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Research Article:

Bone Turnover and the Folate–Homocysteine Pathway in Women Using Combined Oral Contraceptives

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Abstract

Background: The metabolic pathways of the folate-homocysteine pathway including folic acid, vitamin B12, and homocysteine are linked to bone quality and skeletal integrity. The impact of combined oral contraceptives (COC) on this metabolic pathway and its interaction with bone turnover markers remains an area of research. **Objectives:** This study aims to investigate the association of bone turnover markers with folate-homocysteine metabolic pathways in women using COC. Methods: A total of 84 women (42 controls and 42 COCs users) were recruited, blood was withdrawn and serum was separated. Serum folic acid, vitamin B12, homocysteine, and parathyroid hormone were all measured using ELISA technique and bone turnover markers (osteocalcin, bone specific alkaline phosphatase, and C-terminal telopeptide type I collagen) were also measured. **Results:** The use of COC in women was associated with a significant increase in osteocalcin levels (4.83 ± 1.15 ng/ml) compared to controls (3.38 ± 1.13 ng/ml, p = 0.001), while folic acid levels were also significantly higher in COC users (16.40 ± 4.28 ng/ml) than in controls (12.92 ± 4.09 ng/ml, p = 0.02). Positive correlations of both folic acid and vitamin B12 with bone turnover markers (osteocalcin, bone-specific alkaline phosphatase, and C-terminal telopeptide type I collagen) were demonstrated. Homocysteine showed a positive correlation with bone-specific alkaline phosphatase. **Conclusion:** Combined oral contraceptives use is associated with alterations in the bone remodeling process and the folate-homocysteine metabolic pathway. The outcomes of the study suggest that folic acid and vitamin B12 may play a role in modulating bone metabolism, highlighting the importance of considering hormonal and nutritional status in the assessment of bone health in women using combined oral contraceptives.

1. Introduction

Bone is a dynamic tissue that is constantly remodeling through bone resorption and formation. The formation and remodeling of bone tissue is complex and regulated by various factors, including hormonal, dietary, and metabolic variables that preserve calcium homeostasis and bone integrity (1). Bone turnover markers are biomedical indicators such as osteocalcin and bone-specific alkaline phosphatase (bALP) for bone formation, while the bone resorption process is indicated through C-terminal telopeptide type I collagen (bCTX) (2). Osteocalcin is a non-collagenous protein synthesized by osteoblasts during bone formation (3). bALP, a membrane-bound enzyme also produced by osteoclasts, correlates favorably with bone ossification, while bCTX is a degradation product of type I collagen during osteoclast-mediated bone resorption (4). Such biomarkers are widely used in research and clinical studies to evaluate bone status (5). In metabolic bone diseases, variation in these indicators may offer valuable insights into overall bone metabolism or quality, even before detectable changes in bone mineral density (6).

Recent research suggested that the folate-homocysteine metabolic pathway has a significant impact on bone matrix and bone quality (7). Homocysteine is a byproduct of methionine metabolism, which is influenced by folate and vitamin B12 status (8). Numerous observational studies linked the elevated homocysteine levels to lower bone mineral density and higher fracture risks (9–11). Mechanistically, homocysteine interferes with cross-linkage of collagen, which would affect bone matrix, promoting osteoclast activity, thereby favoring bone resorption (12,13). Hyperhomocystenemia, which is connected to epidemiological studies of deteriorating bone health and an increased risk of fracture, may be associated with deficiencies in folate or vitamin B12. Furthermore, elevated levels of homocysteine combined with low vitamin B12 concentrations are associated with high bone turnover and a higher risk of fracture in elderly populations (12,14).

Bone health is also influenced by hormonal factors. Women of reproductive age frequently use combined oral contraceptives (COC), which may modify bone turnover

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markers through changes in estrogen and progesterone levels (15). While the major physiological impact of estrogen on bone is protective by inhibiting bone resorption, the overall potential impact of COC on bone health and biochemical indicators is not fully understood (16). Therefore, the current study aims to evaluate the bone health indicators and the folate-homocysteine metabolic pathway among women on COC, focusing on biochemical markers of bone turnover, vitamin status, and homocysteine levels.

2. Patients and methods

2.1. Study design, settings, and ethical considerations

In this cross-sectional observational study, which was conducted between October 2025 and March 2026, females of reproductive age who were taking COC and matched non users were included. The study was conducted in the family planning units in appropriate health centers namely Al-Wahda, Al-Noor and Al-Qahira at Ninevah Health Doctorate. The study follows the Helsinki Declaration of the World Medical Association for the ethical conduct of research involving human subjects. The work received ethical approval from the Pharmaceutical Research Ethics Committee at the College of Pharmacy, University of Mosul (reference code: PRC-25-3-13), as well as the Nineveh Health Directorate's Local Ethics Committee (code: 2025245). Participants were fully informed about the aim and objectives of the study and a written consent form was obtained. Clinical data were obtained through clinical examinations by family medicine specialists and to ensure the eligibility for the inclusion criteria of the current study, whereas demographic information was gained using a direct interview questionnaire.

2.2. Subjects

The study included a total of 84 premenopausal women aged 18 to 47 years. Control consisted of 42 women who seemed to be clinically healthy, non-obese, had no chronic diseases and were not receiving any long-term medication. COC-users consisted of forty-two participants, all of whom were premenopausal women who used COC with 150µg levonorgestrel and 30µg ethinylestradiol (Bayer, Germany). The use of COC as a contraceptive for all females for at least 6 months. Exclusion criteria comprised of premenopausal women with a history of metabolic disease, endocrine disorders, those with any hormonal therapy, those using alternative hormonal contraceptive methods such as medroxyprogesterone injections, implants, and those with renal or hepatic abnormalities.

2.3. Laboratory tests

All participants, controls and COC-users, had blood drawn for the measurement of biochemical markers. Blood was left to coagulate for 30 minutes in a test tube, and then centrifuged for 10 minutes at 3000 rpm to collect the serum, which was kept at -20°C till used for biochemical analysis. The biochemical parameters were measured using commercially available enzyme linked immunosorbent assay (ELISA) kits from SUNLONG BIOTECH (China) on the ALLSHENG Microplate reader AMR-100 in accordance with the manufacturer's instructions. The assays were osteocalcin (catalogue number: SL3489Hu), bone alkaline phosphatase (catalogue number: SL0358Hu), c-terminal telopeptide type 1 collagen (catalogue number: SL0546Hu), parathyroid hormone (catalogue number: SL1342Hu), vitamin B12 (catalogue number: SL1827Hu), serum folic acid (catalogue number: SL0722Hu), and serum homocysteine (catalogue number: SL2047Hu).

2.4. Statistical analysis

The mean value and standard deviation (mean ± SD) are used to present the data. The Shapiro–Wilk normality test was evaluated for all variables prior to selecting statistical tests. A Student's t-test was used to compare the tested data individually. The Chi-square (and Fisher's exact) test was used for statistical analysis of categorical variables and the multiple regression analysis for BMI adjustment was performed to minimized the potential effect of anthropometric differences between groups. Pearson's correlation coefficient with linear regression and 95% confidence intervals were used to calculate the correlation between the analyzed variables. GraphPad Prism version 8.0.2 was used and the data were considered statistically significant when the p-value was less than 0.05.

3. Results

A total of 84 women were enrolled in the present study. Non users of COC comprise 42 women with a mean age of 30.33 ± 9.35 as control and 42 women on COC with a mean age of 33.19 ± 7.66 as COC-users. The demographic summary in **Table 1** observed non-statistical differences in age, breast feeding history, and number of abortions between the two groups, whereas the body mass index (BMI) was significantly higher in the COC users in comparison to the controls at p <0.001, and a greater proportion of COC users had more than two births (71.43 % versus 35.71%, P<0.01). The mean duration of COC use in user group was 3.66 ± 2.87 years.

Table1. Demographic characteristics of the study participants

Variables	Control (n=42)	COC users (n=42)	P value
Age (years)	30.33 ± 9.35	33.19 ± 7.66	0.12
BMI (kg/m²)	24.05 ± 1.25	28.77 ± 5.05	<0.001*
Duration of use (years)	--	3.66 ± 2.87	--
Breast feeding (Y/N)	24/18	25/17	0.82
Number of births	**≤2**	**>2**	--
Control (No./%)	27 (64.29%)	15 (35.71%)	<0.01*
Users (No./%)	12 (28.57%)	30 (71.43 %)	
Number of abortions	**≤2**	**>2**	--
Control (No./%)	4 (9.53%)	38 (90.47%)	0.24
Users (No./%)	9 (21.43%)	33 (78.57%)	

*Data are expressed as mean ± SD or number (percentage). The control group and COC users were statistically compared using an unpaired t-test. The Chi-square (and Fisher's exact) test is used for statistical analysis of categorical variables. *: significant differences were indicated with a p value less than 0.05, BMI: Body mass index, Y: yes, N: No, %: percentage*

Table 2 showed the bone turnover markers: Osteocalcin was significantly higher in the COC groups (4.83 ± 1.15) compared to controls (3.38 ± 1.13) at a p value of 0.001. There were no significant differences in bALP and bCTX levels when comparing the control group with the COC users. The comparison of parathyroid hormone (PTH) between the control group and COC users revealed a non-significant difference. Regarding the levels of serum folic acid, the COC group showed a significantly higher value in comparison to the control group at p = 0.02. The measurement of vitamin B12 and homocysteine indicates that there is a non-significant difference in levels between the studied groups. Table 3 presents a summary of the comparison of serum levels of PTH, Vitamin B12, folic acid, and homocysteine between the two study groups (**Table 3**).

Table 2. Bone turnover markers in study participants

Variables	Control (n=42)	COC users (n=42)	P value
Osteocalcin (ng/ml)	3.38 ± 1.13	4.83 ± 1.15	0.001*
bALP (mmol/l)	29.03 ± 7.23	32.62 ± 5.90	0.11
bCTX (ng/ml)	4.91 ± 1.83	5.20 ± 1.90	0.67

*Data are expressed as mean ± SD. *: significant differences were indicated with a p < 0.05 using an unpaired t-test. bALP: bone-specific alkaline phosphatase; bCTX: C-terminal telopeptide type I collagen; NS: non-significant.*

Table 3. Serum levels of PTH, vitamin B12, and homocysteine in study participants

Variables	Control (n=42)	COC users (n=42)	P value
PTH (pg/ml)	72.63 ± 14.29	81.78 ± 18.06	0.19
Vit B12 (pg/ml)	1095 ± 286.9	1215 ± 365.2	0.35
Folic Acid (ng/ml)	12.92 ± 4.09	16.40 ± 4.28	0.02*
Homocysteine (umol/ml)	13.32 ± 3.59	12.76 ± 5.02	0.57

*Data are expressed as mean ± SD. *: significant differences were indicated with a p < 0.05 using an unpaired t-test. PTH: parathyroid hormone, Vit: vitamin.*

To determine whether the significant difference of osteocalcin and folic acid between groups could be affected by baseline BMI imbalances, the multiple linear regression analysis with group (COC users versus control) and BMI as predictors is performed (**Table 4**).

Table 4. BMI and COC-adjusted multivariable linear regression analysis of osteocalcin and folic acid

Outcome	Predictor	β (SE)	95% CI	P value
Osteocalcin (R^2 = 0.281, P < 0.001)	Group (COC vs Control)	0.106 (0.046)	0.120 to 2.008	0.028*
	BMI	0.073 (0.038)	-0.004 to 0.151	0.064
Folic Acid (R^2 = 0.183, P < 0.026)	Group (COC vs Control)	2.775 (1.227)	0.287 to 5.262	0.029*
	BMI	0.072 (0.115)	-0.161 to 0.306	0.535

*Data are expressed as a regression coefficient (β) with standard error (SE), 95% confidence interval (CI). *: significant differences were indicated with a p < 0.05 using multiple linear regression analysis. BMI: Body Mass Index, R^2: the coefficient of determination.*

For osteocalcin, the overall model was significant (R^2 = 0.281, P < 0.001). After adjusting for BMI, the group term remained a predictor showing significantly higher osteocalcin levels in COC users compared to controls (P = 0.028). In this model, BMI was a significant predictor (P = 0.064). Similarly, the overall regression analysis model of folic acid was significant (R^2 = 0.183, P < 0.026), with COC users being a predictor that associated with higher folic acid values (P=0.029), while BMI showed no independent predictor (P = 0.535).

Analysis of correlation coefficients shows a significant positive relationship between folic acid and osteocalcin, bALP, and bCTX in the COC users. The scatter plots for these relationships revealed a moderately tight linear cluster of data, demonstrating consistent positive covariation (**Figure 1**). Similarly, a significant positive correlation between vitamin B12 and osteocalcin, bALP, and bCTX was observed in the COC users, with the scatter pattern showing a visible upward linear cluster of data points that reflected consistent positive trends (**Figure 2**). Additionally, a significant positive correlation was noticed between homocysteine and bALP levels in the COC users' group (p= 0.02), the corresponding plot displayed a broad but noticeable upward cluster (Figure 3b). A slight non-significant negative correlation of homocysteine with osteocalcin and bCTX levels in the COC users (p=0.2) was detected, showing a loose and widely scattered distribution (**Figure 3a**, and **3c**, respectively).

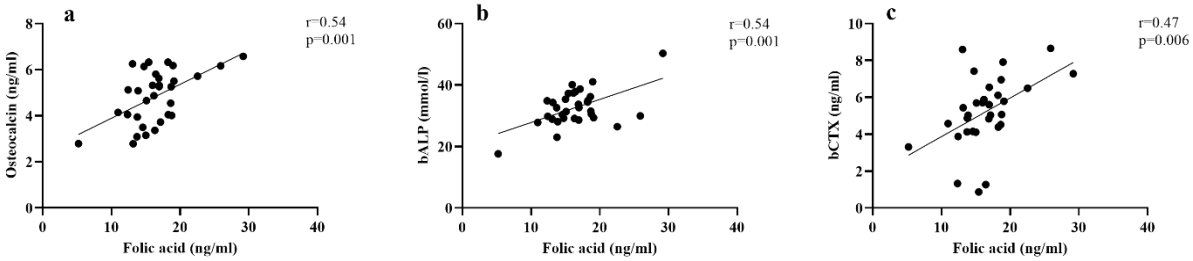

Figure 1. Correlation of serum folic acid with osteocalcin, bALP, and bCTX in users of COC

Pearson's correlation was used to assess the relationship between serum folic acid and bone turnover markers: (a) osteocalcin, (b) bALP, and (c) bCTX in users of COC. A significant positive correlation is seen, as indicated at p< 0.01. bALP: bone-specific alkaline phosphatase; bCTX: C-terminal telopeptide type I collagen.

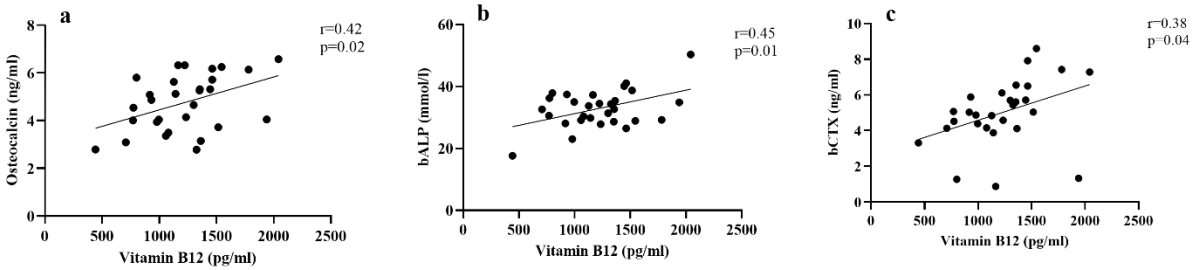

Figure 2. Correlation of serum vitamin B12 with osteocalcin, bALP, and bCTX in users of COC

Pearson's correlation was used to assess the relationship between serum vitamin B12 and bone turnover markers: (a) osteocalcin, (b) bALP, and (c) bCTX in users of COC. A significant positive correlation is seen, as indicated at p< 0.05. bALP: bone-specific alkaline phosphatase, bCTX: C-terminal telopeptide type I collagen.

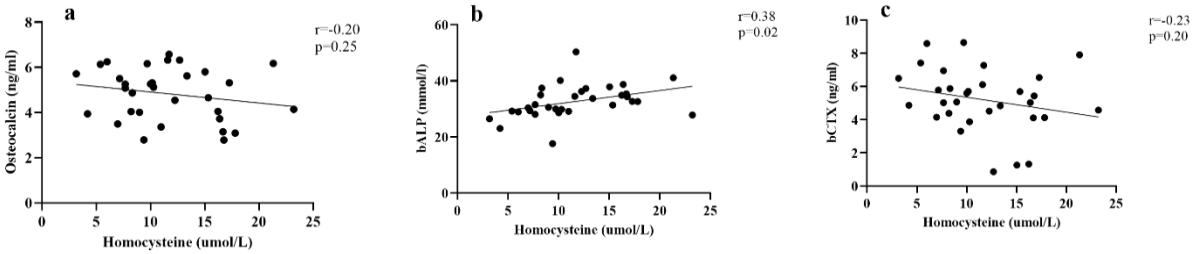

Figure 3. Correlation of serum homocystein with osteocalcin, bALP, and bCTX in users of COC

Pearson's correlation was used to assess the relationship between serum homocysteine and bone turnover markers: (a) osteocalcin, (b) bALP, and (c) bCTX in users of COC. A significant positive correlation is seen, as indicated at p< 0.02 with bALP. bALP: bone-specific alkaline phosphatase, bCTX: C-terminal telopeptide type I collagen.

4. Discussion

The present study evaluates the bone status and folate-homocysteine metabolic pathway in women using COC, with a focus on biochemical markers of bone turnover and vitamin-related metabolism. The current study showed an increase in osteocalcin and folic acid levels among COC users, along with a notable correlation of bone turnover markers with folic acid, vitamin B12, and homocysteine among women using COC, indicating a complex interplay between hormonal, micronutrient, and bone metabolism.

Bone remodeling is a dynamic process that is closely regulated through a coordinated activity of osteoclasts and osteoblasts (17). The current study found that osteocalcin had higher levels in women taking combined oral contraceptive pills, demonstrating a rise in osteoblastic activity. Such a finding is in accordance with the known protective effect of estrogen, a component of the COC, by promoting the osteoblast activity, increasing osteoblast survival and direct anti-resorptive effects on osteoclasts (18). However, the increase in osteocalcin levels could reflect either an increase in bone turnover markers associated with an active bone remodeling state or a compensatory response to acceleration of bone resorption activity (19,20).

Another interesting finding is that there is a significant increase in folic acid levels among COC users. Folate is essential for folate-mediated one-carbon metabolism, and it is required for homocysteine remethylation to methionine (21). Adequate folate concentrations are required for maintaining low homocysteine levels, as elevated homocysteine is associated with impaired collagen cross-

linking and poor bone quality (13). The increase in folic acid could be a result of diet, supplementation or various metabolic processes due to COC. Importantly, such elevation is associated with a positive impact on bone remodeling through modification of homocysteine status (12). Moreover, the lack of significant alterations in PTH levels indicates that the observed variations in bone turnover markers reflect metabolic or cellular disturbances rather than major changes in systemic PTH regulation, while still potentially affected by sex hormones.

The results of the present study revealed a considerable baseline imbalance, with COC users having a significantly higher BMI than controls. Adipose tissue acts as a metabolic organ that can significantly affect bone turnover and circulating folate levels (22), raising the possibility that the observed differences in osteocalcin and folic acid values were cofounded by BMI rather than solely attributable to COC use. Therefore, multivariable linear regression analyses were performed for each outcome to adjust for BMI. The effect of COC use remained significant for both osteocalcin and folic acid, while the BMI was not an independent predictor for either outcome.

The key finding of this research is that there is a positive correlation of folic acid with bone turnover markers (osteocalcin, bALP, bCTX) among COC users. Such a relationship suggests a direct involvement of folic acid with bone remodeling mechanisms. However, available studies on COC reported an impact of sex hormones or hormonal formulation on bone turnover markers rather than an evaluation of folic acid involvement or its correlation with these markers. In a controlled study on COC users, bCTX is significantly decreased, and there was no difference in bALP levels across COC phases, no folate indicators were measured (23). Retrievable meta-analysis reviews reported the association of bone turnover markers (osteocalcin, bALP, and bCTX) in osteoporosis with bone mineral density, fractures, and treatment response, but they do not address correlations of folate or homocysteine in COC users (24,25). One possible explanation for folate's role in bone remodeling mechanisms is that adequate levels of folic acid are required for the methylation process that is required for osteoblast activity and collagen matrix, in addition to the indirect effect on bone turnover markers through maintaining low levels of homocysteine, as mentioned above, hence reducing its negative effect on bone health (13,26). Another systematic review with meta-analysis found that a low level of folate in women is a risk factor for fracture and poor bone quality (27–29). Collectively, these suggest that folic acid status could be considered as a marker of a modest risk factor.

Similarly, this study demonstrates the positive correlation of vitamin B12 with the studied turnover markers in women using COC. Vitamin B12, like folic acid, is a cofactor in one-carbon-metabolism and essential for DNA biosynthesis and cell replication (21). Its correlation with osteocalcin, bALP, and bCTX suggests that vitamin B12 could play a role in bone formation and bone resorption. It has been reported that low vitamin B12 levels were significantly correlated with elevated osteocalcin, bALP, and bCTX (30,31). In postmenopausal women, low bone mineral density, vitamin B12, and folic acid deficiency were associated with clustered bCTX, supporting a link of vitamin B12 with bone resorption (32). Mechanistically, vitamin B12 could regulate bone metabolism through homocysteine-dependent or homocysteine-independent mechanisms (33).

An additional notable finding of the present study is the significant positive correlation of homocysteine with bALP in COC users. Hyperhomocysteinemia is linked to bone fragility mainly by promoting osteoclast-mediated bone resorption and impairing collagen cross-linking rather than a direct effect on bone mineral density (13,32,34). The observed association of homocysteine with bALP, a bone formation marker, likely reflects a compensatory response in osteoblastic activity within an overall high turnover and poor bone quality state, suggesting a complex role of homocysteine in bone metabolism.

The interplay between COC and bone turnover markers is still under investigation. Estrogen is considered bone protective, especially in estrogen deficient states. However, the net effect of COC on bone metabolism may vary in general populations depending on the age, endogenous hormonal status and nutritional adequacy (35,36). The present study finds that the impact of COC on bone health is not only hormone-dependent, but can rely on micronutrient pathways, especially those involving folate and vitamin B12.

It should be acknowledged that there was a limitation for this study including the small sample size and the fact that the cross-sectional design of the present study limits the establishment of causal relationships between the use of COC, micronutrient pathways and bone remodeling markers. Furthermore, the current study only indicates a single point correlation, longitudinal studies are required to assess bone turnover changes over time and to determine the long-term effects of COC on bone health. Moreover, it is impossible to rule out residual cofounder caused by unmeasured dietary and supplement consumption. Lastly, Bone mineral density was not measured; therefore, the clinical implications of changes in bone turnover markers remain unclear.

5. Conclusion

The present study demonstrates that the use of COC is associated with increased osteocalcin and folic acid levels, suggesting accelerated bone turnover and better folate status. Furthermore, there was significant correlation between folic acid and bone turnover markers, as well as vitamin B12 and these markers, indicating a potential involvement of one-carbon metabolism in the underlying mechanisms of the bone remodeling process. The positive correlations of homocysteine with bALP highlight the complexity of increased homocysteine levels in bone metabolism. Collectively, these findings indicate the potential impact of micronutrient status on skeletal health in women using COC through interactions with the homocysteine-dependent pathway.

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صحة العظام ومسار استقلاب حمض الفوليك-هوموسيستين لدى النساء اللواتي يستخدمن موانع الحمل الفموية المركبة

الخلاصة

المقدمة: ترتبط مسارات استقلاب حمض الفوليك-هوموسيستين، بما في ذلك حمض الفوليك وفيتامين ب12 والهوموسيستين، بجودة العظام وسلامة الهيكل العظمي. ولا يزال تأثير موانع الحمل الفموية المركبة على هذا المسار الاستقلابي وتفاعله مع مؤشرات دوران العظام مجالًا بحثيًا. **الأهداف:** تهدف هذه الدراسة إلى بحث العلاقة بين مؤشرات دوران العظام ومسارات استقلاب حمض الفوليك-هوموسيستين لدى النساء اللواتي يستخدمن موانع الحمل الفموية المركبة. الطرق: تم تجنيد 84 امرأة (42 من المجموعة الضابطة و42 من مستخدمات موانع الحمل الفموية المركبة)، وسُحبت عينات دم وفُصل المصل. تم قياس مستويات حمض الفوليك، وفيتامين ب12، والهوموسيستين، وهرمون الغدة الدرقية في مصل الدم باستخدام تقنيةELISA ، كما تم قياس مؤشرات دوران العظام (الأوستيوكالسين، والفوسفاتاز القلوي النوعي للعظام، والببتيد التيلوببتيدي الكربوكسيلي الطرفي للكولاجين من النوع الأول). **النتائج:** ارتبط استخدام موانع الحمل الفموية المركبة لدى النساء بزيادة ملحوظة في مستويات الأوستيوكالسين (4.83 ± 1.15 نانوغرام/مل) مقارنةً بالمجموعة الضابطة (3.38 ± 1.13 نانوغرام/مل، (p = 0.001، بينما كانت مستويات حمض الفوليك أعلى بشكل ملحوظ أيضًا لدى مستخدمات موانع الحمل الفموية المركبة (16.40 ± 4.28 نانوغرام/مل) مقارنةً بالمجموعة الضابطة (12.92 ± 4.09 نانوغرام/مل، .(p = 0.02أظهرت الدراسة وجود ارتباطات إيجابية بين كل من حمض الفوليك وفيتامين ب12 وعلامات دوران العظام (الأوستيوكالسين، والفوسفاتاز القلوي النوعي للعظام، والكولاجين من النوع الأول ذي الببتيد التيلوببتيدي الكربوكسيلي). كما أظهر الهوموسيستين ارتباطًا إيجابيًا مع الفوسفاتاز القلوي النوعي للعظام. **الخلاصة:** يرتبط استخدام موانع الحمل الفموية المركبة بتغيرات في عملية إعادة تشكيل العظام ومسار استقلاب الفولات-الهوموسيستين. تشير نتائج الدراسة إلى أن حمض الفوليك وفيتامين ب12 قد يلعبان دورًا في تنظيم استقلاب العظام، مما يُبرز أهمية مراعاة الحالة الهرمونية والتغذوية عند تقييم صحة العظام لدى النساء اللاتي يستخدمن موانع الحمل الفموية المركبة.

الكلمات المفتاحية: موانع الحمل الفموية المركبة، علامات دوران العظام، صحة العظام، حمض الفوليك، الهوموسيستين