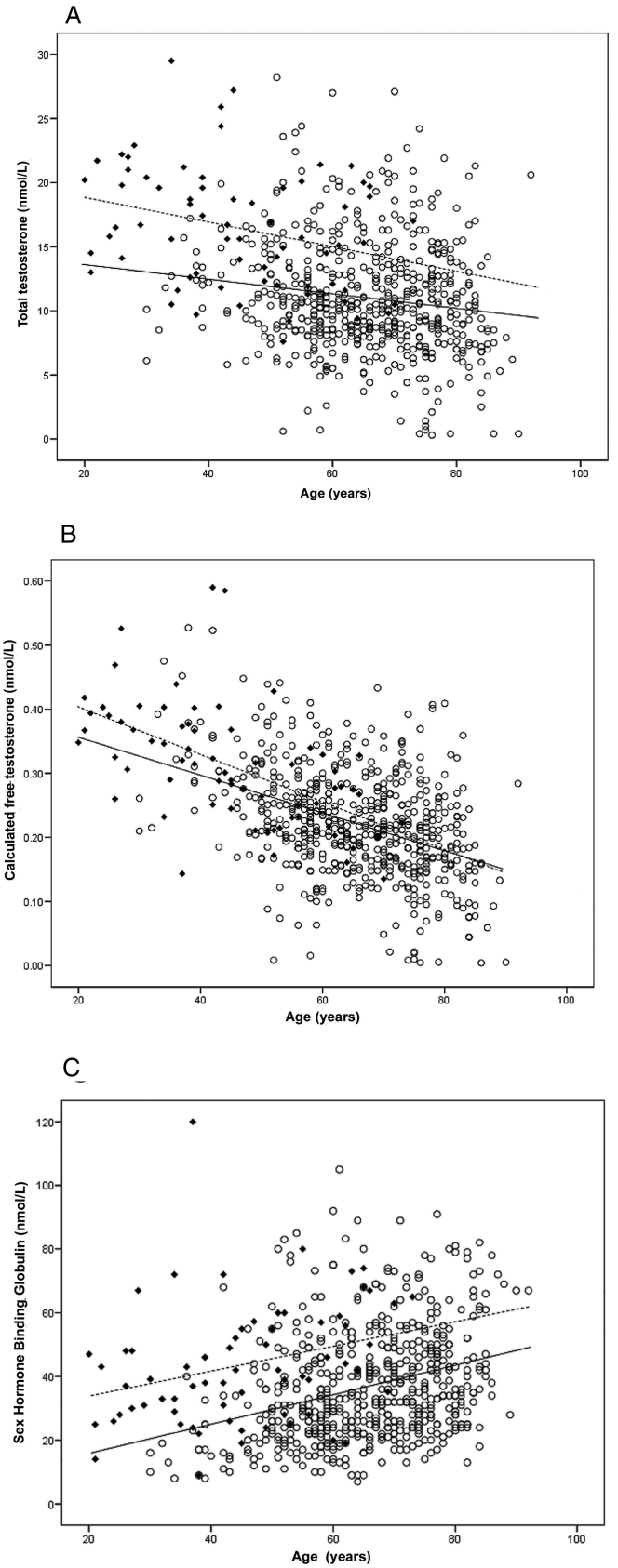

FIG. 2. Correlation between age and TT (A) and cFT (B) and SHBG (C) in patients with diabetes. *Filled symbols* denote men with type 1 diabetes, and *open symbols* denote men with type 2 diabetes. The *dotted line* denotes the correlation for individuals with type 1 diabetes, and the *solid line* denotes the correlation for men with type 2 diabetes.

whom also had low TT (63%) (Fig. 1). More than 85% of men with low TT levels also had a low cFT. The inverse association between cFT levels and age (Fig. 2B) was significantly stronger that that observed for TT ($P < 0.01$), possibly because of the age-associated rise in SHBG (Fig. 2C). The prevalence of low cFT levels was 13% in men with type 2 diabetes younger than 40 yr, 19% in men aged 40–49 yr, 45% in men 50–59 yr old, 60% in men 60–69 yr old, 67% in men 70–79 yr old, and 76% in men with type 2 diabetes aged 80 yr or older. For every decade increase in age, the prevalence of low cFT levels effectively doubled [adjusted odds ratio = 2.0; 95% confidence interval (CI) = 1.4–2.4].

Prevalence of testosterone deficiency in men with type 1 diabetes

Few men with type 1 diabetes had low TT (7.2%, $P < 0.001$, *vs.* type 2 diabetes, Fig. 1). This frequency of low TT levels in men with type 1 diabetes was not significantly greater than observed in reproductively normal young men (21). After adjusting for age, body mass index (BMI), and other confounding factors, the frequency of low TT levels remained significantly higher in men with type 2 diabetes when compared with those with type 1 diabetes (adjusted odds ratio = 4.0; 95% CI = 1.5–10.7; $P = 0.005$). However, when SHBG was included in the model, this difference between type 1 and type 2 diabetes was eliminated ($P = 0.16$).

By contrast, one in five men with type 1 diabetes had low cFT levels (20.3%, Fig. 1), a prevalence significantly higher than normally observed in healthy men (21). This frequency was statistically similar to that observed in age- and BMI-matched men with type 2 diabetes (adjusted odds ratio = 1.4; 95% CI = 0.7–2.9), reflecting the difference in significant SHBG levels in the two groups (Fig. 2C, $P < 0.001$). As in men with type 2 diabetes, the major predictor of cFT levels in individuals with type 1 diabetes was age (Fig. 2B). For each decade of life, the prevalence of low cFT levels effectively doubled (adjusted odds ratio for low cFT levels = 2.4; 95% CI = 1.4–3.9).

Testosterone indices and insulin resistance

In men with type 2 diabetes in our clinic, insulin resistance (as estimated by the HOMA-IR equation) (23) was independently associated with low TT levels (odds ratio = 1.2; 95% CI = 1.0–1.4), after adjusting for age, BMI, treatment regimens, and other potentially confounding variables. Individuals with low TT levels were also more likely to have a BMI higher than 30 kg/m^2 (55 *vs.* 35%, $P < 0.001$), elevated triglycerides higher than 1.7 mmol/liter (45 *vs.* 28%, $P < 0.001$), reduced HDL cholesterol levels (28 *vs.* 17%, $P < 0.001$), and higher hs-CRP levels (median 7.7 *vs.* 4.5, $P < 0.01$). However, there was no difference in glycemic control, blood pressure levels, or the frequency or intensity of antihypertensive treatments between those with and without low testosterone levels. TT levels were also correlated with the HOMA-estimated insulin resistance within the normal range of both parameters after adjusting for age and obesity (partial correlation coefficient = −0.13; $P = 0.002$).

Insulin sensitivity was also independently associated with cFT levels in individuals with type 2 diabetes, such that that men with low cFT levels also tended to be more insulin resistant after adjusting for age, obesity, treatment regimens, and other potentially confounding variables (partial correlation coefficient = −0.10; $P = 0.02$). Individuals with low cFT levels were also more likely to have a BMI higher than 30 kg/m^2 (49 *vs.* 39%, $P = 0.03$) and reduced HDL cholesterol levels (25 *vs.* 17%, $P = 0.03$).

Levels of SHBG were not associated with insulin resistance in men with type 2 diabetes after adjusting for age and BMI ($P = 0.281$). However, low SHBG levels were independently associated with poorer glycemic control (HbA_{1c}) after adjustment for age and BMI ($P = 0.04$). SHBG levels were not associated with type of oral hypoglycemic therapies or the use of statins.

In men with type 1 diabetes, cFT levels were also independently associated with eGDR, a marker of insulin sensitivity in individuals with type 1 diabetes (24), after adjusting for age ($P = 0.04$). There was no statistically significant association between eGDR and TT or SHBG levels.

Changes in testosterone levels over time

In a randomly selected subgroup of 262 men with type 2 diabetes, TT and cFT determinations were repeated at their next routine clinic appointment (median of 6 months; range 1–15 months). The clinical characteristics of this subgroup in which testosterone levels were retested were not significantly different from those of the total cohort of men with type 2 diabetes (Table 1). None of these men received testosterone therapy.

At the second analysis, the prevalence of testosterone deficiency defined by low TT levels (<10 nmol/liter) was not significantly different from obtained at the first estimation (39 *vs.* 42%, $P = 0.2$), and there was a strong correlation between estimations ($r^2 = 0.73$, Fig. 3A). Seventy-three percent of individuals with low TT level on the first estimation had low TT levels on repeat testing. Most of those rising above 10 had borderline levels (8–10 nmol/liter) on initial testing. Although the variability between samples was small, there was some evidence of regression to the mean, with the lowest samples showing a mean increase in levels (Fig. 3B). However, after adjusting for each subject's baseline parameters, age, and the time between clinic visits, we were able to demonstrate a significant inverse relationship between the change in TT level and the change in HOMA-IR during the same follow-up period ($P = 0.01$). In addition, the change in TT level was also independently correlated with the change in HbA_{1c} during the same follow-up period ($P = 0.02$). This was partly explained by the association between SHBG and HbA_{1c} ($P < 0.01$).

At the second analysis, there was also a good correlation between cFT levels obtained at the two time points ($r^2 = 0.57$, Fig. 3C). However, the frequency of testosterone deficiency defined by low cFT levels (<0.230 nmol/liter, 48%) at the second time point was significantly lower than obtained at the first estimation (60% difference, $P < 0.001$). Two thirds (66%) of patients with low testosterone levels at the first estimation continued to have low levels at the second reading. There was some evidence of regression to the mean (Fig. 3D). Nonetheless, after adjusting for each subject's baseline measurements, the change in cFT was inversely correlated with the change in HOMA-IR during the same follow-up period ($P = 0.03$). There was no signif-

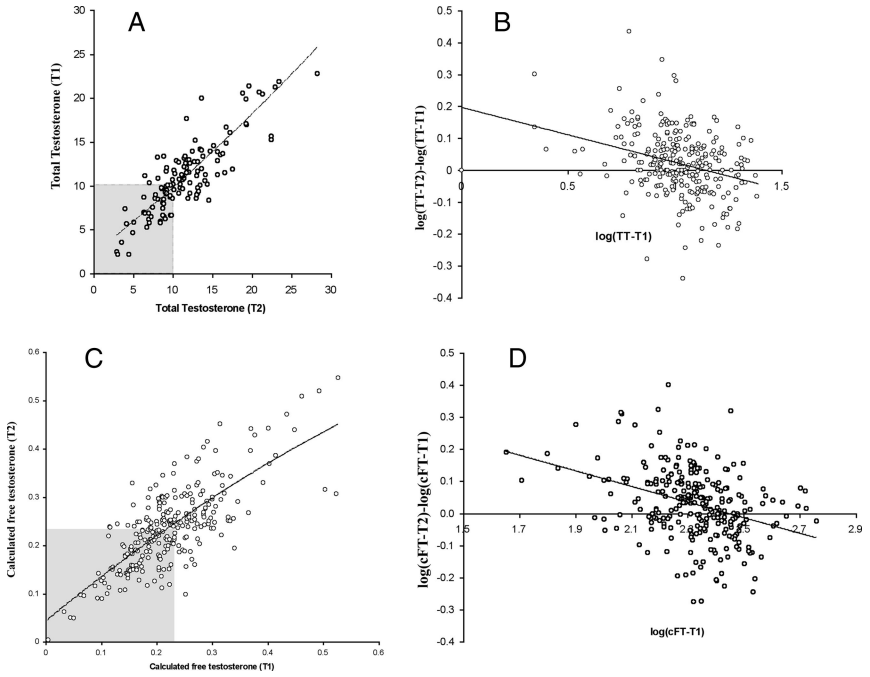

FIG. 3. The correlation between serial measurements of TT (A and B) and cFT (C and D) in 262 men with type 2 diabetes. The *shaded area* denotes men with testosterone deficiency.

icant relationship between the change in cFT level during follow-up and the change in HbA_{1c}.

Discussion

In this cross-sectional analysis of a large unselected cohort of men presenting to a single tertiary referral center, we found that 43% of men with type 2 diabetes had low TT levels, and 57% had low cFT levels. In addition, 20% of men with type 1 diabetes also had low cFT levels, an age-adjusted rate not significantly different from that observed in type 2 diabetes. In our cohort, age and BMI were major factors influencing both TT and cFT levels, consistent with reports from previous studies (2, 7, 25). Because testosterone deficiency may contribute to impaired performance, mood, and libido (2), as well as have adverse impact on cardiovascular risk (3–5), these findings demonstrate the presence of a significant and unrecognized problem. These findings are consistent with a smaller clinic-based study showing a 33% prevalence of low testosterone in men with type 2 diabetes (1) and population-based studies in which reduced testosterone levels are more common in men with type 2 diabetes than in the age-matched general population (8). However, this study is the first to demonstrate a similar prevalence of low cFT levels in individuals with type 1 diabetes, in contrast to previous findings (16), despite otherwise similar demographic and biochemical patient characteristics.

Importantly, we show that free testosterone levels were independently correlated with indices of insulin resistance in men with type 2 diabetes as well as those with type 1 diabetes. Moreover, the change in testosterone levels over time was also independently correlated with changes in insulin sensitivity in the subgroup of men with type 2 diabetes followed longitudinally. Longitudinal changes in testosterone levels in patients with type 1 diabetes remain to be explored in a larger cohort of patients. These data are consistent with findings in nondiabetic men, where cFT levels have been shown to be inversely associated with insulin levels (8), HOMA (25), and visceral adiposity (8, 25). In addition, these findings support the hypothesis that circulating testosterone levels in men with diabetes may be influenced by insulin sensitivity, and vice versa. Although none of the men in our study received testosterone therapy, short-term studies in men have shown that testosterone supplementation may improve insulin sensitivity (11–13, 15). Male mice with a targeted deletion of the androgen receptor have increased blood glucose levels due to insulin resistance (26). Men with Klinefelter syndrome have increased insulin resistance (27), and androgen deprivation therapy in men with prostate cancer increases the risk of developing the metabolic syndrome as well as that of incident diabetes (28, 29). Conversely, interventions to improve insulin sensitivity may also significantly impact on testosterone levels. In particular, visceral adiposity is an important cause of insulin resistance and also decreases testosterone concentrations through conversion to estradiol by aromatase (5). In our study, as well as others (9, 10), testosterone levels in men with type 2 diabetes were correlated with BMI. Although BMI and weight are suboptimal markers of visceral adiposity, previous studies have reported an association of loss of weight in obese insulin-resistant men with increased testosterone levels (30). Although not specifically employed in our study, improved lifestyle factors or altered pharmacological management that contributed to improved insulin sensitivity may also have contributed to an increase in testosterone levels observed in our patients. Similarly, in patients where insulin sensitivity declined, testosterone levels fell on average.

The 4-fold higher prevalence of reduced TT levels observed in men with type 2 diabetes when compared with those with type 1 diabetes was largely driven by reduced levels of SHBG (Fig. 2C), which was present at all ages and across all levels of BMI. When SHBG was included into the model, this difference between type 1 and type 2 diabetes was eliminated ($P = 0.16$). Insulin is known to inhibit hepatic production of SHBG (31), and SHBG levels fall acutely during hyperglycemic-euglycemic clamp studies (32). Indeed, reduced SHBG has been suggested as a surrogate marker for insulin resistance (33). Although insulin resistance in individuals with type 2 diabetes may explain both the high frequency of both low SHBG levels and TT levels in our study, there was no independent association of SHBG levels with

the HOMA index of insulin resistance in men with type 2 diabetes. Moreover, cFT levels, a SHBG-independent testosterone parameter, were still reduced in individuals with both type 2 and type 1 diabetes and independently associated with insulin resistance.

The strengths of this study include the large number subjects, inclusion of a large cohort of patients with type 1 diabetes, measurement of serum testosterone levels at the appropriate time of day (early morning), accurate assays for total and free testosterone levels, and longitudinal follow-up in a substantial number of men with type 2 diabetes. However, it remains to be established whether the biochemical testosterone deficiency observed in this study represents a true hypogonadal state. Guidelines recommend that a diagnosis of hypogonadism be made "only in men with consistent signs and symptoms and unequivocally low serum testosterone levels" (22). Interpretation of our study is therefore limited because we did not obtain a detailed record of symptomatology history. That said, generalized symptomatology in individuals with longstanding diabetes is almost impossible to distinguish from those of hypogonadism.

Findings from the cross-sectional component of our study are also limited because a single low testosterone level is inadequate for making the diagnosis of hypogonadism, given the variability in serum testosterone levels that can result from circadian rhythms, the pulsatile nature of its secretion, use of concomitant medications, and measurement variations (22). To assess this variability, we repeated testosterone determinations in a representative subset of individuals with type 2 diabetes, finding that 27 and 33% of individuals with low TT and cFT levels respectively had levels in the normal range when retested. This is consistent with reports in nondiabetic men, where as many as 30% of men will have normal levels when repeated (34).

Although there is a strong rationale for testosterone replacement, the balance of benefits and risks is currently unknown and still to be defined by large and long-term clinical trials. Certainly, testosterone replacement can improve performance, mood, and libido in men with hypogonadism (22) and augments insulin sensitivity (11, 15). However, testosterone may have deleterious actions on prostate disease, sleep apnea, and possibly cardiovascular risk (35). Although insulin sensitivity is associated with testosterone deficiency, there is no evidence that insulin sensitizers, including metformin and thiazolidinediones, are able to elevate testosterone levels in men with diabetes. Exercise and weight loss appear to be effective, but such lifestyle modifications should already be employed for a range of other reasons. Consequently, the appropriate clinical response to this emerging problem remains to be determined.

Acknowledgments

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This work was supported by a National Health and Medical Research Council Health Professional Research Fellowship (to M.G.).

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