The Effect of Oral Contraceptive: Different Patterns of Use on Circulating IGF-1 and Bone Mineral Density in Healthy Premenopausal Women.

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ABSTRACT

***Background**: Both insulin like growth factor-1(IGF-1) and oral contraceptive (OC) use have been linked to premenopausal breast and colorectal cancers, osteoporosis and cardiovascular disease. Understanding the effects of different patterns of use of OC on IGF-1 levels and bone mineral density (BMD) may offer insight into its influence on osteoporosis. **Methods**: We conducted a cross-sectional study of 135 women who were included into 3 groups (Group A= OC users, 43 women; Group B who never use OC, 51 women; and Group C who were past users, 41 women). Each patient completed a questionnaire on demographic parameters, marital state history, and contraception history including duration of use and type of contraceptive pills or used method. Lower end radius, proximal femur and lumbar spine BMD were measured by dual-energy X-ray absorptiometry. IGF-1 was assessed with chemiluminescent immunometric assay. **Results:** The 3 groups were matched for age and BMI, and nearly similar in total body T- value of BMD (with slight better results in past-users than the other 2 groups but it was statistically insignificant difference), but the other BMD values shows significant difference between the studied groups regarding the measurement at lumbar spine and femur which were statistically significantly better results in Group C (past users). Among past-users women the mean level of circulating IGF-1 was higher than the other 2 groups, and that difference was statistically significant. **Conclusion:** Lower IGF-1 level among current users may also potentially lead to decreased BMD, while the higher levels we observed in older past users may decrease the osteoporosis risk, reflecting observed relationship between IGF-1, BMD, and oral contraceptives.*
***Key words:** IGF-1, BMD and Oral contraceptives.*

INTRODUCTION

Insulin-like Growth Factor 1 (IGF1) is perhaps the most important mediator of muscle and bone growth [(1)]. Systemic IGF1 is synthesized primarily in the liver, where its synthesis is growth hormone (GH) dependant; IGF1 is also produced in multiple extrahepatic tissues, where it acts locally as an autocrine/paracrine growth factor under the control of multiple hormones[(2)].

The GH/IGF1 axis provides the main stimulus for bone growth regulation by activating the osteoblast differentiation program, stimulating chondrocyte proliferation at the

growth plate, and modulating tubular re-absorption of phosphate and 25-hydroxyvitamin D3 1α-hydroxylase activity in the kidney[3]. Consistent with these findings, a decline in GH and IGF1 secretion has been correlated with BMD loss in postmenopausal women [4].

Because of the role IGF1 plays in health and disease, there has been growing interest in understanding factors that influence IGF1 levels. Age is a strong predictor of circulating IGF1; ethnicity, anthropometric indices (body mass index, weight, and height), physical activity, smoking, alcohol and diet can also affect IGF1 levels [5-8].

Low bone density (T-score of less than 1 standard deviation below the mean for young adults) affects approximately 15% of young healthy women between the age of 30 and 40 years [9]. Bone density follows a bell curve distribution, and approximately 0.5% of young healthy women between the ages of 30 and 40 years have T-scores of -2.5 or less [10-11].

The World Health Organization defines osteoporosis as a progressive systemic disease characterized by low bone density and microarchitectural deterioration in bone that predisposes patients to increased bone fragility and fracture. Bone loss is a natural part of aging. Bone mass begins to increase at the time of menarche and continue to rise until the late 20s to early 30s. It is then begins to decrease[11].

In premenopausal women without fragility fractures or height loss, low BMD could simply reflect an underlying low peak bone mass. Low peak bone mass is genetically determined and also affected by environmental factors, such as inadequate exercise and dietary calcium intake, as well as smoking and excess alcohol consumption [9,12,13].

Although it is now 56 years since it was first used (in Puerto Rico, 1956), more than 100 million women worldwide, and about one in three of all females in reproductive age are using oral contraceptives (OC), there are still occasional "Pill Scares" [14].

Considerable controversy exists, however, as to whether Oral contraceptives (OCs) possess positive influences on bone. OCs has been reported to be protective agent against low BMD in several studies [14-16], but there are also conflicting results [17-18]. In a review article **Kuohung** [19] could not find any consensus on whether or not OCs use had a protective effect on BMD and bone metabolism. Conflicting results found between the Canadian multicenter osteoporosis study and the Finish study, both done on selected premenopausal women, the first found negative effect regarding use of OCs on BMD but the other one found positive correlation between OC and adjusted DXA measurements [20, 21].

A small number of studies have examined the effect of current use of OCs on IGF-1 concentrations; when compared to never users current users have significantly lower IGF-1 levels [22-23]. However, to our knowledge the present study is the first one which discusses the relation between different patterns of OCs use, circulating IGF-1 levels and adjusted DXA in premenopausal women.

METHODS

Design and Subjects:

We conducted a cross-sectional study of 135 women who were included into 3 groups (Group A= users, 43 women; Group B= never use, 51 women; and Group C= past users, 41 women). Women selected for the study were recruited from the cities of Ismailia and Port-Said. Informed consent was obtained from all subjects and the study was approved from Ethics Committee of Suez-Canal University Hospital. The exclusion criteria from the study were: (1) smoking; (2) taking drugs known to influence bone density such as corticosteroids, calcium, bisphosphonates, anticoagulants, and hormonal replacement therapy; (3) malignancy, and systemic diseases like diabetes mellitus, adrenal, hepatic and renal diseases.

Data collection and measurements:

Each patient completed a questionnaire on demographic parameters, marital state history, contraception history including duration of use and type of contraceptive pills or method used and Past history of any medical illness or hospitalization.

Bone mineral density measurements (BMD):

Lower end radius, proximal femur (trochanter, femoral neck, head), and whole lumbar spine BMD were measured by dual-energy X-ray absorptiometry with a lunar prodigy densitometer which adjusted for premenopausal women measurement. Daily quality control was carried out by measurement of a lunar phantom.

IGF-1 measurements:

Quantitative measurements of IGF-1 were done by Immulite/Immulite 1000 analyzer, which is a solid phase, enzyme labeled chemiluminescent immunometric assay [(24)].

Statistical analysis:

The primary analysis of the current study compared women who use oral contraceptive pills, women who had never use, and women who had used pills in the past and stop it for at least 2 years. Descriptive statistics are presented as means and standard deviations (SDs) for continuous variables. The ANOVA test was used for matched samples and comparison between means. The factors that remained significant or had strong association with the IGF-1, BMD were tested by multiple linear regression analysis to eliminate potentially confounding factors (age, BMI, duration of use). All analyses were performed using SPSS, version 16.0 for windows. Results with p values < 0.05 were statistically significant.

RESULTS

Table (1) shows the comparison between demographic characteristics of the studied groups. There was no statistically significant difference among the three studied groups regarding age and BMI.

Table (2) showed that there was statistically significant difference in total body T- value of BMD with better results in past-users than the other 2 groups, and the other BMD values showed significant difference between the studied groups regarding

the measurement at lumbar spine and proximal and whole femur which were statistically significant better results in Group C (=past users). The forearm T- value showed statistically significant better measurement in OC non-users and past users than the users group.

In group A the mean duration of OC use was 64.3 (±56.85) month, with a range of 5 to 204 month. There was non-significant relationship between duration of use and level of circulating IGF-1 (Table 3). Also, relationship between duration of use and BMD and T-value of spine, femur or forearm were statistically insignificant. Inspite of that the mean duration of use of OC is increasing with age groups among users (16.66 month in age group 20-25 years, compared to 117.2 month in age group 36-40 years). The relationship with levels of circulating IGF-1 was statistically insignificant ($p= 0.9$).

Among past-users women the mean level of circulating IGF-1 was higher than the other 2 groups, and this difference was statistically significant (p =0.033). Women aged 36-40 years that age group showed the best levels of IGF-1 in past-users group (mean= 202.5ng/ml).

When the correlation between IGF-1 and other parameters in each group separately and in the whole investigated women were studied; there were statistically significant correlation in the total population between circulating levels of IGF-1 and total BMD and also all differential BMD, but among the three groups the statistically significant correlations were found in non-users and past-users groups (Table 3).

Linear regression analysis for most fitting factors affecting BMD showed that the only statistically significant affecting factor was the circulating IGF-1 levels regarding the total T values and also the T-value of BMD of spine, femur and forearm (Tables 4, 5, 6 and 7). The age also was a statistically significant factor affecting the femoral BMD.

Total T value of BMD when compared in the three studied groups after adjustment for age showed statistically significant different results in age group 20-25 years which was better in past users group than other groups (p =0.001). Also, the differential BMD of femur showed the same result, that it was better in young age group of non and past users than the users group (Table 8, 9). Also, BMD of spine and forearm showed better results in nonusers and past users than the users group (Table 10, 11).

We have one women in group A, she is 40 year old, presented with fracture lower end radius, inspite that her IGF-1 circulating level was normal, she was osteoporotic in BMD (T value of forearm was -2.7), she is using OC for the last 60 months.

Table (1): Comparison between three groups regarding demographic characteristics:

	Users (n=43)	**Non users (n=51)**	**Past users (n=41)**	**p-value**
Age (years)	32.16 ± 6.4 20 – 40	32.8 ± 5.7 20 – 40	31.8 ± 6.2 20 – 40	0.7 (NS)
Weight (kg)	72.9 ± 11.4 55 – 100.8	72.3 ± 8.4 55 – 100	70.4 ± 6.08 58 – 87	0.4 (NS)
Height (cm)	160.9 ± 4.2 152 – 172	160.5 ± 3.6 153 – 170	160.6 ± 3.08 152 – 170	0.8 (NS)
BMI (Kg/m^2)	28.1 ± 3.5 20 – 37.6	28.1 ± 2.5 22.6 – 35.8	27.3 ± 2.05 22.4 – 32.7	0.3 (NS)

Data are presented as mean ± SD and range, p-value for analysis of variance test
NS: no statistically significant difference between groups
No statistically significant difference within groups (Post hoc analysis)

Table (2): Comparison between three groups regarding BMD and IGF-1:

	Users (n=43)	**Non users (n=51)**	**Past users (n=41)**	**p-value**
Total T	0.47 ± 1.05 -1.8 – 2.6	0.35 ± 1.02‡ -1.9 – 1.5	0.8 ± 0.9 -1.9 – 2.6	0.1 (NS)
Spine	-0.3 ± 1.13# -3 – 2.4	0.28 ± 0.7 -1.6 – 1.5	0.5 ± 0.8 -1.8 – 1.8	0.001*
Femur	0.2 ± 0.9‡ -1.9 – 2.2	0.5 ± 0.8 -1.6 – 1.7	0.7 ± 0.7 -1.4 – 1.9	0.03*
Forearm	-1.03 ± 0.7# -2.8 – 0.1	-0.3 ± 0.8 -2.2 – 1	-0.3 ± 0.8 -2 – 0.9	0.001*
IGF-1	143.1 ± 72.8‡	166.6 ± 79.7	187.6 ± 77.8	0.03*
	50 – 388	39 – 458	52 – 460	

*Statistically significant difference, # statistically significant difference versus other two groups,
‡ Statistically significant difference versus past users.
NS: no statistically significant difference. Data are presented as mean ± SD and range.

Table (3): Correlation between IGF-1 and other parameters in the whole studied patients and in three groups:

		IGF-1			
		Total (n=135)	**Users (n=43)**	**Non users (n=51)**	**Past users (n=41)**
Age	R p-value	0.2 0.8 (NS)	0.01 0.9 (NS)	-0.1 0.3 (NS)	0.1 0.4 (NS)
Weight	R p-value	-0.2 0.07 (NS)	-0.1 0.4 (NS)	-0.3 0.08 (NS)	0.04 0.8 (NS)
Height	R p-value	-0.1 0.2 (NS)	-0.04 0.9 (NS)	-0.2 0.1 (NS)	-0.1 0.5 (NS)
BMI	R p-value	-0.1 0.1 (NS)	-0.2 0.3 (NS)	-0.2 0.1 (NS)	0.1 0.5 (NS)
Total T	R p-value	0.5 0.001*	0.2 0.3 (NS)	0.6 0.001*	0.6 0.001*
Spine	R p-value	0.4 0.001*	0.2 0.3 (NS)	0.5 0.001*	0.5 0.001*
Femur	R p-value	0.4 0.001*	0.1 0.4 (NS)	0.6 0.001*	0.4 0.001*
Forearm	R p-value	0.5 0.001*	0.3 0.08 (NS)	0.6 0.001*	0.6 0.001*
Duration	R p-value	- -	0.02 0.9 (NS)	- -	- -

*Statistically significant correlation. NS: no statistically significant correlation

Table (4): Linear regression analysis for most fitting factors affecting total T BMD:

	Unstandardized coefficients		**Standardized β coefficients**	**t**	**p-value**
	B	**Standard error**			
Constant	-0.8	1.5		-0.58	0.6 (NS)
Age	-0.02	0.01	-0.13	-1.7	0.08 (NS)
BMI	0.017	0.029	0.047	0.59	0.5 (NS)
IGF-1	0.005	0.001	0.4	4.5	0.001*

*Statistically significant NS: not statistically significant Adjusted R square = 0.22

Table (5): Linear regression analysis for most fitting factors affecting spine BMD:

	Unstandardized		**Standardized β coefficients**	**t**	**p-value**
	B	**Standard**			
Constant	-2.665	1.37		-1.9	0.05 (NS)
Age	-0.02	0.012	-0.136	-1.76	0.08 (NS)
BMI	0.06	0.027	0.175	2.26	0.025
IGF-1	0.004	0.001	0.309	3.38	0.001*

*Statistically significant NS: not statistically significant Adjusted R square = 0.24

Table (6): Linear regression analysis for most fitting factors affecting femur BMD:

	Unstandardized		Standardized β coefficients	t	p-value
	B	Standard			
Constant	-1.189	1.229		-0.967	0.3 (NS)
Age	-0.031	0.011	-0.216	-2.76	0.007*
BMI	0.03	0.024	0.103	1.315	0.1 (NS)
IGF-1	0.004	0.001	0.34	3.69	0.001*

*Statistically significant . NS: not statistically significant Adjusted R square = 0.24

Table (7): Linear regression analysis for most fitting factors affecting forearm BMD:

	Unstandardized coefficients		Standardized β coefficients	t	p-value
	B	Standard			
Constant	-1.704	1.148		1.484	0.1 (NS)
Age	-0.016	0.01	-0.112	-1.5	0.1 (NS)
BMI	0.013	0.023	0.042	0.572	0.5 (NS)
IGF-1	0.005	0.001	0.462	5.3	0.001*

*Statistically significant NS: not statistically significant Adjusted R square = 0.33

Table (8): Total BMD of patients in different groups adjusted for age

Age group	Users (n=43)	Non users (n=51)	Past users (n=41)	p-value
20 – 25	(6) 0.2 ± 0.7	(6) 0.9 ± 0.5	(7) 1.3 ± 0.5‡	0.001*
26 – 30	(14) 0.7 ± 0.9	(14) 0.5 ± 1.1	(7) 1.1 ± 0.5	0.4 (NS)
31 – 35	(6) 0.1 ± 0.8	(12) 0.2 ± 1.02	(14) 0.5 ± 1.08	0.6 (NS)
36 – 40	(17) 0.5 ± 1.3	(19) 0.1 ± 1.05	(13) 0.6 ± 1.06	0.4 (NS)
p-value	0.6 (NS)	0.3 (NS)	0.2 (NS)	

Data are presented as number (mean ± SD) ‡Statistically significant difference versus users

NS: no significant difference

Table (9): Femur BMD of patients in different groups adjusted for age

Age group	Users (n=43)	Non users (n=51)	Past users (n=41)	p-value
20 – 25	(6) 0.1 ± 0.2#	(6) 0.8 ± 0.2	(7) 0.9 ± 0.2	0.001*
26 – 30	(14) 0.5 ± 0.8	(14) 0.8 ± 0.9	(7) 0.9 ± 0.6	0.5 (NS)
31 – 35	(6) 0.5 ± 0.7	(12) 0.4 ± 0.8	(14) 0.7 ± 0.7	0.6 (NS)
36 – 40	(17) -0.04 ± 1.3	(19) 0.3 ± 0.9	(13) 0.5 ± 0.9	0.4 (NS)
p-value	0.4 (NS)	0.3 (NS)	0.5 (NS)	

Data are presented as number (mean ± SD) #statistically significant difference versus other two Groups. NS: no significant difference

Table (10): Spine BMD of patients in different groups adjusted for age

Age group	Users (n=43)	Non users (n=51)	Past users (n=41)	p-value
20 – 25	(6) -0.9 ± 1.1#	(6) 0.6 ± 0.4	(7) 0.7 ± 0.6	0.001*
26 – 30	(14) 0.0 ± 0.8#	(14) 0.5 ± 0.7	(7) 0.8 ± 0.2	0.03*
31 – 35	(6) 0.2 ± 0.9	(12) 0.2 ± 0.8	(14) 0.3 ± 0.8	0.9 (NS)
36 – 40	(17) -0.5 ± 1.3#	(19) 0.04 ± 0.8	(13) 0.5 ± 1.05	0.04*
p-value	0.2 (NS)	0.2 (NS)	0.5 (NS)	

Data are presented as number (mean ± SD) #statistically significant difference versus other two groups
NS: no significant difference

Table (11): Forearm BMD of patients in different groups adjusted for age

Age group	Users (n=43)	Non users (n=51)	Past users (n=41)	p-value
20 – 25	(6) -0.9 ± 0.4#	(6) -0.03 ± 0.5	(7) -0.2 ± 0.5	0.001*
26 – 30	(14) -0.9 ± 0.8#	(14)-0.1 ± 0.9	(7) -0.2 ± 0.7	0.03*
31 – 35	(6) -1.1 ± 0.5	(12) -0.4 ± 0.7	(14) -0.2 ± 0.9	0.07 (NS)
36 – 40	(17) -1.1 ± 0.8	(19) -0.4 ± 0.9‡	(13) -0.5 ± 0.8	0.03*
p-value	0.8 (NS)	0.6 (NS)	0.7 (NS)	

Data are presented as number (mean ± SD) #statistically significant difference versus other two groups
‡statistically significant difference versus users NS: no significant difference

DISCUSSION

Results from one cohort study showed BMD in combined oral contraceptives (COC) users did not change significantly over 5 years follow up, whereas non-users gained 7.8% BMD ($p<0.01$). Moreover, differences between COC users and non-users were significant at 3 years and continued to widen through fourth and fifth year of follow up [25].

The findings of our cross-sectional study of present, never, and past-users of OCs suggest evidence of a significant difference in BMD and IGF-1 levels between the three studied groups.

The past-users group showed higher BMD values either total or differential (except forearm T value which was better in OCs users), Also they showed better circulating levels of IGF-1 in the elder age groups. This result is in agreement with some studies that have found positive effect of previous use of OCs on premenopausal women IGF-1 levels specially older age groups[26], and other studies found better BMD values with OCs use [16,27]. Many other studies suggest no evidence of a significant difference in BMD between the contraceptive past users and never user control groups [28-30]. The divergent results of many previous studies could be attributed to the wide range of studied age groups, duration of studies, dosage and type of OCs.

The very earliest OC pills were a combination of relatively high doses of a chemically altered estrogen, called ethinyl estradiol and a progestin, usually norethindrone. It was not long before multiple side effects were beginning to be noticed, including blood clots, strokes, hypertension, significant mood changes and depression. Early investigators attributed the side effects to the estrogen portion of the Pill and began reducing the dosage levels. Early estrogen doses were approximately 20 times the equivalent synthetic hormone that are now used in hormone replacement therapy (HRT) and ten times what's currently found in OC pills. [28]

Parous women in the general population have lower IGF-1 levels than nulliparous women [31]; after pregnancy, the risk of breast cancer is transiently increased, and is then lower for a period extending into the postmenopausal years [32]. It is possible that the decrease in IGF-1 levels in parous women accounts partially for the protective effect of parity against breast cancer.

Indeed, **Horsman et al.,** reported that postmenopausal women taking doses of estrogen (EE) between 15 and 25 mg daily experienced no bone loss, whereas those taking doses of > 25 mg daily demonstrated net gain of bone [30]. Thus, improved bone mineralization among low dose OC users is biologically plausible. Furthermore, conflicting finding may be due in large part to the longer duration of OC use. Some studies showed results support that the high-dose of OC use for more than 10 years had the greatest protection against low BMD [33,34].

In the present study we did not have the conflict of effect of type of OCs used on levels of circulating IGF-1 because all of our subjects were

third generation OCs users either group A or C. Some studies showed that 3rd generation users have higher levels of circulating IGF-1[26], and other said that the second generation is better regarding the IGF-1 level [23].

Results from one cohort study showed that BMD in combined oral contraceptives (COC) users did not change significantly over 5 years follow up, whereas non-users gained 7.8% BMD ($p<0.01$). Moreover, differences between COC users and non-users were significant at 3 years and continued to widen through fourth and fifth year of follow up [34].

Many studies discussed the effect of OC and IGF-1 levels alone, others showed the relationship between OC and BMD, but to our knowledge this is the first study to discuss the relationship between OC, IGF-1 and BMD in three groups (users, never, and past users). The limitation of our study is the small number of each group.

Conclusion: Based on the findings of the present study and data from earlier ones, it could be concluded that the relationship between OC use and osteoporosis or osteopenia risk is at least in part mediated by the IGF-1 pathway. Lower IGF-1 level among current users may also potentially lead to decreased BMD, while the higher levels we observed in older past users may decrease the osteoporosis risk, reflecting observed relationships between IGF-1, BMD, and oral contraceptives.

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تأثير الأنماط المختلفة لاستخدام حبوب منع الحمل علي مستوى عامل النمو الشبيه بالأنسولين-١ في الدم و علي كثافة العظام في السيدات الأصحاء فى فترة ما قبل انقطاع الطمث

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ان عامل النمو الشبيه بالأنسولين-١ و حبوب منع الحمل قد يكونا لهما علاقة ببعض الأمراض مثل سرطان الثدي ، سرطان القولون و هشاشة العظام. وان الأنماط المختلفة لاستخدام حبوب منع الحمل قد يكون لها تأثير علي مستوى عامل النمو الشبيه بالانسولين-١ فى الدم و كذلك على كثافة العظام وبالتالى قد يكون لها علاقة بمرض هشاشة العظام. لذلك كان الهدف من هذه الدراسة هو توضيح هذا التأثير على مستوى عامل النمو الشبيه بالانسولين-١ وعلى مستوى كثافة العظام فى مجموعة من السيدات الأصحاء فى مرحلة ما قبل انقطاع الطمث و تمت الدراسة على ١٣٥ سيدة تم تقسيمها الى ٣ مجموعات : المجموعة (أ) :٤٣ سيدة من المستخدمات لحبوب منع الحمل، المجموعة (ب) : ٥١ سيدة من غير المستخدمات لحبوب منع الحمل و المجموعة (ج) : ٤١ سيدة من المستخدمات فى الماضى (فى فترة سابقة للدراسة لا تقل عن سنتين). و قد تم قياس عامل النمو الشبيه بالانسولين-١ باستخدام جهاز immulite ، وتم قياس كثافة العظام لكل المشاركات فى الدراسة وتم ملئ استمارة توضح بيانات كل سيدة ونوع الحبوب المستخدمة و مدة استخدامها. و قد أظهرت النتائج فرقا ذا دلالة احصائية بين مجموعات الدراسة بالنسبة لكثافة العظام فى العمود الفقرى و عظمة الفخذ حيث كانت المجموعة المستخدمة في الماضى أكثر كثافة من المجموعات الأخرى. وكذلك مستوى عامل النمو الشبيه بالانسولين-١ كان أعلى فى المجموعة المستخدمة فى الماضى عن المجموعات الأخرى وكانت هذه الزيادة ذات دلالة احصائية و نستنتج من الدراسة أن نقص عامل النمو الشبيه بالانسولين-١ في السيدات المستخدمات لحبوب منع الحمل ربما يؤدى الى نقص كثافة العظام بينما المستويات الأعلى من عامل النمو الشبيه بالانسولين-١ فى السيدات المستخدمات فى الماضى ربما يقلل من خطر الاصابة بمرض هشاشة العظام ولذلك ربما تكون هناك علاقة بين عامل النمو الشبيه بالانسولين-١ و كثافة العظام والأنماط المختلفة لاستخدام حبوب منع الحمل.