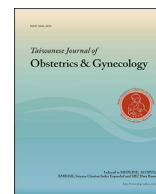




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Original Article

Evaluation of bone mineral density and its associated factors in postpartum women

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ABSTRACT

Objective: Although osteoporosis commonly appears among postmenopausal women, it is rarely diagnosed during the postpartum period as pregnancy-lactation associated osteoporosis (PAO). The aim of the study reported here was to investigate low bone mineral density and its associated risk factors in postpartum women.

Materials and methods: The sample consisted of 93 females aged 18–40 years and in the first month of the postpartum period. All the women had low back pain. The bone mineral density (BMD) Z-score values of the lumbar vertebrae, femur (neck and total) were examined using dual energy x-ray absorptiometry four weeks after birth. Patients body mass index (BMI), 25-hydroxyvitaminD (25-OHD) levels and complete blood counts were recorded. Participants were divided into two groups to their Z scores: the normal group ($n = 71$) and the low BMD group ($n = 22$).

Results: The 25-OHD levels were significantly lower ($p = .02$) in the low BMD group [4.45 (4.0–12.4)] than in the control group [22 (12–48)], however, NLR and PLR values were similar between groups. BMI positively correlated with BMD scores for the lumbar, femoral neck and femoral overall ($p = .011$, $p = .026$ and $p = .026$, respectively).

Conclusion: Vitamin D deficiency and BMI may play a critical role in PAO. Low back pain during postpartum period should be carefully evaluated. Adequate calcium and vitamin D supplementation may prevent possible bone loss.

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Introduction

A major health problem worldwide, osteoporosis (OP) affects an estimated 10 million people older than 50 years and puts another 34 million people, regardless of age, at risk of developing the disease [1]. Although OP commonly appears among postmenopausal women, it is rarely diagnosed in premenopausal women, especially during the postpartum period. To date, however, literature

addressing OP contains little information about pregnancy- and lactation-associated OP (PAO). At the same time, evidence that duration of gestation is a risk factor for low bone mineral density (BMD) remains conflicting [1]. An uncommon condition, PAO typically emerges in the third trimester of pregnancy or in the first 3 months following delivery, especially among primiparous women. Among reasons for its detection at those times, BMD is almost never assessed during pregnancy to avoid the possible teratogenic effect of radiation used in dual-energy X-ray absorptiometry (DXA). Furthermore, because the symptoms of PAO are often confused with muscle–joint pain associated with pregnancy, PAO is an often-overlooked diagnosis. In rare cases, however, PAO can cause severe loss of BMD and pathological fractures in the

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vertebrae, hip and other bones [2,3]. Common risk factors for PAO include anorexia nervosa, vitamin D or calcium deficiency, malabsorption syndromes (e.g. celiac disease), osteogenesis imperfecta, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, depression, alcoholism, low body mass index (BMI) and the use of anticoagulants, anticonvulsants, chemotherapy, immunosuppressive medication, thyroid extracts, proton pump inhibitors, antacids containing aluminium, lithium and selective serotonin reuptake inhibitors [4,5].

Because the primary function of vitamin D is to maintain normal plasma levels of calcium and phosphorus by regulating the small intestines, bones and kidneys. Vitamin D deficiency reduces the absorption of calcium and phosphorus in the intestines and, in compensation, increases parathyroid hormone secretion from the parathyroid glands. Such hormones re-route calcium from the bones to the blood in order to restore local calcium to normal levels, which causes the excessive loss of phosphorus in urine. Since calcium and phosphorus are vital to bones, their reduction weakens the bone structure, and if bone destruction persists, then osteopenia and eventually OP occur [6].

The most recent data suggest that systemic inflammation plays a critical role in OP and bone remodelling [7,9,10]. Some researchers have found that inflammatory bone loss stems from the increased activity of osteoclasts that require the receptor activator of nuclear factor kappa-B ligand (RANKL), in which cases neutrophils were the superior infiltrating cells [7].

The ratio of blood neutrophil to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR) are simple, non-invasive, cost-effective markers of inflammation in various inflammatory diseases [7]. In particular, PLR is used to determine the extent of inflammation in diverse clinical conditions [8]. Many authors have suggested that NLR and PLR are closely associated with OP [9–14], and recent studies have shown that NLR and PLR are higher in postmenopausal patients than in patients with normal BMD [9,10,14].

Because those inflammatory markers could be used together with DXA to diagnosis the PAO earlier, the aim of the study reported here was to investigate low bone mineral density and its associated risk factors in postpartum women. Given the lack of data and studies on the proposed relationship, the study marked the first to assess NLR and PLR in patients with PAO.

Material and methods

The sample consisted of 93 females aged 18–40 years and in the first month of the postpartum period. The sample excluded all individuals currently using antiresorbative drugs or taking vitamin D or calcium medication or with acute or chronic infections, history of trauma or psychiatric disorders or any secondary causes of inflammation (e.g. chronic hepatic, renal or thyroid disease, smoking, diabetes or haematological disease and malignancies). Written informed consent was obtained from all participants.

The study was conducted between October 2017 and January 2018. All participants were recorded as their parity, total duration of pregnancy and breastfeeding, weight and height. The total duration of pregnancy and breastfeeding time was calculated as months by adding up all gestational months and all breastfeeding months until the DXA measurement. Fasting venous blood samples were taken from the patients on the morning of DXA. Their 25-OHD, thyroid stimulating hormone (TSH) and parathyroid hormone (PTH) levels were measured with enzyme-linked immune assay (Advia Centour XP, Siemens, Düsseldorf, Germany) and their calcium levels with spectrophotometry (Advia 1800, Siemens, Düsseldorf, Germany). Complete blood counts were measured using an auto-haematology analyser (BC 6800, Mindray Bio-Medical Electronics, Shenzhen, China). NLR, PLR and the ratio

of monocytes to lymphocytes (MLR) were calculated using different formulae; NLR was recorded as neutrophil count divided by lymphocyte count, PLR as platelet count divided by lymphocyte count and MLR as monocyte count divided by lymphocyte count. BMI was calculated from pre-pregnancy height and weight values. Measurements were taken 4 weeks after childbirth using DXA (XR-600, Norland, Alabama, US) to obtain BMD values (g/cm^2) of the lumbar spine (L1–L4), femoral neck and femoral overall. BMD was expressed as the amount of mineral (g/cm^2) divided by normal reference values. Following the guidelines of the International Society for Clinical Densitometry, a Z score equal to or less than -2.0 indicates PAO, whereas one greater than -2.0 indicates normal BMD.

Once all baseline values were collected, participants were divided into two groups to their Z scores: the normal group ($n = 71$) and the low BMD group ($n = 22$).

Statistical analysis

Regarding the baseline characteristics of participants, values for continuous variables were summarised in $M \pm SD$ values, whereas those for categorical items were summarised in number (n) and percentage (%). The relevance of variance in normal distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Since data were non-normally distributed, the Mann–Whitney U test was used to compare parameters between the groups, after which the Spearman correlation test was administered to test the association between biochemical parameters and BMD. Statistical analyses were performed using the Statistical Package of the Social Sciences version 17.0 (SPSS Inc., IL, USA).

Ethical considerations

All procedures performed involving human participants upheld the ethical standards of the Institutional Ethics Committee and the National Research Committee, in compliance with the 1964 Declaration of Helsinki and its later amendments, or else upheld comparable ethical standards. Approval for the research was obtained from the Ethics Committee of Ankara Health Sciences University Dr. Zekai Tahir Burak Women's Health Training and Research Hospital (decision no. 151, 26 December 2017).

Results

Table 1 presents the blood counts and characteristics of participants ($n = 93$), all of whom had experienced low back pain during pregnancy or the postpartum period. The mean ages of participants in the low BMD group (29.13 ± 5.72 years) and control group (30.25 ± 6.84 years) were similar ($p = .37$), as were their mean BMI values (Low BMD: 28.14 ± 4.52 , Control: 27.46 ± 3.89 , $p = .29$). No differences between the groups in haemoglobin, white blood cell, lymphocyte, neutrophil and platelet levels were significant ($p > .05$), although 25-OHD levels were significantly lower ($p = .02$) in the low BMD group [4.45 (4.0 – 12.4)] than in the control group [22 (12 – 48)]. Although PLR and NLR were lower in the low BMD group than in the control group, the differences were not significant [128 (64 – 200) vs. 144 (71 – 450), respectively, $p = .11$; 3.52 (1.19 – 13.59) vs. 5.33 (1.0 – 37.9), also respectively, $p = .37$]. Likewise, no significant differences appeared in MLR or MPV between the low BMD group and control group [0.33 (0.12 – 0.79) vs. 0.36 (0.17 – 2.55), respectively, $p = .75$; 10.75 ± 1.34 vs. 10.78 ± 1.11 , also respectively, $p = .80$]. BMI positively correlated with BMD scores for the lumbar, femoral neck and femoral overall ($p = .011$, $p = .026$ and $p = .026$, respectively), as shown in Table 2.

Table 1
Demographic characteristics of the patients.

Variables	Normal (n = 71)	Low BMD (n = 22)	p value*
Age (years)	30.09 ± 7.16	29.05 ± 4.14	0.24
Body mass index (kg/m ²)	28.01 ± 4.57	27.6 ± 4.81	0.23
Parity	2 (1–5)	3 (1–4)	0.31
Gravida	2 (1–5)	3 (1–5)	0.63
Total pregnancy month	18 (8–45)	19 (9–36)	0.83
Total breastfeeding month	12 (0–24)	11.5 (0–48)	0.14
Hemoglobin (mg/dl)	11.31 ± 1.33	12.05 ± 1.35	0.09
TSH (mIU/l) ^a (0.5–5.0 IU/mL)	3.21 ± 1.12	2.92 ± 1.35	0.628
Calcium (mg/dl)	8.79 ± 0.57	8.64 ± 0.61	0.36
PTH (ng/ml) ^b (10–65 ng/mL)	42.28 ± 11.20	43.25 ± 12.14	0.326
25-OHVD (ng/ml) ^c (20–100 ng/mL)	22 (12–48)	4.45 (4–12.4)	0.02*
Leukocyte (g/dl)	7646 ± 2110	7984 ± 2433	0.891
Lymphocyte	2320 ± 874	2232 ± 654	0.065
Platelet (μl)	290,120 ± 67230	331,400 ± 56300	0.120
Neutrophil	1070 ± 987	1206 ± 960	0.09
MPV (fL) ^d	10.78 ± 1.11	10.75 ± 1.34	0.80
PLR ^e	144 (71–450)	128 (64–200)	0.11
MLR ^f	0.36 (0.17–2.55)	0.33 (0.12–0.79)	0.75
NLR ^g	5.33 (1–37.9)	3.52 (1.19–13.59)	0.37

Data expressed as Mean ± S.D and absolute count with percentage in parenthesis. Mann Whitney U test and student T test were test used to compare the difference between groups and *p < 0.05 considered significant.

- ^a Thyroid stimulating hormone.
^b Parathyroid hormone.
^c 25 hydroxyvitamin D3.
^d Mean platelet volume.
^e Platelet to lymphocyte ratio.
^f Monocyte to lymphocyte ratio.
^g Neutrophil to lymphocytes ratio.

Table 2
Spearman correlation analysis of body mass index, lumbar, and femur total bone mineral density.

Variables	Lumbar bone mineral density (g/cm ²)		Femur neck bone mineral density (g/cm ²)		Femur total bone mineral density (g/cm ²)	
	r	p	r	p	r	p
BMI ^a	0.262	0.011*	0.231	0.026*	0.231	0.026*

^a Body mass index, *p < 0.05 statistically significant.

Discussion

Results suggest that low BMD is common among patients with low back pain during the postpartum period. Although the data revealed that the prevalence of low BMD was 30.9%, low BMD in puerperal Asian women has been reported as 36.3% [15]. Furthermore, the incidence of possible fractures was lower among premenopausal than postmenopausal participants, possibly due to the former's closer-to-normal trabecular connectivity, greater muscle mass, thicker cortices and fewer falls [15,16]. However, pregnant women are at greater risk of fracture than non-pregnant premenopausal ones due to the high incidence of bone turnover during pregnancy [16]. Even if the risk of fracture is low in premenopausal women, precautions should be taken to increase BMD in all patients with low BMD.

Although no statistically significant difference surfaced in BMI between the groups, correlation analysis revealed that high BMI correlated positively with BMD. Several researchers have reported that low BMI is significantly associated with low BMD, and some have claimed that obesity protects against low BMD [18], though conclusions on that topic remain mixed. Recent clinical studies have shown that a high level of fat mass as well as reduced muscle mass might be a risk factor for OP and fractures due to fragility [19].

Similar to previous findings regarding the relationship of number of pregnancies, number of births and BMD, the results of

the study reported here showed no significant differences among those factors [17,20]. Turan reported that overall femoral BMD was greater among grand–grand multiparas and lumbar vertebral BMD greater in women with three or fewer children, although those differences were not statistically significant [21].

Among other results, no relationship surfaced between duration of breastfeeding and BMD. Although calcium and vitamin D intake is sufficient during lactation, prolonged lactation may also contribute to maternal bone loss [22]. In parallel, loss of BMD becomes more prominent in pregnant women after the lactation period ends [5]. Although the mechanism of that occurrence remains unclear, maternal bone loss has also returned to normal at 6–12 months after breastfeeding ends [23]. In retrospective studies on the duration of breastfeeding in menopausal women, findings that the duration of prolonged lactation did not affect postmenopausal BMD suggest that patients with OP can again have normal BMD levels during the postpartum period [23]. By contrast, however, a study in Turkey revealed that long-term breastfeeding reduced BMD [24].

The level of 25-OHD in pregnant women was significantly lower in low BMD group. In Turkey, Özkan et al. reported that vitamin D deficiency is present in approximately 80% of women of child-bearing age [25], and likewise, the postpartum rate of patients with symptoms of low back pain was as high as 92%. However, reports that serum 25-OHD levels can change in pregnancy remain conflicting; most authors have argued that no such change occurs [26,27], whereas others have observed a decrease [28].

The US Endocrine Society recommends that vitamin D levels should be > 30 ng/mL (>75 nmol/L) during pregnancy and that taking 1500–2000 IU of vitamin D per day to achieve that level is appropriate [29]. Endorsing those recommendations, The American College of Obstetricians and Gynecologists also proposes 1000–2000 IU per day of 25-OHD when a vitamin D deficiency is identified (<20 ng/mL) and recommends 600 IU per day during pregnancy but not routine screening [30].

NLR and PLR between the groups were similar. In other studies on the topic, Özturk et al. reported increased NLR in elderly

osteoporotic individuals, while Yilmaz et al. indicated that NLR might predict more than C-reactive protein (CRP) values in postmenopausal women with OP [9,10]. Several studies have also shown that elevated NLR is associated with poor prognosis in patients with OP [11,12]. However, no researchers have investigated the relationship of low BMD, NLR and PLR during the postpartum period, only in postmenopausal women with OP.

NLR and PLR are simple, easily measurable, cost-effective markers of inflammation in various diseases [12]. Of both markers, PLR, a combination of circulating platelet and lymphocyte counts, is a representative index of systemic inflammation and its severity [8]. Accumulating data suggest that inflammation plays a critical role in bone remodelling and in the pathogenesis of OP. Cauley et al. determined a significant correlation between BMD and inflammatory factors (e.g. IL1, IL-6, CRP and TNF- α) and demonstrated that women with high levels of inflammatory cytokines had an increased risk of hip fracture, which suggests the importance of inflammation in OP and the effect of inflammatory cytokines on bone metabolism [31]. PLR can also rise in postmenopausal women with OP [14]. Ultimately, no significant difference surfaced among NLR, PLR and BMD in normal and osteoporotic postpartum patients. Such findings indicate that inflammation does not play a primary role in the aetiology of premenopausal OP.

The study's limitations included its small sample and cross-sectional design, which precluded the determination of causality. In response, studies on the topic with larger samples are necessary. At the same time, no data were collected about vitamin D and calcium supplementation or exposure to sunlight, although sufficient calcium and vitamin D supplements can prevent OP and associated fractures. Last, pre-pregnancy BMD values of participants were not recorded. Since these patients are in the reproductive period, their BMDs prior to pregnancy are not known. As far as is known, low BMD plays a critical role in bone densitometry reduction, and pre-pregnancy peak bone density implies the importance of elucidating the aetiology of osteoporosis.

Conclusion

Findings indicate that vitamin D deficiency and low BMI plays critical role in OP in patients during the postpartum period. Low back pain during the third trimester of pregnancy or the postpartum period should be carefully evaluated, for distinguishing normal from pathological back pain also distinguishes the potential risk of postpartum osteoporosis, as well as major complications of osteoporotic fractures. It can prevent possible bone loss by providing appropriate doses of calcium and vitamin D supplements to pregnant women and the continuity of appropriate BMI.

Conflicts of interest

The authors declare that they have no conflict of interest.

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None.

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