Quantitative Bone SPECT in Young Males with Delayed Puberty and Hypogonadism: Implications for Treatment of Low Bone Mineral Density

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Constitutional delayed puberty (DP) and idiopathic hypogonadotropic hypogonadism (IHH) lead to osteoporosis in adult men. We were interested in whether response to treatment of these conditions by testosterone could be predicted by in vivo quantitative bone SPECT (QBS) measurement of bone turnover and whether testosterone administration affects bone mineral density (BMD) in these subjects. **Methods:** In vivo QBS and BMD measurements were performed in the lumbar spine (LS) and femoral neck (FN) of 29 young men with DP and 16 young men with IHH. In vivo QBS and BMD values in these patients were compared to the values obtained from 27 age-matched normal controls. The effect of testosterone treatment was determined by measuring changes in QBS and BMD, before and after treatment of 22 patients with DP and of all 16 patients with IHH. Seven patients with DP were not treated. **Results:** In vivo QBS values in patients with DP were significantly higher than those in controls (8.44% ± 2.55%ID/ml compared to 5.63% ± 1.12%ID/ml × 10^{-3}, $p < 0.001$, for the LS; and 7.86% ± 3.01%ID/ml compared to 4.29% ± 1.25%ID/ml, $p < 0.001$, for the FN). One year after testosterone treatment, QBS values in DP were significantly reduced. Pretreatment BMD values in patients with DP were significantly lower than those in normal subjects (0.77 ± 0.11 g/cm^2 compared to 1.03 ± 0.14 g/cm^2, $p < 0.0001$, for the LS; and 0.89 ± 0.11 g/cm^2 compared to 1.08 ± 0.18 g/cm^2, $p < 0.006$, for the FN). One year after treatment, BMD values increased significantly (0.91 ± 0.14 g/cm^2, $p < 0.0001$, for the LS; and 0.97 ± 0.11 g/cm^2, $p < 0.0001$, for the FN). The seven untreated young men with DP still had significantly lower-than-normal BMD values (0.82 ± 0.08 g/cm^2, $p < 0.008$, for the LS; and 0.89 ± 0.05 g/cm^2, $p < 0.04$, for the FN). In patients with IHH, QBS values were not significantly different from those found in normal controls. The values for BMD were significantly lower for both the LS ($p < 0.0001$) and the FN ($p < 0.001$). After treatment, BMD values in patients with IHH were still significantly lower than those of normals ($p < 0.009$ for the LS; and $p < 0.006$ for the FN). **Conclusion:** Young men with maturation abnormalities show low bone density. Patients with DP and high bone turnover, as revealed by high QBS values, respond to testosterone treatment. Patients with IHH have normal bone turnover and do not respond to testosterone.

Key Words: quantitative SPECT; delayed puberty; hypogonadism; bone turnover

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Osteoporosis is a significant health care problem. Because treatment of adults with osteoporosis is often unsuccessful, the prevention of osteoporosis is of great importance (*1*). Reaching a normal peak bone mass is an important factor in prevention of this disease, in both men and women (*2*). Constitutional delayed puberty (DP) and idiopathic hypogonadotropic hypogonadism (IHH) result from gonadotropin-releasing hormone deficiency and, although the diseases are of different etiologies, represent a temporary or permanent lack of gonadal steroids. Patients with IHH have lower-than-normal peak bone mass and an increased rate of fractures (*3*). Recently, it has been found that adult men with a history of DP also have a significantly lower bone density than do matched controls (*4*). Treatment with testosterone increases but does not restore normal peak bone mass in IHH (*5*). The effect of testosterone treatment on the bone in DP has not been investigated.

We were interested in whether, at the time of diagnosis, young men with DP have a lower bone mineral density (BMD) than do normal controls, and we also were interested in whether their bone turnover is different from that of normals. We also were interested in whether testosterone treatment affects BMD in patients with DP and whether measurement of bone turnover (*6,7*) using quantitative bone SPECT (QBS) can predict treatment response. This seemed reasonable because high bone uptake, as measured by SPECT, of ^{99m}Tc-labeled methylene diphosphonate (MDP), which returns to normal after successful treatment, has been found in patients with thyrotoxicosis and primary hyperparathyroidism (*8*), diseases known to have high bone turnover and decreased BMD. High bone turnover and low BMD also have been found in patients with chronic renal disease (*9*). We compared the results of QBS in patients with DP to those in patients with IHH, in whom testosterone is known to not significantly affect BMD.

MATERIALS AND METHODS

Twenty nine-patients with DP, aged 14–19 yr (mean = 15.2 yr), and 16 patients with IHH, aged 16–23 yr (mean = 18.2 yr), were investigated.

None of the patients had a history of renal, liver or endocrine disease or chronic illness. The patients had no history of previous use of hormonal therapy or any medication known to affect endocrine function or bone metabolism. None of the patients was an alcohol or drug abuser or heavy smoker. Physical examination of the patients at the time that they were entered into the study included measurement of height and weight and assessment of pubertal development (*10*). No somatic abnormalities were found. All patients had an initial evaluation of basal serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), dihydroepiandrosterone sulfate, testosterone, prolactin, free thyroxime index (FT_4) and thyrotropin. Serum values of calcium, phosphorus, alkaline phosphatase and parathyroid hormone (PTH) were measured. The LH response to LH-releasing hormone (LHRH) (100 μg, intravenously), the prolactin response to thyroid-releasing hormone (200 μg, intravenously) and the cortical response to adrenocorticotropic hormone (250 μg, intravenously) were evaluated (*11*). The concentrations of serum LH, FSH, prolactin, testosterone, dihydroepiandrosterone sulfate, FT_4, thyrotropin,

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TABLE 1
Morphological and Clinical Data in 29 Patients with Delayed Puberty and 16 Patients with Idiopathic Hypogonadotropic Hypogonadism at Presentation

Data	Delayed puberty	Idiopathic hypogonadotropic hypogonadism
No. of patients	29	16
Age (yr)	15.2 ± 0.3	18.2 ± 2.4
Height (cm)	152.6 ± 10.1	163.1 ± 1.9
Weight (kg)	44.3 ± 12.8	58.4 ± 13.4
Serum levels (normal values)		
Testosterone (3–8 ng/ml)	0.7 ± 0.6	0.4 ± 0.3
FSH (5–15 milliunits/ml)	1.7 ± 2.0	1.4 ± 1.4
LH (5–15 milliunits/ml)	1.2 ± 1.0	0.5 ± 0.5
Prolactin (5–20 ng/ml)	8.0 ± 2.8	7.5 ± 1.73
Peak LH response to LHRH (>10 milliunits/ml)	14.4 ± 6.2	5.1 ± 4.1
Peak prolactin response to thyroid-releasing hormone (>20 mg/ml)	32.5 ± 8.0	27.6 ± 9.7
Peak cortisol response to adrenocorticotropic hormone (>18 μg/dl)	26.3 ± 3.6	26.5 ± 3.8
Calcium (8.2–10.5 mg/dl)	9.2 ± 0.4	9.3 ± 0.2
Phosphorus (2–4 mg/dl)	4.8 ± 0.5	4.1 ± 0.4
Alkaline phosphatase (70–210 units)	253.4 ± 69.5	212.4 ± 67.8
PTH (10–55 pg/ml)	32.1 ± 3.9	32.9 ± 3.2

growth hormone, PTH and cortisol were determined by commercial radioimmunoassays. Patients who had blunted or absent LH response to LHRH stimulation were diagnosed as having IHH. The other patients were considered to have DP. All patients had normal thyroid function and intact adrenal and growth hormone reserves. Their serum calcium, phosphorus and PTH levels were normal. Testosterone serum values were decreased in both groups, and there was no statistically significant difference (Mann–Whitney U test) between the values. CT of the sella turcica was performed and was normal in all patients. Clinical and biochemical data of the patients with DP and IHH at presentation are given in Table 1.

Eleven normal men with a mean age of 15.7 yr (range = 13–18 yr), matched for age with the DP group, served as controls. Sixteen men, with a mean age of 19.7 yr (range = 15–21 yr), served as controls for studies on the IHH patients. Bone scintigraphy and radiographs of the bone were normal. None of the controls had a history of endocrine dysfunction or other health problem or of the use of medication known to affect endocrinological function or bone metabolism. None was an alcohol or drug abuser or heavy smoker.

The patients had initial evaluations by quantitative SPECT scintigraphy and BMD measurement of their lumbar spine (LS) and femoral neck (FN). Planar bone scintigraphy of the whole body also was performed. Twenty-two patients with DP then were treated with testosterone. They received a monthly intramuscular injection of 250 mg Testovirone-Depot (Schering AG, Berlin, Germany). Treatment was discontinued after 6 mo. Seven patients with DP did not receive any testosterone. All patients with IHH received continuous testosterone treatment. Patients were reevaluated after 12 mo. In vivo QBS and BMD studies again were performed. The study protocol was approved by the Institutional Helsinki Committee (Human Studies Committee).

Quantitative bone scintigraphy was performed using a previously described method (*7,12*). SPECT of the pelvis was performed 3 hr after the intravenous injection of 24 mCi ^{99m}Tc-labeled MDP (Soreq Nuclear Laboratory, Yavne, Israel). A large field-of-view (Apex 415) or very large field-of-view (SP-6) digital gamma camera with a rotating gantry (Elscint, Haifa, Israel) was used. A complete rotation of 360°, with 120 projections, 3° apart, was performed over 20 min, with an acquisition of about 6×10^6 counts. Raw data were reconstructed using filtered backprojection with a Hanning filter and a cutoff point of 0.5 cycle/cm using an SP-1 computer (Elscint, Haifa, Israel). After SPECT reconstruction, each image was sectioned at 1-pixel (0.68-cm) intervals in the transaxial, coronal and sagittal planes, using a 64-byte × 64-byte matrix. For concentration measurements, calculations were performed on the reconstructed data using the threshold method. A threshold of 43%, which, in previous studies, was found to give the smallest error in a wide range of phantom studies, was used to measure the concentration of ^{99m}Tc-labeled MDP in the bone (*7,12*). This threshold is suitable for the range of ^{99m}Tc-labeled MDP concentrations that was encountered in this study. Counts/pixel were converted to concentration units (μCi/ml), and the percentage of injected dose (%ID) of ^{99m}Tc-labeled MDP per ml of bone tissue was calculated using the identity line of counts/pixel and μCi/ml.

The %ID of ^{99m}Tc-labeled MDP per ml $\times 10^{-3}$ of bone tissue is defined as the QBS value. Using this method, we have demonstrated a good correlation (r = 0.98) when concentration in phantoms, as measured by SPECT, is compared to known concentrations (*12*). When in vivo SPECT measured concentrations of ^{99m}Tc-labeled MDP in patients are compared to the gold standard, the concentration in the same bones, obtained during surgery and measured in vitro, the correlation (r = 0.96) also is good (*7*). Phantom studies have shown a coefficient of variation for replicate studies of less than 2%, and there is no statistically significant difference between two studies done several months apart in the same group of patients (*13*). QBS of the LS, vertebrae 2, 3 and 4, and the FN were measured. These were the same regions used for densitometry.

Vertebral and FN BMD values were measured using the dual-energy x-irradiation absorptiometry method with a commercial instrument (Lunar, Madison, WI). The results of measurements of the LS, vertebrae 2, 3 and 4, were expressed in g divided by the projected area of these vertebrae in cm^2. For the FN, the commercial computer program was used. Phantom studies showed that the coefficient of variation for same-day replicate measurements was less than 1%. The long-term variability in the stability of the instrument was less than 1%. All young men examined by us were Caucasian, and there was no difference between our values in normal controls and the values given for the same-age and same-sex group by the manufacturer of the instrument. Bone density measurements were performed on the same day as bone scintigraphy, before the injection of the radiopharmaceutical.

Comparison of QBS and BMD measurements in patients with DP and IHH and their respective control groups, at baseline and after 1 yr, were made by using the nonparametric Mann–Whitney U test. Comparisons of baseline and follow-up data were performed using the nonparametric Wilcoxon test. The percentage of change in bone density in each patient was calculated as bone density after 1 yr minus bone density at baseline, divided by bone density at baseline. Comparison of the percentage of change in BMD in patients with treated DP and patients with nontreated DP was performed using the nonparametric Wilcoxon test. A multigroup comparison was assessed by using the analysis of variance (ANOVA) test.

RESULTS

The QBS values of patients with DP were significantly higher than those of normal controls (8.44% ± 2.55%ID/ml compared to 5.63% ± 1.12%ID/ml × 10^{-3}, $p < 0.001$, for the LS; and 7.86% ± 3.01%ID/ml compared to 4.29% ± 1.25%ID/ml × 10^{-3}, $p < 0.001$, for the FN). After treatment, the QBS values declined significantly in DP patients (6.74% ± 1.73%ID/ml × 10^{-3}, $p < 0.001$, for the LS; and 6.04% ± 1.94%ID/ml × 10^{-3}, $p < 0.0001$, for the FN). In patients with DP who did not receive testosterone treatment, the changes in QBS, as compared to the baseline study, in the LS (8.08% ± 3.48%ID/ml × 10^{-3}) and in the FN (6.33% ± 2.08%ID/ml × 10^{-3}) were not statistically significant.

The BMD of patients with DP before treatment was significantly lower than that of normal controls (0.77 ± 0.11 g/cm^2 compared to 1.03 ± 0.14 g/cm^2, $p < 0.0001$, for the LS; and 0.89 ± 0.11 g/cm^2 compared to 1.08 ± 0.18 g/cm^2, $p < 0.006$, for the FN). Bone mineral density in both the LS and FN in DP was significantly higher after treatment than it was before (0.91 ± 0.14 g/cm^2, $p < 0.0001$, for the LS; and 0.97 ± 0.11 g/cm^2, $p < 0.0001$, for the FN). For the LS, the BMD after treatment was still significantly lower than normal ($p < 0.05$). For the FN, it was not significantly different from normal. In the untreated group, BMD values after 1 yr were 0.82 ± 0.08 g/cm^2 ($p < 0.03$) for the LS and 0.89 ± 0.05 g/cm^2 (p was not significant) for the FN, as compared to baseline values. The BMD values of the untreated DP group after 1 yr were still significantly lower than the values of the normal control group ($p < 0.008$ for the LS; and $p < 0.04$ for the FN). An ANOVA test of QBS and BMD values, as measured in the LS and FN, between the different groups in patients with DP was highly significant ($p < 0.0001$). The mean percentages of change in BMD over 12 mo in patients with DP who were treated were 17.2% ± 5.32% for the LS and 8.23% ± 7.64% for the FN. The changes in BMD during the same period in the untreated group were 9.34% ± 5.31% ($p < 0.02$) for the LS and 2.00% ± 4.93% (p was not significant) for the FN.

Values for QBS in IHH patients were not significantly different from those of normal controls (6.20% ± 2.47%ID/ml compared to 5.50% ± 1.15%ID/ml × 10^{-3} for the LS; and 4.56% ± 2.13%ID/ml compared to 3.81% ± 1.28%ID/ml × 10^{-3} for the FN). After treatment, patients with IHH showed no significant decrease in QBS for the LS (5.43% ± 1.58%ID/ml × 10^{-3}) or for the FN (4.19% ± 1.86%ID/ml × 10^{-3}). Bone mineral density in patients with IHH was significantly lower than it was in normal controls (0.82 ± 0.04 g/cm^2 compared to 1.07 ± 0.15 g/cm^2, $p < 0.0001$, for the LS; and 0.87 ± 0.10 g/cm^2 compared to 1.08 ± 0.16 g/cm^2, $p < 0.001$, for the FN). The BMD of patients with IHH increased significantly after treatment (0.93 ± 0.09 g/cm^2, $p < 0.001$, for the LS; and 0.95 ± 0.11 g/cm^2, $p < 0.001$, for the FN), but it was still significantly lower than that of normal controls ($p < 0.009$ and 0.006 for the LS and FN, respectively). An ANOVA test of QBS and BMD measurements in IHH patients, in the LS and FN, between the different groups was significant ($p < 0.0001$). The mean percentages of change in BMD in the IHH group were 13.5% ± 4.3% in the LS and 9.6% ± 6.5% in the FN. The QBS and BMD measurements at baseline and after 1 yr are summarized in Table 2.

TABLE 2
Quantitative Bone SPECT and Bone Mineral Density Measurements at Baseline and After 1 yr in 29 Patients with Delayed Puberty, 16 Patients with Idiopathic Hypogonadotropic Hypogonadism and Their Age-Matched Controls

Measurement	Baseline	At 1 yr
QBS LS (%ID/ml × 10^{-3})		
DP, all patients (n = 29)	8.44 ± 2.55	
Treated DP (n = 22)	8.29 ± 2.15	6.74 ± 1.73
Untreated DP (n = 7)	8.92 ± 3.47	8.08 ± 3.48
DP age-matched controls (n = 11)	5.63 ± 1.12	
IHH (n = 16)	6.20 ± 2.47	5.43 ± 1.58
IHH age-matched controls (n = 16)	5.50 ± 1.15	
QBS FN (%ID/ml × 10^{-3})		
DP, all patients (n = 29)	7.86 ± 3.01	
Treated DP (n = 22)	8.00 ± 2.75	6.04 ± 1.94
Untreated DP (n = 7)	7.45 ± 3.68	6.33 ± 2.08
DP age-matched controls (n = 11)	4.29 ± 1.29	
IHH (n = 16)	4.56 ± 2.13	4.19 ± 1.86
IHH age-matched controls (n = 16)	3.81 ± 1.28	
BMD LS (g/cm^2)		
DP, all patients (n = 29)	0.77 ± 0.11	
Treated DP (n = 22)	0.78 ± 0.12	0.91 ± 0.14
Untreated DP (n = 7)	0.76 ± 0.08	0.82 ± 0.08
DP age-matched controls (n = 11)	1.03 ± 0.14	
IHH (n = 16)	0.82 ± 0.04	0.93 ± 0.09
IHH age-matched controls (n = 16)	1.07 ± 0.15	
BMD FN (g/cm^2)		
DP, all patients (n = 29)	0.89 ± 0.11	
Treated DP (n = 22)	0.90 ± 0.12	0.97 ± 0.11
Untreated DP (n = 7)	0.88 ± 0.06	0.89 ± 0.05
DP age-matched controls (n = 11)	1.08 ± 0.18	
IHH (n = 16)	0.87 ± 0.10	0.95 ± 0.11
IHH age-matched controls (n = 16)	1.08 ± 0.16	

QBS = quantitative bone SPECT; DP = delayed puberty; IHH = idiopathic hypogonadotropic hypogonadism; BMD = bone mineral density; LS = lumbar spine; FN = femoral neck.

DISCUSSION

As yet, there is no completely effective treatment for male osteoporosis (*3*). Therefore, it is important to gain maximal peak bone mass to prevent or delay the appearance of osteoporosis (*1,2*). Diseases due to sex hormone deficiency, such as DP and IHH, are associated in adult men with osteopenia (*3–5*). Sex steroids have a major influence on bone metabolism. Androgens affect osteoblastic activity, including proliferation, growth factors and cytokine and bone matrix protein production. Although reduced bone mass was documented in patients with IHH and hypogonadism due to Klinefelter's or Kalman's syndrome (*14–16*), DP has not been traditionally recognized as being associated with low bone mass. In a retrospective study, it was found that adults with a history of DP had a lower BMD than did a matched normal population (*4*). Patients with DP reach full puberty later than do normal controls, but their sexual characteristics, height and weight reach levels that are not different from those in normal adults. Testosterone treatment in DP has been suggested, but only for patients with social or psychological problems due to the late appearance of sexual

characteristics (*11,17,18*). The present results indicate that testosterone may have a value in elevating BMD in patients with DP. Patients with IHH had normal QBS values and BMD did not reach normal values after treatment.

In this study, young men with constitutional DP had a higher QBS and a lower BMD during puberty than did normal controls of the same chronological age. Bone mineral density increases rapidly in normal young men during puberty (*19–24*). It is this critical period in which peak bone mass is achieved (*25*). It appears that achieving normal bone age at an older chronological age may not be associated with normal peak BMD. Reaching normal BMD during the time of puberty appears to be necessary to achieve a normal peak BMD. Therefore, it is important to diagnose the abnormality in bone mineralization early, so that patients who will respond to testosterone will be treated early during puberty. Measurement of bone turnover has been used to predict osteoporosis in women after oophorectomy (*6*) and in patients with renal failure (*9*). Endocrine abnormalities, such as primary hyperparathyroidism and thyrotoxicosis, also cause elevated bone turnover and, as a result, elevated QBS values. In these conditions, QBS returns to normal levels after correction of the hormonal abnormality (*8*). QBS measures the osteoblastic part of bone turnover, which is coupled with the osteoclastic process. The elevation of QBS values generally seen in osteoporosis is probably secondary to enhanced osteoclasis, to which the osteoblastic process is coupled (*26*). Elevated QBS is, of course, not specific to DP and has been shown in other endocrine abnormalities (*8,9,26*). The return of QBS after treatment to values that are not different from normal values is an indication of the return of bone turnover to normal levels. Patients with DP who had elevated QBS values responded to testosterone treatment by normalizing their bone density after 1 yr. Patients with DP who were not treated had, after 1 yr, a lower BMD than did normal controls. QBS values over the same period did not change significantly in the untreated group. The results suggest that patients with DP should receive testosterone treatment to raise peak bone density and, thus, prevent osteopenia in later life and that patients with abnormalities in maturation and high QBS values are those who respond to testosterone treatment. Larger experience, follow-up for a period longer than 1 yr and comparison with a nontreated matched cohort is still necessary to determine whether testosterone should be recommended as a routine treatment to increase BMD.

CONCLUSION

This study indicates that measurement of QBS can be used to predict the need for treatment with testosterone to prevent osteopenia in young males with DP. A study of a larger population and for a longer period should test the ability of testosterone to prevent patients with high QBS values from developing osteopenia in adulthood.

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