Contrasting Testosterone Concentrations in Type 1 and Type 2 Diabetes

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We have recently reported (1) that male patients with type 2 diabetes have frequent hypogonadotrophic hypogonadism. We have now asked whether a similar defect may be observed in type 1 diabetic males to determine whether diabetes per se is the cause of hypogonadotrophic hypogonadism.

RESEARCH DESIGN AND METHODS

— Fifty patients with type 1 diabetes (age range 23–58 years) and 50 age-matched patients with type 2 diabetes (age range 28–51 years) were included in the study. Patients with known history of hypogonadism, panhypopituitarism, or chronic debilitating disease such as renal failure, cirrhosis, or HIV infection were excluded from the study. Fasting blood samples were obtained from the patients, and total testosterone (TT), free testosterone (FT), sex hormone–binding globulin (SHBG), leutinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured as previously described (1). FT and bioavailable testosterone (bioT) were calculated from SHBG and TT as previously described (1). Hypogonadism was defined as low FT or low calculated FT (2). Mann-Whitney rank-sum test or Student's *t* test for unpaired data, χ^2 test, and Spearman's test were used as appropriate (Sigmastat software).

RESULTS

— The mean TT, FT, calculated FT, and bioT concentrations in type 1 diabetic patients were in the middle of the normal range (Table 1). No patient had subnormal TT concentrations; three patients had supranormal TT, while two patients had subnormal FT and bioT concentrations.

The mean TT concentration in patients with type 2 diabetes was significantly lower than that in type 1 diabetic subjects (Table 1). The prevalence of low TT concentrations was 24 of 50 (48%), while that of low measured and/or calculated FT was 13 of 50 (26%). LH and FSH concentrations in 12 of 13 hypogonadal patients were in the normal range, and were thus inappropriately low. One patient had elevated LH and FSH concentrations and thus had primary hypogonadism. The mean prolactin concentration was lower in type 2 than in type 1 diabetic subjects.

The mean SHBG concentration in type 1 diabetic subjects was at the upper end of the reference range. The level of SHBG was higher than normal in 16 patients. The mean SHBG in type 2 diabetic subjects was significantly lower than that in type 1 diabetic subjects (Table 1).

In type 1 diabetic subjects, plasma TT concentrations were negatively related to BMI ($r = -0.52$, $P < 0.001$), as were FT ($r = -0.36$, $P < 0.05$), calculated FT ($r = -0.36$, $P < 0.05$), and bioT ($r = -0.36$, $P < 0.05$). In type 2 diabetic subjects, BMI was also negatively related to FT ($r = -0.55$, $P < 0.01$), calculated FT ($r = -0.42$, $P < 0.05$), bioT ($r = -0.45$, $P = 0.01$), and TT ($r = -0.382$, $P < 0.01$) (Fig. 1). BMI was also inversely related to SHBG ($r = -0.34$, $P < 0.05$). Plasma FSH concentrations were positively related to age ($r = 0.39$, $P = 0.01$) and to LH concentrations ($r = 0.38$, $P = 0.01$). In type 2 diabetic subjects, FSH was positively related to age ($r = 0.504$, $P < 0.01$) and LH ($r = 0.454$, $P < 0.01$). The total insulin dose and insulin dose per kilogram was significantly related to SHBG ($r = -0.53$, $P < 0.001$). In a multiple linear regression model, only total daily insulin dose, and not BMI, was a significant predictor ($P = 0.04$) of SHBG concentration. HbA_{1c} (A1C) did not relate to any of the parameters in the study either in type 1 or type 2 diabetes.

CONCLUSIONS

— Our data show that in contrast to type 2 diabetes with frequent occurrence of hypogonadotrophic hypogonadism, type 1 diabetes is associated with normal TT concentrations and with consistently high normal or elevated SHBG concentrations. FT, LH, and FSH concentrations also tended to be normal. SHBG tended to be elevated in contrast to the relatively suppressed levels observed in type 2 diabetes.

This pattern of testosterone is therefore different from that in age-matched type 2 diabetic subjects. The prevalence of low TT (48%) and FT (26%) concentrations in type 2 diabetes in this study was associated with inappropriately low LH and FSH concentrations. The prevalence of low TT and FT was 0 and 6%, respectively, in type 1 diabetic patients. Thus, hypogonadotrophic hypogonadism in type 2 diabetes is specific to that condition and is not the effect of diabetes and hyperglycemia per se.

The significance of lower prolactin concentrations in type 2 diabetes than those in type 1 diabetes is not clear but may point to an additional defect in the hypothalamico-hypophyseal axis, possibly at the dopaminergic level. Obesity is known to be associated with diminished prolactin secretion following pharmacological stimuli (3,4). The clinical or pathophysiological significance of this observation is not clear at this time.

It has been suggested that the lack of insulin in type 1 diabetes may contribute to the increase in SHBG concentrations and that treatment with insulin may lower it (5,6). The mean insulin dose per kilogram of body weight has been shown pre-

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Abbreviations: bioI, bioavailable testosterone; LH, leutinizing hormone; FSH, follicle-stimulating hormone; FT, free testosteron; SHBG, sex hormone–binding globulin; TT, total testosterone.

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

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Table 1—*Demographic and biochemical indices in type 1 and type 2 diabetic patients and type 2 diabetic patients with hypogonadotrophic hypogonadism*

	Type 1 diabetes	Type 2 diabetes	*P* value (vs. type 1 diabetes)	Reference range
n	50	50	—	—
Hypogonadal subjects (%)	3 (6)	13 (26)	**<0.01**	—
Age (years)	42.78 ± 1.4	43.74 ± 0.8	0.261	—
BMI (kg/m^2)	26.09 ± 0.75	34.91 ± 1.26	**<0.001**	—
TT (nmol/l)	22.97 ± 0.99	11.20 ± 0.60	**<0.001**	10.4–34.7
FT (nmol/l)	0.382 ± 0.025	0.262 ± 0.022	**0.001**	0.174–0.868
Calculated FT (nmol/l)	0.398 ± 0.019	0.278 ± 0.017	**<0.001**	0.225–0.868
bioT (nmol/l)	9.28 ± 0.44	6.46 ± 0.43	**<0.001**	5.2–17.4
LH (IU/l)	4.12 ± 0.28	3.94 ± 0.33	0.39	1.1–7
FSH (IU/l)	4.46 ± 0.51	5.57 ± 0.61	0.121	1.7–12
Prolactin (mg/l)	11.21 ± 2.1	6.20 ± 0.54	**<0.001**	1.5–19
SHBG (nmol/l)	49.32 ± 2.83	20.44 ± 1.68	**<0.001**	7–50
A1C (%)	7.57 ± 0.20	8.40 ± 0.25	**0.024**	—

Data are means ± SD. To obtain testosterone values in ng/ml multiply by 28.8. $P < 0.05$ is significant (data in bold).

viously to be inversely related to SHBG concentrations in type 1 diabetic patients (7), consistent with our current observations. The degree of hyperglycemia and A1C were not related to the increase in SHBG in type 1 diabetic subjects.

Our data also show for the first time that calculated FT and bioT levels relate negatively to BMI in type 1 diabetic patients (Fig. 1), as previously shown in type 2 and type 1 diabetic patients. A study in TT and calculated FT concentrations on obese type 1 diabetic patients clearly needs to be carried out, especially in view of the increasing rates of obesity and the metabolic syndrome in general and in type 1 diabetic subjects in particular (8). Recent data from an epidemiological study (9) demonstrate that low concentrations of testosterone associated with high concentrations of cortisol (as seen in obesity) predict cardiovascular morbidity and mortality.

In conclusion, type 1 diabetes is associated with increased SHBG; normal TT, LH, and FSH concentrations; and normal FT and calculated FT concentrations in >90% of patients. In contrast, type 2 diabetic patients have frequent hypogonadotrophic hypogonadism and low SHBG concentrations. A higher BMI has a significant effect on calculated FT and FT in both patients with type 1 as well as in those with type 2 diabetes. This suggests that at higher levels of BMI, even type 1 diabetic subjects, may develop hypogonadism.

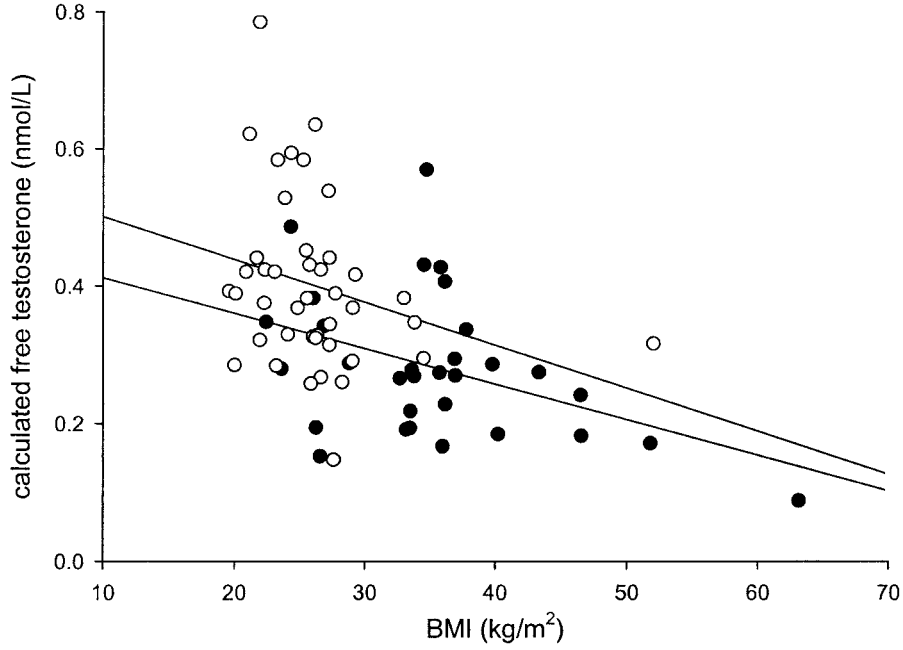

Figure 1—*Correlation of calculated free testosterone (nmol/l) with BMI (kg/m^2) in type 1 (○; r = −0.36, P < 0.05) and type 2 (●; r = −0.42, P < 0.05) diabetic subjects.*

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