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Study on serum phosphate level in surgical and natural menopausal women

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Abstract

Surgical menopause can be defined as cessation of menstruation due to surgical removal of the uterus (hysterectomy), leaving one or both ovaries, or the removal of both ovaries. Women who undergo hysterectomy alone are known to attain menopause 3.7 years earlier than those who attain natural menopause due to decrease blood supply to ovaries. These women face severe postmenopausal symptoms due to deficiency of serum estradiol. Deficiency of serum estradiol is also associated increase bone resorption and decrease renal excretion of phosphate resulting hyperphosphatemia. Thus, increase risk of osteopenia and osteoporosis may present in surgical menopausal women. Very few studies are conducted to know the effect of endocrinological changes associated with hysterectomy on the serum level of phosphate. Hence the present study was conducted to compare the serum phosphate level in surgical (hysterectomies) and natural menopausal women. This cross-sectional study was conducted in the Department of Physiology, Dhaka Medical College, and Dhaka from July 2016 to June 2017. A total number of 60 women were selected with age ranging from 30 to 55 years. Among them, 40 menopausal women were considered as the study group B and 20 apparently healthy pre-menopausal women were considered as control group A. Study group B was again subdivided into group B1 and B2. Group B1 consisted of 20 natural menopausal women and group B2 consisted of 20 surgical menopausal (hysterectomies) women. Serum phosphate level was measured by Beckman Coulter AU680. Statistical analysis was done by one-way ANOVA followed by Bonferroni test. In this study, serum phosphate level was significantly ($p < 0.05$) increase in surgical menopausal women than natural menopausal women. Again, this study showed that 55.0% surgical menopausal and 40.0% natural menopausal women had serum phosphate level >4.7 mg/dl. From this study, it can be concluded that after hysterectomy serum phosphate level significantly increase which might be due to hormonal imbalance.

Keywords: Surgical menopause; Natural menopause; Phosphate level, Hysterectomy

1. Introduction

The term menopause is derived from the Greek words “meno” means month and “pause” to stop. Menopause is defined as permanent cessation of menstruation due to reduction of ovarian follicular activity and occurs naturally [1,2]. Surgical menopause can be defined as cessation of menstruation due to surgical removal of the uterus (hysterectomy), leaving one or both ovaries, or the removal of both ovaries [3].

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Hysterectomy is commonly performed major gynaecological surgeries in many countries of all over the world [4]. Hysterectomy is used to treat dysfunctional uterine bleeding, multiple fibroid, ruptured uterus, cancer of the uterus and ovaries, placenta praevia, postpartum hemorrhage, endometriosis, uterovaginal prolapse, chronic pelvic pain, adenomyosis etc [5].

At least 80% of hysterectomies are done for the treatment of benign gynaecological condition of the female genital tract [6]. The incidence of hysterectomy varies across the countries. Incidence of hysterectomy is about 7-8% in rural women and 5% in urban women in western state of India at an average age of 37 years [7].

When both the ovaries are removed during hysterectomy, ovarian hormones (estradiol, progesterone & testosterone) level decrease abruptly. About one- third of hysterectomized women may lose their ovarian function following one to two years, even after preservation of both ovaries during operation [8]. The mechanism by which the ovarian hormones level decrease is not clear. But it is thought that decrease level of ovarian hormones is due to interruption in ovarian blood flow. The ovary is supplied by the ovarian artery and uterine artery. The ovarian artery makes an anastomosis with the uterine artery. During hysterectomy this anastomosis is disrupted, therefore decreased blood supply to the ovary and subsequent reduction in ovarian hormone production [9].

Moreover, the uterus is the target site for the action and regulation of female hormones especially estradiol. The presence of a functional uterus is vital for the normal physiological functioning of the musculoskeletal system. Thus, surgical menopausal women have three times greater risk of weakened bone than natural menopausal women [10,11].

Bone formation is a process in which deposition of inorganic mineral is controlled by an organic matrix. The mineral phase is composed of calcium and phosphate. The concentrations of these ion in the extracellular fluid influence the rate at which mineral is formed. When bone is resorbed calcium and phosphate ions are released into the ECF and the organic matrix is resorbed.There are several hundred grams of phosphate in adult human body. Approximately 85% of phosphate is present in bone or teeth as hydroxyapatite and ~15% is present within cells. Therefore, extracellular inorganic phosphate is <1% of total phosphate [12,13]. Serum phosphate is maintained by intestinal phosphate absorption, renal phosphate handling and equilibrium of extracellular phosphate with that in bone or intracellular fluid. Phosphate is an essential nutrient required for important biological function of the body. Phosphate is necessary for proper mineralization of bone as a constituent of hydroxyapatite crystal. Several phosphorylated proteins like osteopontin and dentin matrix protein 1 (DMP1) have been shown to regulate bone mineralization. In addition, it is the major component of building blocks of DNA, phospholipids, and high-energy compounds such as ATP. Impaired phosphate balance can affect the functionality of almost every human system, including musculoskeletal and cardiovascular systems, leading to increase in morbidity and mortality of the affected patients. Decreased estradiol affects the serum and urinary level of phosphate indirectly at various levels. Decreased estradiol also alters the intestinal absorption, bone resorption and renal reabsorption of phosphate [14,15].

Several studies reported that serum phosphate level was significantly increased in surgical and natural menopausal women than healthy premenopausal women, which may increase the future risk of development of postmenopausal osteopenia and osteoporosis [16,17]. On the other hand, some researchers did not find significant change in serum phosphate level in surgical and natural menopausal women [18].

Sreekantha et al. conducted a study on 34 hysterectomized women, 34 natural menopause and 28 premenopausal women to observe the serum phosphate level. The study results showed serum phosphate level was significantly increased hysterectomized and natural menopausal women than premenopausal women which might be due to hormonal imbalance [16].

Perez, Mercer & Cano conducted a study on 147 surgical and natural menopausal womento assess their serum phosphate level. Study result revealed that serum phosphate level increase in surgical than natural menopausal women [17].

In India, Yeldose et al. conducted a case control study on 69 women. Among them 26 healthy premenopausal, 22 hysterectomized and 21 was natural menopausal women. Study result showed that no significant change in serum phosphate level in hysterectomized women compared to natural and pre-menopausal women [18].

So, it has been observed that, the result is conflicting. Several studies have been done in abroad about hormonal imbalance and mineral status in patients of surgical and natural menopause but very few published data are available in our country. Therefore, on the basis of this background, the present study is designed to see the effect of decreased estradiol levels associated with hysterectomy on serum levels of phosphate.

2. Methods

The present cross-sectional study was carried out in the Department of Physiology, Dhaka Medical College, Dhaka from July 2016 to June 2017. The protocol was approved by the Research Review committee and Ethical Review committee of Dhaka Medical College, Dhaka. A total number of 60 women were selected and divided into group A and group B. Group A consisted of 20 apparently healthy premenopausal women with age ranging from 30 to 35 years. Group B consisted of 40 menopausal women age ranging from 45 to 55 years. Study group B was again subdivided into group B_1 (20 women with natural cessation of menstruation in past 2-5 years) and group B_2 (20 women with surgical removal of uterus without any oophorectomy in past 2-5 years). The subjects were selected from Outpatient Department (OPD) of Dhaka Medical College Hospital. Subjects with unilateral or bilateral oophorectomy, taking hormone replacement therapy (HRT), steroid containing drug, polycystic ovarian syndrome, renal disease, diabetes mellitus, thyroid or parathyroid disease, ovarian malignancy, treated with chemotherapy or radiotherapy, smoking, family history of early menopause were excluded from the study. Informed written consent was taken from the each subject after proper briefing about the nature, purpose and benefit of the study. Before taking blood, detailed personal history and family history were taken. Anthropometric measurement of the subjects was done and blood pressure was measured. With all aseptic precaution, 2ml of venous blood was collected by a disposable plastic syringe from each subject for estimation of biochemical tests. Collected blood was transferred in a de-ionized glass test tube and was kept in slanted position till formation of clot. The blood sample was centrifuged at a rate of 3000rpm for 10 minutes for separation of serum. After that, supernatant serum was collected in leveled eppendroff tube and stored in a refrigerator at - 20^{o}c until estimation of serum phosphate level. The study parameterwas estimated in the Department of Biochemistry and Molecular Biology, BSMMU, Dhaka by Beckman Coulter- AU680.All the parameter was expressed as mean ± SD. One-way ANOVA followed by Bonferroni test was performed as applicable.*P* value < 0.05 was accepted as level of significance. Statistical analyses were performed by using a computer based statisticalprogram SPSS (Statistical package for social science) version 22.0.

3. Results

In this study, statistically significant differences were observed in mean age and BMI among control and study groups. There was no significant difference in mean systolic and diastolic blood pressure among different groups (Table 1). Table 2 showed themean (±SD) serum phosphate level of control group A and study subgroups B1 and B2 were2.84 ± 0.62, 3.78 ± 0.97 and 4.62 ± 0.91 mg/dl respectively. The mean (±SD) serum phosphate level in the subgroup B_2 was higher than group A and group B_1 which was statistically significant *(p*<0.001). The mean (±SD) serum phosphate level in the subgroup B_1 was higher than group A which was also statistically significant *(p*< 0.001).

Table 1 General characteristics of the subjects in different groups (N=60)

Parameters	Groups			p value
	A (n=20)	B1 (n=20)	B2 (n=20)	
Age (years)	32.05 ± 2.09	49.65 ± 3.01	47.05 ± 3.15	0.001
Height (cm)	158.12 ± 4.87	156.46 ± 4.47	158.50± 4.97	0.366
Weight (kg)	54.05 ± 5.01	61.25 ± 6.31	57.15 ± 7.69	0.003
BMI (kg/m2)	21.65 ± 2.07	25.04 ± 2.70	22.78 ± 3.22	0.001
Systolic BP (mm Hg)	110.50 ± 8.09	114.00 ± 9.82	115.25± 7.34	0.174
Diastolic BP (mm Hg)	75.25 ± 5.95	72.63 ± 6.70	73.00 ± 5.71	0.144

Results are expressed as mean ± SD. ANOVA test was performed to compare among groups. The test of significance was calculated and *p* value <0.05 was accepted as level of significance. N=Total number of subjects, n=number of subjects in each group, Group A=Pre-menopausal women, Group B_1=Natural menopausal women, Group B_2= Surgical menopausal women, BMI=Body mass index

Table 2 Mean serum phosphate level in different groups (N=60)

Parameters	Groups			
	A (n=20)	B1 (n=20)	B2 (n=20)	p value
Phosphate (mg/dl)	2.84 ± 0.62	3.78 ± 0.97	4.62 ± 0.91	<0.001***

Table 3 Statistical analysis

Groups	p value
	Phosphate
A vs B1 vs B2	<0.001***
A vs B1	0.001***
A vs B2	<0.001***
B1vs B2	0.008***

One way ANOVA followed by Bonferroni test was performed to compare among groups. The test of significance was calculated and *p* value < 0.05 was accepted as level of significances.

- N= Total number of subjects
- n= number of subject in each group
- Group A: Pre-menopausal women
- Group B_1: Natural menopausal women
- Group B_2: Surgical menopausal women

4. Discussion

In the present study, the mean serum phosphate level was significantly increased in surgical menopausal (hysterectomies) women 2 to 5 years after surgery than that in the post-menopausal women at similar periods after natural menopause. This finding is in consistent with that of some other researchers [16,17]. But some investigators did not find significant change in serum phosphate level in menopausal women than premenopausal women [18,19].

Onset of natural menopause is associated with various endocrinological changes and alteration in bone and mineral metabolism. Estradiol levels decrease significantly after menopause. Decrease estradiol affects the serum and urinary levels of phosphate at various levels. Decreased estradiol alters the intestinal absorption, bone resorption and renal reabsorption of phosphate. All these changes are gradual after natural onset of menopause. However after hysterectomy blood supply to the ovaries is affected hence the onset of endocrinological changes after surgical menopause is very sudden unlike natural menopause [20]. Cai & Sun suggested that the uterus is the target site for the action of ovarian hormone especially estradiol and also has close connection with the ovary for anatomical and endocrine functions. The ovary is mainly supplied by the ovarian artery and also by a collateral branch from uterine artery. During hysterectomy, the bilateral uterine artery is cut off. Thus, the anastomosis between ovarian and uterine artery is disrupted leading to decrease in ovarian stromal blood flow result in ovarian follicular degeneration and subsequent decrease in ovarian hormone production [21].

Estradiol is a major estrogen produce by the ovaries mainly acts on reproductive system and secondary sexual organs. Estradiol act on bone, intestine and kidney through estradiol receptors ERα and ERβ. It exerts direct effects as well as indirect transcriptional effects on various proteins involved in the metabolism of phosphate. Estradiol promotes bone mineralization by stimulating the action of osteoblasts and inhibiting the action of osteoclasts. It also decreases the reactive oxygen species concentration and decrease the bone demineralization. Estradiol inhibits bone resorption by controlling the timing of osteoclast apoptosis. It decreases the secretion of IL-I and IL-6 which inhibit bone resorption by decreasing osteoclastic activity. Decrease in estradiol causes decrease in the activity of osteoblasts and increase in the activity of osteoclasts and hence causing demineralization and eventually in postmenopausal osteoporosis [22,23,24]. This is corroborated by our study, observed increase serum phosphate levels could be due to increased demineralization in surgical menopausal women secondary to decreased serum estradiol level after hysterectomy.

Phosphate and calcium are the two major minerals that play an important role in bone matrix and bone mineralization. Sex steroids deficiency, mainly estradiol has been suggested as a major factor in bone minerals loss in postmenopausal women [25]. The renal regulation of phosphate is principally achieved through the sodium phosphate co-transporter type IIa (NaPi-IIa) in the proximal convoluted tubule. Estradiol decreases NaPi-IIa mRNA and protein levels and induces phosphaturia. In rats, Faroqui et al. observed that treatment with 17 beta-estradiol for three days decreased NaPi-IIa mRNA and protein levels, resulting in lower serum phosphorus levels and enhanced urinary phosphate loss [22]. Again,

in rats, Carrillo-Lopez et al. showed that estradiol increased serum Fibroblast growth factor 23 (FGF23) levels in vivo, and increased FGF-23 mRNA and protein levels in a rat-derived osteoblast cell line in vitro. Because FGF-23 decreases NaPi-IIa levels in the proximal tubule and induces phosphaturia this finding suggests that estradiol may induce phosphaturia indirectly, through upregulation of FGF-23. Therefore, estradiol deficiency after hysterectomy may decrease renal excretion of phosphate resulting hyperphostaemia [26,27].

In the present study, increased serum phosphate level was observed in surgical than natural menopausal women. This may be due to estradiol deficiency, because deficiency of estradiol may increase bone resorption and decrease renal excretion of phosphate. But the exact mechanism is not elucidated in this study as the serum PTH, Vit D and urinary phosphate level were not assessed due to time and financial constraints.

5. Conclusion

After analyzing the result of the study, it can be concluded that serum phosphatelevel was significantly increase in surgical than natural menopausal women which might be due to estradiol deficiency after hysterectomy. Therefore, the findings of this study may be helpful to explore knowledge about the hormonal imbalance and mineral status in this group of patients and may act as guide for appropriate patient management.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

Ethical approval obtained from Dhaka medical college, Dhaka, Bangladesh with Memo no. MEU-DMC/ECC/2017/92 dated on 30/04/2017.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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