The Pituitary-Gonadal Axis and Health in Elderly Men

A Study of Men Born in 1913

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The results of recent studies suggest that a relative hypogonadism in men is associated with several established risk factors for prevalent diseases. Therefore, we determined total and free testosterone, luteinizing hormone (LH), and sex-hormone binding globulin (SHBG) in a cohort of randomly selected men (n = 659) at 67 years of age. These data were analyzed cross-sectionally in relation to blood glucose and serum insulin, which were measured while fasting and after an oral glucose tolerance test, in addition to plasma lipids and blood pressure. The data were also analyzed in relation to impaired glucose tolerance (IGT) and diabetes, which were discovered at examination or earlier diagnosis. Risk factors for the development of diabetes up to 80 years of age were analyzed with univariate and multivariate statistics. Total and free testosterone and SHBG concentrations correlated negatively with glucose and insulin values; total testosterone and SHBG, with triglycerides; and SHBG, with blood pressure (from $P < 0.05$ to $P < 0.01$). Men with IGT or newly diagnosed diabetes had higher BMI values (26.2 ± 0.31 and 27.0 ± 0.59 [mean ± SE], respectively) and waist circumference (99.0 ± 1.03 and 100.5 ± 1.57) than nondiabetic men (BMI, 25.1 ± 0.14; waist circumference, 95.4 ± 0.47; $P < 0.05$), indicating abdominal obesity. Such men and men with previously diagnosed diabetes had, in general, lower total and free testosterone and SHBG levels, while those for LH were not different. In multivariate analyses that included BMI, waist-to-hip ratio, total and free testosterone, and SHBG, the remaining independent predictors for the development of diabetes were low total testosterone (P = 0.015) and, on the borderline, low SHBG (P = 0.053). In relation to nondiabetic men, the risk ratio for mortality, myocardial infarction, and stroke increased gradually and significantly from 1.18 to 1.68, from 1.51 to 1.78, and from 1.72 to 2.46 in men with IGT, newly diagnosed diabetes, and previously known diabetes, respectively. It was concluded that low testosterone and SHBG concentrations in elderly men are associated with established risk factors for diabetes and in established diabetes. Moreover, low testosterone levels independently predict the risk of developing diabetes. In different degrees of expression, the diabetic state predicts strongly (and gradually mortality from) myocardial infarction and stroke. It has been suggested that a relative hypogonadism might be a primary event, because other studies have shown that testosterone deficiency is followed by insulin resistance, which is ameliorated by testosterone substitution. The data suggest that the relative hypogonadism involved might be of both central and peripheral origin. *Diabetes* 45:1605–1609, 1996

In women, the production of sex steroid hormones from the ovaries is diminished abruptly at menopause. There is a fairly extensive literature on the consequences of this change for well-being, body composition, and risk for disease (1). In contrast, the production of testosterone in men diminishes slowly with age, and the consequences thereof are less well-known. A male "andropause" is a much-debated problem that has poorly defined psychological and physiological consequences (2). The diminution of muscle mass with age in men has been attributed, at least in part, to hormonal deficiencies (2). In one recent study (3), negative relationships were reported between a relative hypogonadism and lung function in middle-aged men who also had higher fibrinogen concentrations. Recent evidence also suggests that the deficiency of testosterone in men is associated with insulin resistance. Testosterone concentrations in serum have been reported to be inversely related to fasting insulin concentrations (4–6) and to insulin sensitivity, measured with euglycemic clamp technique (7). When substituted with testosterone, not only is insulin sensitivity improved, but plasma lipid concentrations and blood pressure become lower (7). In addition, men with NIDDM seem to have lower testosterone and sex-hormone binding globulin (SHBG) concentrations (8). There is also a report that suggests that men who have had a myocardial infarction have abnormally low testosterone values (9).

With this background, it seemed of interest to examine the relationship between the activity of the pituitary-gonadal axis and diabetes in elderly men. Therefore, we determined total and free testosterone and luteinizing

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IGT, impaired glucose tolerance; LH, luteinizing hormone; SHBG, sex-hormone binding globulin; WHR, waist-to-hip ratio.

TABLE 1
Characteristics of the men (n = 651) at 67 years of age

Height (cm)	174.6 ± 0.2
Weight (kg)	77.4 ± 0.4
BMI (kg/m^2)	25.4 ± 0.12
WHR	1.02 ± 0.003
Subscapular skinfold (mm)	18.0 ± 0.2
Systolic blood pressure (mm Hg)	154.8 ± 0.9
Diastolic blood pressure (mm Hg)	85.5 ± 0.4
Cholesterol (mmol/l)	6.7 ± 0.05
Triglycerides (mmol/l)	1.75 ± 0.05
Fasting glucose (mmol/l)	4.8 ± 0.06
Fasting insulin (mU/l)	13.7 ± 0.04
Total testosterone (nmol/l)*	16.9 ± 0.30
Free testosterone (pmol/l)	68.0 ± 0.9
LH (mU/l)	4.0 ± 0.15
SHBG (nmol/l)	49.3 ± 1.3

Data are means ± SE. *n = 536.

hormone (LH) concentrations in a population cohort, selected at random, of men at 67 years of age. SHBG binds primarily androgens, but it also binds other steroids (10). Thus, by determining SHBG concentrations, information on testosterone-binding capacity was obtained. These values were analyzed in relation to body composition and risk factors for cardiovascular disease, diabetes, and stroke, as well as prevalence and incidence data for these diseases up to 80 years of age. In addition, relationships to mortality, myocardial infarction, and stroke were analyzed prospectively.

RESEARCH DESIGN AND METHODS

In 1963, all men living in Gothenburg, Sweden, who were born on dates that were divisible by 3 during 1913 were invited to a health screening. The total number was 973, and the attendance was 88% (11). These men were subsequently followed and reexamined. If a subject died, the cause of death was registered. The cross-sectional data presented here were collected in 1980, and the prospective data were collected in 1993, when these men were 67 and 80 years of age, respectively. The number of participants in 1980 was 659, constituting 79% of the men who were still alive at this point in time.

Height to the nearest centimeter and body weight to the nearest 0.1 kg were recorded, and BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist and hip circumferences were measured, providing a waist-to-hip circumference ratio (WHR) (12).

Blood pressure was measured in the sitting position with a mercury manometer on the right arm after 5 min rest. Diastolic blood pressure was recorded at Korotkoff, phase V.

Incidence data are for diseases developing between 67 and 80 years of age. Diabetes and impaired glucose tolerance (IGT) were defined according to World Health Organization criteria (13). It was not possible to separate IDDM and NIDDM, but it is most likely that the study was largely dominated by the latter, considering the age-span examined (14). Myocardial infarction was diagnosed by criteria including chest pain, enzyme elevations, and/or typical changes in an electrocardiogram (15). Stroke was diagnosed clinically by conventional criteria.

Fasting venous blood was obtained in the morning for the determination of blood glucose, serum triglyceride, and cholesterol levels by automated enzymatic methods (Boehringer, Mannheim, Germany) and the determination of serum insulin by radioimmunoassay (Phadebas, Pharmacia, Uppsala, Sweden). Free testosterone was determined by ligand analog radioimmunoassay (Coat-A-Count Free Testosterone, Diagnostic Products, Los Angeles, CA; the central 90% interfractile interval for 60- to 69-year-old men is stated by the manufacturer to be 38–90 pmol/l); LH, by a chemoluminescent enzymatic assay (Immulite LH, Diagnostic Products; calibrated against the 1st International Reference Preparation, World Health Organization 68/40; normal reference interval in middle-aged men was reported by the manufacturer as 1.4–7.7 mU/l); and SHBG, by radioimmunoassay (Orion Diagnostica, Turku, Finland). These variables were determined retrospectively after sera were stored at −70°C. An oral glucose tolerance test was performed with 100 g glucose, and blood glucose and serum insulin were measured in samples taken after 60 and 120 min.

Statistical methods. Differences between means were evaluated with a two-tailed analysis of variance, and correlations were evaluated with conventional methods, utilizing the SAS JMP program on an IBM computer. P values <0.05 were considered statistically significant.

RESULTS

Table 1 shows the average values (± SE) of the measured variables. Correlations between the endocrine variables and anthropometric measurements and hemoglobin, hematocrit, and total serum protein values are found in Table 2. Both BMI and WHR correlated significantly and negatively with free testosterone SHBG and LH. Inverse relationships were found between total and free testosterone and SHBG concentrations on the one hand and between blood glucose and serum insulin values during fasting and after glucose load on the other. Furthermore, triglycerides correlated negatively with total testosterone and SHBG, and blood pressure correlated negatively with SHBG. No significant correlations were found with cholesterol.

TABLE 2
Correlation coefficients (r values) between endocrine, anthropometric, metabolic, and blood pressure variables

	Total testosterone	Free testosterone	LH	SHBG
BMI	−0.18†	−0.12†	−0.10*	−0.24†
WHR	−0.23†	−0.16†	−0.10*	−0.26†
Cholesterol	NS	NS	NS	NS
Triglycerides	−0.09*	NS	NS	−0.12*
Fasting insulin	−0.11*	−0.10*	NS	−0.10*
Insulin 60 min.	−0.14*	−0.12*	NS	NS
Fasting glucose	−0.19*	−0.13*	NS	−0.20†
Glucose, 60 min	−0.18†	−0.11*	NS	−0.18†
Glucose, 120 min	−0.18†	−0.11*	NS	−0.17†
Systolic blood pressure	NS	NS	NS	−0.11*
Diastolic blood pressure	NS	NS	NS	−0.15†

Time points given are after oral glucose ingestion in glucose tolerance test. Abbreviations: T: Testosterone. Other abbreviations as in Table 1. *P < 0.05, †P < 0.01.

TABLE 3
BMI, the waist-to-hip ratio, and waist circumference in nondiabetic men, IGT, diabetes diagnosed at examination (new diabetes), and previously known diabetes

	n	Mean ± SE	Difference from nondiabetic	95% confidence interval
BMI (kg/m^2)				
Nondiabetic	536	25.1 ± 0.14	—	—
IGT	95	26.2 ± 0.31	−1.07	−1.77–−0.36
New diabetes	35	27.0 ± 0.59	−1.89	−3.01–−0.76
Previously known diabetes	41	25.6 ± 2.87	−0.45	−1.48–0.58
Waist circumference (cm)				
Nondiabetic	397	95.4 ± 0.47	—	—
IGT	66	99.0 ± 1.03	−3.55	−5.96–−1.14
New diabetes	27	100.5 ± 1.57	−5.10	−8.72–−1.47
Previously known diabetes	27	96.9 ± 1.73	−1.43	−50.1–2.21
Waist-to-hip circumference ratio				
Nondiabetic	429	1.018 ± 0.078	—	—
IGT	73	1.031 ± 0.061	−0.013	−0.030–0.005
New diabetes	30	1.043 ± 0.066	−0.025	−0.050–0.003
Previously known diabetes	32	0.976 ± 0.061	0.042	0.010–0.069

Table 3 shows the anthropometric measurements in men with IGT, newly diagnosed diabetes at examination, and previously known diabetes. Men with IGT and newly diagnosed diabetes had higher BMI and waist circumference than nondiabetic men, while men with previously known diabetes were not different from nondiabetic men. The WHR was lower in men with previously diagnosed diabetes than in all other groups that showed no difference between groups.

Results of similar analyses in relation to endocrine variables are shown in Table 4. Total testosterone was lower in men with IGT or diabetes than in nondiabetic men. Free testosterone was significantly lower in men with previously known diabetes than in nondiabetic control subjects and the IGT group. LH showed no significant differences. SHBG values were significantly lower in men with newly discovered diabetes than in the nondiabetic and IGT groups.

Multiple regression analyses of factors which from these analyses seemed to predict diabetes, including BMI, WHR, free and total testosterone, and SHBG, showed independent contributions to risk by low total testosterone (P = 0.015) and, on the borderline, by low SHBG (P = 0.053).

The risk of mortality, myocardial infarction, and stroke between 67 and 80 years of age in relation to diabetic state is shown in Table 5. The risk ratio for mortality, myocardial infarction, and stroke increased with IGT, newly discovered diabetes, and previously known diabetes.

DISCUSSION

The men studied in this cohort were examined first in 1963 (11) and then repeatedly on later occasions. The results described in this study are those that were collected in 1980 and 1993 when the men were 67 and 80 years of age, respectively. For this study, the pituitary-

TABLE 4
Total and free testosterone, LH, and SHBG concentrations in nondiabetic men, men with IGT, diabetes diagnosed at examination (new diabetes), and previously known diabetes

	n	Mean ± SE	Difference from nondiabetic	95% confidence interval
Total testosterone (nmol/l)				
Nondiabetic	411	17.3 ± 0.26	—	—
IGT	68	15.2 ± 0.67	2.18	0.28–4.42
New diabetes	27	13.6 ± 0.70	3.80	1.76–5.83
Previously known diabetes	27	15.0 ± 1.06	2.35	0.28–4.42
Free testosterone (pmol/l)				
Nondiabetic	487	69.0 ± 1.02	—	—
IGT	88	69.0 ± 2.75	0	—
New diabetes	35	61.4 ± 3.52	7.60	−0.10–15.3
Previously known diabetes	39	58.8 ± 2.65	10.2	3.00–17.5
Luteinizing hormone (mU/l)				
Nondiabetic	487	4.06 ± 0.18	—	—
IGT	88	3.63 ± 0.31	0.43	−0.46–1.32
New diabetes	35	4.23 ± 0.65	−0.17	−1.56–1.22
Previously known diabetes	39	4.51 ± 0.59	−0.45	−1.76–0.86
Sex hormone binding globulin (nmol/l)				
Nondiabetic	487	51.5 ± 1.38	—	—
IGT	88	48.3 ± 5.38	3.13	−4.68–10.9
New diabetes	35	39.9 ± 1.97	18.6	8.37–28.7
Previously known diabetes	40	41.1 ± 3.87	10.4	0.70–20.1

TABLE 5
Relative risks for mortality, new myocardial infarction, or stroke from 67 to 80 years of age in nondiabetic men, men with IGT, diabetes diagnosed at examination (new diabetes), and previously known diabetes

	n	Risk ratio	95% confidence interval
Mortality			
Nondiabetic	534	1.00	—
IGT	95	1.18	0.96–1.45
New diabetes	35	1.51	1.18–1.92
Previously known diabetes	41	1.72	1.42–2.07
Myocardial infarction			
Nondiabetic	496	1.00	—
IGT	89	1.25	0.80–1.92
New diabetes	32	1.74	1.00–3.01
Previously known diabetes	34	2.46	1.60–3.75
Stroke			
Nondiabetic	522	1.00	—
IGT	90	1.68	1.04–2.70
New diabetes	33	1.78	0.89–3.59
Previously known diabetes	37	2.28	1.28–4.06

gonadal axis served as the focus because several previous studies of the cross-sectional or case-control type indicated that, when peripheral testosterone concentrations are low, various health variables seem to deteriorate (2–8). A decrease in testosterone levels seems to occur with higher age, but is highly variable among individuals (2). Therefore, the question of the consequences of a failing pituitary-gonadal axis was analyzed in a fairly large cohort of elderly men.

LH controls the testicular production of testosterone. To examine the potential causes of relative hypogonadism, which could be of central (pituitary) or peripheral (testicular) origin, both LH and testosterone were examined. Free testosterone was examined because it gives a measurement of the concentrations of the fraction of testosterone that is considered physiologically active.

In addition to these hormones, SHBG was determined since it is the protein that carries a major part of testosterone in circulation in a presumably inactive form. Because testosterone itself seems to regulate the production and/or elimination of SHBG (16–19) and therefore may modify the fraction of free active testosterone, it was considered of interest to examine also possible relationships to SHBG.

As expected, free testosterone, LH, and SHBG showed close interrelationships statistically, probably explained by their interdependent regulation (not shown). Both total and free testosterone and SHBG showed negative correlations with glucose and insulin values in the fasting state and after a glucose load, and total testosterone and SHBG showed negative correlations with triglycerides. This is in agreement with previous reports in studies of younger men (4–6). LH showed no such relationships. This finding is in agreement with cross-sectional studies of men with clinically overt NIDDM, where both total and free testosterone and SHBG were lower in subjects than control subjects (8).

Cross-sectional analyses revealed several characteristics of men with IGT, newly diagnosed diabetes, or previously known diabetes in comparisons with nondiabetic men. Men with IGT and newly discovered diabetes had a higher BMI than control subjects, indicating that these men were more obese. Waist circumference and WHR measurements suggested that their obesity was mainly centrally localized, although the increase in WHR was not significant. This was, however, not found in previously diagnosed diabetes. These findings suggest that, in prediabetic and early diabetic states, abdominal obesity is prevalent, in accordance with previous reports (8,20). In diabetes of longer duration, this disappeared, which could possibly be explained by treatments that attempt to lower body weight.

Total testosterone was significantly lower in all three prediabetic or diabetic groups than in control subjects. Free testosterone and SHBG were, however, not different between control subjects and men with IGT, but were apparently lower in both groups with established diabetes, although this was not fully significant for new diabetes and free testosterone and for known diabetes and SHBG. LH showed no differences between groups.

The lack of difference in LH might mean that the central regulation of testosterone secretion is not involved in the peripheral androgenic status of these men and that the relative hypogonadism of prediabetic and diabetic men is attributable to aberrations in the regulation of the testicular secretion of testosterone. The lower free testosterone in established diabetes might be a consequence of this. However, free testosterone is dependent on SHBG binding, and SHBG was also lower. SHBG concentration is regulated negatively by testosterone and insulin (16–24), in accordance with the negative correlations between insulin and SHBG in this study. The data presented suggest that this complex regulation results in low SHBG and low free testosterone.

In a prospective analysis of the incidence of diabetes between 67 and 80 years of age, both SHBG and total testosterone concentrations were lower in men who had developed diabetes during this period. In multivariate analyses including body fat and fat distribution variables and total and free testosterone and SHBG, the factors remaining independently predictive for development of diabetes were, particularly, total testosterone and, to some extent, low SHBG. Thus, it is apparent that a relative hypogonadism in elderly men predicts the development of diabetes.

One might speculate about the mechanisms that are involved. Low total and free testosterone were associated with high insulin levels, suggesting insulin resistance. Insulin resistance is a powerful predictor of NIDDM (25). However, elevated insulin levels may be followed by elevated testosterone concentrations (10), suggesting that insulin resistance might not be a primary factor. The absence of testosterone is, however, followed by insulin resistance that is localized to diminished insulin-sensitive glycogen synthase activity and is totally reversible by testosterone substitution (26). Furthermore, viscerally obese men with a relative hypogonadism and insulin resistance show a marked improvement in insulin sensitivity upon testosterone substitution (7). These observations, taken together, suggest that a relative hypogonadism may be a primary factor,

followed by insulin resistance, which is a precursor state to NIDDM.

Analyses of risk for mortality, myocardial infarction, and stroke in the men with IGT, newly diagnosed diabetes, and previously known diabetes were performed. There was an increasing risk from nondiabetic men through all these conditions, which might be considered a gradient of the impact of the diabetic state on the development of the diseases mentioned. These results then suggest that the diabetic state is a powerful predictor of mortality, myocardial infarction, and stroke, a finding that has been observed previously (27). Whether the diabetic state as such or elevated triglycerides, insulin, blood pressure, or the associated relative hypogonadism are the trigger factors alone or in combination is not known.

Previous studies have shown that the androgenic status in women is also important for the relative risk to develop NIDDM (20,28) and myocardial infarction (L. Lapidus, C. Bengtsson, P.B., L. Lissner, G.L., unpublished observations). In women, however, a relative hyperandrogenicity is correlated with established risk factors for these diseases, in addition to insulin resistance, dyslipidemia, hypertension, and abdominal obesity (20,28,29). The androgenic status in both sexes thus appears to be an important factor for the development of serious diseases, although in different directions for men and women.

In conclusion, elderly men with low total and free testosterone and SHBG concentrations had signs of glucose intolerance, insulin resistance, and diabetes in cross-sectional analyses. A relative hypogonadism, apparently mainly of peripheral origin, was also a predictor of the development of diabetes. The diabetic state then predisposes to premature mortality, myocardial infarction, and stroke. The cause-effect relationship is not clear, but other data from intervention studies suggest that the low secretion of testosterone might be a primary event in the pathogenesis of insulin resistance, because the replacement of testosterone to normal values reverts insulin resistance.

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