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Ovarian aging and bone metabolism in menstruating women aged 35–50 years

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Abstract

Objectives: The aim of this study was to investigate the relationships between the levels of gonadotrophins, estradiol, inhibin-b and bone mass and turn-over in regularly menstruating women aged 35–50 years.
Methods: The study group included 87 healthy volunteers from the community aged 35–50 years. Bone mineral density of lumbar vertebras, wards triangle, throchanter, femur neck, bone resorption and formation markers were studied as well as the serum levels of gonadotrophins, estradiol and inhibin-b on the day 3 of menstrual cycle.
Results: The gonadotrophin levels showed significant positive relation with age, whereas inhibin-b and estradiol levels showed significant negative correlation with age. The gonadotrophins and estradiol levels had no significant association with bone mass and bone formation markers. Increased gonadotrophin ($p < 0.001$) levels and decreased inhibin-b ($p < 0.01$) levels independent from age were correlated with increased bone resorption. Gonadotrophins, estradiol, age, inhibin-b, body mass index (BMI) were the confounding factors for bone resorption ($p = 0.015$, $R^2 = 0.190$) and lumbar bone mass ($p = 0.041$, $R^2 = 0.148$). Multivariate analysis showed an independent contribution of inhibin-b and BMI in the prediction of lumbar bone mass.
Conclusion: This findings suggested that estradiol was not the only factor responsible for bone loss and decrease in reproductive function because increased gonadotrophins and decreased inhibin-b levels might trigger some changes in bone metabolism prior to the menopause.

Keywords: Gonadotrophins; Inhibin-b; Estradiol; Bone turnover; Bone mass; Ovarian aging

1. Introduction

The net result of interaction of the various endocrine, paracrine and autocrine factors, mechanical stresses is that bone is in a constant dynamic equilibrium. Metabolic bone disease results when any one of these

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factors or any combination of them becomes abnormal [1]. Osteoporosis is a condition refers to loss of both mineral and matrix that renders residual quantities of mineralized bone inadequate to withstand minor trauma without fracture [1]. Osteoporosis is a significant public health problem, particularly among postmenopausal women with subsequently increased risk of fracture impacting morbidity and mortality and decreased quality of life in affected person [1,2]. The incidence and cost of the disease are rising as the life-span of the population increases. It is difficult to restore large quantities of bone once the bone mass is lost especially after trabecular connectivity has been lost. Therefore it is appealing to design programs prevent osteoporosis rather than treat symptomatic disease [1]. Since osteoporosis is a multifactorial silent disease which can progress asymptomatically for years [1], knowledge of risk factors would provide us with new insights into the development of new methods for early detection of osteoporosis.

Age dependent changes and sexual differences in bone mass suggest that hormonal factors may play major role in the pathogenesis of osteoporosis [3]. The effects of menopause on bone metabolism and the protective effects of postmenopausal estrogen replacement therapy have been clearly demonstrated [4]. Although there are several studies of bone metabolism in peri and postmenopausal women [5–8], the relationship between reproductive potential and bone turnover or bone mass is still matter of debate.

The decrease in reproductive potential occurs in the late thirties of women. Several markers of ovarian aging have been identified. Early follicular serum FSH and inhibin-b levels are known to change as a function of a woman's age; other change noted in the follicular phase is earlier elevations of estradiol level in the aging process [9,10]. One of the earliest finding of decreased reproductive potential is a rise in FSH concentrations during early follicular phase. Elevated FSH level is an indirect measure of ovarian function, reflecting decrease in negative feedback mechanism of the ovaries on the pituitary gonadotrophin secretion. It has been suggested that decreased ovarian inhibin-b secretion is primarily responsible for the monotropic rise in FSH and inhibin-b is a direct product of ovarian granulosa cells [9,11,12].

The changes in bone metabolism with increasing levels of gonadotrophin and decreasing level of estradiol have been well documented. However, the mechanism of perimenopausal bone loss is uncertain, since it occurs before serum estradiol concentrations changed. This suggested that changes in ovarian activity before major changes in estradiol levels may effect bone metabolism in the premenopausal women. There was no study on dimeric inhibin-b and bone metabolism in regularly menstruating women. In this study, the effects of gonadotrophins, estradiol and inhibin-b levels on bone metabolism were investigated.

2. Materials and methods

2.1. Participants

The study group included 87 healthy volunteers from the community aged 35–50 years. Among 120 women admitted to the study, 87 were suitable for inclusion criterias. Each women was given verbal and written information on the study and informed consent was obtained from each participant woman in accordance with Ethical Committee of Kocaeli. University Medical Faculty. The study was conducted at Kocaeli University School of Medicine Gynecology and Obstetrics Department between March 2002 and November 2002. The urinary *N*-telopeptide level, serum osteocalcin and serum inhibin-b levels were studied in Microbiology–Immunology Department of Medical School of Istanbul University. The inclusion criterias were as follows:

a. All women had spontaneous (without medications) regular menstrual bleeding (21–35 days interval). None of the women had previous amenorrhea periods (loss of menses more than 3 months) or fertility problem (all had at least one previous pregnancy)
b. None of the women had diseases or medications known to influence bone mineral or calcium metabolism, and none was taking oral contraceptive pills or any other hormonal preparations.
c. All subjects had both ovaries and none had undergone ovarian surgery before.
d. None of the patients had previous diagnosis of osteoporosis or had undergone bone mineral density measurements.
e. Blood samples were taken for hepatic, renal and thyroid functions, prolactin and androgen (DHEAS and