Original Study

Effect of Antiandrogen Treatment on Bone Density and Bone Geometry in Adolescents with Polycystic Ovary Syndrome

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A B S T R A C T

Study Objectives: To determine the impact of antiandrogen treatment on bone density and geometry.
Design: Prospective cohort investigation.
Setting: Academic research institute.
Participants: 38 (age 14.96 ± 1.42 yr) subjects with PCOS.
Interventions: Treated with metformin (n = 17) or metformin and antiandrogen (n = 21).
Main Outcome Measure: Bone density and geometry parameters at baseline and after a mean duration of 1.92 ± 0.88 years using peripheral quantitative computed tomography of the forearm.
Results: At baseline, z-scores for trabecular (0.53 ± 1.02) and cortical BMD (0.79 ± 1.55) as well as total (0.62 ± 1.07) and medullary cross sectional area (CSA) (0.79 ± 1.29) were elevated. Cortical CSA (−0.01 ± 1.10) and bone strength strain index (SSI) z-scores (−0.01 ± 1.10) were normal. Muscle CSA z-score (0.12 ± 1.70) was normal, but grip strength (−1.60 ± 1.15) was significantly reduced. There were no significant changes within and between the two treatment options in respect to bone density and bone geometry parameters. With antiandrogen treatment, free androgen index (FAI) was significantly lower and grip strength further decreased ($P < .001$).
Conclusions: No significant changes in bone mineral density and geometry parameters took place in PCOS women irrespective of treatment followed over a time of almost two years. General muscle weakness expressed as low grip strength may influence further bone development in PCOS.
Key Words: Bone mineralization, Bone geometry, Polycystic ovary syndrome, Antiandrogen, Peripheral quantitative computed tomography

Introduction

Polycystic ovary syndrome (PCOS) is a unique endocrine disorder among the causes of oligo-menorrhea characterized by chronic anovulation, relatively high estradiol levels, androgen excess and higher incidence of insulin resistance. In addition, obesity is a very common clinical feature in women affected by PCOS, more than 50−60% of PCOS women being obese.[1] The feature of polycystic appearance of the ovaries may essentially be a late epiphenomenon of an early-onset disorder.[2,3] Physical signs of women with PCOS are excess of central fat, deficit of lean mass, even in the absence of obesity, as well as hirsutism and acne.[4,5]

The static levels of estradiol, with the absence of estradiol peak associated with ovulation in PCOS women, may negatively affect bone density and geometry.[6,7] Although conflicting results have been reported so far bone mass and density in PCOS women appear to be maintained at a level comparable to normal ovulatory women or even higher.[8−10] A higher bone mass might be related to a higher body mass index (BMI), higher estrogen and androgen levels and hyperinsulinemia.[11] In peripheral quantitative computed tomography (pQCT) studies a trend for higher cortical and total bone cross-sectional area (CSA) was found in lean and obese PCOS women.[7]

At present there is no approved therapy for PCOS in adolescents. Ibáñez et al described a treatment combination of low-dose flutamide, metformin and etinylestradiol-drosperinone (oral contraception with antiandrogen effect).[12]

Puberty and adolescence are critical periods with major increase in bone mass.[13] Menstrual dysfunction, hyperandrogenism and treatment interventions may affect bone mass accrual in these young women. No data are available on the effect of treatment options in PCOS on bone density and geometry development in this age group.

The aim of our investigation was to look for changes in bone geometry and density parameters. We hypothesize that with antiandrogen treatment periosteal bone apposition is decreased leading to a smaller total bone cross-sectional area and a reduction in bone strength.

To address the hypothesis we used pQCT, which images a cross-sectional view of the limb and provides volumetric, 3-dimensional assessment of the structural and geometric properties (bone mineral density, bone size) of the appendicular skeleton. A further advantage of pQCT is its ability to measure muscle and fat cross-sectional area (CSA) of the limb which is accepted as a reasonable surrogate for total body muscle and fat mass.

The authors indicate no conflicts of interest.

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Materials and Methods

In this retrospective analysis performed between 2005 and 2009 the population consisted of 38 young patients with PCOS (mean age at baseline 14.96 ± 1.42 yr; range 12.4 to 18.04 yr) followed in a university outpatient clinic. The mean BMI was elevated with 27.05 ± 5.05 kg/m^2 (range 20.00 to 41.43). Diagnostic criteria for PCOS were hyperandrogenism as defined by hirsutism (Ferriman-Gallwey score above 8), menstrual irregularities, elevated serum androstenedione (>268 ng/dl) or testosterone levels (>50 ng/dl) or free androgen index (>6) and hyperinsulinemia on a standard 2-h oral glucose tolerance test, defined as fasting insulin of >15 μU/ml, peak insulin of >150 μU/ml and / or mean insulin levels of >84 μU/ml.[14] A non-classical adrenal hyperplasia was excluded by a basal level of 17-OH progesterone < 217 ng/dl. If 17-OH-P levels were equal or higher an ACTH stimulation test was performed and with an increase in 17-OH-P of < 260 ng/dl a heterozygous status of 21-OH-deficiency was excluded. At baseline none of the patients were receiving contraceptive treatment or another medication known to affect carbohydrate metabolism or adrenal or gonadal function. The HOMA index [(fasting glucose (mmol/l) × fasting insulin (pmol/l))/135] and the insulin sensitivity index due to Matsuda, [10 000 / square root of (fasting glucose × fasting insulin) × (mean glucose × mean insulin during oGTT)], were calculated.[15] A homeostatic model assessment (HOMA) index above 2.5 and insulin sensitivity index (ISI) below 5 were defined as a state of insulin resistance. Patients obtained off-label either metformin (850 mg two times a day) (n = 17) or metformin combined with a monophasic anti-androgenic oral contraceptive (OC) and low dose flutamide (62.5 mg) (n = 21) after pretreatment consultation in accordance with data by Ibáñez et al.[16]

Patients were reevaluated at a mean age of 16.84 ± 1.41 years, being treated for at least one year. Height was measured in a standing position to the next 1 mm using a digital telescoping wall-mounted stadiometer (Ulmer Stadiometer, Prof. E. Heinze, Ulm, Germany). Weight was determined to the nearest 0.1 kg using an electronic scale (Seca 753 E, Vogel and Hanke, Hamburg, Germany) with the adolescent clothed in underwear. The body mass index (BMI) was calculated using the formula weight/height (m^2). Data for height, weight and BMI were compared to German normative data.[17] Waist was measured at the level midway between the lower rib margin and the iliac crest. Hip was measured as the maximum circumference over the buttocks.[18] Forearm length was measured at the non-dominant forearm as the distance between the ulnar styloid process and the olecranon using a caliper. In all patients sexual development corresponded to Tanner stage 4 or 5 using grading system by Tanner for breast development in girls[19] and the growth velocity of the previous 6 months was ≤ 2 cm per year indicating near final height.

The pQCT results were compared to those in a German reference population using identical methodology (XCT 2000) and analysis protocol.[20,21] Reference data are available for age and height as well as pubertal status, with about 30 female patients in each age group.

Maximal isometric grip force of the non-dominant hand was determined with a standard adjustable handle Jamar Dynamometer (Preston, Jackson, MI) as previously described.[22] The handle was adjusted to Setting 2 in all. The subjects were told to put maximal force on the dynamometer. The maximal value of three trials was noted. Reference data were taken from the participants in the DONALD study.[22]

Endocrine and Metabolic Assessment

At the time of oral glucose tolerance testing routine blood analysis (blood cell count, electrolytes, and liver and renal function tests) was obtained. Fasting blood glucose, serum insulin, androstenedione, dehydroepiandrosterone sulfate (DHEAS) and thyroid stimulating hormone were measured by commercial enzyme labeled immunometric chemiluminescense assay (Immulite, Siemens, Eschborn, Germany) and testosterone, SHBG and prolactin were assayed by commercial enzyme labeled immunometric chemiluminescense assay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany) in our laboratory.

It was the patient's decision which treatment they preferred and informed consent was obtained from patients and parents. Further, pQCT measurement was approved by the University's ethics committee and informed consent was obtained from all patients and/or their parents.

Peripheral Quantitative Computed Tomography

Two sites of the non-dominant radius were analyzed by pQCT, the distal metaphysis (“4% site”) and the proximal diaphysis (“65% site“) as described before. A XCT scanner (XCT 2000, Stratec Inc; Pforzheim, Germany) was used, which is equipped with a low energy (38keV) X-ray tube. For the measurement, the scanner was positioned at the distal forearm and a scout view was carried out to position the scanner at a distance of 4% and 65% of forearm length proximal to the radial articular surface. At both sites a 2mm-thick single tomographic slice was sampled at a voxel size of 0.4 mm. Image processing and calculation of numerical values was done using the manufacturer's software package (version 5.40). The measurement sites, parameters and devices were identical with those for the reference data.

At the metaphysis (4% site), the trabecular bone mineral density (BMD) was measured and at the diaphysis (65% site), total and cortical BMD as well as total, cortical and marrow cross-sectional area (CSA), muscle and fat CSA were measured. Data on bending strength or the SSI of long bone diaphysis, a measure of bone stability, related to its diameter raised to the third power were derived from primary measures and calculated by the manufacturer's software.[23]

Statistics

Patients` data were compared with age- and sex-matched reference data. Results were converted into sex- and age-specific standard deviation scores (Z-scores) using the formula: Z-score = [(test result for a patient) − (age-specific mean in reference population)]/(age-specific standard deviation in reference population).