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Increased Risk of Falls and Increased Bone Resorption in Elderly Men with Partial Androgen Deficiency: The MINOS Study

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The goal of this study was to identify the clinical and biological patterns of hypogonadism in a cohort of 1040 elderly men. Residual androgenic activity was estimated by total testosterone as well as the apparent free testosterone concentration (AFTC) and free testosterone index (FTI) calculated on the basis of concentrations of SHBG and total testosterone using appropriate formulae. The lower limit of the normal range defined by 2 SD below the mean in 150 healthy, nonobese, and nonsmoking men, aged 19–40 yr, was calculated for total testosterone (9.26 nmol/liter), AFTC (146 pmol/liter), and FTI (0.14 nmol/nmol). The prevalence of hypogonadism increased with ageing. Hypogonadal men were older and heavier (due to a higher fat body mass) and had lower concentrations of 17β-estradiol and androstenedione than men with normal androgenic activity. Men with decreased AFTC had a slightly lower bone mineral density (BMD) at certain sites. Men with decreased FTI had lower appendicular skeletal muscle mass and relative skeletal muscle index. For all three measures of androgenic activity, hypogonadal men had increased levels of the markers of bone resorption. In the multiple regression models including both 17β-estradiol and testosterone (total, AFTC, or FTI), 17β-estradiol was the only significant determinant of BMD. In the multiple regression models including 17β-estradiol and AFTC or FTI, only testosterone was a significant determinant of the variability in bone formation markers, whereas both 17β-estradiol and testosterone were significant determinants of the variability of the markers of bone resorption. Hypogonadism was associated with an increase in the risk of falls, an impairment of static and dynamic balance, as well as the inability to stand up from a chair and to perform the tandem walk. Decreased AFTC (<146 pmol/liter) discriminated best men with functional disabilities (odds ratio, 1.54–7.95; $P < 0.05$–0.0001). Hypogonadal elderly men had increased bone resorption that was not adequately matched by an increase in bone formation, lower muscle strength, impaired static and dynamic balance, a higher risk of falls, and, in men with low AFTC, a slightly lower BMD. Low AFTC seems to have the best discriminative power for densitometric, biochemical, and functional parameters, followed by FTI, whereas total testosterone was the least discriminative. In multiple regression models, 17β-estradiol was the strongest determinant of BMD, and AFTC and FTI were significant determinants of the variability in bone formation markers, whereas both 17β-estradiol and testosterone determined the variability in bone resorption markers. (*J Clin Endocrinol Metab* 88: 5240–5247, 2003)

PARTIAL ANDROGEN DEFICIENCY in ageing men (PADAM) is characterized by an age-related decrease in testicular secretion of testosterone (1, 2). Although PADAM contributes to the age-related decrease in bone mineral density (BMD), the positive correlation between testosterone concentration and BMD in men is weak (3–5) or not significant (6, 7). In contrast, many studies indicate a positive correlation of 17β-estradiol and BMD in men (5–8). Muscle mass and strength decrease with age in men (9, 10). This decrease, along with an impairment of static and dynamic balance, contributes to the increased risk of falls (11, 12). As testosterone has a powerful effect on the striated muscles (13), PADAM may contribute to this decrease in muscle mass and strength and to the higher risk of falls and fractures in elderly men (14, 15).

Circulating total testosterone consists of three fractions: free testosterone, testosterone bound weakly and nonspecifically to albumin, and testosterone bound strongly and specifically to SHBG (16). Given the age-related decrease in testicular secretion and increase in SHBG concentration, the serum free testosterone level decreases with ageing more than that of total testosterone (7, 8). As the SHBG-bound fraction of testosterone does not enter cells and is largely inactive, the total testosterone concentration is not a sufficiently sensitive hormonal parameter of PADAM. In contrast, the concentration of free testosterone, which enters the cells, better reflects the residual androgenic activity. The free testosterone fraction can be measured in serum or approximated using the free testosterone index (FTI = total testosterone/SHBG).

However, measurement of the free testosterone level presents certain difficulties. Equilibrium dialysis and centrifugal ultrafiltration are reliable, but expensive and time-consuming (17, 18). Direct measurement of free testosterone in serum is inaccurate (19, 20). In comparison with the equilibrium dialysis, not only does it underestimate the level of free testosterone, but the correlation between these methods is not linear. We calculated the apparent free testosterone concentration (AFTC) using the levels of total testosterone and

Abbreviations: AFTC, Apparent free testosterone concentration; BAP, bone-specific alkaline phosphatase; BMD, bone mineral density; βCTX-1, β-isomerized C-terminal telopeptide of collagen type I; DPD, deoxypyridinoline; FTI, free testosterone index; 25OHD, 25-hydrocholecalciferol; PADAM, partial androgen deficiency in ageing men; PINP, propeptide of type I collagen; SSMB, Société de Secours Minière de Bourgogne.

SHBG as described by Vermeulen *et al.* (21). This method correlates well with the equilibrium dialysis (16).

Thus, the aim of this study was to evaluate the correlation of different determinants of the fracture risk (BMD, bone turnover, muscle strength, and balance) with the age-related decrease in the testosterone concentration in a large cohort of men and to verify which parameter of androgenic activity (total testosterone, AFTC, or FTI) discriminates best elderly men at risk.

Subjects and Methods

Cohort

The MINOS study is a prospective study of osteoporosis and its determinants in men that was initiated in 1995 (22). It is a collaboration between INSERM and Société de Secours Minière de Bourgogne (SSMB) in Montceau les Mines. Montceau les Mines is a town situated 130 km northwest of Lyon in the Department (District) of Saône et Loire. Its population is 21,000 inhabitants, including 7,150 men aged more than 19 yr. SSMB is one of the largest health insurance companies in this town. The MINOS cohort is composed of 2 groups: men aged 19–50 yr and men aged 51–85 yr. Invitations to our study with information about its aim were sent to a random sample of men aged 51–85 yr ensured by SSMB. Among 841 men who responded to the invitation, 786 consented to participate and had all the diagnostic examinations including bone densitometry at four sites of measurement. A group of 254 men aged 19–50 yr was recruited among male residents of Montceau les Mines who were contacted using several ways of information: men ensured by SSMB, families of the SSMB staff, all enterprises of Montceau les Mines (factories, firemen, national education, regional administration), sport and social associations, and announcement in a newspaper. All men responded to an epidemiological questionnaire covering demographic and behavioral information as well as detailed medical history.

Reference values for testosterone were calculated in 150 healthy, nonobese, nonsmoking men aged 19–40 yr. Then the analyses were performed in men aged 50–85 yr. In this age range, 818 men had hormonal and biochemical measurements as well as bone densitometry (at least at three sites). Among them, we excluded 26 men receiving oral glucocorticoids, gonadoliberine analogs, antiresorptive medications, and fluoride, leaving 792 men in whom the analyses were performed.

Clinical tests

Getting up from a chair and sitting down allows to evaluate the strength of knee extensors and flexors (23–25). The participants were seated on a hard chair and asked to stand up and sit down from a chair five times as quickly as possible. The examiner recorded the number of chair-stands, the time required to perform the test, and the degree of difficulty (pushes up with arms, moves forward in chair first, unsteady on first standing). The inability to perform the test was diagnosed when the subject got up less than five times (zero to four times). If the subject made this test with difficulty but managed to get up five times regardless of the time he required, he was classified as able.

Standing balance was evaluated based on standing with the feet in the side by side position (24, 26). Participants were evaluated for 10 sec with eyes open and for 5 sec with eyes closed. The timing was stopped when the participant moved his feet or grasped the examiner for support or when the time (10 or 5 sec, respectively) had elapsed. The participant was scored as able if he could stand for 10 sec with eyes open or 5 sec with eyes closed, otherwise, he was classified as unable.

To test dynamic balance, participants performed a 10-step tandem walk on the line drawn on the floor (11). The examiner recorded the time, the number of steps really performed, and the number of errors (stepping off the line, grabbing an object, and taking steps with the heel and toe visibly separated). After the subject had finished the tandem walk forward, he was asked to perform the same 10-step tandem walk backward. Similarly, the examiner recorded the time, the number of steps really performed, and the number of errors.

Participants were interviewed about the falls during the 12 months preceding the questionnaire. We recorded all falls from standing height or less then standing height.

Biochemical measurements

Fasting serum as well as 24-h urine were collected and stored at −80 C until assayed.

Serum total osteocalcin was measured with a human-specific, two-site immunoradiometric assay (ELSA-OSTEO, CIS BioInternational, Bagnols/Cèze, France) that recognizes a large N-terminal midfragment in addition to the intact molecule (27). Intra- and interassay coefficients of variation are less than 4% and 6%, respectively, and the sensitivity is 0.4 ng/ml. Serum bone-specific alkaline phosphatase (BAP) was measured with an immunoassay using a monoclonal antibody directed against BAP purified from human SAOS-2 osteosarcoma cells as a standard, followed by a conventional colorimetric detection using paranitrophenyl phosphate (Alkphase-B, Metra Biosystems, Inc., Mountain View, CA) (28). This assay has a low cross-reactivity with the circulating liver, placental, and intestinal isoenzymes (<15%). The sensitivity of the assay is 0.7 U/liter. Intra- and interassay coefficients of variation are less than 6% and 8%, respectively. Serum N-terminal extension propeptide of type I collagen (PINP) was measured by a new RIA that recognizes the intact circulating form of PINP (Intact PINP, Farmos Diagnostica, Uppsala, Sweden) (29). Intra- and interassay coefficients of variation are less than 5% and 8%, respectively, and the detection limit is 1 ng/ml.

Urinary β-isomerized C-terminal telopeptide of collagen type I (βCTX-I) was measured with an ELISA (CrossLaps ELISA, Osteometer BioTech A/S, Rodovre, Denmark) as described previously (30, 31). The antigen Glu-Lys-Ala-His-β-Asp-Gly-Gly-Arg is a fragment of the C-telopeptide of the α1-chain of type I collagen (32). The sensitivity of the assay is 0.5 μg/liter. Intra- and interassay coefficients of variation are less than 10% and 15%, respectively. This assay does not react with free cross-links, and its cross-reactivity with αCTX is less than 1%. Serum βCTX-I was measured with an ELISA (CrossLaps One Step ELISA, Osteometer BioTech A/S) as described previously (33, 34). The sensitivity of the assay is 92 pmol/ml. Intra- and interassay coefficients of variation are less then 8%. Free deoxypyridinoline (DPD) was measured by an ELISA (Pyrilinks-D, Metra Biosystems Inc.) that uses a monoclonal antibody with less than 1% cross-reactivity with free pyridinoline and 10% cross-reactivity with cross-linked polypeptides (35). The sensitivity of the assay is 3 nM. Intra- and interassay coefficients of variation are less than 10%. Urinary total DPD was measured with the same assay after acid hydrolysis. Urinary peptide-bound DPD was defined as the difference between total and free DPD in the same 24-h sample, and it corresponds to different DPD-containing peptides, being a product of collagen type I catabolism.

BMD measurement

BMD was measured at the lumbar spine, right hip, and whole body using dual energy x-ray absorptiometry (QDR-1500, Hologic, Inc., Waltham, MA). Distal and ultradistal sites of nondominant forearm were measured using single energy x-ray absorptiometry (Osteometer DTX 100). Both bone densitometers were calibrated daily using a phantom of the lumbar spine for the QDR 1500 and a calibration standard for the DTX 100 as described previously (22). Appendicular skeletal muscle mass was estimated as a sum of the lean tissue mass of four limbs (36, 37). Relative skeletal muscle index was calculated as appendicular skeletal muscle mass divided by the square of body height (38).

Hormones

Serum total 17β-estradiol and total testosterone were measured by tritiated RIA after diethyl ether extraction (39). For testosterone, the limit of detection is 0.06 nM/liter, and the interassay coefficient of variation is 10% for a concentration of 1 nM/liter and 7.8% for 6 nM/liter. For 17β-estradiol, the limit of detection is 11 pM/liter, and the interassay coefficient of variation is 9.4% for a concentration of 169 pM/liter and 6.2% for 510 pM/liter. SHBG was measured by immunoradiometric assay (125 I SBP Coatria, Bio-Mérieux, Marcy l'Etoile, France) with an interassay coefficient of variation of 4.1% for a concentration of 16 nmol/liter and 5.3% for 100 nmol/liter. The limit of detection is 0.5 nmol/liter. The AFTC was calculated as described previously by Vermeulen *et al.* (16, 21). The FTI was calculated as total testosterone/SHBG and expressed as nanomoles/nanomoles. Serum androstenedione was measured by tritiated RIA after diethyl ether extraction (39). The inter-

assay coefficient of variation is 6% for a concentration of 1.96 nM/liter and 8.3% for 3.98 nM/liter. Serum 25-hydrocholecalciferol (25OHD) was measured by RIA (Incstar Corp., Stillwater, MN), which excludes any interference from lipids (40). Intra- and interassay coefficients of variation were 5% and 11%, respectively. The detection limit was 7.5 nmol/liter.

Statistical methods

All calculations were performed using SAS software. Some biochemical and BMD measurements could not be performed in some participants due to insufficient volume of serum, lack of reliable and full 24-h urine collection, or prostheses of both hips. The number of subjects in different analyses may vary slightly, but the number of measurements lacking did not exceed 10%. Given the skewed distribution of the concentrations of total testosterone, AFTC, and FTI, the reference normal ranges were calculated after the logarithmic transformation. Pearson's simple correlation coefficients were calculated for continuous variables. BMD at different sites and serum concentrations of biochemical markers of bone turnover were compared in men with normal and low AFTC using the analysis of covariance adjusted for age, body weight, tobacco smoking, concentration of 25OHD, and comorbidities. For urinary levels of the markers of bone resorption, the analysis of covariance was adjusted for lean body mass (source of creatinine) instead of body weight. Analyses of body composition were also adjusted for the professional physical activity (scored as low, medium, high, or very high) and for body height (except relative skeletal muscle index), but not for body weight. The inability to perform clinical tests, expressed as an increase of risk per decrease in AFTC by 1 SD, was evaluated using the logistic regression adjusted for age, body weight, tobacco smoking, 25OHD concentration, and comorbidities. Comorbidities included arterial hypertension, coronary heart disease, chronic pulmonary disease necessitating corticosteroid treatment, liver cirrhosis, diabetes mellitus, vascular brain disease, hemiplegia, Parkinsonism, and treatment with psychotropic medicines. For both the analysis of covariance and the logistic regression, a backward procedure was used; first all of the independent variables were introduced, then removed progressively, leaving in the final model only the independent variables for which $P < 0.2$.

Results

Descriptive characteristics

Reference values for testosterone were calculated in 150 healthy, nonobese, nonsmoking men aged 19–40 yr (Table 1). Descriptive data for 792 men aged 50–85 yr in whom subsequent analyses were performed are also presented. In the entire cohort, the concentration of total testosterone, AFTC, and FTI decreased with ageing (Table 2). At the age of 80 yr, average levels of total testosterone, AFTC, and FTI were lower by 14.1%, 41.5%, and 44.7%, respectively, compared with those in young men. These decreases correspond to 0.43, 1.82, and 1.56 SD below the mean in young men.

Hypogonadism was defined after logarithmic transformation as the concentration more than 2 SD below the mean in young men for total testosterone, AFTC, and FTI (Table 1). In men more than 50 yr of age, the prevalence of hypogonadism increased with ageing (Fig. 1). For a given age range, the percentage of hypogonadal men was lowest for total testosterone and highest when AFTC was used for the diagnosis of hypogonadism. Hypogonadal men were older and heavier (Table 3). For all three diagnostic thresholds, levels of all hormonal parameters were significantly lower than in men with normal values.

Unexpectedly, the SHBG concentration was lower in men with a decreased total testosterone level (<8.92 nmol/liter). However, these men were older, more obese, and had a lower concentration of 17β-estradiol. After adjustment for these determinants of SHBG level, the serum SHBG concentration did not differ in men with low and normal total testosterone concentrations (80.4 ± 64.5 *vs.* 85.1 ± 40.7 nmol/liter; partial $F = 0.70$; $P = 0.40$).

The 17β-estradiol concentration was correlated positively with total testosterone, AFTC, and FTI ($r = 0.48$, $r = 0.30$, and $r = 0.18$, respectively; $P < 0.0001$). However, for the three testosterone parameters, about 22–23% of eugonadal men had 17β-estradiol concentrations below the first quartile, and 46–64% of hypogonadal men had 17β-estradiol concentrations in the three highest quartiles.

BMD

After adjustment for age, body weight, and comorbidities, BMD did not differ between men with normal and decreased total testosterone concentrations or FTI at any site of measurement. Differences in average BMD between the healthy and hypogonadal men were less than 1.6% ($P > 0.27$) for total testosterone and less than 2.8% ($P > 0.08$) for FTI. In contrast,

TABLE 1. Descriptive characteristics of 150 men, aged 19–40 yr (control group), and of 792 men, aged 50–85 yr, in whom the subsequent analyses were performed

Parameter	Men aged 19–40 yr (mean ± SD)	Men aged 50–85 yr	
		Mean ± SD	Median (IQ)
Age (yr)	32 ± 7	65 ± 7	65 (58, 71)
Body weight (kg)	75 ± 11	80 ± 13	79 (71, 87)
Body height (cm)	176 ± 7	169 ± 6	169 (165, 173)
Body mass index (kg/m^2)	24.5 ± 3.4	28.1 ± 3.8	27.6 (25.6, 30.2)
Lean body mass (kg)	56.4 ± 6.5	54.5 ± 6.8	54.2 (50.0, 58.3)
Fat body mass (kg)	14.8 ± 6.8	22.1 ± 7.7	21.2 (17.0, 26.4)
Appendicular skeletal muscle mass (kg)	24.3 ± 3.1	22.9 ± 3.2	22.9 (20.8, 24.8)
Total testosterone (nmol/liter)[a]	18.94 ± 5.01	17.69 ± 7.00	17.4 (13.2, 21.5)
AFTC (pmol/liter)[a]	268 ± 61	200 ± 79	192 (151, 236)
FTI (nmol/nmol)[a]	0.32 ± 0.09	0.24 ± 0.10	0.22 (0.17, 0.28)
17β-Estradiol (pmol/liter)	110 ± 28	114 ± 29	110 (95, 128)
Androstenedione (nmol/liter)	2.16 ± 0.59	1.66 ± 0.60	1.60 (1.21, 2.02)
SHBG (nmol/liter)	66.0 ± 32.8	84.7 ± 43.6	75.6 (57.4, 100.9)
25OHD (nmol/liter)	71.4 ± 27.8	67.7 ± 29.0	65 (47, 85)

FTI = total testosterone/SHBG; IQ, interquartile range.
[a] Given the skewed distribution, the normal range was calculated after logarithmic transformation.

TABLE 2. Correlation of hormone concentration and parameters of body composition with age

Parameter	Age[a]	Change until 80 yr[b]	
		%	SD
Total testosterone	−0.16	−14.1	−0.43
AFTC	−0.44	41.5	−1.82
FTI	−0.44	−44.7	−1.56
SHBG	0.28	48.5	0.99
Androstenedione	−0.37	−38.4	−1.41
Total 17β-estradiol	0.04	3.7	0.14
Lean body mass	−0.24	−12.8	−1.07
Fat body mass	0.27	43.7	0.95
Appendicular skeletal muscle mass	−0.29	−16.2	1.29

[a] $P = 0.0001$ for all except total 17β-estradiol.
[b] Compared with reference data in Table 1.

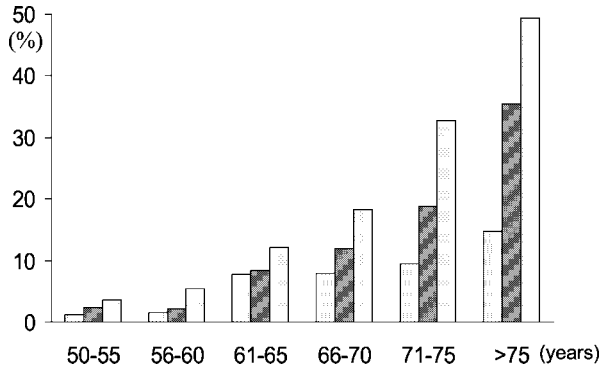

FIG. 1. Prevalence of hypogonadism in the MINOS cohort according to age group and testosterone parameter: *first bar*, total testosterone less than 8.92 nmol/liter; *second bar*, FTI less than 0.14 nmol/nmol; *third bar*, apparent free testosterone concentration less than 146 pmol/liter.

after similar adjustments, BMD was lower at several sites in men with decreased AFTC (Table 4).

Explanatory contributions of AFTC and 17β-estradiol for the BMD variability was evaluated using multiple regression models, including AFTC, 17β-estradiol, age, and body weight as independent variables. For all sites, 17β-estradiol was a significant determinant (partial $t = 2.58–4.50$; $P = 0.01–0.0001$), whereas AFTC was not significant (partial $t = 0.06–1.29$; $P = 0.20–0.95$). In the models including fat mass and lean mass, 17β-estradiol was a significant determinant of BMD for all sites, whereas AFTC was not significant. In the analysis of covariance, AFTC, used as a dichotomous variable, was a borderline significant determinant of BMD of total hip and ultradistal radius ($P < 0.05$) in the models including body weight.

Body composition

Lean body mass and appendicular skeletal muscle mass decreased, whereas fat body mass increased with age (Table 2). After adjustment for age, body height, and comorbidities, fat body mass (in absolute values and as a percentage of body weight) was higher in hypogonadal men (Table 3). In hypogonadal men discriminated using AFTC or total testosterone, lean body mass and appendicular skeletal muscle mass were slightly higher than in eugonadal men. In contrast, men with low FTI had a lower appendicular skeletal muscle mass and relative skeletal muscle index. However, hypogonadal men discriminated using AFTC or total testosterone were heavier. When lean mass was expressed as a percentage of body weight, AFTC and total testosterone discriminated better than FTI the men with a decreased fraction of lean mass (Table 3).

Biochemical markers of bone turnover

After adjustment for age, lean body mass, and comorbidities, men with the decreased total testosterone concentration (<8.92 nmol/liter) had higher urinary excretion of DPD (Table 5). Men with decreased AFTC (<146 pmol/liter) had increased urinary and serum levels of bone resorption markers as well as slightly increased concentrations of BAP and PINP. Similar differences of the levels of bone markers were found when FTI (0.14 nmol/nmol) was used as the diagnostic threshold for hypogonadism.

Explanatory contributions of testosterone and 17β-estradiol to the variability in biochemical bone markers was evaluated by multiple regression models, including testosterone (total, AFTC, or FTI), 17β-estradiol, age, as well as body weight or fat mass and lean mass. Both models provided very similar results and are presented jointly. In the models including total testosterone, 17β-estradiol was a determinant of the variability of bone resorption markers, except for free DPD (partial $t = -2.57$ to -3.68; $P = 0.01–0.002$), but not of bone formation markers. Total testosterone was not a significant determinant for any marker. In the models including FTI and 17β-estradiol, FTI determined the variability in bone formation markers (partial $t = -2.26$ to -4.10; $P < 0.03–0.0001$), whereas 17β-estradiol did not. Both FTI and 17β-estradiol were determinants of the variability in bone resorption markers (partial $t = -2.64$ to -4.69; $P < 0.01–0.0001$). Similarly, AFTC, but not 17β-estradiol, was a determinant of the variability in bone formation markers (partial $t = -2.06$ to -3.24; $P < 0.05–0.002$). Variability in bone resorption markers was explained by AFTC (partial $t = -2.01$ to -4.14; $P < 0.05–0.0001$) and by 17β-estradiol (partial $t = -2.19$ to -3.01; $P < 0.03–0.003$).

Functional capacity

The risk of inability to perform clinical tests was evaluated by logistic regression after adjustment for age, body weight, 25OHD level, and comorbidity for total testosterone, AFTC, and FTI below the threshold of hypogonadism and for these parameters examined as continuous variables (Table 6). Total testosterone poorly discriminated men who were unable to perform clinical tests (five consecutive chair stands, standing with the feet in the side by side position for 10 sec with open eyes and for 5 sec with closed eyes, and forward or backward tandem 10-step walk) or had fallen during a preceding year. In contrast, a decrease in AFTC was associated with a significantly higher risk of inability to perform the clinical test and with a higher risk of falls when it was introduced as dichotomous or continuous variable. FTI disclosed a similar or a slightly lower discriminative power for different clinical tests and falls. Interestingly, low AFTC and FTI were associated with a higher risk of inability to perform the tests, but

TABLE 3. Comparison of the hormonal parameters in 792 men aged 50–85 yr divided according to the levels of total testosterone, AFTC, and FTI

Parameters	Testosterone <8.92 nmol/liter (n = 68)	Testosterone ≥8.92 nmol/liter (n = 724)	*P*	AFTC <146 pmol/liter (n = 177)	AFTC ≥146 pmol/liter (n = 615)	*P*	FTI <0.14 nmol/nmol (n = 91)	FTI ≥0.14 nmol/nmol (n = 701)	*P*
Age (yr)	67 ± 8	65 ± 7	<0.03	69 ± 8	64 ± 7	<0.0001	71 ± 8	64 ± 7	<0.0001
Body weight (kg)	89 ± 17	79 ± 12	<0.0001	83 ± 16	79 ± 12	<0.002	79 ± 14	80 ± 13	0.24
Body height (cm)	170 ± 6	169 ± 6	0.34	169 ± 6	169 ± 6	0.54	168 ± 6	169 ± 6	0.15
RASM (kg/cm^2)	30.5 ± 4.4	27.8 ± 3.6	<0.0001	28.8 ± 4.6	27.8 ± 3.4	<0.001	27.8 ± 4.2	28.1 ± 3.7	0.53
Testosterone (nmol/liter)	5.93 ± 2.65	18.71 ± 6.30	<0.0001	12.09 ± 5.94	19.32 ± 6.42	<0.0001	12.97 ± 6.89	18.44 ± 6.67	<0.0001
AFTC (pmol/liter)	91 ± 56	209 ± 74	<0.0001	107 ± 35	226 ± 67	<0.0001	87 ± 38	214 ± 70	<0.0001
FTI (nmol/nmol)	0.14 ± 0.12	0.24 ± 0.10	<0.0001	0.13 ± 0.04	0.27 ± 0.09	<0.0001	0.10 ± 0.04	0.25 ± 0.09	<0.0001
Total 17β-Estradiol (pmol/liter)	88 ± 28	116 ± 28	<0.0001	103 ± 29	117 ± 29	<0.0001	98 ± 31	116 ± 28	<0.0001
Androstenedione (nM/liter)	1.47 ± 0.63	1.68 ± 0.60	<0.005	1.40 ± 0.52	1.73 ± 0.60	<0.0001	1.33 ± 0.53	1.70 ± 0.60	<0.0001
SHBG (nmol/liter)	68.7 ± 60.0	85.9 ± 40.6	<0.005	103.3 ± 59.1	79.0 ± 35.4	<0.0001	126.5 ± 67.8	79.2 ± 35.3	<0.0001
Fat body mass (kg)[a]	28.3 ± 9.7	21.5 ± 7.3	<0.0001	25.2 ± 9.5	21.2 ± 6.8	<0.0001	23.6 ± 8.9	21.9 ± 7.5	<0.06
Lean body mass (kg)[a]	56.8 ± 8.6	54.3 ± 6.5	<0.003	55.4 ± 7.6	54.2 ± 6.5	0.12	53.8 ± 6.9	54.6 ± 6.7	0.27
ASM (kg)[a]	23.9 ± 4.0	22.9 ± 3.1	<0.02	23.3 ± 3.6	22.8 ± 3.1	0.12	22.2 ± 3.0	23.0 ± 3.2	<0.02
RASM (kg/m^2)[a]	8.22 ± 1.08	7.98 ± 0.87	<0.04	8.01 ± 1.07	8.00 ± 0.82	0.80	7.71 ± 0.89	8.04 ± 0.87	<0.001
Fat mass/weight (%)	31.6 ± 6.1	26.9 ± 5.5	<0.0001	29.6 ± 6.6	26.6 ± 5.7	<0.0001	28.9 ± 7.0	27.1 ± 5.9	<0.02
Lean mass/weight (%)	64.3 ± 5.9	68.8 ± 6.0	<0.0001	66.1 ± 6.5	69.1 ± 5.7	<0.0001	67.1 ± 6.8	68.6 ± 5.9	<0.04

Thresholds of normality correspond to 2 SD below the mean in young men aged 19–40 yr. ASM, Appendicular skeletal muscle mass; RASM, relative skeletal muscle index.

[a] Adjusted for age.

TABLE 4. Comparison of BMD in men according to the AFTC by analysis of covariance adjusted for age, body weight, and comorbidities

Site of measurement	AFTC <146 pmol/liter (n = 177)	AFTC ≥146 pmol/liter (n = 615)	*P*
Lumbar spine (g/cm^2)	1.021 ± 0.205	1.036 ± 0.181	0.35
Total hip (g/cm^2)	0.943 ± 0.146	0.973 ± 0.130	<0.01
Femoral neck (g/cm^2)	0.831 ± 0.139	0.846 ± 0.114	0.12
Trochanter (g/cm^2)	0.720 ± 0.124	0.743 ± 0.104	<0.02
Whole body BMC (g)	2645.5 ± 490.6	2716.3 ± 396.6	<0.02
Whole body BMD (g/cm^2)	1.194 ± 0.129	1.213 ± 0.105	<0.05
Distal forearm (g/cm^2)	0.513 ± 0.070	0.525 ± 0.063	<0.03
Ultradistal radius (g/cm^2)	0.416 ± 0.067	0.432 ± 0.064	<0.005

BMC, Bone mineral content.

TABLE 5. Comparison of the levels of biochemical markers of bone turnover according to the AFTC

Parameter	Testosterone <8.92 nmol/liter (n = 68)	Testosterone ≥8.92 nmol/liter (n = 724)	*P*	AFTC <146 pmol/liter (n = 177)	AFTC ≥146 pmol/liter (n = 615)	*P*	FTI <0.14 (n = 91)	FTI ≥0.14 (n = 791)	*P*
Osteocalcin (ng/ml)	20 ± 10	19 ± 7	0.21	20 ± 9	19 ± 7	0.39	20 ± 10	19 ± 7	0.16
BAP (U/liter)	18 ± 6	17 ± 6	0.41	18 ± 9	17 ± 5	<0.03	18 ± 7	17 ± 6	<0.09
PINP (ng/ml)	38 ± 19	36 ± 18	0.61	39 ± 23	36 ± 16	<0.02	40 ± 22	36 ± 17	<0.05
Total DPD (nM/mM cr)	8.38 ± 4.20	6.98 ± 2.76	<0.001	7.95 ± 3.88	6.89 ± 2.60	<0.0001	8.69 ± 4.33	6.92 ± 2.67	<0.0001
Free DPD (nM/mM cr)	3.87 ± 1.46	3.46 ± 1.12	<0.01	3.79 ± 1.54	3.42 ± 1.08	<0.001	4.01 ± 1.67	3.43 ± 1.12	<0.0001
Bound DPD (nM/mM cr)	4.47 ± 2.98	3.55 ± 1.99	<0.002	4.19 ± 2.69	3.49 ± 1.97	<0.001	4.73 ± 3.06	3.51 ± 1.98	<0.0001
β-CTX-I (μg/mg cr)	147.2 ± 99.0	124.3 ± 78.0	<0.04	142.1 ± 100.9	121.0 ± 72.0	<0.005	158.2 ± 126.9	121.5 ± 70.2	<0.0001
β-CTX-I (nM/liter)	2.67 ± 1.87	2.45 ± 1.25	0.23	2.64 ± 1.57	2.39 ± 1.21	<0.05	2.89 ± 1.95	2.40 ± 1.18	<0.002

Calculations were adjusted for age, body weight, and comorbidities for serum markers and for age, lean body mass, and comorbidities for urinary markers. cr, Creatinine.

not with the difficulty of performing the test (*e.g.* longer time required to perform the test and number of different errors).

Discussion

Hypogonadal elderly men had a higher risk of falls, lower muscle strength, impaired static and dynamic balance, increased bone resorption not adequately matched by an increase in bone formation, and, in men with low AFTC, lower BMD. AFTC had the best discriminative power for densitometric, biochemical, and functional parameters, followed by FTI, whereas total testosterone was the least discriminative. FTI better discriminated men with low muscle mass but total testosterone, and AFTC better discriminated men with low fraction of lean mass. In multiple regression models, 17β-estradiol was the strongest determinant of BMD, AFTC and FTI were determinants of the variability in bone formation markers, and both 17β-estradiol and testosterone determined the variability in bone resorption markers.

The age-related decrease in testicular secretion of testosterone and the increase in SHBG concentration result in a decrease in the concentrations of total and free testosterone (41). The decreased total testosterone level reflects the decrease in testicular secretory activity, whereas free testoster-

TABLE 6. Risk of inability to perform clinical tests in men as a function of total testosterone, AFTC, or FTI adjusted for age, body weight, concentration of 25OHD, and comorbidities

Clinical test	Total testosterone	AFTC	FTI
A) Odds ratio of the risk in men with decreased level of hormone *vs.* men with normal level of hormone			
Five chair stands	3.04 (1.08–8.59)[a]	7.95 (2.78–22.8)[b]	4.61 (1.78–12.0)[c]
Static balance[d] with open eyes (10 sec)	1.54 (0.44–5.40)	2.96 (1.19–7.38)[a]	2.40 (0.89–6.50)
Static balance[d] with closed eyes (5 sec)	1.73 (0.66–4.54)	2.68 (1.29–5.55)[c]	1.62 (0.72–3.66)
Tandem walk forward (10 steps)	2.25 (0.92–5.51)	2.64 (1.34–5.21)[c]	1.94 (0.93–4.05)
Tandem walk backward (10 steps)	1.31 (0.52–3.32)	2.09 (1.13–3.87)[a]	1.56 (0.76–3.22)
Falls during last yr	1.16 (0.63–2.12)	1.54 (1.01–2.33)[a]	2.20 (1.31–3.70)[c]
B) Odds ratio of the risk per 1 SD decrease in hormone concentration			
Five chair stands	1.60 (1.15–2.22)[c]	2.47 (1.52–3.99)[e]	3.28 (1.82–5.90)[b]
Static balance[d] with open eyes (10 sec)	1.19 (0.86–1.64)	1.65 (1.06–2.58)[a]	2.18 (1.24–3.83)[c]
Static balance[d] with closed eyes (5 sec)	1.30 (1.01–1.68)[a]	1.51 (1.07–2.12)[a]	1.58 (1.03–2.42)[a]
Tandem walk forward (10 steps)	1.31 (1.01–1.70)[a]	1.52 (1.10–2.10)[a]	1.74 (1.16–2.61)[c]
Tandem walk backward (10 steps)	1.21 (0.98–1.51)	1.23 (0.93–1.61)	1.18 (0.84–1.65)
Falls during last yr	1.10 (0.98–1.26)	1.20 (1.03–1.40)[a]	1.21 (1.03–1.41)[a]

[a] $P < 0.05$.
[b] $P = 0.0001$.
[c] $P < 0.01$.
[d] Static balance was evaluated by standing with the feet in the side by side position.
[e] $P < 0.001$.

one corresponds better to the residual androgenic activity (16, 42).

Osteoporosis is one of the manifestations of hypogonadism in men. However, data on osteoporosis in elderly hypogonadal men are limited (14, 15). In elderly men, the correlation of BMD with testosterone was relatively weak or not significant (3–7). In contrast, total and bioavailable 17β-estradiol were correlated positively with BMD and negatively with levels of bone markers and the rate of bone loss in elderly men (5–8, 43, 44). Our data also indicate that a low 17β-estradiol level is a strong determinant of BMD. Two mechanisms may lead to a low concentration of 17β-estradiol in hypogonadal men: 17β-estradiol is cosecreted with testosterone by testicles and is also a product of the peripheric aromatization of testosterone; in addition, hypogonadal men had a lower concentration of androstenedione, which is also a substrate of aromatase.

In elderly men, severe osteoporosis due to hypogonadism is observed in patients with prostate cancer receiving antiandrogen therapy (45–48). They have a barely detectable testosterone concentration, but also a markedly decreased 17β-estradiol level. They have increased bone resorption, which results in accelerated bone loss, decreased BMD, and increased risk of fractures. These observations confirm the importance of sex steroids for bone turnover in elderly men. However, this drug-induced, rapidly developing, and severe hypogonadism is different from the progressively developing, less severe hypogonadism in elderly men.

Our cross-sectional data suggest that in hypogonadal elderly men, increased bone resorption not matched by an adequate increase in bone formation is the mechanism leading to bone loss. Both young and elderly hypogonadal men had increased levels of bone markers, mainly those of bone resorption (45, 49). In elderly men, increased levels of bone resorption markers are correlated negatively with BMD (4, 50). Despite a marked difference in bone resorption marker levels between hypogonadal and eugonadal men, BMD was only slightly lower in men with decreased AFTC, but not in men with hypogonadism diagnosed using total testosterone or FTI. Moreover, hypogonadal men can have low or normal concentrations of 17β-estradiol. Multiple regression models show that a low testosterone level is associated with an acceleration of both bone formation and bone resorption, whereas in men with low 17β-estradiol levels, increased bone resorption may not be matched by increased bone resorption. Thus, low 17β-estradiol may be a stronger determinant of low BMD than a low testosterone level. These results seem interesting, but must be interpreted cautiously. They are based on the cross-sectional associations, which do not necessarily prove causation. A part of circulating testosterone will be aromatized to 17β-estradiol in fat tissue before entering bone cells, and a part of testosterone entering bone cells will be aromatized and act as 17β-estradiol. Moreover, only a part of 17β-estradiol will enter bone cells. Thus, circulating levels of sex steroids do not necessarily reflect the biological reality at the tissue level.

Hypogonadal men were older and heavier. After adjustment for age, they had higher fat body mass than eugonadal men. Lean body mass, appendicular skeletal muscle mass, and relative skeletal muscle index were comparable in both groups when hypogonadism was diagnosed using total testosterone or AFTC, but was lower when hypogonadism was diagnosed using FTI.

Main findings of our study are lower muscle strength, impaired static and dynamic balance, and increased risk of falls in elderly hypogonadal men. Hypogonadal men failed to perform five chair stands more often than eugonadal men. Thus, they had less muscle strength despite similar appendicular skeletal muscle mass and relative skeletal muscle index.

This discrepancy between decreased muscular strength and preserved skeletal muscle mass is the most intriguing point of our study. The age-related decrease in muscle strength is higher than that in muscle mass (51). Lower extremity performance is correlated with muscle strength, but not with muscle mass, in elderly men (52). Several mechanisms result in the age-related decrease in muscle mass and strength: decreased number of muscle fibers (mainly of type

IIA), loss of contractile proteins (mainly myosin heavy chains), lower activity of mitochondrial enzymes, and changes in the motor units innervating muscles (9, 53). Consequently, single fibers develop lower maximal force in older men compared with younger ones even after adjustment for fiber size (54). Thus, decreased muscle strength is not necessarily accompanied by a detectable decrease in muscle mass. Hypogonadal men were heavier due to a higher body fat mass; thus, their normal muscle mass may not be able to develop the strength sufficient to carry a heavier body.

In cross-sectional studies, appendicular skeletal muscle mass was weakly positively correlated with the testosterone concentration (55). In longitudinal studies performed in both young and elderly men, drug-induced severe, rapidly developing hypogonadism resulted only in a mild decrease in lean body mass (56, 57). Several studies indicated a positive correlation of the bioactive fraction of testosterone with muscle strength and static balance (3, 57, 58). In hypogonadal men, testosterone replacement increased the synthesis of mixed muscle proteins, including that of myosin heavy chains, which determine the strength of striated muscles (59).

These pathophysiological observations should be discussed in the context of therapeutic studies. In young hypogonadal men, testosterone replacement therapy increases both muscle mass and strength (49, 60). In contrast, in elderly men with PADAM, hormone replacement therapy increased muscle mass, whereas its effect on muscle strength was very weak or not significant (61–63). Thus, testosterone replacement therapy can increase the synthesis of muscle protein and skeletal muscle mass, but it may not be able to entirely restore the functional integrity of skeletal muscle (especially the levels of motor units) that has deteriorated due to the ageing process.

In conclusion, elderly men with partial androgen deficiency have markedly higher bone resorption that is not adequately matched by increased bone formation, decreased muscle strength (but not mass), impaired static and dynamic balance, increased risk of falls, and, in men with low AFTC, a slightly lower BMD. Thus, they can have an increased risk of osteoporotic fractures. Low AFTC is more discriminative for densitometric, biochemical, and functional parameters than FTI or total testosterone, whereas FTI is more discriminative for muscle mass. In multiple regression models, 17β-estradiol was the strongest determinant of BMD; AFTC and FTI were significant determinants of the variability in bone formation markers, whereas both 17β-estradiol and testosterone determined the variability in bone resorption markers.

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