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Obesity and Insulin Resistance, Not Polycystic Ovary Syndrome, Are Independent Predictors of Bone Mineral Density in Adolescents and Young Women

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Keywords
Adolescents · Body mass index · Polycystic ovary syndrome · Bone mineral density

Abstract
Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders that affects females of reproductive age. The characteristic features of PCOS individually have opposing effects on bone mineral density (BMD); however, their cumulative effect on BMD has not been clearly defined. Adolescence and young adulthood span a crucial period in achieving peak bone mass. Thus, a better understanding of the impact of PCOS on BMD in this age group is needed. ***Objectives:*** To determine whether BMD is different between young females with PCOS and controls and to identify factors that influence BMD in this population. ***Methods:*** Data from four cross-sectional studies with a total of 170 females aged 12–25 years with PCOS (n = 123) and controls (n = 47) with a wide range of BMIs (18.7–53.4 kg/m^2) were analyzed. Participants had fasting glucose, insulin, and free and total testosterone concentrations measured. HOMA-IR was calculated. Whole-body BMD was assessed by dual-energy X-ray absorptiometry. Multiple regression analysis for predicting BMD included PCOS status, menstrual age, obesity, HOMA-IR, and free testosterone. ***Results:*** HOMA-IR and total and free testosterone were significantly higher in PCOS compared to controls but there was no difference in BMD z-score between PCOS (0.8 ± 1.0) and controls (0.6 ± 1.0) (p = 0.36). Obesity (p = 0.03) and HOMA-IR (p = 0.02) were associated with BMD z-score. ***Conclusions:*** Obesity status and insulin resistance, but not PCOS status, were each independently associated with BMD in adolescents and young women who spanned a wide range of BMIs.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects up to 15% of females of reproductive age and frequently presents in adolescence

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and young adulthood [1, 2]. It is characterized by menstrual dysregulation manifesting as oligomenorrhea and amenorrhea (oligo-/amenorrhea), signs of hyperandrogenism such as hirsutism and acne, and polycystic ovarian morphology. Comorbidities of PCOS include insulin resistance, cardiovascular disease, and obesity; however, little is known about the effect of PCOS on bone health. Understanding the effect of PCOS on bone health in young patients is crucial since peak bone mass is reached by the beginning of the third decade of life and is a strong predictor of osteoporosis risk [3, 4]. Dual-energy X-ray absorptiometry (DXA) is a validated method to assess bone mineral density (BMD) in young patients [5]. Determining the effect of PCOS on BMD is challenging because of its many associated metabolic abnormalities, some of which have opposing effects on BMD. Hyperandrogenism [6, 7] and hyperinsulinism [7–10] have been described to have beneficial effects on BMD, whereas oligo-/amenorrhea is associated with deleterious effects on BMD due to relative estrogen deficiency [11–13]. Available data are conflicting regarding the effect of PCOS on BMD as some studies show decreased BMD in PCOS [8, 14] while others show no difference in BMD between PCOS and controls [15–18]. The varied findings among studies may be due to differences in diagnostic criteria for PCOS used, skeletal sites studied, and study population characteristics such as age and body mass index (BMI).

Estrogens, and to a lesser extent androgens, contribute to bone mineral accrual and maintenance in both males and females [6, 19]. Estrogens influence osteoblast, osteoclast, osteocyte, and T-cell activity resulting in inhibition of bone remodeling, decrease in bone resorption, and maintenance of bone formation [20]. Low estrogen states have been associated with low BMD as seen in hirsute oligo-/amenorrheic women when compared to hirsute eumenorrheic women [11, 12]. The effect of androgens on BMD is mediated by androgen receptors expressed at bone remodeling sites, hypertrophic chondrocytes, and mononuclear and endothelial cells of blood vessels within the bone marrow. Additionally, androgens indirectly affect BMD by inhibiting bone resorption mediated by reduction of prostaglandin E_2 production and by effects of PTH on osteoblasts and osteoclastogenesis [21].

In the pediatric population, subtotal whole-body BMD and posterior-anterior lumbar spine are the preferred sites to evaluate areal BMD [5]. Since soft tissue may interfere in BMD measurement accuracy, higher fat mass could confound the determination of DXA [22, 23]. Historically, obesity has been considered to be a protective factor in bone [8, 11, 24–26]; however, the positive effect of obesity on BMD has been questioned [27–31] and in adolescents, the association between obesity and BMD is weaker [32, 33]. The potential effect of obesity on BMD is particularly significant in this study because obesity is a prevalent condition; in the USA 20.9% of female adolescents are obese [34] and 57.3% of adolescents with PCOS are obese [35].

Insulin resistance and concomitant hyperinsulinemia is associated with both obesity and PCOS [35] and has also been associated with a positive effect on BMD. Insulin has direct effects on bone through osteoblast receptors [8, 11] and promotes proliferation and differentiation of bone and decreases bone turnover [12]; however, hyperinsulinemia decreases the osteoprotegerin to RANKL ratio, which leads to osteoclast differentiation and bone resorption [7]. Indirect positive effects of insulin on bone include the stimulation of IGF-1 production [8, 10] and suppression of SHBG production, which increases free testosterone [9].

Considering the metabolic and hormonal features associated with PCOS and their potential effects on bone health during a unique period of bone accrual, the primary aim of our study was to determine whether there is a difference in BMD between adolescents and young women with and without PCOS in a cohort that spans a wide range of BMIs. Our secondary aim was to investigate factors that may influence BMD such as obesity, insulin resistance measured by HOMA-IR, and free testosterone. To date, there are no studies that analyze BMD in adolescents and young adults with PCOS and class 3 obesity [36].

Materials and Methods

Participants included 170 females aged 12–25 years with and without PCOS who were enrolled in one of four cross-sectional studies: (1) The PCOS study conducted at Columbia University Irving Medical Center (CUIMC); (2) Androgens and Insulin Sensitivity (ARIS), prior to NCT; (3) APPLE NCT02157974; and (4) PLUM NCT03041129. The latter three studies were conducted at the Children's Hospital of Colorado (CHC). Participants from the CUIMC study were recruited from pediatric endocrinology and adolescent clinics and general practices at CUIMC as well as Listserv postings and flyers from 2006 to 2019. Participants from the CHC studies were recruited from the pediatric endocrinology and lifestyle medicine outpatient clinics at the Children's Hospital Colorado from 2012 to 2018.

Inclusion criteria for the CUIMC study were age 12–25 years, nonobese (BMI <95th percentile for participants less than 20 years old and <30 kg/m^2 for participants 20 years old or older). For the CHC studies, the inclusion criteria were age 12–20 years, overweight/obesity (BMI >90th percentile), and sedentary status (<3 h of regular exercise/week; validated with a 3-day activity recall).

Table 1. Descriptive statistics

Characteristics	PCOS (n = 123)	Control (n = 47)	p value
Age, years			0.03*
Mean ± SD	16.5±2.2	17.7±3.5	
Median (IQR)	16.3 (15.2–17.7)	17.1 (15–20.4)	
Menstrual age, years			<0.01*
Mean ± SD	4.77±2.02	5.97±2.81	
Median (IQR)	4.33 (3.33–6.0)	5.33 (3.75–8.17)	
Race			0.78
African American	16 (13)	6 (13)	
Asian	3 (2)	3 (6)	
Caucasian	45 (37)	16 (34)	
Hispanic	54 (44)	21 (45)	
Multiracial	5 (4)	1 (2)	
BMI, kg/m^2	32.6±7.1	30.5±7.6	0.09
Obese	88 (72)	27 (58)	0.08
% body fat	41.7±5.9	41.4±8.1	0.82
BMD, g/cm^2	1.1±0.1	1.1±0.1	0.55
BMD z-score	0.8±1.0	0.6±1.0	0.36
HOMA-IR	5.25±3.7	3.6±2.4	<0.01*
Free testosterone, pg/mL	8.26±4.6	3.6±1.9	<0.0001*
Testosterone, ng/dL	45.4±19.5	32.9±20.1	<0.001*

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. BMD, bone mineral density. * p < 0.05. p values were generated by t tests or χ^2/Fisher's exact test.

Exclusion criteria for this analysis were the presence of diabetes mellitus, nonclassical congenital adrenal hyperplasia, thyroid disease, current or past pregnancy, chronic glucocorticoid use, and use of hormonal contraception or metformin within 3 months of enrollment.

The diagnosis of PCOS for all participants was based on the NIH criteria which requires both oligo-/anovulation and hyperandrogenism and does not include polycystic ovarian morphology [37, 38]. Using the phenotypic approach, patients with PCOS would be characterized as phenotypes A and B [39]. Controls were eumenorrheic and without evidence of hyperandrogenism. All patients were at least 18 months postmenarche.

Height was measured using a stadiometer to the nearest 0.1 cm; weight was measured using a digital readout scale to the nearest 0.1 kg and BMI was calculated. Fasting labs included insulin, glucose, and total and free testosterone. For the CUIMC study, insulin was measured using immunochemiluminescence and glucose was analyzed using the glucose hexokinase method (Biomarkers Core Laboratory at CUIMC). For the CHC studies insulin was measured by radioimmunoassay (Millipore, Billerica, MA, USA) and glucose was analyzed using Yellow Spring Instrument (YSI) for AIRS and Statstrip hospital grade glucometer (Novo Biomedical, Waltham, MA, USA) for APPLE and PLUM. Total testosterone was measured by liquid chromatography-mass spectrometry and free testosterone was measured by equilibrium dialysis (Esoterix, Calabasas Hills, CA, USA) in both the CUIMC and the CHC studies.

For all 170 participants, whole-body BMD and percentage body fat were determined by DXA (Lunar Prodigy, GE Healthcare). Whole-body BMD was used; given our young study population, its measurements are feasible and can provide reproducible measurements in the pediatric population [5].

Data Analysis

Descriptive statistics were used to summarize all variables of interest. Continuous variables were described using means (standard deviations) and/or medians (interquartile ranges). Comparisons between the two groups (PCOS vs. control) were assessed using two-sample independent t tests or equivalent nonparametric tests upon distributional constraints. Categorical variables were summarized by frequencies (percentages). Associations were evaluated using χ^2 or Fisher's exact tests. Based on these comparisons, all characteristics that significantly differed between the groups or had specific clinical relevance (obesity) were entered in simple and multiple regression models to further identify factors associated with BMD z-score (main outcome of interest). If two variables were highly correlated (age and menstrual age; testosterone and free testosterone), in order to prevent multicollinearity, only one of them was chosen for modeling purposes. Data analysis was performed using SAS v 9.4 (Cary, NC, USA) with a level of significance of 0.05.

Results

Descriptive statistics are shown in Table 1. For the primary analysis, participants were divided into two groups: PCOS and controls. Of the 170 participants, 123 had PCOS

Table 2. Simple and multiple regression analyses to identify factors associated with BMD z-score

Variable	Simple linear regression		Multiple regression	
	Estimate (SE)	*p* value	Estimate (SE)	*p* value
PCOS vs. non-PCOS (ref.)	0.16 (0.17)	0.36	–0.08 (0.18)	0.66
Obese vs. non-obese (ref.)	0.74 (0.15)	<0.0001*	0.41 (0.19)	0.03*
Menstrual age (years)	–0.09 (0.03)	<0.01*	–0.02 (0.04)	0.63
Free testosterone (pg/mL)	0.05 (0.02)	<0.01*	0.01 (0.02)	0.57
HOMA-IR	0.10 (0.02)	<0.0001*	0.06 (0.03)	0.02*

Simple linear regression represents the variable related to BMD. Variables included in the multiple regression include PCOS status, obesity status, menstrual age, free testosterone, and HOMA-IR. BMD, bone mineral density. SE, standard error. * $p < 0.05$.

and 47 were controls. PCOS patients were younger than controls ($p = 0.03$). Menstrual age – time in years from menarche to age at the time of the study – was also lower in PCOS compared to controls ($p < 0.01$). Seventy-five participants (45%) were Hispanic, 61 (36%) were Caucasian, 22 (13%) were African-American, 6 (3%) were Asian, and 6 (3%) were multiracial. There was no difference in the ethnic distribution between PCOS and controls ($p = 0.78$).

Participants had a wide range of BMIs, which spanned from 18.7 to 53.4 kg/m^2 and there was a statistical trend of a greater frequency of obesity in PCOS (88/123) than in controls (27/47) ($p = 0.08$). Mean percentage body fat was similar between the groups ($p = 0.82$). Whole-body BMD was similar in PCOS and controls ($p = 0.55$) as was BMD z-score ($p = 0.36$). (Table 1).

Laboratory evaluation showed that HOMA-IR, testosterone, and free testosterone were higher in PCOS compared to controls ($p < 0.05$ for all) (Table 1).

Linear regression analyses were fitted to identify potential predictive factors of BMD z-score (the main outcome of interest). HOMA-IR, free testosterone, obesity status, PCOS status, and menstrual age were first tested using simple regressions, and then combined in a multiple regression (adjusted) model (Table 2). PCOS status was not found to be a predictor for BMD z-score as a single predictor or in the adjusted model. Free testosterone was a significant predictor of BMD z-score when analyzed as a single predictor, and for each unit increase in free testosterone BMD z-score increased by 0.05 ($p < 0.01$) on average; however, after adjusting for the other covariates, free testosterone was no longer an independent predictor of BMD z-score ($p = 0.66$). In contrast, obesity status was an independent predictor of BMD z-score in both the simple and multiple regression models. The interaction between PCOS and obesity was also tested in the multiple regression model, but it was not significant. Being obese increased one's BMD z-score by 0.41 ($p = 0.03$) on average. HOMA-IR was also found to be an independent predictor of BMD z-score, and for each unit increase in HOMA-IR BMD z-score increased by 0.06 ($p = 0.02$).

Discussion

In this ethnically diverse cohort of adolescents and young women with a wide range of BMIs, there was no difference in BMD between PCOS and controls. Additionally, obesity status and insulin resistance were shown to have independent, positive effects on BMD z-score, whereas PCOS status and total and free testosterone levels did not independently affect BMD.

The current understanding of bone health in patients with PCOS is limited, likely due to the complexity of PCOS and the paucity of studies in this area. Our study cohort has unique characteristics such as young chronological and menstrual ages and bone mass that has not yet reached its peak. In agreement with some prior studies, we have found that there is no difference in BMD between PCOS and controls. Nonobese adolescents with PCOS have been reported to have lower BMD than controls [8, 40, 41]. One study showed comparable BMD in obese adolescents with and without PCOS, but lower BMD in nonobese PCOS compared to controls [41]. Another study showed that nonobese PCOS had lower lumbar spine BMD than controls but no between-group difference in obese subjects [40]. In a slightly older population, there were no differences in total and regional BMD (L2–L4, femoral neck, trochanter, and Ward's triangle) between PCOS and controls [17].

A defining feature of PCOS is androgen excess. Testosterone levels correlate with BMD in premenopausal women, even when adjusted for BMI [11, 15, 16]. Additionally, it has been hypothesized that bone androgen receptors in hirsute patients may be more sensitive [13]. In contrast to prior studies, total and free testosterone levels were not independent predictors of BMD z-score when adjusting for obesity status, menstrual age, HOMA-IR, and PCOS status.

Insulin resistance is a common feature of PCOS and the prevalence of insulin resistance among patients with PCOS measured by HOMA-IR has been reported to be 64% in adult females [42] and common in youth with PCOS [43, 44]. The relationship of insulin resistance and BMD has been reported as positive in different populations [45, 46]. In young overweight and obese women with PCOS, BMD was negatively correlated with hirsutism and positively correlated with fasting insulin and HOMA-IR, regardless of BMI [40]. Another study with young women with PCOS found a positive correlation between whole-body BMD and fasting insulin and an inverse correlation between fasting glucose-to-insulin ratio and L2–L4 BMD, after adjusting for age and BMI [17]. Similarly, our study demonstrated a positive relationship between BMD and HOMA-IR when adjusting for obesity, PCOS status, free-testosterone, and menstrual age.

Obesity is a complex and multifactorial disease itself. Nonetheless, its relationship with BMD is also complex. Several studies have reported a positive relationship between obesity and BMD; however, more recent data have questioned this association. Fracture risk was traditionally thought to be negatively associated with BMI, a belief supported by several studies [46–48]; however, lower BMD in patients with central obesity has been reported [50]. A U-shaped relationship between BMI and fracture risk has been described and could partially explain the discrepancy in results from different studies [50]. In the present study, we found similar results as obesity was found to be an independent predictor of BMD z-score.

Finally, when all the above features were analyzed together, PCOS status was not a predictor of BMD z-score, while obesity and insulin resistance were. Obesity and insulin resistance do not universally affect all patients with PCOS. Since obesity and insulin resistance both positively predicted BMD z-score, one can hypothesize that other factors might be attenuating the effects associated with obesity and insulin resistance on BMD of patients with PCOS. This is extremely relevant, given the high prevalence of PCOS and the impact in fracture risk in women's health.

Limitations of our study are mainly related to its retrospective design leading to inherent potential biases, as well as secondary analysis of the CHC dataset. Related to this, we lack dietary and physical activity assessments in the CUIMC cohort and laboratory bone evaluation in the CHC participants, in particular measures of vitamin D concentrations. An additional limitation is the use of whole-body BMD including head rather than subtotal whole-body BMD, or more precise hip or spine bone measurements. Despite these limitations, the present study has strengths, including the unique young subject population, a large multi-site cohort to allow for a more diverse and representative patient population, PCOS defined by the most stringent guidelines, gold standard testosterone measurements,, and a wide range of BMIs, which enabled us to evaluate how those characteristics affect BMD.

Conclusions

In summary, we found that in young females with a wide span of BMIs, PCOS status was not an independent predictor of whole-body BMD z-score, while obesity and insulin resistance were. These findings suggest that in this population PCOS is not associated with low BMD despite the presence of oligo-/amenorrhea and that obesity and insulin resistance may in fact have beneficial effects on BMD. Further studies examining bone microarchitecture such as pQCT and studying subtotal whole-body and lumbar spine DXA may provide a deeper understanding of the effects of PCOS on bone health.

Statement of Ethics

The CUIMC study was approved by the Institutional Review Board at CUIMC and the CHC studies were approved by the University of Colorado Anschutz Medical Campus Institutional Review Board and the CHC Scientific Advisory Review Committee. Informed consent was obtained from all participants 18 years and older and parental consent and participant assent from all participants <18 years of age.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Study design: A.B.S. and C.F.P.-E. Data collection: R.H.T., Y.D.N, A.P., C.F.P.-E., A.B.S., I.F., and M.C.-G. Coordination of research: R.H.T. Data analysis: M.M., C.C., and Y.Z. Data interpretation: A.B.S., .C.F.P.-E., S.E.O., and I.F. Drafting of the manuscript: C.F.P.-E. and A.B.S. Revision of content: A.B.S., S.E.O., I.F., M.C.-G., C.C., and YZ. All authors read, edited, and approved the manuscript.

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