

Effects of long-term testosterone substitutive therapy on bone mineral content in men with hypergonadotrophic hypogonadism

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Summary. Hypogonadism is one of the crucial risk factors for male osteopenia and osteoporosis. There are few studies on the effects of long-term and consistently administered testosterone substitutive therapy on bone mineral density in men with gonadal androgen deficiency, and their results have been susceptible to various interpretations. The aim of our study was an evaluation of bone mineral content in 26 men, aged 18–57 years, with hypergonadotrophic hypogonadism who underwent long-lasting androgen replacement therapy with testosterone esters (Omnadren 250), which conditioned proper psychosomatic androgenization. The control group comprised 405 healthy men, aged 20–60 years, a representative sample of the local male population. Among all examined men and in the control group, trabecular, cortical and total bone mineral content at the distal radius of the non-dominant hand were assessed by peripheral quantitative computed tomography using the Stratec 960 apparatus. In 11 hypogonadal men (42.3%), the trabecular bone mineral content was found to be within normal ranges; in 15 patients (57.7%) its values were below -1 standard deviation (SD) (osteopenia). In six patients (23.1%), the cortical bone mineral content was between $+1$ SD and the arithmetic mean, \bar{X} ; in 13 examined men (50%), the cortical bone mineral content was below \bar{X} and above

-1 SD. Osteopenia was diagnosed in six hypogonadal males, whereas osteoporosis was found in one man (cortical bone mineral content below -2.5 SD). Only in seven of the examined men (26.9%) was the total bone mineral content found within normal ranges, whereas in 19 men (73.1%) the total bone mineral content was below -1 SD (osteopenia). Despite the testosterone replacement in hypogonadal men, the greatest reduction of bone mineral content was found in its trabecular and total values. Among all the men examined, the trabecular and total bone mineral contents were below the mean of our own reference values. The results show that long-term and consecutively administered testosterone replacement in conventional doses, despite the normalization of serum androgen levels and the promotion of proper somatic development, does not simultaneously eliminate hypogonadal osteopenia in every case. The individually differentiated response to exogenous androgens is a characteristic feature of male hypogonadism. This study emphasizes the necessity of regular measurements of bone mineral density in hypogonadal men, as the densitometric parameters should be accepted as an osteologic (and very important) marker of androgenization of the male organism.

Introduction

It is well established that in young men the skeletal maturation and the acquisition of optimal peak bone mass is conditioned by the increase of androgen levels during male puberty (Finkelstein *et al.*, 1992; Orwoll & Klein,

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1995; Vanderschueren & Bouillon, 1995; Eastell *et al.*, 1998; Katznelson, 1998; Winters, 1999). The subsequent persistence of normal testosterone secretion during male adulthood is required for the maintenance of proper bone mineral density (BMD) during the entire lifetime, even until old age (Finkelstein *et al.*, 1992; Orwoll & Klein, 1995; Vanderschueren & Bouillon, 1995; Eastell *et al.*, 1998; Katznelson, 1998; Winters, 1999).

Prominent symptoms of male hypogonadism can be osteopenia and even osteoporosis (Finkelstein *et al.*, 1987; Orwoll & Klein, 1995; Holmes & Shalet, 1996; Behre *et al.*, 1997; Eastell *et al.*, 1998; Katznelson, 1998), hence both the development of osteopenia in hypogonadal men and the preservation of bone mass by restoration of proper testosterone levels confirm the importance of androgens for male bone metabolism (Holmes & Shalet, 1996). Sometimes values of male BMD below normal ranges, found accidentally, can suggest the existence of androgen deficiency, and such a densitometric measurement can finally lead to the diagnosis of male hypogonadism which itself, in fact, has resulted in the above-mentioned osteopenia or osteoporosis.

To date, the issue of suitable therapy for osteoporosis (or osteopenia) in hypogonadal males has not been comprehensively and clearly resolved (Orwoll & Klein, 1995; Vanderschueren & Bouillon, 1995; Eastell *et al.*, 1998; Francis, 1999; Winters, 1999). There is, in particular, a lack of precise information on the optimal kind of testosterone preparation, individual doses, the total duration of therapy, and the proper monitoring of bone metabolism during testosterone

replacement. It has not been established whether, in hypogonadal males with reduced BMD, androgen supplementation is sufficient for the maintenance of optimal bone density, or whether testosterone replacement should be accompanied by other medicaments to improve male bone metabolism.

Some studies have demonstrated a significant improvement of densitometric parameters after the administration of testosterone derivatives in men with gonadal insufficiency (Behre *et al.*, 1997; De Sanctis *et al.*, 1998; Leifke *et al.*, 1998). In contrast, other authors have emphasized the slight increase in BMD of hypogonadal males during long-term gonadal androgen supplementation (Finkelstein *et al.*, 1989; Devogelaer *et al.*, 1992).

The aim of our study was an evaluation of bone mineral content (BMC) in men with androgen deficiency resulting from hypergonadotrophic hypogonadism who underwent long-lasting androgen replacement therapy with testosterone esters.

Materials and methods

The study group comprised 26 men with primary gonadal insufficiency (hypergonadotrophic hypogonadism), aged 18–57 years, inhabitants of the region, who over periods of 3–20 years were treated with Omnadren 250 (Przedsiębiorstwo Farmaceutyczne, Wincentego, Poland) (active substances: testosterone propionicum 30 mg, testosterone phenylpropionicum 60 mg, testosterone isocaproicicum 60 mg, and testosterone caproicicum 100 mg), one ampoule administered intramuscularly every 3–4 weeks, without simultaneously receiving any other medicaments used in the therapy of osteoporosis (for example, calcium or vitamin D). During the hormonal substitutive treatment, all of the men stu-

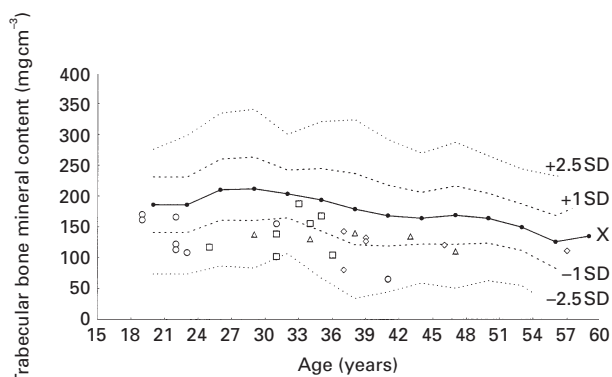


Figure 1. Trabecular BMC at the distal radius of 26 hypogonadal males compared with the normal ranges of healthy men, inhabitants of Wrocław. Legend: open circles – hypogonadal men treated with testosterone over a period of 3–4 years; open squares – hypogonadal men treated with testosterone over a period of 5–7 years; open triangles – hypogonadal men treated with testosterone over a period of 8–11 years; open diamonds – hypogonadal men treated with testosterone over a period of 12 years or longer.

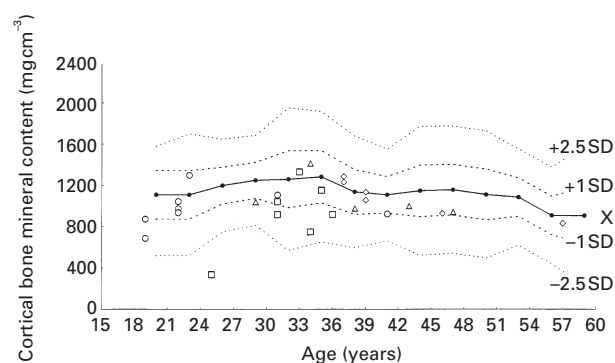


Figure 2. Cortical BMC at the distal radius of 26 hypogonadal males compared with the normal ranges of healthy men, inhabitants of Wrocław. Legend as in Fig. 1.

Table 1. Trabecular, cortical and total BMC at the distal radius of hypogonadal men

No.	The patient's initials	Age during examination (years)	Period of testosterone substit. (years)	Trabecular BMC			Cortical BMC			Total BMC		
				mg cm ⁻³	% peak mass	% age-matched	mg cm ⁻³	% peak mass	% age-matched	mg cm ⁻³	% peak mass	% age-matched
1	BK	25	5	116.9	55.2	55.6	333.8	26.0	27.9	236.3	57.5	60.0
2	BH	38	8	140.1	66.2	75.4	979.6	76.3	88.4	290.5	70.6	80.5
3	FP	29	9	137.9	65.1	65.1	1042.7	81.2	83.5	304.1	74.0	74.0
4	GW	34	11	130.2	61.5	67.2	1417.5	110.4	110.4	387.9	94.3	94.3
5	GA	39	14	132.2	62.4	74.0	1056.6	82.3	93.0	304.9	74.1	78.1
6	HZ	39	20	126.1	59.6	70.6	1134.8	88.4	99.9	320.3	77.9	82.0
7	HJ	57	20	110.8	52.3	88.4	831.5	64.8	91.7	242.9	59.1	87.0
8	HW	31	6	138.1	65.2	67.9	917.1	71.4	72.8	275.1	66.9	67.7
9	JG	19	3	169.8	80.2	91.4	872.0	67.9	78.7	278.9	67.8	77.3
10	JJ	37	17	142.2	67.2	79.6	1285.8	100.2	113.2	362.7	88.2	92.9
11	JK	43	10	134.6	63.4	82.2	1001.2	78.0	87.3	293.0	71.3	80.8
12	KM	46	16	120.0	56.7	71.2	928.7	72.4	80.1	269.6	65.6	73.2
13	LB	22	4	121.9	57.6	65.6	973.2	75.8	87.8	280.9	68.3	77.8
14	MT	22	3	112.8	53.3	60.7	935.3	72.9	84.4	268.2	65.2	74.3
15	PM	35	7	167.6	79.2	86.5	1153.1	89.8	89.8	343.3	83.5	83.5
16	PP	34	5	155.1	73.3	80.1	749.5	58.4	58.4	243.8	59.3	59.3
17	PZ	41	3	65.0	30.7	38.7	922.0	71.8	83.2	243.3	59.2	66.2
18	PJ	31	6	101.6	48.0	50.0	1042.4	81.2	82.7	287.8	70.0	70.8
19	RJ	36	5	104.0	49.1	53.7	918.0	71.5	71.5	259.9	63.2	63.2
20	RA	37	14	79.9	37.7	44.7	1232.5	96.0	108.5	322.2	78.4	82.5
21	SM	19	3	161.2	76.1	86.7	685.8	53.4	61.9	231.7	56.3	64.2
22	SP	31	3	155.0	73.2	76.2	1107.1	86.2	87.9	326.9	79.5	80.4
23	SD	33	7	187.3	88.5	92.1	1331.8	103.8	105.7	393.6	95.7	96.8
24	WC	47	10	110.0	52.0	65.2	944.3	73.6	81.6	268.8	65.4	73.0
25	WM	22	3	165.8	78.3	89.3	1044.3	81.4	94.2	317.0	77.1	87.8
26	WR	23	4	108.1	51.1	58.2	1298.6	101.2	117.2	350.5	85.2	97.0

died remained under the medical attention of the same physician. The patients were comprehensively informed about the nature of their disease, the necessity of long-term androgen replacement and the detrimental effects of giving up the testosterone substitutive therapy. Periodically, every 6–8 months, the patients underwent medical examination. Their psychosomatic appearance, the degree of androgenization, LH, FSH and testosterone levels (assessed approximately 10 days after the Omnadren 250 injection) were evaluated. Such a procedure allowed the firm conclusion that the therapy performed was completely sufficient in the context of psychosomatic androgenization of hypogonadal patients. Information concerning compliance with the therapeutic regimen was obtained from all of the men; these data enabled us to state that only in isolated cases, once or twice per year, was a testosterone injection not administered to a particular hypogonadal man for reasons beyond his control.

The control group comprised 405 healthy men, aged 20–60 years, occupationally active inhabitants of our region, who were a representative sample of the local male population. As it was concluded that there were significant

inter-population differences in BMD, and also discrepancies between the reference BMC values provided by the manufacturer of the densitometer and the densitometric data obtained from healthy male inhabitants of the local population (Rogucka *et al.*, manuscript in preparation), for the purpose of this study it was decided to compare the densitometric parameters of hypogonadal patients with the BMC values of their own control group.

In all patients studied and in the control group, trabecular, cortical and total BMC at the distal radius of the nondominant hand were assessed by peripheral quantitative computed tomography (pQCT) using the Stratec 960 apparatus (Stratec Medizintechnik GmbH, Germany). The pQCT method measures bone density with a high degree of precision. The short-term and long-term reproducibilities of this device are 0.5% and 0.73%, respectively (Talajko, 1998).

It is worthy of note that the cortical BMC at the distal radius is a good predictor of the vertebral fracture status and a reliable indicator of general age-related skeletal deterioration (Grampp *et al.*, 1995). In addition, the correlations between pQCT and dual-energy X-ray absorptiometry measurements (Lunar DPX,

Madison, WI) of the lumbar spine were $r \approx 0.8$ (Hasegawa *et al.*, 1997). A comprehensive study of the comparison between different sites and techniques revealed that the correlations ranged from $r=0.10$ to 0.93 (Grampp *et al.*, 1997).

Because of the inter-population variation of densitometric parameters (resulting, among other causes, from nutritional factors, physical activity, environmental pollution, and alcohol and nicotine abuse), the BMC values (mg cm^{-3}) obtained for hypogonadal men were compared with our own reference ranges (the control group) and expressed as: (1) the percentage of the BMC of age-matched controls; and (2) the percentage of the peak values of particular BMCs. Additionally, in order to evaluate the BMC of hypogonadal males in comparison with the healthy local male population, the mean values, ± 1 and ± 2.5 SD (below -2.5 SD, osteoporosis is diagnosed) of trabecular, cortical and total BMC were calculated in particular age categories of the local population of healthy male inhabitants of the city of Wroclaw.

Results

Table 1 presents the values of trabecular, cortical and total BMC at the distal radius of hypogonadal men expressed as: (1) mg cm^{-3} ; (2) the percentage of the BMC of age-matched controls; and (3) the percentage of BMC peak values (compared with our own reference ranges).

In the group of hypogonadal men, the range of variation of the trabecular BMC was $65.0\text{--}187.3 \text{ mg cm}^{-3}$ (38.7–92.1% of the trabecular BMC of age-matched Polish male controls), the range of variation of the cortical BMC was $333.8\text{--}1417.5 \text{ mg cm}^{-3}$ (27.9–117.2% of the cortical BMC of age-matched Polish male controls), and the range of variation of the total BMC was $231.7\text{--}393.6 \text{ mg cm}^{-3}$ (59.3–97.0%

of the total BMC of age-matched Polish male controls).

The mean values of the trabecular, cortical and total BMC in all patients examined with androgen deficiency were, respectively, 130.5 mg cm^{-3} (68.8% as compared with our own control group), $1005.4 \text{ mg cm}^{-3}$ (87.5% as compared with our own control group) and 296.3 mg cm^{-3} (78.4% as compared with our own control group).

Figures 1, 2 and 3 present, respectively, the trabecular, cortical and total BMC of hypogonadal men compared with the densitometric reference ranges [arithmetic mean (\bar{X}), ± 1 SD, ± 2.5 SD] established for the local male population.

In 11 hypogonadal men studied (42.3%), the trabecular BMC was found to be within normal ranges (above -1 SD); in 15 patients (57.7%), values of the trabecular BMC were below -1 SD (osteopenia); osteoporosis was not diagnosed in any patient (trabecular BMC below -2.5 SD).

Values of the cortical BMC of hypogonadal males as compared with reference ranges for the healthy male population of the city of Wroclaw were as follows: in six subjects (23.1%) this densitometric parameter was between $+1$ SD and \bar{X} (relatively high, but within the normal range); in 13 men (50%), the cortical BMC was below \bar{X} and above -1 SD (slightly lower than average, but normal). Osteopenia was diagnosed in six hypogonadal males (cortical BMC below -1 SD), whereas osteoporosis was found in one man (cortical BMC below -2.5 SD).

Only in seven of the patients studied (26.9%) was the total BMC found to be within normal ranges (above -1 SD), whereas, in 19 males (73.1%), values of the total BMC were below -1 SD (osteopenia). Osteoporosis was not diagnosed in any hypogonadal patient (total BMC below -2.5 SD).

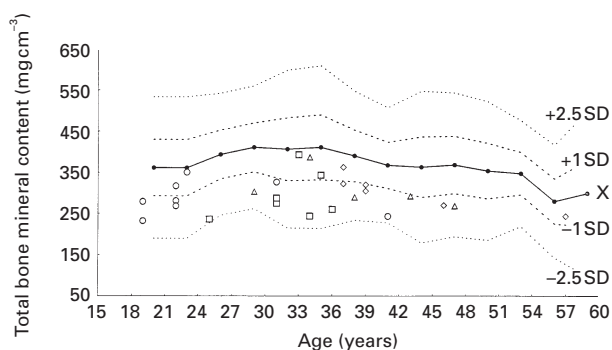


Figure 3. Total BMC at the distal radius of 26 hypogonadal males compared with the normal ranges of healthy men, inhabitants of Wroclaw. Legend as in Fig. 1.

Discussion

Reduced BMC is observed in men with various types of hypogonadism (Orwoll & Klein, 1995; Eastell *et al.*, 1998), hypo- and hypergonadotrophic hypogonadism, hyperprolactinaemic hypogonadism (Greenspan *et al.*, 1989), androgen deficiency after orchidectomy or in Klinefelter's syndrome (Foresta *et al.*, 1983)]. According to Finkelstein *et al.* (1992), the timing of puberty is an important determinant of peak bone mass in men, and hence also adult men with a history of delayed puberty have decreased radial and spinal BMD and are at increased risk of

osteoporotic fractures in later life. Abnormal bone development plays an important role in osteopenia of adult men with idiopathic hypogonadotrophic hypogonadism (Finkelstein *et al.*, 1987).

Male hypogonadism is considered to be one of the most demonstrable risk factors for the development of osteopenia and osteoporosis (Ringe & Dorst, 1994); hence in that particular case of secondary male osteoporosis, aetiological therapy should be started (Ringe & Dorst, 1998). Unfortunately, only a few studies concerning the treatment of male osteoporosis and osteopenia have been published so far (Ringe & Dorst, 1998). In particular, there is a shortage of publications about the effects of long-term and consistently administered testosterone substitutive therapy on BMD in men with gonadal androgen deficiency.

Few authors have emphasized that long-lasting androgen replacement (resulting in normotestosteronemia) significantly improves the densitometric parameters of hypogonadal men (Behre *et al.*, 1997; De Sanctis *et al.*, 1998).

Behre *et al.* (1997) evaluated the effects of testosterone replacement therapy on BMD in 72 hypogonadal patients continued for up to 16 years. Among all of the men examined, the androgen supplementation resulted in both normotestosteronemia and improvement of densitometric parameters. The greatest increase of BMD was seen during the first year of therapy, and the long-lasting testosterone substitutive treatment maintained bone density within the normal reference ranges (Behre *et al.*, 1997).

De Sanctis *et al.* (1998) reported effective therapy with a nonscrotal testosterone transdermal system for hypogonadotrophic hypogonadal adolescents and young men with beta-thalassemia major. That treatment resulted in promoted growth, virilization, appropriate testosterone and sex hormone binding globulin (SHBG) levels and increased BMD. Also Leifke *et al.* (1998) found, in 32 men aged 18–74 years with various types of hypogonadism, who were treated with testosterone preparations for 3.2 ± 1.7 years, a significant increase of the trabecular and cortical BMD of the spine, independently of age and type of hypogonadism.

Apart from authors reporting positive relationships between androgen substitutive therapy and BMD values in hypogonadal men, there are also some studies that do not confirm the correlation between testosterone levels and BMD in such patients (Devogelaer *et al.*, 1992). In some studies, testosterone replacement resulted in only a slightly increased BMD in hypogonadal men (Finkelstein *et al.*, 1989; Devogelaer *et al.*, 1992).

Finkelstein *et al.* (1989) evaluated BMC changes in 21 men with idiopathic hypogonadotrophic hypogonadism who were treated with testosterone preparations while serum testosterone levels were maintained within male adult normal ranges. The cortical BMD at the distal radius increased in men who had open and fused epiphyses, whereas the trabecular BMD of the lumbar spine increased only in the patients with open epiphyses. Despite those positive changes, neither the cortical nor the trabecular BMD returned to normal values (Finkelstein *et al.*, 1989).

According to Devogelaer *et al.* (1992), in 16 hypogonadal males the BMD at the beginning of the study (assessed by single photon absorptiometry at the nondominant radius) was lower in the examined patients as compared with the controls, to a similar extent at both the distal and midshaft radius. At the same time, there was no correlation between testosterone levels and BMD at both the distal and midshaft radius. Testosterone substitutive therapy was followed by a slight increase of BMD at the distal radius (only 1.4% per year) and at the midshaft radius (only 1.1% per year) (Devogelaer *et al.*, 1992). When the hypogonadal men who had achieved full bone age maturity were taken into consideration, the increase in BMD persisted at significant levels only at the distal radius (Devogelaer *et al.*, 1992). The study by Devogelaer *et al.* (1992), similarly to that by Finkelstein *et al.* (1989), indicates that the BMD of hypogonadal males increases in particular in those men who during testosterone supplementation are skeletally immature (i.e. their bones have open epiphyses).

In our study the greatest reduction of bone density was found within the trabecular and total BMC of hypogonadal men, despite the testosterone replacement. Among all the patients examined, the values of the trabecular and total BMC were below the mean values of the respective densitometric parameters assessed in particular age categories of healthy men, inhabitants of the city of Wrocław. Taking the trabecular BMC into consideration, osteopenia was diagnosed in 15 patients. When values of the total BMC were evaluated, osteopenia was found in 19 patients. The results concerning the cortical BMC of hypogonadal males are comparatively good.

Among others, the study by Leifke *et al.* (1998) suggests that the trabecular part of the bone structure responds much better to androgen substitution than other parts. This fact is in agreement with the generally accepted view that the trabecular bone compartment is more metabolically active and more susceptible to various

influences of factors modifying the bone structure during the entire lifetime (and also hormonal alterations).

Our results show that long-term and consecutively administered testosterone substitutive therapy, despite the normalization of serum androgen levels and the promotion of proper somatic development, does not simultaneously eliminate hypogonadal osteopenia in every case (the reduction of BMD is most markedly seen within its trabecular part).

Our results have particular relevance for a clinically crucial problem of the risk of osteopenia (or even osteoporosis) in hypogonadal males, although long-term androgen supplementation has been performed. Testosterone replacement in conventional doses (which result in normalization of hormonal parameters and are required for proper somatic development) is not always associated with the simultaneous significant improvement of BMD. The individually differentiated response to exogenous androgens is a characteristic feature of male hypogonadism. In the present study, perhaps androgen supplementation should have been administered in higher doses at the beginning of the therapy.

Administration of one ampoule of Omnadren 250 (containing 250 mg of testosterone esters) results in the maintenance of testosterone levels of 3–7 ng ml⁻¹ (assessed approximately 10 days after the injection), thus within the lower values of normal adult ranges. The application of increased doses of androgen preparations is not always possible (in particular, among elderly men); in such cases other medicaments for the therapy of osteoporosis should be additionally used.

This study emphasizes the necessity of regular measurements of BMD in hypogonadal men, as the densitometric parameters should be accepted as an osteologic (and very important) marker of androgenization of the male organism.

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