Diabetes mellitus is associated with subnormal serum levels of free testosterone in men

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OBJECTIVE

To evaluate the relationship between diabetes mellitus (DM) and serum levels of free (FT) and total (TT) testosterone.

PATIENTS AND METHODS

A cross-sectional study was carried out including 746 men, of whom 116 (15.6%) were diabetics. Both groups, diabetic and nondiabetic, were paired according to age. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated, and a stratification analysis correlating DM and elevated BMI (>25 kg/m^2) and WHR (>1) with the presence of subnormal FT and TT levels was performed.

RESULTS

FT and TT serum levels were subnormal in 46% and 34% of diabetics, respectively, and in 24% and 23% of nondiabetics. Subnormal FT levels were strongly correlated with DM (odds ratio (OR) 2.7; 95% confidence interval (CI) 1.8–4.1) but not with elevated BMI (OR 1.4; 95% CI 1.0–2.0). Subnormal TT levels were more strongly associated with elevated BMI and WHR (OR 2.6; 95% CI 1.7–3.9 and 2.0; 1.4–2.9) than with DM (1.7; 1.1–2.6 and 2.0; 1.3–3.2).

CONCLUSION

These data strongly suggest that DM is associated with subnormal FT levels, and that TT levels are influenced more by obesity and central adiposity.

KEYWORDS

testosterone, diabetes mellitus, body mass index, obesity

INTRODUCTION

The prevalence of both hypogonadism and diabetes mellitus (DM) increase with age [1–4], and the association between these conditions has recently received great attention [5–7]. The Massachusetts Male Aging Study prospectively found that, for each decrease of 1 SD in free testosterone (FT), there was a 1.58-fold greater risk of developing DM after a median interval of 8.9 years [8]. Some authors suggest that, at physiological levels, testosterone has a role in maintaining normal insulin sensitivity in men, an effect that is lost at low or high concentrations [9]. Other studies have shown that administration of testosterone to hypogonadal middle-aged men improves insulin sensitivity and glucose homeostasis [10,11]. On the other hand, suppression of insulin production by diazoxide reduces FT and total testosterone (TT) levels, and adult men with type 1 diabetes have lower FT levels, suggesting that insulin has a regulatory effect on testosterone secretion and/or metabolism [12,13]. Whether this association results from a direct interaction between serum androgen levels and glucose control, or whether there is a third factor causing both to develop is unresolved [5,14]. For example, male obesity and central adiposity are associated with DM and low serum testosterone levels [15,16]. Thus the purpose of the present study was to evaluate the relationship between DM and serum testosterone levels.

PATIENTS AND METHODS

This cross-sectional study included 824 consecutive men (mean age 55.2 years, SD 13.6, range 15–90) who attended a urological medical centre in Porto Alegre, Brazil, from January 2000 to December 2001. All patients had first been seen by their primary-care physicians, who referred them for a urological appointment for a variety of urological complaints. Screening for DM was routinely performed by the primary-care physicians, based on fasting serum glucose levels. Patients were questioned about their use of insulin or hypoglycaemic agents. Glycosylated haemoglobin and fasting serum glucose levels were measured in all diabetic men. The same examiner (E.R.) measured the patients' height, weight, waist and hip circumferences, with the men in lightweight clothing and no shoes. The body mass index (BMI) was calculated for each subject, as the weight (kg)/height^2 (m^2), while the waist-to-hip ratio (WHR) was available in only 622 men. A BMI of >25 kg/m^2, which included overweight (25–30 kg/m^2) and obese (>30 kg/m^2), and a WHR > 1, representing abdominal fat accumulation, were considered as elevated [17]. In all men, the morning (08.00–10.00 hours) TT and FT levels were measured after an overnight fast. FT was measured by radio-immunoassay (Coat-a-Count®; DPC, Los Angeles, CA), with an intra-assay coefficient of variation of 6.3% and an interassay coefficient of variation of 6.5%. Normal levels of TT were 13.9–34.7 nmol/L and normal levels of FT were 0.043–0.14 nmol/L.

Patients receiving testosterone replacement or androgen suppression therapy were excluded. The nondiabetic and diabetic groups were paired by age range. As the diabetic group were aged 33–83 years, 61 nondiabetic men aged < 33 years and seven aged > 83 years were excluded from the study.

The 746 remaining men were classified into two groups, 'with' and 'without' DM. The mean values of TT, FT, BMI and WHR in these groups were compared, and the association of elevated BMI and WHR and subnormal FT and TT levels with DM was assessed. Also, every combination between normal/subnormal FT and normal/subnormal TT was compared in the diabetic and nondiabetic groups. Finally, we carried out a stratification analysis

correlating DM and elevated BMI and WHR with the presence of subnormal FT and TT levels. The results were assessed statistically using Student's *t*-test for continuous variables and the odds ratio (OR) with CI for categorical variables. For the stratified analysis, the Mantel-Haenszel (MH) estimator of the common OR and the chi-square for differentiating the OR by stratum were calculated. Statistical significance was defined as $P < 0.05$.

Variable	Mean (SD, range)
Total number	746
Age, years	57.2 (10.8, 33–83)
FT, nmol/L	0.06 (0.02, 0.005–0.16)
TT, nmol/L	17.95 (5.98, 3.17–47.31)
Height, cm	170 (10, 150–200)
Weight, kg	78.7 (13.8, 46.5–160)
BMI, kg/m^2	27 (4.3, 17.2–54.7)
Waist, cm	97.7 (11.4, 64–148)
Hip, cm	97.56 (8.5, 63–127)
WHR	1 (0.06, 0.8–1.5)

TABLE 1
General characteristics of the study population

RESULTS

In all, 746 men were analysed; the mean (SD) age was 57.3 (10.8) years, and 116 men (15.5%) had type 2 DM. The study included 594 Caucasian men (79.6%) and 152 African-Brazilian men (20.4%); 178 (23.9%) were cigarette smokers and 60 (8.0%) were heavy alcohol drinkers. Of the diabetic men, 83 (71.5%) were on oral hypoglycaemic agents, 13 (11.2%) on insulin use, and 20 (17.2%) were off treatment. The mean (SD, range) fasting serum glucose level was 206.3 (73.8, 70–417) mg/dL and the glycosylated haemoglobin level 9.6 (2.3, 4.9–18.8)%. The overall mean (SD, range) BMI was 27 (4.3, 17.2–54.7) kg/m^2 and the WHR 1.0 (0.06, 0.8–1.5), while the FT and TT were 0.057 (0.02, 0.005–0.16) and 17.95 (5.98, 3.17–47.31) nmol/L, respectively (Table 1). FT levels were subnormal in 203 men (27.3%) and TT levels in 183 men (24.5%). BMI was elevated in 479 of 746 men (64.2%) and WHR in 285 of 621 men (45.8%).

TABLE 2 Laboratory and clinical variables stratified by the presence or not of DM in the study population. Values are given as mean (SD, range)

Variable	DM present	DM absent	P
N	116	630	
Age, years	57.9 (9.0, 33–83)	57.1 (11.1, 33–83)	0.46
FT, nmol/L	0.05 (0.03, 0.007–0.16)	0.06 (0.02, 0.005–0.16)	0.03
TT, nmol/L	16.32 (4.93, 3.17–31.57)	18.24 (6.11, 4.51–47.31)	0.001
BMI, kg/m^2	28.7 (4.4, 19.2–40.8)	26.6 (4.3, 17.2–54.7)	<0.001
WHR*	1.03 (0.07, 0.85–1.18)	0.99 (0.06, 0.8–1.5)	<0.001

**WHR obtained from 108 men with DM and 514 without DM*

Group	DM present N (%)	DM absent N (%)	OR (95% CI)
Frequency of subnormal FT and TT levels			
Total N	116	630	
FT < 0.043 nmol/L	53 (45.7)	150 (23.8)	2.7 (1.8–4.1)
TT < 13.87 nmol/L	39 (33.6)	144 (22.9)	1.7 (1.1–2.6)
BMI > 25 kg/m^2	95 (81.9)	396 (62.9)	2.7 (1.6–4.4)
WHR > 1*	78 (72.2)	247 (48.1)	2.8 (1.8–4.4)
Association of FT and TT levels with DM			
FT↓ TT↓	24 (20.7)	71 (11.3)	2.1 (1.2–3.4)
FT↓, normal TT	29 (25)	79 (12.5)	2.3 (1.4–3.8)
Normal FT, TT↓	15 (12.9)	73 (11.6)	1.1 (0.6–2.1)
Normal FT and TT	48 (41.4)	407 (64.6)	0.4 (0.3–0.6)

TABLE 3
Frequency of subnormal FT and TT levels, elevated BMI and WHR in men with and without DM and the association of FT and TT levels with DM

*↓, subnormal levels; *WHR obtained from 108 men with DM and 514 without DM*

FT levels of <0.043 nmol/L, TT levels of <13.87 nmol/L, a BMI of >25 kg/m^2 and WHR of >1 were all significantly associated with DM when independently analysed (Table 3). FT and TT levels were subnormal in, respectively, 46% and 34% of diabetic men, and in 24% and 23% of nondiabetics. The OR (95% CI) for the various combinations of FT and TT in men with DM or not are also shown in Table 3.

The crude ORs of diabetic men having subnormal FT and TT levels are shown in Table 4, with the values when stratified by BMI and adjusted using the MH. The chi-square *P* values for differentiating the OR by stratum (interaction) were 0.70 and 0.52, respectively. When only men with WHR measured were analysed, the crude ORs of diabetics having subnormal FT and TT levels were 3.0 (2.0–4.6) and 2.0 (1.3–3.2). Their OR adjusted for WHR (MH estimator of the common OR) were not significant for the interaction ($P = 0.18$ and 0.59; Table 4).

Men with an elevated BMI and WHR had crude ORs for having subnormal FT levels as shown in Table 4 (*P* interaction, 0.70 and 0.18). After MH adjustment for DM, the OR values remained similar. For subnormal TT levels, the crude ORs for an elevated BMI and WHR were not significantly different, and nor when MH-adjusted (*P* for interaction 0.52 and 0.59; Table 4).

DISCUSSION

In the present study, men with DM had lower mean levels of FT and TT than nondiabetic

TABLE 4 Association of DM, BMI and WHR with subnormal FT and TT levels, stratified by BMI and WHR and by presence of DM

	FT levels <0.043 nmol/L		TT levels <13.87 nmol/L	
Group	N	OR (95% CI)	N	OR (95% CI)
Stratified by BMI and WHR				
DM present (crude OR)	53	2.7 (1.8–4.1)	39	1.7 (1.1–2.6)
BMI > 25 kg/m^2	45	2.7 (1.7–4.3)	34	1.4 (0.9–2.2)
BMI ≤ 25 kg/m^2	8	2.2 (0.9–5.6)	5	2.0 (0.7–6.0)
Adjusted for BMI (MH)		2.6 (1.7–3.9)		1.5 (1.0–2.3)
DM present* (crude OR)	50	3.0 (2.0–4.6)	39	2.0 (1.3–3.2)
WHR > 1	41	3.4 (2.0–5.7)	30	1.6 (1.0–2.8)
WHR ≤ 1	9	1.7 (0.7–4.0)	9	2.2 (0.9–5.0)
Adjusted for WHR (MH)		2.8 (1.8–4.3)		1.8 (1.1–2.8)
Stratified by presence of DM				
BMI > 25 kg/m^2 (crude OR)	144	1.4 (1.0–2.0)	147	2.6 (1.7–3.9)
DM present	45	1.5 (0.6–3.9)	34	1.8 (0.6–5.3)
DM absent	99	1.2 (0.8–1.8)	113	2.6 (1.7–4.0)
Adjusted for DM (MH)		1.2 (0.9–1.8)		2.5 (1.7–3.7)
WHR > 1 (crude OR)	102	1.7 (1.2–2.5)	98	2.0 (1.4–2.9)
DM present	41	2.6 (1.1–6.4)	30	1.5 (0.6–3.6)
DM absent	61	1.3 (0.9–2.0)	68	1.9 (1.3–2.9)
Adjusted for DM (MH)		1.5 (1.0–2.2)		1.8 (1.2–2.7)

*MH, Mantel-Haenszel estimator of the common OR; *of the 622 men with WHR measured.*

men, and higher mean BMI and WHR values. When the data were independently analysed, diabetic men had a higher risk of having subnormal levels of FT and TT than nondiabetic men. Diabetic men had a higher risk of having an elevated BMI and WHR. An important finding was that subnormal FT had a stronger correlation with DM than subnormal TT levels (OR 2.7 vs 1.7). Consistent with this, the combination of normal TT and subnormal FT levels was significantly associated with DM, while the combination of normal FT and subnormal TT levels was not.

A higher prevalence of subnormal TT levels and obesity in diabetic men has been reported by several authors [18–20], but there is still controversy about whether subnormal FT levels are associated with DM [21]. The low reported TT levels could be merely a manifestation of reduced sex-hormone-binding globulin (SHBG), as 58% of serum TT is bound to SHBG [21]. Andersson *et al.* [22] found an inverse correlation of DM with TT and SHBG levels, but not with FT levels. Haffner *et al.* [23] showed an inverse association of FT, TT and SHBG with insulin concentrations. Two longitudinal studies reported conflicting results [8,24]; in the Massachusetts Male Aging Study [8], low FT and SHBG levels at baseline were both risk factors for DM, whereas in the Rancho Bernardo Study [24] low TT, but not bioavailable testosterone, was associated with future DM development.

Obesity is at the centre of these interrelated conditions, and has been implicated as a common factor for developing DM and low androgen levels. Obesity is also associated with lower SHBG concentrations, possibly as a consequence of the increased insulin levels in obese individuals [19,25]. Men with mild-to-moderate obesity often have low TT but normal FT concentrations, a condition explained at least in part by the lower SHBG concentrations [3,19]. Nevertheless, Dhindsa *et al.* [26] found a weak correlation between FT levels and BMI ($r = -0.382$; $P < 0.01$) in diabetic patients with a mean (SD) BMI of 33.4 (0.8) kg/m^2. Also, in very obese men there is a decrease in FT levels, resulting from the peripheral conversion of testosterone into oestrogens, which decreases the amplitude of LH pulses, promoting central inhibition of androgenic production [27]. Conversely, testosterone supplementation in obese individuals has been shown to increase lipolysis of abdominal fat, reducing body weight, body fat and WHR [11,28].

In the present study, the correlation between DM and subnormal FT levels was unchanged after adjusting for elevated BMI (OR 2.6) and WHR (OR 2.8), suggesting that obesity and central adiposity are unlikely to be important confounding factors of these associations. However, the lower correlation of DM with subnormal TT levels did not remain significant (OR 1.5, 1.0–2.3) after adjusting for BMI.

A second important finding was that elevated BMI and WHR were significantly associated with subnormal TT levels but not with subnormal FT levels after adjusting the OR for DM. Also, the correlation of subnormal TT levels with BMI and WHR was stronger than with DM.

One limitation of the present study was that FT levels were measured by radio-immunoassay, a method that has been criticized for its great variability [29]. Unfortunately, equilibrium dialysis, the method considered to be the 'gold standard' for measuring FT, was not available. SHBG and albumin levels also could not be determined, making it impossible to calculate the FT levels from TT levels. Nevertheless, the present report is unique in comparing FT levels in diabetic and nondiabetic men, correcting for obesity and central adiposity. Despite the limitations of radio-immunoassay for measuring FT, we consider that the main results of the present study are valid, considering that the presence of a nondiabetic control group has reduced associated biases.

In conclusion, this study suggests that subnormal FT levels and DM are directly associated, whereas TT levels appear to be more strongly related to obesity and central adiposity than to DM.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **DM**, diabetes mellitus; **FT**, free testosterone; **TT**, total testosterone; **BMI**, body mass index; **WHR**, waist-to-hip ratio; **OR**, odds ratio; **MH**, Mantel-Haenszel; **SHBG**, sex-hormone-binding globulin.