Advance Research Journal of medical and clinical science
Received 16 Jun 2022 | Revised 28 Jun 2022 | Accepted 5 Jul 2022 | Published Online 18 Jul 2022

DOI: https://doi.org/10.15520/arjmcs.v8i07.455

ARJMCS 08 (07), 912–925 (2022)

ISSN (O) 2455-3549

ICV 2020 = 86.28

ORIGINAL ARTICLE

Bone Mineral Density in Women with Polycystic Ovary Syndrome- Baghdad

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Abstract

Background: Polycystic ovary syndrome is a serious public health concern through its symptomology, complications and comorbidities. Many researcher reports a statistically significant positive correlation between decrease bone mineral density and polycystic ovary syndrome as various features of this disorder may have an influence on bone metabolism.
Aim of study: To evaluate bone mineral density in women suffering from polycystic ovary syndrome and determine the associations between Bone mineral density and insulin resistance, hyperandrogenemia, Body mass index, and sex hormones.
Study design: A cross sectional study.
Setting: Department of Obstetrics and Gynecology at Baghdad Teaching Hospital / Medical city.
Patients and Methods: During a period of seven months that was conducted from April till November 2018. It included 30 women suffering from polycystic ovarian syndrome attended the outpatient clinic of the hospital seeking for management. Patients with Cushing`s syndrome, androgen producing adrenal tumors, congenital adrenal hyperplasia (CAH), thyroid disease, hyperprolactinemia, current use of contraceptive pills in the last six months, anti-diabetic treatment, and patients on restrictive diet were excluded from this study. Serum concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), 17 β-estradiol (E2), testosterone dehydroepiandrosterone sulfate (DHEAS), thyroid stimulating hormone (TSH), free thyroxin (fT4), fasting insulin and fasting glucose were determined using electrochemiluminescence immunoassay. Level of serum calcium, 25- hydroxy vitamin D was measured as it considered the best indicator of vitamin D level which reflects the stored vitamin D level. Bone mineral density values also were measured by Dual Energy X-Ray Absorptiometry scan (DEXA).
Results: The highest proportion of study patients showed low Bone mineral density level (73.3%). The highest prevalence of low level of bone mineral density was found significantly ($P < 0.05$) in patients with normal Body mass index , high insulin resistance, low estrogen level, low vitamin D level, and low serum calcium level (90%, 82.6%, 90%, 100%, and 100% respectively).
Conclusion: Bone mineral density decrease in a women with polycystic ovary syndrome due to low estrogen level, VIT D3 deficiency and insulin resistance
Keyword: SPCOS, BMD, vitamin D, insulin resistance, Estrogen

Effect of hormones of polycystic on BMD

PCOS is a complex disorder and various features of this disorder may have an influence on bone-metabolism. Peak bone mass is the maximal amount of bone tissue at the end of skeletal maturation, which is an important determinant of the (potential) development of osteoporosis. Many factors are supposed to influence bone deposition during growth [1]. Genetic factors are responsible for about 60–80 %, and hormonal and nutritional factors 20–40 % for the development of peak bone mass. Many previous studies have suggested that a relatively high estrogen concentration, higher insulin concentration,hyperandrogenemia and obesity are crucial bone growth stimulating factors in women with PCOS [2]. Due to its extreme variability, PCOS is a difficult syndrome to understand and much of the research available about its effect on BMD appear contradictory. Most research suggests that certain symptoms of PCOS, such as hyperanderogenemia, hyperinsulinemia (Insulin Resistance), and obesity, may positively affect bone growth and mineral accumulation [3]. For instance, weight gain and obesity may cause patients with PCOS to have higher BMD in load- bearing regions of the skeleton, like the femoral head or lumbar spine, since load-bearing bone density increases as weight increases. The visceral fat associated with PCOS weight gain can cause excessive free androgen production, which may be associated with increased BMD in non-load-bearing areas of the skeleton. [3,4] However, many researches does not show whether the effect of PCOS related obesity on bone density is a localized effect (increasing BMD only in specific areas of the body), or a systemic one.

ESTROGEN & ANDROGEN: Estrogens play a key role in the development and maintenance of the appropriate bone mass in women, by acting on osteoblasts, as well as on osteoclasts [1].

Estrogen actions on bone are complex. the major physiological effect of estrogen is to inhibit bone resorption. Bone cells have two kinds of intracellular steroid receptors for estrogen. When estrogen bind to receptors, various genes become active.Estrogen effects may be mediated in part by growth factors and interleukins. Interleukin 6 is apotent stimulator of bone resorption, estrogen bloacks osteoblast synthesis of interleukin 6. [3]

Osteoclast apoptosis is regulated by estrogens. With estrogen deficiency, the osteoclasts live longer and are therefore able to resorb more bone. In response to the increased bone resorption, there is increased bone formation and a high- turnover state develops which leads to bone loss and perforation of trabecular plates [5].

Moreover, all bone-forming cells have receptors for both androgens and estrogens with a predominance of androgen receptors on osteoblast cells [6].

Androgen influences bone metabolism through various pathways including inhibition of bone resorption, by decreasing interleukin 6 and prostaglandin E production, inhibiting the effect of PTH, by increase calcium resorption from the intestine and preventing it is excretion and by increasing vitamin D3 production.[7]

Hyperandrogenemia helps to preserve bone mass in PCOS women. But androgen has positive effect on bone only in the presence of estrogen. Without the estradiol peak or progesterone production associated with normal menstrual cycle, there is no net positive effect for androgen on bone. All these findings suggest that both estradiol and androgen have a critical role in maintaining bone mass. Studies have shown that androgen receptors are up regulated by androgen in bone and also by exposure to glucocorticoids, estrogen and 1, 25-dihydroxyvitamin D3. All of which are found to be reduced in PCOS condition, thus adversely affecting the regulation of BMD by androgens.[6]

Supplementary information The online version of this article (https://doi.org/10.15520/arjmcs.v8i07.455) contains supplementary material, which is available to authorized users.

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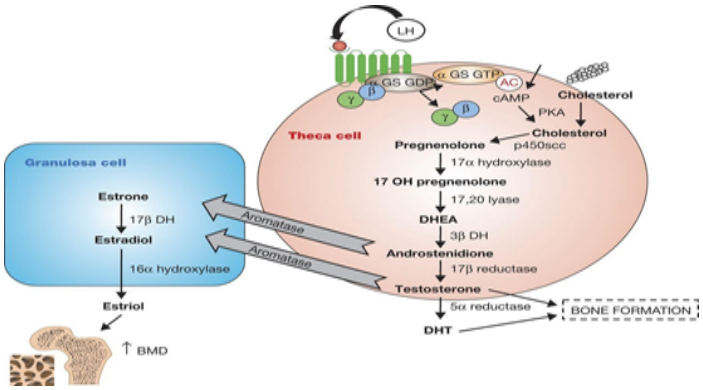

Figure 1-3 Schematic representation showing the effects of androgen/(s) on BMD. AC, acetylate cycles; c AMP, cyclic adenosine mono phosphate; PKA, Protein kinase A; DHEA, ehydroepidandroster one [8]

INSULIN: has an anabolic effect on bone, through the stimulation of osteoblast differentiation, which enhances production of osteocalcin. They reduce the ability of PTH to activate protein kinase C in osteoblasts and inhibit bone resorption [9].
Furthermore, the elevated circulating insulin levels often associated with PCOS may influence the osteoblast cells activity through direct stimulation or indirectly by reducing production of the sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein (IGFBP) [10].

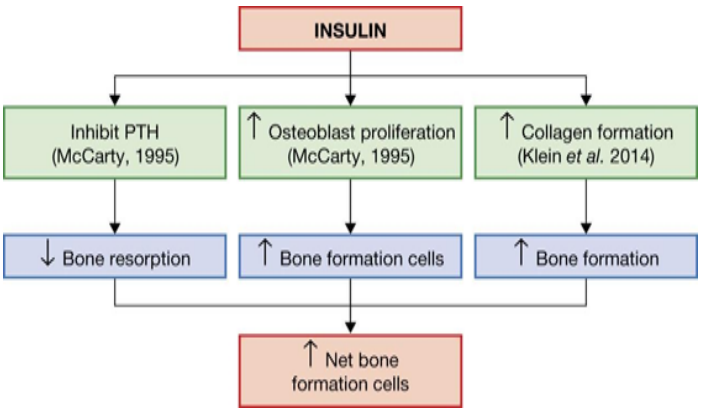

Figure 1-5 Schematic representation showing the effects of insulin on bone formation at physiological level.[11]

PCOS -Menstruation and BMD
Individuals with a known history of amenorrhea related to PCOS may not have vertebral bone density loss, or may have an increased rate of vertebral bone density loss than either healthy individuals or those with amenorrhea unrelated to PCOS. Unfortunately, research comparing vertebral bone mineral density of women with PCOS-related amenorrhea and healthy controls is lacking [7]

Vitamin D and Comorbid Conditions Deleterious Effect on BMD

There are specific comorbid conditions and treatment options that may have a deleterious effect on bone mineralization.

• First, chronic and severe vitamin D deficiency is common in patients with PCOS, and is associated with osteomalacia.[7,11]

• Secondly, Auto Immune Thyroiditis and hypothyroidism- associated BMD loss may occur through thyroxin deficiency, while BMD loss associated with thyroxin replacement therapy may be caused by thyroxin toxicity [12]. It seems that the effect of low progesterone in PCOS is primarily that it increases the risk factor of patients with PCOS for pregnancy-related disorders and loss of pregnancy [13] However, because progesterone plays a role

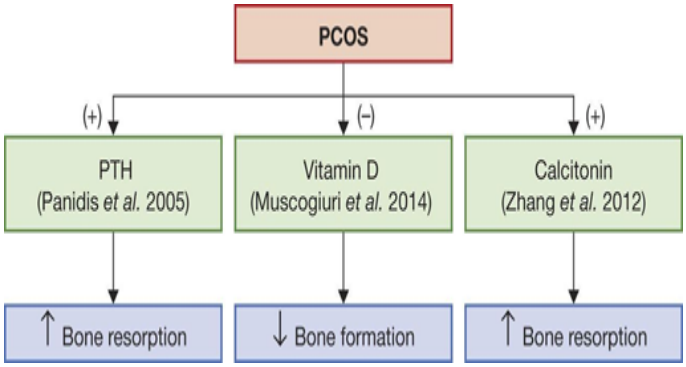

Figure 1-6 Schematic representation of the effect of PCOS on bone in relation to vitamin D, PTH and calcitonin. [11]

Bone Mineral Density: can be measured by a variety of techniques at several skeletal sites. Once measured, the manufacturers" software uses the BMD to calculate a T-score and/or Z-score. Both T-scores and Z- scores are derived by comparison to a reference population on a deviation scale. T-scores and Z-scores are widely quoted in scientific

publications on osteoporosis and BMD studies, and are the values used for DEXA diagnostic criteria and current clinical guidelines for the management of osteoporosis [14].

2 | DEXA BONE DENSITOMETRY:

DEXA is now the most commonly used technique for measuring BMD throughout the world and measurements of the lumbar spine [PA and lateral] ,hip, forearm, heel ,and total body in adults and children can be obtained, also measurement of total body composition(lean and fat body mass). The technique is simple to use with short scanning time and low radiation dose. [15].

Noninvasive bone densitometry utilizing X-ray absorptiometry enables accurate evaluation of bone mass and the diagnosis of BMD defect in asymptomatic individuals prior to fracture [16]. There is a strong inverse relationship between bone mineral density and fracture risk [14]. This relationship between BMD and fracture risk has been confirmed prospectively in a number of large well-designed studies (II-1) [14]

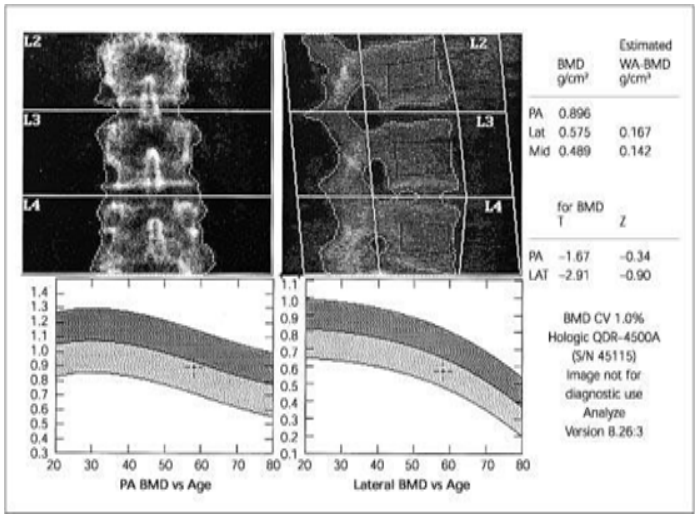

Figure 1-7 Different DEXA scans section.

Common Treatments in BMD defects: Treatment plans include lifestyle changes and exercise. In addition, patients are commonly treated with one or more of the following medications: insulin sensitizing agents, androgen blocking medication s, or hormonal contraceptive medications.

These therapies may affect the way in which PCOS affects BMD:

First, women with PCOS may be treated with oral, implantable, or injectable contraceptives as exogenous sex hormones. oligo- and amenorrhea in premenopausal women with PCOS are commonly treated by Hormonal oral contraceptives.[7] These contraceptives may prevent the BMD loss that is associated with menstrual and ovulatory dysfunction In women with oligo- or amenorrhea that is not associated with PCOS.[17] However, positive effect on BMD due to increased estrogen secretion in patients with PCOS-related amenorrhea. This may mean that any positive impact on BMD associated with hormonal oral contraceptives is absent, or that oral contraceptives do not have a similar effect in PCOS patients as the effect observed in non-PCOS patients. The bone density effect of injectable and implantable contraceptives are the subject of some medical professionals debate [18]. Treatment of PCOS-associated oligo- and amenorrhea with injectable or implantable forms of contraceptives may have an effect on the BMD of patients.

Secondly, insulin sensitizing medications like metformin hydrochloride are useful in treating PCOS, making them a common addition to many patient treatment plans. The medications are meant to staunch excessive insulin production as a response to Insulin Resistance (IR), and mitigate the production of excessive male sex hormones and follicle stimulating hormone.[17] Therefore, insulin sensitizing agents may counteract the effect of IR and hyperanderonege -mia on bone growth and development [19].

3 | LITERATURE REVIEW

• Sarah Bruckler (2017) find that no correlation was observed between cranial BMD and total BMD in the PCOS sample, but was observed in the control sample. These results suggest that

PCOS has a systemic effect on BMD independent of weight [20]

- A Katulski study (2014) show The PCOS women had lower BMD values as compared to the controls (1.057 ± 0.1260 vs. 1.210 ± 0.1805 g/cm2, p \0.0002). In the analysis of PCOS patients according to BMI, only in the subgroup of the normal weight PCOS we find significantly lower BMD in comparison to controls (p = 0.0049). In patients with PCOS, BMD was positively correlated with insulin concentration and HOMA–IR. In the controls Z-score values were positively correlated with insulin concentration and HOMA–IR.[1]
- In a study by Douchi and colleagues (2001), free androgens associated with visceral fat increased lean muscle mass in arms, legs, and the trunk, and that increased lean muscle mass was significantly associated with increased regional BMD, regardless ofload-bearing. However, the same study showed that serum androgen levels were not associated with increased BMD.[21]
- A later study determined that patients with PCOS who are lean, or whose fat is distributed more peripherally, did not have the same regionally increased BMDs as patients with viscerally distributed fat [22] It was determined that the cause of this anomaly was that peripheral fat does not produce free androgens the way visceral fat does, and the authors determined that this non-load-bearing effect of visceral fat was more significantly associated with increased BMD than its load-bearing effects.[23]
- According to Davies, Hall, and Jacobs studies, there is a significant correlation between amenorrhe a and vertebral bone mineral density loss in premenopausal women, except in women with PCOS. that hypothesize that the cause of bone mineral density loss in most cases of amenorrhea is due to estrogen deficiency.[24]
- Overall, evidence from previous studies, randomized, placebo- controlled clinical trials suggests a positive relationship between BMD and Ca intake of 1377.8 ± 631.9 in premenopausal women and to smaller extend in women around the onset of menopause [34,35]. While some other studies reported no significant association between daily dietary Ca intake of 1088 ± 489 and BMD values in premenopausal women [33]. Shapses et al. had noticed, in obese premenopausal women, negative relationships between the number of times women dieted to lose weight, the cognitive dietary restraint score and the current BMD. This may be due to insufficient amount of Ca and Vit. D intake, in absence of minerals supplementation, during the diet restrain periods as it was reflected by the high prevalence of osteoporosis (31%) [26].

4 | THE AIM OF THE STUDY

To evaluate bone mineral density in women suffering from polycystic ovary syndrome and determine the associations between Bone mineral density and insulin resistance, hyperandrogenemia, Body mass index, and sex hormones.

5 | PATIENTS AND METHODS

Study Design, Setting and Data Collection Time

This is a cross sectional study that was conducted in the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital/ Medical city during a period of seven months from April till November 2018.

Study patients and sample size

This study included 30 women diagnosed as polycystic ovarian syndrome (PCOS) attended to the outpatient clinic of gynecological department seeking for management. The data were arranged on a questionnaire paper which was designed for the study.

Exclusion criteria

Diabetes mellitus (DM), Congenital adrenal hyperplasia (CAH), Cushing`s syndrome, Androgen producing adrenal tumors, Patients with vit D3 deficiency, Pregnancy, Thyroid

disease, Hyperprolactinemia, Current use of contraceptive pills in the last six months, Patients on restrictive diet.

Diagnosis of PCOS:

Diagnosis of PCOS was done according to Rotterdam Criteria as two of the following three criteria are required [52]:

1. Oligo / anovulation,
2. Hyperandrogenism

- Clinical (hirsutism or less commonly male pattern alopecia) or
- Biochemical (raised FAI or free testosterone)

3. Polycystic ovaries on ultrasound: (an ovary with 12 or more follicles measuring 2-9 mm in diameter and\ or increased ovarian volume >10 cm3)

Clinical assessment

Detailed history including: Demographic data, Menstrual history: (Regularity and date of menarche), History of infertility: Primary or secondary, Past medical history, Past surgical history, Family and drug history.

General examination: Systemic examination and vital signs.

Body Mass Index (BMI): Is calculated by weight in (kilograms) divided by the square of height in (meters). Weight and height are measured by the same scale for all the subjects. BMI = Weight (Kg) / Square height (m^2), Participants were classified according to BMI as:

Normal ($\leq$ 24.99 kg/m^2), Overweight (25 - 29.99 kg/m^2) and Obese ($\geq$ 30 kg/m^2)

Blood sample collection and preparation (investigations)

From each polycystic woman, blood samples, which were obtained from the antecubital area early in the morning, followed 10 hours of fasting using disposable syringe on the second or third day of menstrual cycle. Withdrawal bleeding was done for patients with amenorrhea, and then blood sample obtained on the second or third day. These samples were left to stand at room temperature for 30 minutes to allow the blood to clot and then centrifuged for 10 minutes then freezing at -20 Co until assayed. Serum concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), 17 β- estradiol (E2), Testosterone (T),dehydroepiandrosterone sulfate (DHEAS), thyroid stimulating hormone (TSH), free thyroxin (fT4), fasting insulin and fasting glucose were determined. Level of 25 (OH) D was measured as it considered the best indicator of vitamin D level that give impression about the stored vitamin D level.

According to normal value of our laboratory kits; persons are at risk of vitamin D deficiency at serum 25 (OH) D concentrations < 30 nmol/L (< 12 ng/mL). Some are potentially at risk for inadequacy at levels ranging from 30 – 50 nmol/ L (12 – 20 ng/mL) .

Serum calcium levels were also measured in present sera and recorded as milligram per deciliter units (mg/dl). The normal range of serum Ca is 8.6–10.2 mg/dl . LH and FSH hormones measured to find the LH / FSH ratio.

A normal level of estradiol (E2) for menstruating women is 15 to 350 (pg/mL) .

The insulin resistance (IR) was calculated by using the homeostatic model assessment (HOMA) –IR as:

IR= Fasting blood sugar (mg/dl) * fasting insulin (µU/l) / 405 Any value ≥ 2.6 mmol/dl was considered IR[50]

1. Examination done by trans-abdominal ultrasound machine Philips HD 11 XE, using the biconvex probe C52 (frequency 3.5 MHz): (Feature of PCOS in U/S) Figure (2.1).
2. Bone mineral density (BMD) values measurement: Done by STRATOS DR Device figure (2.2).

- Lumbar spine → Effective / input dose (1.95 µSv / 41µGy).
- Femur → Effective / input dose (0.31 µSv / 20 µGy).

It measured in the lumbar spine (L1–L4) by the Dual Energy X-ray Absorptiometry (DEXA) scan. The results are expressed as BMD and the Z-SCORE in absolute values (g/cm2). Calculated Z-scores matched for age and weight. The coefficient of variation was 1.0%.

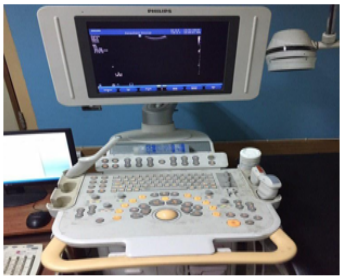

Figure (2-1) ultrasound machine

Figure (2-2) STRATOS DR Device

Statistical analysis: The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Pearson's Chi–square test was used to assess statistical association between BMD level and other variables. A level of P – value less than 0.05 was considered significant.

Ethical considerations and official approvals: Verbal permission was obtained from each patient prior to collecting data, and the information were registered. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes.

Administrative approvals were granted from the following

1. The Council of Iraqi Board of medical specialization.
2. Approval of the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital / Medical city.

6 | RESULTS

The total number of study patients was 30. All of them were diagnosed with PCOS.

... Age and BMI level

The distribution of study patients by BMI level is shown in Table (3.1). Study patient's age was ranging from 18 to 42 years with a mean of 29.1 years and standard deviation (SD) of ± 7.6 years.Concerning BMI level, it was ranging from 19.3 to 35.4 with a mean of 26.7 and SD of ± 7.33. The highest proportion of study patients was overweighed (43.3%).

Table 3.1: Distribution of study patients by BMI level

BMI Level	No.(n=30)	Percentage (%)
Normal	10	33.3
Overweight	13	43.3
Obese	7	23.4

3.2 Clinical Information

Table 3.2 shows the distribution of study patients by clinical information. In this study, the highest proportion of study patients complained from anovulation (53.3%). Concerning U/S finding, 73.3% of study patients showed features of PCOS by U/S.

Table 3.2: Distribution of study patients by clinical information

Variable	No.(n=30)	Percentage (%)
Patient History		
Amenorrhea	16	53.3
Oligo-menorrhea	14	46.7
U/S Finding		
PCOS	22	73.3
Normal Findings	8	26.7

3.3 Insulin Resistance Level

The distribution of study patients by insulin resistance level is shown in figure (3.1).it shows (76.7%) of women with PCOS had insulin resistance.

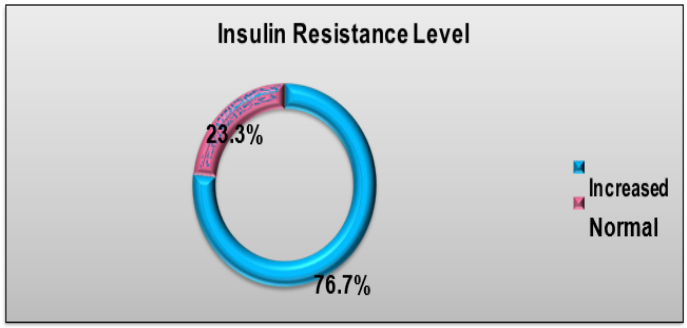

Figure 3.1: Distribution of study patients by insulin resistance levell

3.4. Investigations

The distribution of study patients by result of investigations is shown in table (3.3). We noticed that the highest proportion of study patients showed normal serum calcium level (60%); LH / FSH ratio of 3:1 (50%), low estrogen level (66.7%), and low vitamin D level (56.7%).

Table 3.3: Distribution of study patients by investigations

Investigation	No.(n=30)	Percentage (%)
Serum Calcium Level		
Low (<8.6mg/dl)	12	40.0
Normal (8.6-10.2mg/dl)	18	60.0
LH /FSH Ratio		
2:1	6	20.0
3:1	15	50.0
4:1	9	30.0
Estrogen Level		
Low (<15pg/ml)	20	66.7
Normal (15-350pg/ml)	10	33.3
Vitamin D Level		
Low (<30nmol/L)	17	56.7
Normal (>30nmol/L)	13	43.3

3.5 Bone Mineral Density (BMD) Level

Figure 3.2 shows the distribution of study patients by BMD level. The highest proportion of study patients showed low BMD level (73.3%).

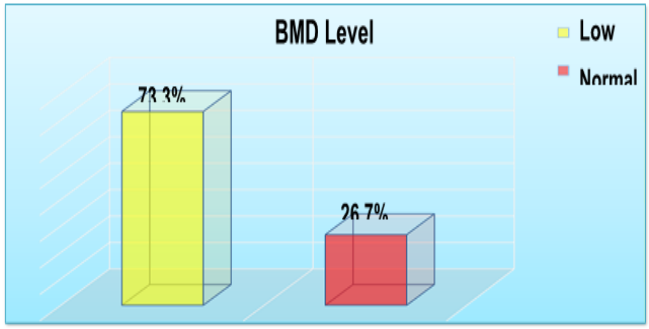

Figure 3.2: Distribution of study patients by BMD level

Table 3.4 shows the association between bone mineral density and BMI level. The highest prevalence of low level of bone mineral density was found in patients with normal BMI level (90%) with a significant association between BMI level and bone mineral density level (P= 0.008).

Table 3.4: Association between bone mineral density and BMI

BMI Level	Bone Mineral Density Level		Total (%) n= 30	P- Value
	Low n= 22	Normal n= 8		
Normal	9 (90.0)	1 (10.0)	10 (33.3)	0.008
Over weight	11 (84.6)	2 (15.4)	13 (43.3)	
Obese	2 (28.6)	5 (71.4)	7 (23.4)	

Table 3.5 shows the association between bone mineral density and insulin resistance. The highest prevalence of low level of bone mineral density was seen in patients with increase insulin resistance (82.6%) with a significant association between insulin resistance and low bone mineral density level (P= 0.037).

Table 3.5: Association between bone mineral density and insulin resistance

Variable	Bone Mineral Density Level		Total (%) n= 30	P- Value
	Low n= 22	Normal n= 8		
Insulin Resistance				
Increase	19 (82.6)	4 (17.4)	23 (76.7)	0.037
Normal	3 (42.9)	4 (57.1)	7 (23.3)	

Table 3.6 shows the association between bone mineral density and result of investigations. It was obvious that 90% of patients who had low estrogen level were showed low bone mineral density level with a significant association (P=0.003) between estrogen level and bone mineral density level. Regarding vitamin D, all patients who had low vitamin D level showed low bone mineral density level with a significant association (P= 0.001) between vitamin D level and bone mineral density level.Concerning serum calcium level, all patients with low serum calcium level were showed low bone mineral density level with a significant association (P= 0.007) between serum calcium level and bone mineral density level.

There was no significant association between bone mineral density level and LH / FSH ratio (P = 0.691)

Table 3.6: Association between bone mineral density level and investigations

Variable	Bone Mineral Density		tal (%) n= 30	P- Value
	Decrease n= 22	Normal n= 8		
Estrogen Level				
Low	18 (90.0)	2 (10.0)	20 (66.7)	0.003
Normal	4 (40.0)	6 (60.0)	10 (33.3)	
Vitamin D Level				
Low	17 (100.0)	0 (0)	17 (56.7)	0.001
Normal	5 (38.5)	8 (61.5)	13 (43.3)	
Serum Calcium Level				
Low	12 (100.0)	0 (0)	12 (40.0)	0.007
Normal	10 (55.6)	8 (44.4)	18 (60.0)	
LH /FSH Ratio				
2:1	5 (83.3)	1 (16.7)	6 (20.0)	0.691
3:1	10 (66.7)	5 (33.3)	15 (50.0)	
4:1	7 (77.8)	2 (22.2)	9 (30.0)	

7 | DISCUSSION

Overview

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder characterized by multiple hormonal imbalances and had a manifestation of Hyperandrogenism, which had a consequence on female health [27]. It affects 5–15% of premenopausal women worldwide [28]. In the current study, thirty patients participated. All of them had PCOS.

Bone Mineral Density (BMD) Level

In the this study, as shown in Figure (3.2), low BMD level found in the majority of study patients (73.3%); the highest prevalence of low level of BMD was found those with normal BMI (90%), with a significant association between BMI and BMD level (P= 0.008), as shown in table (3.4).

These results agreed with Kassanos et al study in 2010, in which mean and standard deviation (SD) of BMI in the lean PCOS women was significantly lower than the obese PCOS women (22.3 ± 2.6 vs. 32.3 ± 2.87 Kg/m2, P < 0.001) [29].

Agreement also noticed in Ganie et al study in 2018, in which lean subjects with PCOS when compared to the overweight and obese PCOS counterparts had a significant lower BMD at the hip ($p< 0.001$), neck of femur ($p=0.005$) and lumbar spine ($p< 0.001$) [30].

Similarly, Karadağ and his colleagues found in their study in 2017, that Women with BMI higher than 25 kg/m2, irrespective of whether they had PCOS or not had significantly higher lumber BMD values than those women who had BMI lower than 25 kg/m2 [(1.19 ± 0.10 versus 1.05 ± 0.10; $p<0.01$) and (1.27 ± 0.11 versus 1.15 ± 0.08; $p<0.01$), respectively], concluded that women with PCOS with normal BMI have a significant lower BMD of the lumbar spine and femur neck than over weight/ obese women and BMI was one of the determinants of BMD in PCOS women.[31].

Agreement observed in results obtained in Katulski et al study in 2014, as he found that in the subgroup of overweight/obese PCOS women, the BMD values were significantly higher in comparison to the normal weight PCOS women (1.09 ± 0.16 vs. 1.045 ± 0.11g/cm2, $P>0.05$) [32].

The postulated mechanisms of action of the excessive body weight on BMD are the insulin resistance, increase of the biomechanical forces, and increased conversion of androgens to estrogens [33]. In the present study, low level of BMD was seen significantly in patients with increase insulin resistance (82.6%, $P= 0.037$), as shown in table (3.5). Disagreement to Ganie et al study in 2018 they found no correlation between BMD at any site and fasting insulin level or insulin resistance [30].

Disagreement also found with Noyan et al results in 2004, in which a significant positive correlation between fasting insulin and total BMD and significant inverse correlation between fasting glucose/insulin ratio and lumber spine BMD after adjustment for age and BMI might indicate hyperinsulinemia and insulin resistance to be associated with higher BMD in patients with PCOS [34].Katulski and his colleagues in their study in 2014, disagreed to the current result, as found that BMDs in patients with PCOS were positively correlated with insulin concentration ($r = 0.25$, $p = 0.0347$) and insulin resistance ($r = 0.29$, $p = 0.017$) [32], similar to Karadağ and his colleagues in their study in 2017, as noticed that in PCOS group, there was a significant positive correlation between insulin resistance and lumber BMD ($r = 0.617$; $p<0.01$) and femoral neck BMD ($r = 0.654$; $p<0.01$) [31].Hyperinsulinemia often associated with PCOS may influence the osteoblast cells activity through direct stimulation or indirectly by reducing production of the sex hormone binding globulin (SHBG) in the liver and insulin-like growth factor binding protein (IGFBP) [35]. In the current study, as shown in table (3.6), low estrogen level found in 66.7% of patients and vast majority of them (90%) showed low BMD level with a significant association between estrogen level and BMD level ($P=0.003$).

Agreement noticed in Karadağ et al study in 2017, as found that, despite the positive effects of hyperandrogenemia and hyperinsulinemia, PCOS patients have lower bone mineral density due to hypoestrogenism, when found in their results, in PCOS group, lumber and femoral neck BMD value was significantly correlated with serum estradiol ($r = 0.488$; $p < 0.01$) [31].

Disagreement to the results observed in Noyan et al study in 2004, as found that estradiol levels had a positive correlation with BMD but this correlation was not statistically significant after controlling for age and BMI [34] It is well known that estrogen deficiency might result in a decline in bone mass by demineralization of the bone, leading to osteoporosis [62]. In this study, in table(3.6), LH / FSH ratio of 3:1 found in 50% of patients but no significant relation between BMD level and LH / FSH ratio ($P = 0.691$) observed. This finding agreed to Kassanos et al study in 2010, when found that LH/ FSH > 2 was higher in Lean PCOS women, while 6.66% of the obese women with PCOS had this ratio and no significant relation observed between them [29].

Finally, in regard to vitamin D and serum calcium level in the current study, all patients with low vitamin D level and low serum calcium level had a significant low BMD level (100%, $P< 0.005$) as shown in table (3.6).

Insulin Resistance Level

In the present study in Fig. (3.1), 76.7% of the patients had an increased insulin resistance. In comparison to other studies, higher results observed in Stepto et al study in 2013, which conducted on 20 overweight and 20 lean PCOS patients, 14 overweight and 19 lean body mass index (BMI)-matched control non-PCOS women, that insulin resistance was present in 62% of overweight controls and 95% of overweight PCOS, Also, concluded that overweight women with PCOS were significantly more insulin resistant than all groups including overweight controls [37].

Dissimilarity found in Chiware et al study in 2013, as observed a lower result, when they found only 34% of patients were insulin resistance [38]. Agreement to the current results found in other studies, in Cresswell et al study, they found that presence of PCOS increases insulin resistance and its presence appears to have a stronger influence than obesity on insulin resistance, as found that patients with a body mass index >25 and with PCOS were the most insulin resistant, while those with a body mass index of ≤25 and with normal ovaries were the most insulin sensitive [39] and in Rabøl et al study in 2011, as found in their study that insulin sensitivity decreased with PCOS [40] and finally, Li et al study in 2012, observed that insulin resistance and deregulation of glucose metabolism were common in PCOS women with normal glucose tolerance.They concluded that BMI ≥ 25.5 kg/m2 indicated impaired β cell function in PCOS women with normal glucose tolerance [41].

These discrepancies in reported insulin resistance prevalence in PCOS women cannot only be attributed methodological differences but also to other factors play an important role as, the lack of a consistent definition of insulin resistance between contributing studies, accuracy of the investigation used in each study and the different variable used among contributing patients.

Age and BMI level

In this study patient's age mean and standard deviation (SD) was 29.1 ± 7.6 years, ranging from 18 to 42 years. Half of patients were aged < 30 years and the other half were aged ≥ 30 years,

This result was similar to Hanan Al-Taee study in 2013, in which the mean of the participant's age was 28.4 years [42]. Dissimilarity found in Farhood study in 2017, when lower results observed, in which mean and SD of age was 25.48±3.56 years [43].

Additionally, In the Ramanand et al study in 2013, a younger PCOS patients were observed, in which found that mean and SD of age of the included patients was 22.05 ± 4.649 years, in which age group 19-22 years had the highest proportion (30.8%) [44]. Concerning BMI level in this study (table 3.1), the mean and SD was 26.7 ± 7.33, ranging from to 35.4. The highest proportion of study patients was overweighed (43.3%), while normal weight (33.3%), and (23.4%) were obese. Similarity observed to Haghnazari et al study in 2016, in which mean BMI of the PCOS patients was 26.62 kg/m2 [45]. While dissimilarity to this result observed in other studies, lower results obtained from Kensara study in 2018; in which mean body mass index of the patients participated in his study was 22.2 ± 2.6 kg/m2 [46]. While, higher results observed in a study conducted in 2017 by Kumar and their colleagues, in which the mean of BMI was equal to 30.4 kg/m2 [47].

Differences observed between studies are multifactorial, among the important factors were sample size of each study add to this, socio-economic status of the participants and the degree of education.

8 | CONCLUSION

Bone mineral density decrease in a woman with polycystic ovary syndrome due to low estrogen level, VIT D3 deficiency and insulin resistance.

Recommendations

• Large sample size in multicenter study must be included in further research.

• Early detection and treatment of low estrogen, VIT D3 deficiency, and insulin resistance in women with polycystic ovary syndrome lead to

prevent demineralization of bone and preserve the bone mineral density.

• We recommend comparing Bone mineral density between normal and PCOS women.

• Evaluation of Bone mineral density in PCOS women without VIT D3 deficiency.

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How to cite this article: Dr.Dina Faiz Dahash ET AL Bone Mineral Density in Women with Polycystic Ovary Syndrome- Baghdad Advance Research Journal of medical and clinical science. 2022;912−925. https://doi.org/10.15520/arjmcs. v8i07.455