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Original Article

Hyperemesis gravidarum is not a negative contributing factor for postpartum bone mineral density

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Abstract

Background: Hyperemesis gravidarum (HG), related to protracted vomiting and nausea, is a common cause of hospitalization during the first trimester of pregnancy. It can be accompanied by ketonuria, dehydration, and weight loss. Our aim was to investigate bone loss in patients with HG.

Methods: In our study, we investigated decreased bone mineral density (BMD)in a total of 79 patients (40 HG and 39 control) by means of dual energy X-ray absorptiometry (DEXA) measurements and laboratory parameters related to HG. All patients received DEXA measurement during the early postpartum period (usually two days after delivery, prior to discharge).This study was registered in the database via the Protocol Registration and Results System (PRS) (NCT03127293).

Results: There was no significant difference in DEXA results (lumbar spine and total hip) and laboratory parameters between case and control groups, although a significant difference in vitamin intake was identified between cases and controls (65% vs. 92%, respectively, $p = 0.003$). Except for low serum levels of vitamin D, other laboratory parameters were in normal range in both groups.

Conclusion: Pregnancies complicated by HG did not have decreased bone mineral density compared to those without HG. There is no evidence to relate HG to future osteoporosis.

Keywords: Decreased bone mineral density; DEXA; Hyperemesis gravidarum; Vitamin D

1. Introduction

Hyperemesis gravidarum (HG) is a disorder that is characterized by severe nausea and vomiting in the early period of pregnancy. Definition of HG includes protracted vomiting and nausea accompanied by weight loss, ketonuria, and disturbance of electrolyte balance due to dehydration. Most cases require hospitalization during pregnancy.[1] The prevalence of HG is about 0.3–2% of pregnancies.[1] However, the etiology is not well understood, and data about maternal outcomes of HG in literature are limited.[1] HG may be a heterogeneous medical condition and is mainly thought to have a genetic basis.[2]

As mentioned above, HG can cause severe electrolyte disturbances and malnutrition or even weight loss during pregnancy in some patients.[3] Mineral metabolism also changes during pregnancy, such that both excretion of urinary calcium and absorption of intestinal calcium tend to increase gradually.[4]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Elevated absorption of intestinal calcium increases when the first trimester ends. It is reported that calcium storage in the maternal skeleton accelerates during the first trimester.[4] As a consequence of prolonged fasting in HG, physical activity decreases, and the levels of hormones also change.[5] Therefore, all these metabolic fluctuations may lead to decreased BMD, which is a systemic skeletal disease characterized by low bone mass with deterioration of microarchitectural bone tissue.[4,6] On the other hand, pregnancy is a physiological event that almost every woman will experience during her life. About 50–80% of pregnant women have daily nausea and occasional vomiting in the first half of gestation.[7] The question is whether hyperemesis gravidarum is really a risk factor for decreased BMD in young adults. Although HG is a very short-term condition, might it cause decreased BMD during pregnancy? Unfortunately, an exact definition and cut-offs for intervention in decreased BMD for young adults do not yet exist.[8]

Since HG may induce alterations in bone-mineral metabolism and maternal serum hormone levels, the outcome of HG on bone mineral metabolism was investigated in this study. As HG is common and there has not been any research on its association with decreased BMD, we have concentrated on this issue. This is the first study about this topic in the literature.

2. Methods

Fourty pregnant women with a history of severe HG and 40 gestational-age-matched healthy pregnant women were enrolled in this study between June and December 2015 in Kayseri Education and Research Hospital, a tertiary teaching hospital in Kayseri, Turkey. Ethics approval for the study was obtained from Erciyes School of Medicine. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all subjects. This study was registered in the database via the Protocol Registration and Results System (PRS) (NCT03127293).

2.1. Patient selection

A total of 40 consecutive primigravid patients aged over 18 years with singleton pregnancy diagnosed with severe hyperemesis gravidarum were included in our study as the HG Group. Considering a power of 90% and Altman monogram, a minimum of 21 subjects per group sample size was determined for the study. Severe HG was defined if the following symptoms were present: admission to the hospital one or more times mostly before 20 completed weeks of gestation because of protracted vomiting and nausea accompanied by weight loss, disturbance of electrolyte balance, ketonuria, or dehydration. Because of one missed laboratory analysis, the control group comprised 39 primigravid singleton gestational-age-matched healthy pregnant women.

Patients with diagnostic confounders such as overt hyperthyroidism, stomach disease, cholelithiasis, or gastroenteritis; patients with chronic illness; patients with history of thyroid surgery, calcium and/or hormone producing tumors, systemic lupus erythematosus; and patients with eating disorders were excluded from the study. Patients with usage of steroids (including for fetal lung maturation),antiepileptic drugs, and/or low molecular weight heparin (a long-term medication known to affect bone metabolism); patients with history of osteoporosis, bone fracture at young ages in the family, and multi gestational pregnancies were also excluded from study.

2.2. Study design

All patients gave birth between 37 and 40 gestational weeks. Data regarding demographic variables including age, body mass index (BMI), parity, gravida, abortions, and vitamin usage in pregnancy were asked and recorded.

All patients underwent Standard dual energy X-ray absorptiometry (DEXA, Hologic Discovery Wi S/N 80848) during the early postpartum period (frequently within two days after birth, prior to discharge) by a single technician. Results for bone area, bone mineral density (BMD), bone mineral content (BMC), T and Z scores for lumbar spine (antero posterior projection at L1–L4) and right hip were recorded. The radiation dose for all of the scans for lumbar spine and right hip were 4.3 μSv and 4.9 μSv, respectively. According to the World Health Organization (WHO) classification system,[9] a T-score ≤ -2.5 is classified as osteoporosis and a T-score between -2.5 and -1 is classified as osteopenia. Z score is the number of standard deviations above or below the mean for patient's age, sex, and ethnicity, while T score is the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity.[9]

2.3. Biochemical analysis

Blood samples (10 mL) were drawn at the time of DEXA scans in early postpartum period and collected into ethylenediaminetetraaceticacid (EDTA)-containing sterile tubes and serum separator tubes (SSTs). Samples were centrifuged at 3000 g for 10 min at room temperature. A single technician separated the serum and plasma of samples, and samples were stored at −80 °C until the assay. Serum phosphorus (P) and calcium (Ca) were measured by ionselective electrode (ISE), and alkaline phosphatase (ALP) activity was measured by kinetic enzymatic method with reagents from Beckman Coulter on an auto-analyzer (Olympus AU5400, Beckman Coulter, Inc., U.S.A.). Serum intact parathyroid hormone (PTH) was analyzed by two-site immune enzymatic method, and 25-hydroxy D level was analyzed by competitive immune enzymatic method on a UniCel DxI 800 Immunoassay System (Beckman Coulter, Inc., U.S.A.).

2.4. Statistical analysis

All statistical analyses were performed using PASW Statistics for Windows, Version 18, SPSS, Inc. Chicago, IL, USA. Descriptive statistics of all variables were calculated.

Continuous, normally distributed data are reported as mean ± SD, while categorical data are reported as percentage. *T*-test was performed to compare means between two groups for normally distributed data, and Mann–Whitney U test was used for non-normally distributed data. $\chi 2$-test was used to compare proportions among groups for categorical data. Values of $p < 0.05$ were accepted as statistically significant.

3. Results

A total of 79 patients were included in our study. Baseline characteristics and laboratory measurements of patients are compared in Table 1. There were no significant differences concerning maternal age and BMI ($p = 0.96, p = 0.52$). Control Group had significantly higher history of vitamin usage compared to HG Group ($p = 0.003$).Serum levels of Ca, P, ALP, vitamin D, and PTH were similar between groups ($p = 0.19, p = 0.88, p = 0.96, p = 0.55, p = 0.54$, respectively). Except for low serum levels of vitamin D, other laboratory parameters were in the normal range in both groups. There were no significant differences between gravidity and parity as expected, since all patients in our study were primigravid.

DEXA results (BMC, BMD, Z and T scores) of patients are listed and compared between groups in Table 2. Mean lumbar spine (L1–L4) T and Z scores were lower than mean total hip (neck and wards) T and Z scores. Total hip score mean for all T and Z scores was within normal range, while the lumbar spine T score mean was slightly matched with osteopenia. T score is number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as mentioned above. There were no significant differences in DEXA reports and scores regarding lumbar spine and total hip between HG and control groups.

4. Discussion

The major finding of our study was that there was no clear association between HG and postpartum bone mineral density. There was no significant difference in DEXA results (lumbar spine and total hip) and laboratory parameters between HG and control groups, although a significant difference in vitamin intake was identified between groups.

Table 1
Comparisions of laboratory parameters and characteristics between groups.

	HG group N = 40 ± SD	Control group N = 39 ± SD	*p*
Age (years)	22 ± 4.20	21.82 ± 3.53	0.96
BMI	25.73 ± 4.0	26.34 ± 4.4	0.52
History of vitamin usage	65%	92%	0.003
Ca (mg/dl)	8.43 ± 0.38	8.54 ± 0.37	0.19
P (mg/dl)	3.51 ± 0.67	3.49 ± 0.56	0.88
ALP (u/L)	185 ± 45.8	184 ± 53.6	0.96
D vit (ng/ml)	14.15 ± 11.45	12.13 ± 6.22	0.55
PTH (pg/ml)	29.62 ± 18.20	32.54 ± 25.79	0.54

SD = Standard deviations, BMI = Body Mass Index, Ca = Calcium, P = phosphorus, ALP = Alkaline phosphatase, PTH = parathyroid hormone.

Table 2
Comparisions of DEXA parameters between groups.

	HG group N = 40 ± SD	Control group N = 39 ± SD	*p*
Lumbar Spine BMD (gr/cm^2)	0.925 ± 0.11	0.916 ± 0.08	0.705
Lumbar spine BMC (gr)	50.75 ± 9.15	51.07 ± 7.22	0.860
Lumbar spine T score	−1.10 ± 1.05	−1.18 ± 0.81	0.727
Lumbar spine Z score	−0.90 ± 1.03	−1.01 ± 0.83	0.654
Total hip BMD(gr/cm^2)	0.89 ± 0.12	0.87 ± 0.10	0.508
Total hip BMC(gr)	26.54 ± 4.59	26.33 ± 4.94	0.847
Total hip T score	−0.42 ± 0.99	−0.54 ± 0.89	0.596
Total hip Z score	−0.40 ± 1.0	−0.70 ± 0.80	0.232

BMC = bone mineral content, BMD = bone mineral density, SD = Standard deviations.

Bone metabolism and bone density change during pregnancy. This has been the subject of various studies in the literature.[4,10] It was suggested that pregnancy was associated with process of alterations and/or worsening in bone metabolism of the mother. Calcium transfer to fetal bones accelerates drainage of calcium from mother to fetus. Therefore in this stage, especially during third trimester, maternal bones may be prone to osteoporosis if compensatory mechanisms (such as PTH and other regulators) do not work.[4] However the process seems to be transient, as was shown in several case series studies.[11,12] Osteoporosis might be easily ignored or misdiagnosed because of similarly appearing pains in late pregnancy. After delivery, symptoms of patients typically resolved without clinical intervention within several months.[12,13] Because of its transient effects, pregnancy is not considered as a risk factor for postmenopausal osteoporosis. Therefore, routine evaluation of bone density during pregnancy did not seem to be logical or cost effective. On the other hand, it may still be reasonable in women with risk factors such as glucocorticoid therapy, restricted physical exercise, nicotine consumption, and malnutrition.[10]

Vanderspank et al.[14] reported that activity restriction, which is one of the most common treatments used in high-risk pregnancies, might accelerate decreased BMD in pregnancy. Increased bone resorption in these hospitalized pregnant patients may lead to osteopenia or osteoporosis. Moreover, women who breastfed, women with twin pregnancies, women with anorexia nervosa, and women with low BMI seem to have an increased risk of osteoporosis or decreased BMD.[14]

In this study, DEXA was performed in the early postpartum period (two days after delivery, prior to discharge). There were no significant differences in DEXA results and scores regarding lumbar spine and total hip between groups. The ages of our patients (since women in our area usually give birth at the ages of 18–20) may contribute to our results, as the rate of bone turnover in adolescents is greater than adults, and this may influence the results in DEXA and laboratory examinations. Fat and lean body mass were shown to be the predictors of bone mass in adolescents for later in life.[15] As BMI were similar between groups, the fat and body mass had no effect on the results.

Although our control group had a significantly higher history of vitamin usage compared to HG group ($p = 0.005$), serum levels of Ca, P, ALP, vitamin D, and PTH were similar between them. Therefore, we suggest that vitamin usage does not affect laboratory parameters related to bone metabolism during pregnancy. Kalkwarf et al.[16] and Sowers et al.[17] had similar results in their studies and reported that decreased BMD due to lactation could not be reversed by calcium intake. Serum vitamin D and PTH levels were not connected to bone mass turnover over the lactation period. In contrast, Aksakalet al.[18] suggested that calcium supplementation can overcome the negative effects of lactation on bone mass.

Serum levels of vitamin D were lower in both of our groups. It is already known that racial differences may occur in calcium and vitamin D metabolism. Actually, vitamin D deficiency is very common in our population.[19] Intake of vitamin D supplementation was 600−800 IU per day, and most of our patients could not orally intake enough vitamin D during pregnancy because of the wrong habitual nutrition in our country. This may be an explanation for lower vitamin D levels in our study results.

There were no significant differences in DEXA reports and scores regarding lumbar spine and total hip between groups. However, mean lumbar spine (L1−L4) T scores and Z scores were lower than mean total hip (neck and wards) T and Z scores in both groups. It has been demonstrated that trabecular bone (lumbar spine) is much more susceptible to metabolic changes than cortical bone (femoral neck, distal radius).[5,12]

The means of lumbar spine T scores were slightly matched with osteopenia in both groups. The mean ages of the groups were 22 ± 4.20 and 21.82 ± 3.53 years (HG and control group; respectively). Therefore, T scores may be misleading because these women had not yet reached peak bone mass. This may be the reason for slightly lower T scores of total lumbar spine in both groups (-1.10 ± 1.05, -1.18 ± 0.81, HG and control group, respectively).

The major limitation of our study was the small sample size. We had no data about gestational weight gain and perinatal outcome of the two groups. Also, we had no data on serum estradiol, progesterone, and beta-HCG during first trimester and postpartum period.

In conclusion, pregnancies complicated by HG showed no signs of higher risk of postpartum BMD, which would therefore not likely increase future osteoporosis risk, either. Study results indicated that there was no significant difference in postpartum BMD either in lumbar spine or total hip between HG and control groups. Because of the small sample size, the impact of HG on decreased bone mineral density should be evaluated in larger prospective trials with new bone markers.

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