



RESEARCH ARTICLE

MICRONUTRIENT ALTERATIONS IN HORMONAL CONTRACEPTIVE USE

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ABSTRACT

The study investigated effects of contraceptives on the concentration of calcium, magnesium and phosphorus. Taking advantage of the variability of contraceptives and duration of usage, the three parameters were analyzed spectrophotometrically with the O-cresolphthalein complexon, Xyldyl blue and Molybdated UV methods respectively. Values obtained were analyzed statistically using analysis of variance (ANOVA) statistics. Results show the mean concentration of calcium was significantly higher ( $p < 0.05$ ) in women on oral (combination 3) contraceptives when compared with the control group. The mean concentration of phosphorus and magnesium obtained from subjects on oral (combination 3) were significantly lower ( $p < 0.05$ ) than group. In participants on injectables (depo-provera and noristerat) contraceptives when compared with control group. However, mean serum calcium was significantly lower ( $p < 0.05$ ) in participants on injectables (depo-provera and noristerat) contraceptives when compared with control group. The mean concentration of phosphorus and magnesium levels on injectable (depo-provera and noristerat) and implant (Jadelle) were similar in control and participants. Correlation analysis show significant association between magnesium and phosphorus and the duration of contraceptive usage. Hormonal contraceptives show no correlation with body mass index of participants. Complications usually associated with hypo or hyperstates of these micronutrients are of grave medical concern. The need for caution, monitoring and their intermittent evaluation among contraceptive users especially in long term is strongly advocated.

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INTRODUCTION

Contraceptives are compounds with oestrogen- progesterone-like actions. They are generally used as devices or techniques and or pharmaceutical drugs that permits sexual union but prevent pregnancy. The use of contraceptives have spanned over several years, however, their effective and safe method of use was made manifest in the 20<sup>th</sup> century (Hansen *et al.*, 2010). There are several hormonal contraceptives which includes pills, patches, vaginal rings and injections. Sterilization utilizing the method of vasectomy in male is common while methods using intrauterine devices (IUDs), implants and tubal ligation are common in females. Other methods such as the use of spermicides, withdrawal by males on ejaculation and such barriers as condom, diaphragms, contraceptive sponge and fertility awareness advocacy are also available. The prevalence of contraceptive use have increased worldwide due to the development and introduction of modern contraceptives and the establishment of organized family planning programmes. As shown by Carr *et al.* (2012), over 222 million who want to avoid pregnancy in developing

countries are not using modern contraceptive. Contraceptive use in developing countries have however decreased the number of maternal deaths by 40% (Almed *et al.*, 2012). Several factors are known to modulate the distribution of micronutrients. These factors are either environmental, or genetic. Moreover, changes in life style and dietary habits and active ingredient of hormonal agents have been known to affect status of micronutrients in human. As earlier observed by (Abou-skakar *et al.*, 1989; Akinloye *et al.*, 2005) some evidence has been shown that contraceptive use interfere with absorption of some micronutrients. Some micronutrients are known to act as co-factors and co-enzymes while others are potent micronutrients known to be involved in preventing free radical induced damages, preventing the formation of reactive oxygen species, scavenging them or promoting free radical decomposition in the body. Calcium is known to play major role in skeletal mineralization, as well as a wide range of biological function. Its requirement is largely dependent on the state of calcium metabolism, which is in turn regulated by mechanisms such as intestinal absorption, renal absorption and bone turnover. Moreover some hormones also intervene to interplay in this biochemistry. Parathyroid hormones (PTH), 1,25 -dihydroxyvitamins D (1,25(OH)<sub>2</sub>D), ionized calcium itself and their corresponding receptors in the gut, kidney and bone are major players. A vast majority of total calcium is

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present in the skeleton as calcium – phosphate complexes, primary as hydroxyapatite which is responsible for much of the material properties of bones (Rose *et al.*, 2011). Magnesium as an essential element in biological system have been proved by Palmeny *et al.* (2013).

It ligand with Adenosine triphosphate (ATP), the main energy source of cells to enhance its biological activities. Many enzymes require the presence of magnesium ions for this catalytic activity (Cowan, 1995). Inadequate magnesium intake frequently cause muscle spasm and has been associated with cardiovascular, blood pressure, anxiety disorder, osporosis and cerebral infarction (Gums, 1983) Phosphorus is an essential components of cellular membrane lipid bilayer (phospholipids) and ultracellular compounds like nucleic acid and nucleoprotein. Most ultracellular phosphates exist as organic phosphates in creatinine phosphate adenine triphosphate (ATP) and 2,3diphosphoglycerates. As shown by Raina *et al.* (2012), changes in serum phosphate level do not necessarily reflect the body's total store of phosphorus. Possible changes in serum micronutrients biomolecules of woman on contraceptive have been postulated (Fallah *et al.*, 2009; Berg *et al.*, 1998). We evaluated the concentration of calcium, magnesium and phosphorus in women taking injectable, implant and oral contraceptives over a period of time to assess possible alteration in the concentration of the ions.

authorities concerned. Consent were also obtained from all subjects. The Height and Weight of subjects were also obtained and duration of drug usage recorded. 5.0mls of blood was collected, allowed to clot and spun to remove serum which was used for the analysis.

### Analytical Methods

Calcium. Calcium was analyzed by the 0-cresolphthalein complexon (CPC) method (Kessler *et al.*, 1964) based on the reaction of calcium in the alkaline solution to form an intense violet coloured complex which gives a maximum absorbance at 578nm wavelength on spectrophotometer (S23A) Medfield Equipment and scientific Limited. Magnesium was measured by the Xyldyl blue method (Farrel *et al.*, 1984). Principle depend on the fact that magnesium in serum sample react with xyldyl to form coloured compound in alkaline solution which was measured at 546nm wavelength. Phosphorus concentration was estimated by the molybdate uv method (Tietz, 1883) when ammonium molybdate react with sulphuric acid in the presence of phosphorus phosphomolybdic complex which was measured at 340nm.

### Statistical analysis

The concentration of analyses, were expressed as mean  $\pm$  standard deviation. The data obtained were analyzed using two

**Table 1. Effect of Contraceptive on Serum Calcium, Magnesium and Phosphorus**

Parameter	Control X $\pm$ SD	Depo- provera X $\pm$ SD	Noristerat X $\pm$ SD	Jadelle X $\pm$ SD	Oral (combination 3) X $\pm$ SD
Calcium (mmo/L)	2.24 $\pm$ 0.23 <sup>a</sup>	1.92 $\pm$ 0.39 <sup>b</sup>	1.2 $\pm$ 0.39 <sup>b</sup>	2.14 $\pm$ 18 <sup>c</sup>	3.32 $\pm$ 0.52 <sup>d</sup>
Magnesium (mmo/L)	0.85 $\pm$ 0.16 <sup>e</sup>	0.74 $\pm$ 0.17 <sup>f</sup>	0.77 $\pm$ 0.22 <sup>f</sup>	0.82 $\pm$ 0.20 <sup>e</sup>	0.30 $\pm$ 0.06 <sup>h</sup>
Phosphorus (mmol/L)	1.06 $\pm$ 0.23 <sup>j</sup>	1.18 $\pm$ 0.31 <sup>k</sup>	1.20 $\pm$ 0.25 <sup>k</sup>	1.28 $\pm$ 0.63 <sup>k</sup>	0.45 $\pm$ 0.25 <sup>l</sup>

At (P<0.05) values with the same superscript are not significant, those with different superscript are significant. A correlation co-efficient done for the subject age and duration of contraceptive use against calcium, magnesium and phosphorus show a positive correlation for age in all three parameters. A negative correlation was however observed for magnesium in respect of duration of use.

**Table 2. Correlation between Age and duration of contraceptive usage on concentration of calcium magnesium and phosphorus levels**

Parameter	Age (Year)	Duration
Calcium (mmo/L)	0.20P<0.05	0.43 p > 0.05
Magnesium (mmo/L)	0.03 p < 0.05	- 0.37 p < 0.05
Phosphorus (mmo/L)	0.24 P > 0.05	0.54P < 0.05

Significant positive correlation observed between serum phosphorus and magnesium levels and duration of contraceptive (r = 0.54 p < 0.05) significant correlation observed between age and serum calcium and magnesium (r=0.20p<0.05 and r=0.03p < 0.05). No observable significant difference was reflected on the body mass index (BMI)

**Table 3. Effect of Contraceptives (Depo-Provera, Noristerat, Jadele and Combination 3 Oral) on Body Mass Index (BMI)**

Parameter	Control X $\pm$ SD	Depoprovera X $\pm$ SD	Noristerat X $\pm$ SD	Jadele X $\pm$ SD	Combination 3 X $\pm$ SD
BMI	25.66 $\pm$ 4.32	26.29 $\pm$ 4.24	25.64 $\pm$ 5.05	25.86 $\pm$ 5.68	27.62 $\pm$ 4.78
p-Value	-	1.00	1.00	1.00	1.00

No significant difference observed between contraceptive (Depaprovera, Noristerat, Jadele and oral) and body mass index (BMI) (P>0.05)

## MATERIALS AND METHODS

The study was carried out in Yenagoa, Bayelsa State of Nigeria. Four identified Health facilities where family planning programmes are in place: Federal Medical Centre (FMC), DieteKookie Memorial Hospital (DKMH), Women Affairs Clinic (FSP–WAC) and Comprehensive Health Centre Agudama were used. Subjects were 220 women, out of which 120 were on contraceptives (40 on oral contraceptive combination 3) 40 on implant (Jadele) and 40 on injectable (depo-provera and noristerat). A second group of 100 women were non- users of contraceptives. The age range of all subjects were between 20 – 45 years. Ethical issues were handled and approval was obtained from institutional

way analysis of variance (ANOVA) using the SPSS statistical package (version. 20). The means were separated and compared at 0.05 level of significance. Pearson correlation was used to determine association between the various parameters with age and duration of contraceptive use.

## RESULTS

Our findings from the Biochemical analysis of the various micronutrients of interest in this study are shown in Tables 1, 2 and 3 below. With a confidence value set at (P<0.05) results show a slight fall in calcium levels among Depoprovera (1.92 $\pm$ 0.39mmol/l) Norister at (1.93 $\pm$ 0.1mmol/l) when

compared with the control (non users)  $2.24 \pm 0.23 \text{ mmol/l}$ . There was however a significant rise in calcium among oral (combination 3) up to  $3.32 \pm 0.56 \text{ mmol/l}$ . There was no significant difference observed between control and the contraceptive Jadele. Magnesium exhibited a significant fall from control. A similar scenario was observed for phosphorus among users of oral (combination 3).

## DISCUSSION

The result obtained in this study have confirmed that alterations occurs among contraceptive users as it relates to the concentration of calcium, magnesium and phosphorus. The alterations were age and duration dependent. Our findings in this work agrees with the observation of Akinloye *et al.* (2011) and Gulia *et al.* (2014). These alterations may imply a reduction in the probability of having a pregnancy and / or an increase of serious illness for the unborn. Our findings are however at variance with the earlier findings of Hameed *et al.* (2001) and Simpson *et al.* (1972) where they have reported a decrease in serum calcium level among contraceptive users while injectable depo-provera and noristeract show significant increases in serum calcium level. Some other studies have shown that women using oral contraceptive have had their concentration of trace elements altered. It has been observed however, that the magnitude of alteration in variable. Changes in the tissue level or bioavailability of such micronutrients could play a significant role in health as well as in the pathology of some disorders. Other hormones could also trigger calcium metabolism and these include estrogen, prolactin and growth hormones. Where they are able to increase  $1,25 \text{ (OH)}_2\text{D}_3$  production, there will be an increase in calcium absorption. The consequences of most disturbance of calcium can be predicated from knowledge of actions of parathyroid hormones (PTH) on bone and on renal tubular cells, and also from plasma concentration of calcium and phosphate. It has been known that a decrease concentration of calcium could excite PTH secretion which in turn result in phosphaturia. The loss of urinary phosphate overrides the tendency to hyperphosphataemia due to the influence of PTH on bone. Knowledge of the fact that an increase in concentration of PTH reduces phosphate concentration has brought to the fore the need to explain the interplay of these biomolecules in modulating the behavior of calcium and phosphates. An increase in calcium concentration unless due to inappropriate excess of PTH, inhibit PTH secretion and a high plasma phosphate concentration. As a result of this, plasma calcium and phosphate concentration usually vary in the some direction unless renal glomerular dysfunction is severe enough to impair phosphate excess or deficiency of PTH. Calcium in known to stimulate gastrin (and therefore gastric acid) secretion. An association has been established between chronic hypercalcaemia and peptic ulceration. Our understanding from this study have shown the need for caution in administration of contraceptives especially when we consider the side effect of increase or decrease of these trace elements studied.

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