Original Article

Serum Calcium Level is Associated with Lipids in Young Nigerian Women Using Low-Dose Oral Contraceptive Pills

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ABSTRACT

Background: The formulation of low-dose oral contraceptive pill (OCP) has not been able to completely eliminate the cardiovascular risks associated with its use. Studies have associated serum calcium with metabolic syndrome, high blood pressure and lipids in the general population. Aim**:** To examine the association of serum total calcium with lipids levels and blood pressure in young Nigerian women who use OCP. **Subjects and Methods:** Fasting serum triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), very low-density lipoprotein cholesterol (VLDL-c), total lipids and total calcium were assayed in 160 young women (110 OCP users and 50 controls) using colorimetric methods. Body mass index (BMI) and blood pressure were also measured. **Results:** Serum triglyceride (1.19(0.01) vs 0.94(0.02), total cholesterol (4.08(0.06) vs 3.52 (0.05), LDL-c (1.79(0.04) vs 1.24 (0.02), VLDL-c (0.25(0.02) vs 0.18(0.03), total lipids (7.55(0.2) vs 6.26(0.2), total calcium (2.25(0.01) vs 2.06(0.03), systolic (108.9(0.9) vs 103.1(0.9) and diastolic (67.7(0.7) vs 65.0(0.5) blood pressures were significantly higher ($P < 0.001$) in OCP users than non-users. Conversely, HDL-c levels in OCP users were lower (1.77(0.08) vs 1.84(0.02); $P = 0.30$) compared with non-users. Serum calcium positively correlated with blood pressure and lipid parameters except HDL-c in women OCP users. Women on OCP who had lower serum total calcium levels had statistically significant lower lipid parameters while those women on OCP who had higher serum calcium levels had significantly higher lipid parameters. The BMI of both study population and control was not significantly different. **Conclusion:** Low-dose OCPs induce increased levels of serum lipids, calcium and blood pressures. Serum total calcium level was positively associated with blood pressure, measured lipid parameters except HDL-c in women on OCP. These data suggest that serum calcium may have some influences on lipids and blood pressure in subjects who use OCP irrespective of their BMI.

KEY WORDS: Blood pressure, oral contraceptive pill, serum total calcium, total lipids and lipoproteins

INTRODUCTION

The use of oral contraceptive pills (OCP) by Nigerian women has increased over the years. The report of the family planning Survey carried out by the Federal Office of Statistics indicated a substantial increase in the rate of OCP use among Nigerian women of reproductive age.[1] Prior to the introduction of low-dose OCP, the first generation of OCP which contained high dose ethinyl estradiol (≥50 μg) and progestin were associated with several adverse effects including cardiovascular risk factors.[2] In order to minimize the adverse effects, low-dose OCP was formulated.[2-4] The introduction of this low-dose OCP did not completely eliminate the association of OCP use with cardiovascular and other risks.[5] We previously reported on the effect of OCP on some lipids and electrolytes levels in women of different hemoglobin genotypes[6] and effect of duration of OCP use on lipid levels.[7] Tanis *et al.*[8] reported that hypercholesterolemia was the most important risk factor for myocardial infarction in women who are users of OCP. It was observed that association of OCP with other risk factors may lead to changes in the cardiovascular risk profile. Studies that investigated arterial events in OCP users have shown some associations with clinical identifiable risk factors such as obesity and hypertension.[9,10]

Serum calcium plays an important pathophysiologic role in cardiovascular[11] and kidney functions.[12] Studies have reported an association between serum calcium and

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metabolic syndrome,[13] high blood pressure,[14] and lipids[15] in the general population. Calcium deficiency may lead various diseases such as osteoporosis, arthritis, hypertension[16] while its excess also has negative consequences on the reproductive health in experimental animals.[17] Excess calcium salt in the body has been reported as castrative agent[18] but others contradict its chemocastrative role.[19] Calcium has been reported to have oxidative and nitrosative stress effects in the body.[20] High calcium levels in the body main lead to decrease body weight of testes and other accessory sex organs in a dose- and time-dependent manner. The mechanism by which excess calcium correlates negatively with body weight could be either by increasing core body temperature[21] or reduced body fat accumulation.[22] Excess calcium has also been reported to affect the concentration of sex hormones in rats.[9] Report on the association of serum calcium with lipids and blood pressure in women who are users of low-dose OCP is scarce. High serum calcium levels were observed to be positively associated with high blood pressure in a representative sample of United States of American adults without cardiovascular diseases (CVDs) which was independent of age, sex, race, alcohol, smoking, diabetes, lipids, serum albumin, serum vitamin D and phosphorus.[23] Calcium is an important intracellular messenger that is involved throughout the life cycle of an organism to control very many biological processes.[24] Subjects with calcium intake above the estimated average requirement (EAR) exhibited significantly greater serum high-density lipoprotein cholesterol (HDL-c) levels than those with a calcium intake below EAR.[25] It was suggested that diabetes mellitus and CVDs are linked by a common defect of divalent cation metabolism including calcium.[26] Epidemiological evidence shows link between abnormality of lipid profile and variations in calcium levels. There is need to know whether an increase in the levels of serum calcium are associated with changes in lipid concentrations in women who are users of OCP. This study therefore examines any possible association between serum total calcium and lipid levels as well as blood pressure in ambulatory young Nigerian women who were current users of OCP.

SUBJECTS AND METHODS

Subjects' preparation

After ethical approval by relevant authorities, all subjects who gave informed consent and met the inclusion criteria were consecutively recruited in the study. They consisted of 110 young women on OCP and 50 young women non-OCP users who were on typical Nigerian diet of high carbohydrate and low fat. The study group was receiving combined biphasic lo femenal tablets (Wyeth Laboratory Inc. Philadelphia, USA) which contains 0.03 mg ethinyl estradiol and 0.3 mg norgestrel for a minimum of 6 months. They were subjects with regular menstruation, no history of metabolic disease and were not on calcium supplementation. The control group was young women with consistent menstrual cycle for the last six consecutive months, no history of metabolic disease, not on calcium supplementation and no history of hormonal therapy within the last 6 months before investigation. Demographic data were obtained with the help of structures questionnaires. The height, weight and blood pressure of both study subjects and controls were measured. Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg in light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). Blood pressure was measured twice and the latter was used in the analysis, in a sitting position after a minimum of 10 minutes of rest using a mercury sphygmomanometer.

Laboratory methods

After an overnight fast, venous blood sample was collected into plain tube in order to obtain serum for lipids and total calcium determinations. The blood was allowed to clot at room temperature and serum collected after centrifugation at 3000 rpm for 10 minutes. The serum was stored at -20°C and analyzed within 5 days. Serum triglyceride, total cholesterol and HDL-c were assayed by enzyme catalyzed colorimetric technique using kits supplied by Randox Laboratories, UK. While low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation. Total lipid was determined using the method of Zollner and Kirsch.[27] Total lipids react with sulfuric acid, phosphoric acid and vanillin to form a pink colored complex. A 50 µl of serum or standard lipid was added to 2 ml concentrated sulfuric acid. The tube was mixed, plugged with cotton wool and stand in a boiling water bath for 10 minutes. After 10 minutes, the test-tube was removed and then cooled in a cold water bath. A 10 µl of the mixture from the above solution was added to 2.5 ml of color reagent. This was mixed and allowed to stand at room temperature for 30 minutes. The absorbance was then read at 540 nm against a reagent blank. Serum total calcium was assayed by end point colorimetric method using *o*-cresolphthalein complex one reagent. Quality control sera were included in the assays to ensure accuracy of measurements.

Statistical analysis

Data are presented as mean (SEM). The Students *t*-test was used to compare the mean values of measured variables between the study group and controls. Pearson correlation coefficient was calculated to evaluate the relationship between serum calcium and other measured variables. Statistical analysis was performed using the statistical package for social sciences (SPSS-16, Chicago, USA) and a *P* value less than 0.05 was considered significant.

RESULTS

A total of 160 ambulatory young Nigerian women (110 °OCP users, 50 controls, mean (SEM) age 24.1(4) vs 25.2(3), BMI 28.7(1.2) vs 27.8(1.5) were included in the study. Table 1 shows the general characteristics and measured biochemical variables in women who are current OCP users compared with non-OCP users (Controls). The mean age of the 110°CP users was not significantly lower ($P = 0.80$) compared to the control subjects. The BMI of both study population and controls was not significantly different ($P = 0.50$). Both systolic and diastolic blood pressures of OCP users was significantly higher ($P < 0.001$) compared to non-OCP users. Similarly, serum triglyceride, total cholesterol, LDL-c, VLDL-c and total lipids were significantly higher in OCP users than non-OCP users. Serum total calcium levels was significantly higher ($P < 0.001$) in the study group compared with the control group. Conversely, HDL-c levels in OCP users were lower compared to non-OCP users. The different was however not statistically significant ($P = 0.30$). Serum total calcium correlated positively ($P = 0.05$) with blood pressures, triglyceride, total cholesterol, total lipids and LDL-c ($P = 0.04$), but HDL-c did not correlate with serum total calcium in women OCP users. Only total lipids significantly correlated ($P = 0.05$) with serum calcium in non-OCP user [Table 2]. In order to better appreciate the relationship between serum total calcium and measured lipid parameters, the serum levels of triglyceride, total cholesterol, HDL-c, LDL-c, VLDL-c and total lipids were stratified based on serum total calcium levels. Women OCP users who had serum total calcium concentrations of 2.0-2.05 mmol/L had significantly lower ($P < 0.001$) levels of triglyceride, total cholesterol, LDL-c, VLDL-c and total lipids compared to those women OCP users who had serum total calcium levels of 2.06-2.30 mmol/L. Those with lower serum total calcium levels had slightly higher but not statistically significant HDL-c level compared with women on OCP who had higher serum total calcium levels. When the mean values of lipid parameters in subjects who had serum calcium concentrations of 2.0-2.05 mmol/L were compared with those who had higher calcium levels (2.06-2.30 mmol/L), statistically significant differences were observed at various levels of significance. Among the control subjects, those who had serum calcium levels of 2.06-2.30 mmol/L have elevated levels of measured parameters when compared with those who lower calcium levels (2.0-2.05 mmol/L), but only triglyceride and VLDL-c were statistically significant ($P = 0.02$) [Table 3]. Higher atherogenic lipid indices were observed in OCP users with higher serum calcium levels than those with lower serum calcium levels. Serum calcium failed to show a significant correlation with systolic ($P = 0.92$), diastolic ($P = 0.91$) blood pressure, triglyceride ($P = 0.09$), total cholesterol ($P = 0.98$), HDL-c ($P = 0.93$), LDL-c ($P = 0.08$) and VLDL-c ($P = 0.09$).

Table 1: General characteristics and measured biochemical variables in women on low-dose OCP compared with control subjects (mean±SEM)

Measured variables	Women on OCP	Controls	*P* value
Age (years)	24.1 (4.0)	25.2 (3.0)	0.80
Body mass index	28.7 (1.2)	27.8 (1.5)	0.50
Systolic blood pressure (mmHg)	108.9 (0.9)	103.1 (0.9)	<0.001
Diastolic blood pressure (mmHg)	67.7 (0.7)	65.0 (0.5)	<0.001
Triglyceride (mmol/l)	1.19 (0.01)	0.94 (0.02)	<0.001
Total cholesterol (mmol/l)	4.08 (0.06)	3.52 (0.05)	<0.001
HDL-c (mmol/l)	1.77 (0.08)	1.84 (0.02)	0.30
LDL-c (mmol/l)	1.79 (0.04)	1.24 (0.02)	<0.001
VLDL-c (mmol/l)	0.25 (0.02)	0.18 (0.03)	<0.01
Total lipids (g/l)	7.55 (0.20)	6.26 (0.20)	<0.001
Total calcium (mmol/l)	2.25 (0.01)	2.06 (0.03)	<0.001

OCP – Oral contraceptive pill; HDL – High-density lipoprotein cholesterol; LDL – Low-density lipoprotein cholesterol; VLDL – Very low-density lipoprotein cholesterol; SEM – Standard error of mean

Table 2: Relationship between serum calcium and other measured variables in women on OCP and controls

Parameters	Women on low-dose OCP (*n*=110)		Control subjects (*n*=50)	
	r value	*P* value	*r* value	*P* value
Calcium and systolic blood pressure	0.199	0.05	0.168	0.46
Calcium and diastolic blood pressure	0.198	0.05	0.166	0.48
Calcium and triglyceride	0.217	0.043	0.170	0.45
Calcium and total cholesterol	0.223	0.042	0.168	0.46
Calcium and LDL cholesterol	0.234	0.02	0.166	0.48
Calcium and HDL cholesterol	0.196	0.06	0.169	0.46
Calcium and total lipids	0.218	0.043	0.276	0.05

OCP – Oral contraceptive pill; HDL – High-density lipoprotein cholesterol; LDL – Low-density lipoprotein cholesterol

Table 3: Serum lipids levels in relation to calcium concentration in women on OCP and controls

Measured parameters	Mean calcium levels in OCP users			Mean calcium levels in non-OCP users		
	2.0-2.05 mmol/l (*n*=66)	2.06-2.30 mmol/l (*n*=44)	*P* value	2.0-2.05 mmol/l *n*=41	2.06-2.30 mmol/l *N*=09	*P* value
Triglyceride (mmol/l)	0.98 (0.08)	1.50 (0.04)	<0.001	0.94 (0.02)	1.00 (0.02)	0.02
Total cholesterol (mmol/l)	3.71 (0.04)	4.60 (0.02)	<0.001	3.45 (0.02)	3.83 (0.20)	0.08
LDL-cholesterol (mmol/l)	1.74 (0.05)	1.86 (0.04)	0.004	1.17 (0.02)	1.38 (0.14)	0.06
HDL-cholesterol (mmol/l)	1.78 (0.02)	1.74 (0.60)	0.5	1.81 (0.01)	2.07 (0.12)	0.07
VLDL-cholesterol (mmol/l)	0.20 (0.01)	0.32 (0.05)	0.04	0.44 (0.01)	0.47 (0.01)	0.02
Total lipids (g/l)	6.82 (0.20)	8.64 (0.20)	<0.001	6.30 (0.95)	6.67 (1.91)	0.08

OCP – Oral contraceptive pill; HDL – High-density lipoprotein cholesterol; LDL – Low-density lipoprotein cholesterol

DISCUSSION

These data indicate an association between serum calcium and measured lipid levels in women on OCP. A positive correlation was observed between triglyceride, total cholesterol, LDL-c, VLDL-c, total lipids and total calcium levels in women who use OCP. The present study is consistent with others.[28,29] Abdel-Barry *et al*.[28] observed that serum triglyceride, total cholesterol, HDL-c and VLDL-c levels were significantly higher in OCP users compared

to non-OCP users, but LDL-c level was significantly lower. This observation of lower LDL-c in OCP users disagreed with ours where LDL-c was equally higher in OCP users. Some authors[1] reported that African American women who use low-dose OCP had worse glucose tolerance and triglyceride levels. It was also stated that the differences between OCP users and non-OCP users in cardiovascular risk factors were greater in the subgroup of non-obese women on OCP. This observation may indicate additional health risks for non-obese women on OCP. This is important because our study participants were non-obese judging from their BMI values. The observed increased in triglyceride, total cholesterol, LDL-c and VLDL-c in OCP users may be attributed to enhanced hepatic synthesis and secretion of triglyceride-rich particles,[30] total cholesterol and modulation of LDL receptor activity.[28-31] Several authors have shown that increased triglyceride levels are independent risk for CVD[32] and total cholesterol a strong predictor of coronary risk especially at young age.[33] The observed decrease in HDL-c may be due to up-regulation of hepatic lipase activity by androgenic effect of progestin leading to increased clearance of HDL-c, thereby lowering the circulating HDL-c levels.[30] Even though estrogen has the ability to inhibit hepatic lipase activity, it is our belief that the overall net effect favors progestin in the regulation of HDL-c in users of OCP. This observation is slightly different from that reported by Kim *et al.*[25] They observed that in patients with diabetes mellitus, calcium was protective against decreasing HDL-c levels without elevating total cholesterol levels. The proposed mechanisms by which total calcium affects lipid metabolism are that calcium interferes with lipid absorption in the gut since it can bound to fatty acids and bile salts hydrolase.[15] While HDL-c increasing effect of calcium may be through a reduction in the activity of plasma cholesteryl ester transport protein (CETP).[25]

We observed a significant association between measured lipoproteins except HDL-c and serum total calcium in OCP users. A subgroup of women OCP users with calcium levels of 2.0-2.05 mmol/L had the lowest concentrations of total lipids and lipoproteins, while those with higher total calcium levels (2.06-2.3 mmol/L) had the highest concentrations of the measured lipids. Similar associations between lipids and total calcium were reported in a number of studies[34,35] even in the general population without any observed confounders. Calcium has been reported to modulate lipid metabolism in both experimental animals and human studies.[25] Cobb *et al.*[36] observed that OCP use may be detrimental to bone health in exercising women with normal menstrual cycles. Studies have also shown that physically active women on low-dose OCP had reduced bone mineral density (BMD) compared with physically active women who do not use OCP.[37,38] Studies associating OCP use and calcium are inconsistent, while some linked OCP use to decrease in stress fracture risk[39] others observed no association.[40] Subjects treated with gonadal steroid combination were reported to achieve a positive calcium balance with occasional concomitant fall in serum calcium levels.[40] The observed association of OCP use with serum calcium in this study is agreement with other studies.[41-43] It was suggested that OCP may play some roles in calcium homeostasis bringing about an overall increase in calcium mobilization from the bone resulting in bone demineralization, which may predisposes subjects on OCP to osteoporosis.[41] The mechanism by which OCP usage affects calcium levels is by increasing intestinal absorption of dietary calcium and tubular re-absorption through the actions of parathyroid hormone (PTH). The Estrogen content of OCP appears to inhibit bone mineralization perhaps by reducing the response of bone to circulating PTH or by directly altering PTH levels. Parathyroid hormone increases the activity of 1α-hydroxylase enzyme, which converts 25 hydroxy cholecalciferol to 1,25 dihydroxycholecalciferol. This active form of vitamin D regulates serum calcium levels by increasing calcium absorption from diet in the intestine and tubular re-absorption of calcium in the kidney.[15,25]

A large Swedish health screening survey reported that changes in calcium metabolism, even within the physiological range, were related to increased blood pressure, impaired glucose tolerance and dyslipidaemia.[44] The increased serum total calcium levels in some subjects on low-dose OCP may be due to increased intestinal absorption, renal absorption, increased skeletal resorption or a combination of these factors since these activities are mediated by parathyroid hormone (PTH).[10] However, several studies on cardio-metabolic outcomes failed to observe clinically significant effects of vitamin D supplementation.[18] The positive association between total calcium and blood pressure as observed in this study is consistent with others.[19,45] Yao *et al*.[45] reported that serum calcium may have an influence on blood pressure of older male subjects with hypertension and in blood lipid profile of normotensive subjects. Willett *et al*.[46] previously reported an increased risk of hypertension among current users of low-dose OCP, a frequency that was highest among long-term users. Women with a history of high blood pressure may respond readily to the hormonal stimulus of OCP with greater increase in blood pressure.[46] It was concluded that subjects who use OCP may be monitored more closely and thus are more likely to be diagnosed with increased blood pressure than non-OCP users. Even though the mechanisms involved in the production and maintenance of OCP-induced high blood pressure are not fully understood, the rennin angiotensin system has been implicated.[46] The good news is that changes in blood pressure induced by OCP are reversible in a short time. Some authors reported that increased blood pressure returned to pre-treatment levels within 3 months in

a group of women who discontinued OCP after 1-3 years of use.[46] On the other hand, a cross-sectional study of women on OCP did not observed any significant differences in mean systolic and diastolic blood pressure.[47] Bloch[48] even observed a slight fall (<2 mmHg systolic and <4 mmHg diastolic) in blood pressure among women on OCP which contain different doses of progestin.

The limitations of this study are the sample size and the inability to measure ionized calcium. Serum total calcium is a combination of three forms in the circulation: Ionized or free (50%), protein-bound (40%) and soluble form complexed with anions such as bicarbonate and phosphate (10%). The ionized calcium is the physiologically active form in the circulation which is an accurate indicator of calcium homeostasis.[49] But its measurement is not readily done in our setting; hence, total calcium is routinely used in clinical practice to assess calcium status. In studies that evaluated ionized calcium levels, no association was reported between ionized calcium and blood pressure in several studies.[50,51]

CONCLUSION

Serum calcium, measured lipid parameters, except HDL-c and blood pressure were elevated in subjects using low-dose OCP. Among OCP users, the sub-group of women with higher serum calcium levels had increased atherogenic lipid indices compared to those with low serum calcium levels. Serum total calcium level correlated positively with blood pressure, measured lipid parameters except HDL-c in women on OCP. These data suggest that serum calcium may exert some influences on lipids and blood pressures in women who use OCP irrespective of their BMI.

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REFERENCES

1. Planned News. A newsletter of the planned parenthood federation of Nigeria. June 1993;6:1-3.
2. Frempong BA, Ricks M, Sen S, Sumner AE. Effect of low-dose oral contraceptives on metabolic risk factors in African-American women. J Clin Endocrinol Metab 2008;93:2097-103.
3. Godsland IF, Crook D, Wynn V. Clinical and metabolic considerations of long-term oral contraceptive use. Am J Obstet Gynecol 1992;166:1955-63.
4. Piper JM, Kennedy DL. Oral contraceptives in the United States: Trends in content and potency. Int J Epidemiol 1987;16:215-21.
5. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. Ann Intern Med 1998;128:467-77.
6. Uadia PO, Famodu AA, Emokpae MA. Effect of oral contraceptive pills on some lipids and electrolytes levels in women with haemoglobin genotype AA and AS. Med Sci Res 2000;1:9-11.
7. Emokpae MA, Uadia PO, Osadolor HB. Effect of duration of use of hormonal contraceptive pills on total lipid and lipoproteins in Nigerian women. Int J Pharm Biol Sci 2010;1:1-5.
8. Tanis BC, Van de Bosch MA, Kemmeren JM, Manger CV, Helmerhoest FM, Algra A, *et al*. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001;345:1787-93.
9. Machado RB, Bernardes CR, de Souza IM, Santana N, Morimoto M. Is lipid profile determination necessary in women wishing to use Oral Contraceptives. Circulation 2013;87:801-5.
10. Baillargeon JP, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: A meta-analysis. J Clin Endocrinol Metab 2005;90:3863-70.
11. Resnick LM. Cellular ions in hypertension, insulin resistance, obesity and diabetes: A unifying theme. J Am Soc Nephrol 1992;3:S78-85.
12. National Kidney FoundationK/DoQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Dis 2002;39:S1-266.
13. Saltevo J, Niskaneni L, Kautiainen H, Teittinen J, Oksa H, Korpi-Hyovalti E, *et al*. Serum calcium level is associated with metabolic syndrome in the general population: FIN-D2D study. Eur J Endocrinol 2011;165:429-34.
14. Sabanayagam C, Shankar A. Serum calcium levels and hypertension among US adults. J Clin Hypertens (Greenwich) 2011;13:716-21.
15. Kennedy A, Vasdev S, Randell E, Xie Y, Green K, Zhang H, *et al*. Abnormality of serum lipids areIndependently associated with increased serum calcium level in the adult Newfoundland population. Clin Med: Endocrinol Diabetes 2009;2:15-23.
16. Weaver CM, Heaney RP. Calcium and Human Health. 1st eds. Totowa, New Jersey: Humana Press Inc,. p. 313-8.
17. Chandra AK, Sengupta P, Goswami H, Sarkar M. Excessive dietary calcium in the disruption of structural and functional status of adult male reproductive system in rat with possible mechanism. Mol Cell Biochem 2012;364:181-91.
18. Canpolat I, Gur S, Gunay C, Bulut S, Eroksuz H. An evaluation of the outcome of bull castration by intra-testicular injection of ethanol and calcium chloride. Rev Med Vet 2006;157:420-5.
19. Murono EP, Payne AH. Testicular maturation in rats: *In vivo* effect of gonadotrophins on steroidogenic enzymes in hypophysectomized immature rats. Biol Reprod 1979;20:911-6.
20. Annunziato L, Cataldi M, Pignataro G, Secondo A, Molinaro P. Glutamate-independent calcium toxicity: Introduction. Stroke 2007;38:661-4.
21. Welberg JW, Monkelbaan JG, de Vries EG, Muskiet FA, Cats A. Effect of supplemental dietary calcium on quantitative fecal fat excretion in man. Ann Nutr Metab 1994;38:185-91.
22. Zemel MB, Morgan K. Interaction between calcium, dairyband dietary macronutrients in modulating body composition in obese rats. Fed Am Soc Exp Biol J 2002;16:A369.
23. Ermak G, Davis KJ. Calcium and oxidative stress: From cell signaling to cell dealth. Mol Immunol 2002;38:713-21.
24. Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signaling. Nat Rev Mol Cell Biol 2000;1:11-21.
25. Kim J, Hwang JY, Kim KN, Choi YJ, Chang N, Huh KB. Relationship between Milk and Calcium intake and lipid metabolism in female patients with type 2 diabetes. Yonsei Med J 2013;54:626-36.
26. Resnick LM. Hypertension and abnormal glucose homeostasis: Possible role of divalent ion metabolism. Am J Med 1989;87:17-22.
27. Zollner N, Kirsch K. Colourimetric estimation of total lipid in biological systems. Ges Exp Med 1962;135:546-8.

28. Abdel-Barry JA, Flafl MS, Al-Namaa LM, Hassan NA. Lipoprotein changes in women taking low dose combined oral contraceptive pills: A cross sectional study in Basra, Iraq. Eastern Med Health J 2011;17:684-8.
29. Hennekens CH, Evans DA, Castelli WP, Taylor JO, Rosner B, Kass EH. Oral contraceptive use and fasting triglyceride, plasma cholesterol and HDL cholesterol. Circulation 1979;60:486-9.
30. Krauss RM, Burkman RT Jr. The metabolic impact of oral contraceptives. Am J Obstet Gynecol 1992;167:1177-84.
31. Brogan K. Oral contraceptives: Mind body Poison. Altern Integ Med 2013;2:124-5.
32. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, *et al*. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007;115:450-8.
33. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease: New perspectives based on the Framinghan study. Ann Intern Med 1979;90:85-91.
34. Lind L, Jakobsson S, Lithell H, Wengle B, Ljunghall S. Relation of serum calcium concentration to metabolic risk factors for cardiovascular disease. BMJ 1988;297:960-3.
35. Rychewaert A, Richet G, Lemaire V, Begue MC, Fenelon JP. Serum calcium levels in a population of 6048 men; variations with age and correlation with other biological data. Rev Rhum Mal Osteoartic 1974;41:473-8.
36. Cobb KL, Bachrach LK, Sowers M, Nieves J, Greendale GA, Kent KK, *et al*. The effect of Oral contraceptives on Bone Mass and stress fractures in female runners. Med Sci Sport Exerc 2007;39:1464-73.
37. Hartard M, Kleinmond C, Kirchbichler A, Jeschke D, Wiseman M, Weissenbacher ER, *et al*. Age at first oral contraceptive use as a major determinant of vertebral bone mass in female endurance athletes. Bone 2004;35:836-41.
38. Hartard M, Bottermann P, Bartenstein P, Jeschke D, Schwaiger M. Effects on BMD of low-dosed oral contraceptives compared to and combined with physical activity. Contraception 1997;55:87-90.
39. Barrow GW, Saha S. Menstrual irregularity and stress fractures in collegiate female distance runners. Am J Sport Med 1988;16:209-16.
40. Birge SJ, Avioli LV. The effect of oral contraceptives on calcium absorption In: Salhanick HA, editor. Metabolic Effects of Gonadal Hormones and Contraceptive steroids. New York: Plenum Press; 1995. p. 485-92.
41. Akinloye O, Adebanyo TO, Oguntibeju OO, Oparinde DP, Ogunyemi EO. Effects of Contraceptives on serum trace elements, calcium and phosphorus levels. West Indian Med J 2011;60:308-15.
42. Hergenroeder AC, Smith EO, Shyallo R, Jones LA, Klish WJ, Ellis K. Bone mineral changes in young women with hythalamic amenorrhea treated with oral contraceptives medroxyprogesterone or placebo over 12 months. Am J Obstet Gynecol 1997;176:1017.
43. Hartard M, Bottermann P, Bartenstein P, Jesehke D, Sehwaiger M. Effects on bone mineral deposit of low-dose contraceptives compared to and combined with physical activity. Contraception 1997;55:87-90.
44. Sun G, Vasdev S, Martin GR, Gadag V, Zhang H. Altered calcium homeostasis is correlated with abnormalities of fasting serum glucose, insulin resistance and cell function in the Newfoundland population. Diabetes 2005;54:3336-9.
45. Yao Y, He L, Jin Y, Chen Y, Tang H, Song X, *et al*. The Relationship between serum calcium level, blood lipids and blood pressure in hypertensive subjects who come from a normal University in East China. Biol Trace Elem Res 2013;153:35-40.
46. Chasan-Taber L, Willet WC, Manson JE, Spiegelman D, Hunter DJ, Curhan G, *et al*. Prospective study of oral contraceptives and Hypertension among women in the United States. Circulation 1996;94:483-9.
47. Khaw KT, Peart WS. Blood pressure and contraceptive use. Br Med J 1982;285:403-7.
48. Bloch B. The effect of cyclical administration of levonorgestrel and ethinyloestradiol on blood pressure, body mass, blood glucose and serum triglycerides. S Afr Med J 1979;56:568-70.
49. Calvi LM, Bushinsky DA. When is it appropriate to order an ionized calcium? J Am Soc Nephrol 2008;19:1257-60.
50. Buckley BM, Smith SC, Beevers M, Beevers DG, McKiernan MJ. Lack of evidence of low ionized calcium levels in systemic hypertension. Am J Cardiol 1987;59:878-80.
51. Fogh-Andersen N, Hedegaard L, Thode J, Siggaard-Andersen O. Sex-dependent relation between ionized calcium in serum and blood pressure. Clin Chem 1984;30:116-8.

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