Prevalence of Undiagnosed Testosterone Deficiency in Aging Athletes: Does Exercise Training Influence the Symptoms of Male Hypogonadism?

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ABSTRACT

Introduction. Worldwide many aging males practice sports. A high prevalence of late-onset male hypogonadism has been observed in general population. Sport-participation influences the neuroendocrine system and may decrease serum testosterone.

Aim. This preliminary study was designed to estimate the prevalence and the symptoms of undiagnosed testosterone deficiency in aging athletes.

Methods. This observational survey was performed in 183 caucasian male athletes >50 years, in the setting of pre-participation screening. Pituitary–gonadal hormones and symptoms of hypogonadism were investigated. Serum total testosterone (TT), sex hormone binding globulin, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), *free*-T4, and thyroid stimulation hormone (TSH) were assayed, and free T, bioactive T, and the LH/TT ratio were calculated. The International Index of Erectile Dysfunction (IIEF-15) and the Center for Epidemiological Studies Depression Scale (CES-D) were administered. Hypogonadal athletes were compared with eugonadal athletes as controls.

Main Outcome Measures. Prevalence and clinical symptoms of severe (TT < 8 nmol/L) or mild (8 nmol/L ≤ TT < 12 nmol/L) testosterone deficiency were investigated.

Results. The mean sample age was 61.9 ± 7.5 years (range 50–75). Severe or mild testosterone deficiency was observed in 12% and 18%, respectively, of overall athletes, with the highest prevalence in athletes >70 years (27.5% and 25.0%, respectively). TT did not correlate with age, training duration, or questionnaire scores. No differences were observed for nonspecific symptoms of hypogonadism, IIEF-15 and CES-D scores between eugonadal and severe hypogonadal athletes.

Conclusions. Independently of its etiology, a significant percentage of aging athletes had undiagnosed testosterone deficiency. In a relevant number of these cases, testosterone deficiency was not overtly symptomatic. Our results suggest that sport-participation per se can influence the symptoms of hypogonadism. The history of clinical symptoms may be inaccurate to diagnose testosterone deficiency in aging athletes. Future research should address the clinical relevance and the specific risks of testosterone deficiency in aging athletes, and the need of a systematic pre-participation serum testosterone evaluation. **Di Luigi L, Sgrò P, Fierro V, Bianchini S, Battistini G, Magini V, Jannini EA, and Lenzi A. Prevalence of undiagnosed testosterone deficiency in aging athletes: Does exercise training influence the symptoms of male hypogonadism? J Sex Med 2010;7:2591–2601.**

Key Words. Testosterone Deficiency; Sport; Sexual Desire; Erectile Dysfunction; Hypogonadism; Stress

Introduction

The relationships between male reproduction and physical training have mainly been evaluated in terms of exercise-related modifications of the hypothalamus–pituitary–gonadal (HPG) axis and in terms of the possible effects of lifestyle on sexual function [1–4].

While moderate training in males is useful in the prevention and treatment of sexual disorders [1], increasing evidence points to high intensity endurance training as having detrimental effects on the HPG axis. In highly trained individuals, exposure to intense training can affect gonadotropins secretion and reduce serum testosterone [2–4]. Such an "exercise-hypogonadal male condition" is characterized by stable, reduced, serum free, and total testosterone (TT) without concurrent luteinizing hormone (LH) elevation, and is reported as being detrimental to both health and performance [4].

The prevalence and symptoms of male hypogonadism have been evaluated in the general population and in cohorts of subjects at higher risk for testosterone deficiency (e.g., aging, depression, metabolic diseases, individual or couple sexual dysfunctions) [5–10]. Insufficient investigation has been focused on the prevalence of testosterone deficiency in athletes, particularly in subjects involved in competitive sports at advanced ages.

In fact, in general population serum testosterone in males declines gradually after age 40, by decreasing 0.4–2.6 per year [11–13], and the prevalence of late-onset hypogonadism (LOH) in men over 45 years ranges from <10% to about 40% [5,14,15]. Owing to the effects of testosterone on the central nervous system, muscles, and metabolism [16–20], it is essential for physical performance. However, in asymptomatic adults involved in physical training, serum testosterone is not routinely measured. The evaluation of serum testosterone in males is commonly indicated only if symptoms or signs suggestive of testosterone deficiency appear, or when a subject is at high risk of hypogonadism. Furthermore, perhaps as a result of limited sexual opportunity, to the paucity of symptoms or to their absence [5], individuals have no reason to check serum testosterone, and so a high prevalence of undiagnosed testosterone deficiency probably exist.

It is possible therefore that also a noteworthy number of aging individuals doing training or practicing sports are affected by undiagnosed testosterone deficiency. Owing to the association between the reduced effects of testosterone and increased body demands, hypogonadal athletes are exposed to further specific health risks, depending on the type of performed physical activity.

There has not been adequate research into the prevalence and symptoms of testosterone deficiency in males practicing sports in advanced age.

Aim

The aim of this preliminary observational survey was to study the serum HPG axis hormones and the prevalence and clinical symptoms of undiagnosed testosterone deficiency in a group of apparently healthy competitive athletes over 50 years.

Methods

Participants and Inclusion Criteria

The athletes were progressively recruited during the mandatory pre-participation screening performed to evaluate health risks contraindicating sport participation. To be included, athletes had to meet the following criteria: Caucasian race, age 50–80 years, participation in the same sport in the last 10 years, no decreased sport performances in the previous 3 months, willingness to answer questions related to medical and sexual history, and stable living situation with a partner in the previous 2 years. Exclusion criteria were: the practice of cycling; previous diagnoses of sexual disorders or diseases affecting the HPG axis or sexual behavior; and taking supplements, doping substances, or other drugs influencing the study.

After recruitment, "theoretically" healthy male athletes (N = 183) from different sports (tennis, swimming, and track and field) volunteered to participate in this study. The characteristics of the research were thoroughly explained and written informed consent was obtained. Approval was obtained from the University Scientific-Ethic Committee.

The day after inclusion, all enrolled athlete underwent further clinical evaluations and answered a series of questionnaires after a morning blood sample collection was taken.

Main Outcome Measures

Clinical Evaluations

All the volunteers underwent an in-depth clinical history and a careful evaluation of anthropometric and sexual characteristics. Nonspecific nonsexual symptoms of male hypogonadism (e.g., osteoporosis or fractures after age 50 years, sleep distur-

bances, reduced sense of energy) were investigated as described by Araujo et al. [5].

Weight was measured on a digital scale with an accuracy of 0.1 kg. A Harpenden's stadiometer (St. Albans, UK) was used for height measurement. Waist circumference was measured with a calibrated tape at the midpoint between the lowest rib and the iliac crest with the subject standing at the end of gentle expiration. Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2).

Questionnaires

The self-administered International Physical Activity Questionnaire was used to measure individual physical activity level [21]. The International Index of Erectile Dysfunction (IIEF-15) was used to evaluate sexual symptoms of testosterone deficiency (e.g., low libido, erectile dysfunction): we focused our attention on the erectile function domain (EF) (score range 1–30, no dysfunction if score >25) [22], and sexual desire domain (SXD) (score range 2–10, we arbitrary considered no dysfunction if score >8). The Center for Epidemiological Studies Depression Scale (CES-D) was used to assess depressive symptoms (score range 0–60, no psychological distress or depression if score <16, psychological distress or mild depression if score 16–21, and overt depression if score >21) [23].

Hormones Assays

After 60 minutes in a sitting position, all the volunteers underwent a single venous blood sample collection after an overnight fast, between 08:30 AM and 09:00 AM Serum samples were frozen at −30°C until analyses for TT, LH, follicle stimulating hormone (FSH), dehydroepiandrosterone sulphate (DEAS), sex hormone binding globulin (SHBG), *free*-T4 (FT_4), thyroid stimulation hormone (TSH), and prolactin (PRL) concentrations were performed. All samples were analyzed in duplicate within the same assay.

TT and DHEAS were measured by radioimmunoassay (Orion, Espoo, Finland). FSH, LH, and SHBG were measured by the immunoradiometric method (Immunotech, Prague, Czech Republic and Orion, Espoo, Finland, respectively). The sensitivity of the assay methods were: 0.1 nmol/L for TT, 0.2 IU/L for FSH, 0.2 IU/L for LH, 0.03 μmol/L for DHEAS, and 1.3 nmol/L for SHBG. The intra-assay and the inter-assays coefficients of variation were: 5.5% and 4.8% for TT, 2.6% and 6.3% for FSH, 6.7% and 3.7% for LH, 7.5% and 7.0% for DHEAS, and 5.3% and 3.3% for SHBG.

Serum free testosterone (cFT) and bioavailable testosterone (cBioT), were calculated from TT and SHBG concentrations, assuming an albumin concentration of 4.3 g/dL, by using published equations [24].

We classified severe testosterone deficiency when TT < 8 nmol/L and mild testosterone deficiency a TT between 8 and 12 nmol/L; furthermore, we identified the subjects with low cFT as those having calculated values below the threshold value of 225 pmol/L [25].

FT_4, TSH, and PRL were measured by radioimmunoassay and immunoradiometric methods (IMMUNOTECH a.s. Radiova, Prague, Czech Republic; BIOSOURCE Europe S.A., Nivelles, Belgium; and ICN Pharmaceuticals, Costa Mesa, CA, USA, respectively).

Statistical Analyses

The primary statistical analyses focused on descriptive statistics and the evaluation of prevalence. All parameters were analyzed in the overall athletes sample and in cohorts derived from age-class distribution (age groups: 50–59, 60–69, and 70–79 years) and from TT concentrations (TT groups: $TT \geq 12$, $8 \leq TT < 12$, and $TT < 8$ nmol/L). In addition, we also stratified overall athletes based on cFT concentration ($cFT < 225$ and $cFT \geq 225$ pmol/L). Athletes with testosterone deficiency were compared with eugonadal athletes.

Kolmogorov–Smirnov test has been used to evaluate the parameters distribution. Data are expressed as mean ± standard deviation (SD) when normally distributed, and as median (quartiles) if not normally distributed. One-way ANOVA and post hoc analysis of significant differences between parameters were used. Unpaired two-sided Student's *t*-test has been used for comparison of means of normally distributed parameters, and in all other cases we used the Mann–Whitney *U*-test. Chi-squared test was used for comparison. Pearson's or Spearman's correlations among questionnaire scores, age, exercise training (hours/week), BMI, and serum HPG hormones were calculated. A level of $P < 0.05$ was selected to infer statistical significance. Statistical analyses were performed using the SPSS statistical package (Version 17.0 for Windows; SPSS Inc., Chicago, IL, USA).

Results

The study sample characteristics are reported in Table 1. All the athletes were regularly trained,

Table 1 Study sample characteristics, performed training, nonspecific symptoms of testosterone deficiency, and concomitant morbidities in athletes over 50 years, overall and stratified by age group

	Mean ± standard deviation or N (%)			
Variable	Overall N = 183	Age 50–59 N = 73 (39.8)	Age 60–69 N = 70 (38.2)	Age 70–79 N = 40 (21.8)
Age (year)	61.9 ± 7.5	54.5 ± 3.1	64.5 ± 3.4*	72.8 ± 1.7*
Weight (kg)	78.8 ± 8.6	76.3 ± 8.0	81.1 ± 9.5	79.9 ± 7.3
Height (cm)	174.4 ± 5.4	166.0 ± 34.3	176.2 ± 5.3	172.3 ± 4.4
BMI ($kg \cdot m^{-2}$)	25.9 ± 2.5	25.2 ± 2.2	26.2 ± 2.8	26.7 ± 2.4
Systolic blood pressure (mm Hg)	133.5 ± 10.5	132.3 ± 9.1	132.7 ± 10.0	136.8 ± 13.6
Diastolic blood pressure (mm Hg)	79.6 ± 6.3	76.9 ± 5.5	80.5 ± 6.3	83.1 ± 6.0*
Resting heart rate (beats/min)	72.8 ± 6.5	72.5 ± 7.2	71.5 ± 7.1	75.3 ± 2.4#
IPAQ-training (hours/week)	7.1 ± 3.3	7.8 ± 3.9	7.2 ± 2.9	5.8 ± 2.6
Alcohol consumption (1/2 drinks)	126 (68.8)	58 (79.4)	40 (57.1)*	28 (70.0)
Smoking status, current	54 (29.5)	24 (32.8)	15 (21.4)	11 (27.5)
Osteoporosis fractures	0 (0)	0 (0)	0 (0)	0 (0)
Nonspecific symptoms (two)	15 (8.1)	6 (8.2)	5 (7.1)	4 (10)
Positive history for hypertension	47 (25.6)	10 (13.6)	12 (17.1)	25 (62.5)**##

*$P < 0.05$ vs. age 50–59; **$P < 0.01$ vs. age 50–59; #$P < 0.05$ vs. age 60–69; ##$P < 0.01$ vs. age 60–69.
BMI = body mass index; IPAQ = International Physical Activity Questionnaire.

with a mean training duration of 8.1 ± 3.3 hours/week (2–3 hours/day for 3–5 days/week) during the last 2–3 years. Based on the pre-participation screening (i.e., without knowing individual TT) nobody was affected by diseases contraindicating sport-participation.

Age Groups

The age groups were comparable for anthropometry, performed physical activity and clinical characteristics, even though there was a higher prevalence of history of hypertension and a higher resting heart rate in athletes aged 70–79 years ($P = 0.04$ vs. 60–69 years) (Table 1).

Serum Hormones

Mean TT were in the normal range for athletes overall and stratified for age, and no differences were observed between age groups (Table 2).

Based on individual TT, we observed a severe or mild testosterone deficiency in the 12% and 18% of the athletes overall, respectively, and the highest prevalence in athletes aged 70–79 years (27.5% and 25.0%, respectively) (Table 2).

A lower mean cFT, cBioT, and DHEAS and a higher mean gonadotropins concentrations and LH/TT ratio were observed in the advanced ages (Table 2). FT_4, TSH, and PRL were normal for all the athletes, and no differences were observed between age groups (*data not shown*).

Symptoms of Testosterone Deficiency

None of the athletes reported a history of osteoporosis or fractures, and no differences in the prevalence of other nonspecific symptoms of male hypogonadism were observed between the age groups (Table 1).

Table 2 Serum hormones/proteins concentrations and prevalence of testosterone deficiency in athletes over 50 years, overall and stratified by age group

	Mean ± standard deviation (min–max) or median (quartiles) or N (%)			
Variable	Overall N = 183	Age 50–59 N = 73 (39.8)	Age 60–69 N = 70 (38.2)	Age 70–79 N = 40 (21.8)
TT (nmol/L)	14.8 ± 5 (6.2–25.7)	16.0 ± 5.6 (7.1–25.7)	14.9 ± 4.1 (8.2–23.6)	12.6 ± 4.4 (6.2–18.4)
cFT (pmol/L)	263.6 ± 85.1 (0.1–0.5)	300.1 ± 96.1 (0.1–0.5)	250.5 ± 72.0 (0.1–0.3)	215.4 ± 50.4 (0.1–0.3)*
cBioT (nmol/dL)	6.18 ± 2.01 (3.0–12.2)	7.0 ± 2.3 (3.0–12.2)	5.8 ± 1.6 (3.3–9.3)	5 ± 1.1 (3.5–7.0)*
FSH (IU/L)	7.0 (4.6–10.6)	4.9 (3.9–8.2)	7.0 (4.8–10.9)	11.7 (9.9–20.5)**#
LH (IU/L)	6.5 (4.4–9.3)	4.5 (3.2–7.3)	6.9 (4.8–10.6)*	8.1 (6.9–11.3)**
LH/TT	0.4 (0.2–0.7)	0.3 (0.2–0.5)	0.4 (0.3–0.8)	0.6 (0.4–1.1)**
DHEAS (μmol/L)	2.8 ± 1.3 (0.8–7.1)	3.5 ± 1.1 (1.7–6.3)	1.5 ± 1.6 (0.9–7.1)*	1.6 ± 0.8 (0.8–3.4)*#
SHBG (nmol/L)	42.4 ± 14.2 (20.2–91.4)	39.2 ± 15.1 (20.2–91.4)	46.5 ± 12.9 (28.5–74.2)	41.7 ± 14.0 (20.2–65.3)
TT ≥ 12 nmol/L	128 (69.9)	58 (79.4)	51 (72.8)	19 (47.5)**##
8 nmol/L ≤ TT < 12 nmol/L	33 (18.0)	11 (15.0)	12 (17.1)	10 (25.0)
TT < 8 nmol/L	22 (12.0)	4 (5.4)	7 (10.0)	11 (27.5)**##
TT < 12 nmol/L	55 (30.0)	15 (20.4)	19 (27.1)	21 (52.5)**##

*$P < 0.05$ vs. age 50–59; **$P < 0.01$ vs. age 50–59; #$P < 0.05$ vs. age 60–69; ##$P < 0.01$ vs. age 60–69.
cBioT = calculated bioavailable testosterone; cFT = calculated free testosterone; TT = total testosterone; FSH = follicle stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone binding globulin; DHEAS = dehydroepiandrosterone sulphate.

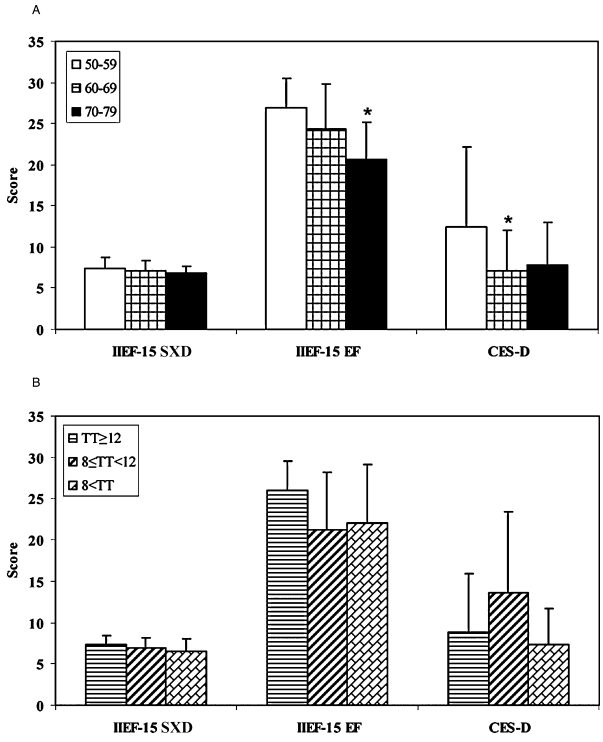

Figure 1 Absolute questionnaire scores (mean ± standard deviation) in athletes over 50 years (N = 183) stratified by age group (A) and by serum total testosterone levels (TT, nmol/L) (B). IIEF = International Index of Erectile Dysfunction; SXD = sexual desire domain; EF = erectile function domain; CES-D = Center for Epidemiological Studies Depression Scale. *$P < 0.05$ vs. age 50–59.

No differences in the mean IIEF-15/SXD scores were observed between age groups. The lowest mean IIEF-15/EF score was observed in athletes aged 70–79 years ($P = 0.001$ vs. 50–59 years) (Figure 1A). The highest mean CES-D score was observed in athletes aged 50–59 years ($P = 0.03$ vs. 60–69 years) (Figure 1A).

At an individual level, very few of the athletes had an IIEF-15/SXD score of >8 (i.e., from 28.7% in the 50–59 years to 2% in the 70–79 years group, $P = 0.0002$) (Figure 2A). An absolute IIEF-15/EF score suggestive of erectile dysfunction was observed from about 7% of the younger to 72.5% of the older athletes ($P = 0.0001$) (Figure 2A). A CES-D score suggestive of overt depression was observed in 13.6% of athletes aged 50–59 years and only in one subject of the 60–69 years group ($P = 0.005$); nobody in the 70–79 years group had a CES-D score suggestive of overt depression (Figure 2A).

Testosterone Groups

When the sample was stratified by TT and cFT concentration, except for HPG hormone concentrations, the groups resulted comparable for anthropometry, performed physical activity, and main clinical characteristics, even if a difference in the history for smoking and hypertension was observed between TT groups (Table 3). No effects of positive history for hypertension and smoking have been observed when data were adjusted for these parameters. In fact, all the smokers consumed a maximum of four to six cigarettes per day and the mean blood pressures showed not differences between TT groups (Table 3). Furthermore, to obtain sport-eligibility all the hypertensive athletes were adequately treated in previous years, and did not use β-blockers or diuretics because these are prohibited by the World Anti-Doping Agency.

Serum Hormones

No differences in mean gonadotropins concentrations were observed between eugonadal and severe

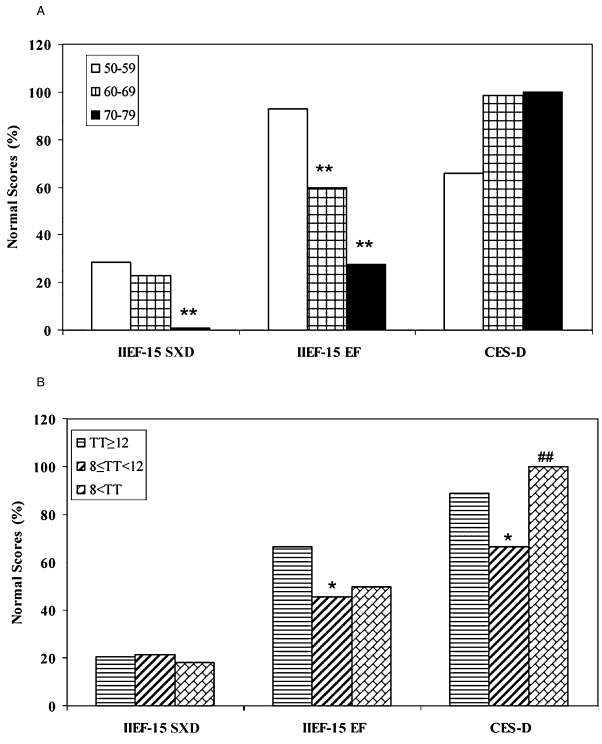

Figure 2 Percentage of subjects with normal absolute questionnaire scores between athletes over 50 years (N = 183) stratified by age group (A) and by serum total testosterone levels (TT, nmol/L) (B). IIEF = International Index of Erectile Dysfunction; SXD = sexual desire domain (arbitrary normal score >8); EF = erectile function domain (normal score >25); CES-D = Center for Epidemiological Studies Depression Scale (normal score <16). (A) **$P < 0.01$ vs. age 50–59; (B) *$P < 0.05$ vs. TT ≥ 12 nmol/L, ##$P < 0.01$ vs. 8 ≤ TT < 12 nmol/L. [Correction added after online publication 5-Feb-2010: The normal score and the arbitrary normal score have been transposed in the legend for Figure 2.]

Table 3 Study sample characteristics, performed training, nonspecific symptoms of testosterone deficiency, medical history, and serum hormones in athletes over 50 years stratified by serum total testosterone concentration

	Mean ± standard deviation or median (quartiles) or N (%)		
Variable	TT ≥ 12 nmol/L N = 128 (69.9)	8 ≤ TT < 12 nmol/L N = 33 (18.0)	TT < 8 nmol/L N = 22 (12.0)
Age (years)	61.0 ± 7.2	63.8 ± 8.0	64.1 ± 9.2
Age groups:			
50–59 years	58 (45.3)	11 (33.3)	4 (18.1)
60–69 years	51 (39.8)	12 (36.3)	7 (31.8)
70–79 years	19 (14.8)	10 (30.3)*	11 (50.0)
Weight (kg)	79 ± 8.6	78.5 ± 9.0	82.0 (6.0)
Height (cm)	171.3 ± 2.7	172.4 ± 3.9	170.8 ± 2.0
BMI (kg/m^2)	25.5 ± 2.1	26.8 ± 3.1	28.3 ± 2.7
Waist circumference (cm)	90.5 ± 7.4	89.6 ± 10.9	91.2 ± 8.1
Systolic blood pressure (mm Hg)	132.4 ± 10.4	136.6 ± 11.9	135.0 ± 8.9
Diastolic blood pressure (mm Hg)	79.2 ± 5.8	81.6 ± 7.0	79.1 ± 8.6
Resting heart rate (beast/min)	72.1 ± 7.0	75.3 ± 3.0	73.0 ± 6.7
IPAQ-training (hours/week)	6.8 ± 3.2	7.7 ± 4.5	8.1 ± 2.4
Alcohol consumption (1/2 drinks)	86 (67.1)	21 (63.6)	19 (86.3)
Smoking status, current	31 (24.2)	13 (39.3)	10 (45.4)*
Positive history for hypertension	29 (22.6)	7 (21.2)	11 (50.0)**#
Osteoporosis fractures	0 (0)	0 (0)	0 (0)
Nonspecific symptoms (two)	9 (7.0)	4 (12.2)	2 (9.0)
cFT (pmol/L)	301.2 ± 7.15	186.7 ± 37.6**	159.5 ± 18.4**
cBioT (nmol/dL)	7.0 ± 1.6	4.4 ± 1.0**	3.6 ± 0.5**
FSH (IU/L)	6.7 (4.2–10.2)	7.8 (4.7–18.7)	11.6 (5.2–22.0)
LH (IU/L)	4.9 (3.8–8.1)	9.3 (6.3–11.1)*	7.0 (4.5–10.6)
LH/TT	0.3 (0.2–0.4)	0.9 (0.6–1.2)**	1.12 (0.5–1.5)**
DHEAS (μmol/L)	3.0 ± 1.4	2.3 ± 1.2	2.5 ± 1.1
SHBG (nmol/L)	45.6 ± 14.0	39.1 ± 13.0	28.5 ± 7.3*#

*$P < 0.05$ vs. TT ≥ 12 nmol/L; **$P < 0.01$ vs. TT ≥ 12 nmol/L; #$P < 0.05$ vs. 8 ≤ TT < 12 nmol/L.
BMI = body mass index; cBioT = calculated bioavailable testosterone; cFT = calculated free testosterone; IIEF = International Index of Erectile Dysfunction; IPAQ = International Physical Activity Questionnaire; TT = total testosterone; FSH = follicle stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone binding globulin; DHEAS = dehydroepiandrosterone sulphate.

hypogonadal athletes (Table 3). In the hypogonadal athletes, overall (TT < 12 nmol/L) LH and FSH concentrations were elevated in 47.2% and in 40% of the cases, respectively, and normal in 52.7% and in 60% of the cases, respectively.

Absolute cFT was <225 pmol/L in 90.9% of athletes with mild testosterone deficiency (30/33) and in all athletes with severe testosterone deficiency.

No differences for mean FT_4, TSH, and PRL were observed between TT groups (*data not shown*).

Symptoms of Testosterone Deficiency

No differences in the prevalence of nonspecific nonsexual symptoms of testosterone deficiency (Table 3) and in mean absolute IIEF-15/SXD, IIEF-15/EF, and CES-D scoring were observed between groups stratified for TT (Figure 1B). Similar results have been observed when athletes were stratified based on cFT less than or greater than 225 pmol/L (*data not shown*); in fact, cFT was <225 pmol/L in the 94.5% of athletes with TT < 12 nmol/L.

At an individual level, the percentage of athletes with absolute IIEF-15/SXD score of >8 did not differ between TT groups. No difference in the percentage of athletes with normal absolute IIEF-15/EF score was observed between eugonadal athletes and athletes with severe testosterone deficiency (Figure 2B). Interestingly, no athletes with severe testosterone deficiency had absolute CES-D scores indicative of depression ($P = 0.002$ vs. mild testosterone deficiency) (Figure 2B).

The percentage of athletes with normal IIEF-15/EF score was higher in eugonadal athletes with respect to athletes with testosterone deficiency overall (i.e., TT < 12 nmol/L) (66.4% vs. 47%; $P = 0.015$), and no differences for IIEF-15/SXD and CES-D scores were observed (20.3% and 89% vs. 20% and 80%, respectively; $P = 0.961$ and $P = 0.101$, respectively).

The IIEF-15 and CES-D scores did not correlate with TT, even though the IIEF-15 scores correlated with the LH/TT ratio and the IIEF-15/EF score with cFT (Table 4).

Discussion

The main results of this exploratory study are the unexpectedly high prevalence of undiagnosed tes-

Table 4 Multivariate regression analysis (r) considering serum hormones and proteins, questionnaires scores, age, exercise training (hours/week), and BMI in athletes over 50 years

Department variable	Age	Training	BMI	TT	cFT	cBioT	LH/TT
TT	–0.177	–0.137	–0.262		0.817**	0.814**	–0.674**
cFT	–0.345*	–0.132	–0.207	0.817**		0.998**	–0.548**
cBioT	–0.341*	–0.125	–0.225	0.814**	0.998**		–0.545**
LH	0.451**	0.580	0.277	–0.269	–0.164	–0.159	0.829**
LH/TT	0.410**	0.071	0.313*	–0.674**	–0.548**	–0.545**	
SHBG	0.174	–0.087	–0.137	0.579**	–0.548**	0.013	–0.423**
DHEAS	–0.409**	0.200	–0.253	0.169	0.253	0.250	–0.236
IIEF-15 SXD score	–0.295*	0.031	–0.090	0.126	0.095	0.086	–0.309*
IIEF-15 EF score	–0.425**	0.180	–0.127	0.231	0.328*	0.308*	–0.381**
CES-D score	–0.243	–0.006	0.124	–0.192	0.042	0.044	0.004

*$P < 0.05$; **$P < 0.001$ (data are adjusted for hypertension and smoking).
BMI = body mass index; cBioT = calculated biovailable testosterone; CES-D = Center for Epidemiological Studies Depression Scale; cFT = calculated free testosterone; EF = erectile function; IIEF = International Index of Erectile Dysfunction; SXD = sexual desire; TT = total testosterone; LH = luteinizing hormone; SHBG = sex hormone binding globulin; DHEAS = dehydroepiandrosterone sulphate.

tosterone deficiency in aging athletes, and the lack of differences in the prevalence of symptoms of male hypogonadism between eugonadal and severe hypogonadal athletes.

Our data suggest that exercise training can influence some of the symptoms of male hypogonadism and may be a confounding factor in suspecting testosterone deficiency. Actually, owing to the lack of knowledge or adequate evidence-based criteria, it is only possible to make hypotheses or to speculate in analyzing our results.

The Nature of Testosterone Deficiency

Despite the lack of correlation between TT and age, based on the presence of symptoms, we diagnosed an LOH or an age-related biochemical testosterone deficiency in all the athletes with reduced testosterone concentration [25]. In fact, both an age-related increase in gonadotropins concentrations was observed (Table 2), and cFT, cBioT, and gonadotropins concentrations and the LH/TT ratio significantly correlated with age (Table 4).

We excluded the diagnosis of purely exercise-related testosterone deficiency since our overall athletes with low testosterone had normal/elevated LH and FSH concentrations. We indirectly excluded also the abuse of androgenic anabolic steroids [26] because all the athletes denied taking prohibited drugs, nobody showed inhibition of gonadotropins and significantly higher LH/TT ratios were observed in athletes with testosterone deficiency (Table 3).

The unexpected lack of correlation between TT and age and the observed homogeneity in mean TT between age groups (Table 2) could be related both to the sample characteristics and/or to possible combinations of the TT lowering effect of age and exercise-related HPG axis modifications. Even though no correlations between HPG hormones and training duration were observed (Table 4), we cannot exclude, owing to exercise intensity, that in some athletes physical training could also have contributed to influence serum testosterone, apart from age.

Depending on the characteristics of performed exercise and on individual characteristics and responsiveness, the stress hormones mediators (e.g., corticotrophin-releasing hormone, adrenocorticotrophic hormone, cortisol, catecholamines, growth hormone, PRL, β-endorphins, *and so forth*) [27,28] may differently influence the HPG axis. Long-term exercise-stress may reduce serum testosterone [4], as a result of increased peripheral catabolism and/or HPG axis inhibition [2,3]. Moreover, exercise training could increase serum testosterone in older men [29] or modify androgen receptors expression [30]. Interestingly, the testosterone response to training in aging is also linked to an age-related variation in the HPG axis response to physical stress [31].

Based on our evaluated parameters, it was difficult to identify at an individual level the exact role of physical training in influencing the HPG axis. Considering that no differences in mean gonadotropins concentrations were observed between eugonadal and severe hypogonadal athletes, one possible hypothesis is that in advanced ages exercise training, even if not sufficient per se to induce a true hypogonadism, in some subjects might partially inhibit the hypothalamus–pituitary feedback response to the age-related decreased testosterone production.

The Symptoms of Testosterone Deficiency

This study showed that in aging athletes the prevalence of the clinical symptoms associated to test-

osterone deficiency increased with age but was not substantially influenced by serum testosterone levels.

No differences in the evaluated IIEF-15 domains were observed between eugonadal and severe hypogonadal athletes. Even if depression was found in 24% of nonathletes with hypogonadism [32,33], we found the lowest prevalence of abnormal CES-D scores in athletes with severe hypogonadism. Moreover, although the prevalence of nonspecific symptoms in nonathletes with LOH ranges between 17% and 42% [5], we observed a lower prevalence of these symptoms in severe and mild hypogonadal athletes (9% and 12.2%, respectively), and no differences were observed with respect to eugonadal athletes (Table 3).

Even though BMI is of reduced significance in athletes, no differences in mean BMI and in mean waist circumference were observed between eugonadal and hypogonadal athletes (Table 3). Furthermore, despite a possible increased risk [34], none of the hypogonadal athletes showed cardiovascular diseases contraindicating sport-participation.

Various mechanisms could be hypothesized to explain the possible relationships between sport-participation and the symptoms of male hypogonadism. The neuroendocrine and tissues modifications induced by exercise training and/or the type of sport (e.g., mechanical factors in cyclists) could cause per se hypogonadism-like symptoms (e.g., altered sexual desire, erectile dysfunction, decreased hematocrit, *and so on*) and/or might attenuate or mask the biological consequences of testosterone deficiency.

An inhibited sexual behavior (e.g., decreased libido, loss of erection) in eugonadal athletes could be also considered as a physiological mechanism of adaptation to exercise-related stress and might represent one of the biological effects of stress hormones [35,36].

Conversely, exercise training per se increases lean mass and reduces fat mass, improves strength and the sense of well-being, improves mood and cognitive processes, increases insulin sensitivity, increases the number of erythrocytes, increases bone mineral density, may favor sexual behavior, and protects the cardiovascular system. At least in theory, all of these biological effects of exercise result in potential for the improvement of common symptoms and signs of testosterone deficiency.

On these bases, we believe that an accurate history for specific symptoms of hypogonadism might be useful in raising suspicions of testosterone deficiency in athletes, but clinical symptoms alone may produce many false negatives (i.e., in the case of biochemical testosterone deficiency) or positives (i.e., in the case of eugonadal athletes with pure exercise-related sexual dysfunctions or symptoms).

As further confounding factor, we highlight that in athletes also many prohibited drugs can mask the symptoms of a true hypogonadism or cause hypogonadism-like symptoms.

The Risks for Athletes with Testosterone Deficiency

Because testosterone influences body composition and physiology [17,37–41] differently from sedentary hypogonadal individuals, untreated hypogonadal athletes are theoretically exposed to further specific risks for health and performance.

For example, hypogonadal athletes can be at increased risk of fractures in case of falling or trauma (e.g., cyclists, combat sports), of cardiovascular accidents related to high exercise-strain, and of worsened sport-related anemia. In addition, because of the possible role of androgens in modulating the hypothalamus–pituitary–adrenal response to stress and in counterbalancing the biological effects of cortisol, hypogonadal athletes might be at increased risk of stress-related diseases.

Testosterone deficiency also influences the endocrine and metabolic adaptations to exercise, reduces muscles strength, aggressiveness in competition and proteins resynthesis during recovery, and increase the risk of overtraining, thus altering the biologically normal physical capacities and performances in athletes.

Unfortunately, there are no data from cross-sectional or longitudinal studies addressing the consequences of testosterone deficiency on athletes' health and performance, and the impact of untreated hypogonadism on morbidity in athletes remains unknown.

Although different treatments have been proposed to improve symptoms of male hypogonadism [42,43], in our opinion, even though evidence-based criteria do not exist and while waiting for definitive criteria, in order to guarantee a physiological adaptation during sport-participation and to reduce all possible risks, competitive athletes with testosterone deficiency should undergo testosterone replacement therapy. Testosterone should be administered independently of the presence of symptoms of hypogonadism, if there are no con-

traindications [42,44] and after receiving a therapeutic use exemption by the respective antidoping organization.

On these bases, for ethical and legal considerations, it could be extremely useful to check serum testosterone concentration in athletes over 50 years during the periodical pre-participation screening independently of the presence of symptoms of hypogonadism, or whenever there is a suspicion of testosterone deficiency.

Limitations of the Study

The lack of specific questionnaires (e.g., Aging Male Symptoms Score) for evaluating nonspecific nonsexual symptoms of male hypogonadism and the arbitrary identification of a threshold value for IIEF-15/SXD score might be considered as possible limitations of the study. Furthermore, being this study a first exploratory survey, we did not evaluate body composition, bone mineral density, muscles strength, hematocrit, LH pulsatility, and LH biological activity.

Conclusions

Independently of the relative roles of aging and exercise training, a good number of aging athletes in this preliminary study were affected by undiagnosed testosterone deficiency. As in the general population [5], not all athletes with low testosterone were overtly symptomatic, and sport-participation resulted to influence some of the symptoms of male hypogonadism. Consequently, the clinical symptoms could be misleading in suspecting testosterone deficiency in athletes, and their possible paucity or absence could delay or make difficult the diagnosis of male hypogonadism.

Considering the potential spin-off, if serum testosterone is evaluated in the millions of adults that worldwide practice sports, further studies are needed to investigate on the prevalence and on the risks of testosterone deficiency in aging athletes. If a marked prevalence of testosterone deficiency is further confirmed, then it would be necessary to standardize the criteria [45] for suspecting testosterone deficiency and for addressing serum testosterone evaluations in athletes (serum TT alone or with cFT), together with sport eligibility and treatment criteria. Particularly, it should also be established if the current testosterone threshold values for diagnosing testosterone deficiency in the general population ought to be identical in male athletes.

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