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Review article

Hormonal contraception and bone metabolism: a systematic review

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Abstract

Background: Although a large amount of studies in the literature evaluated the effects of hormonal contraception on bone, many questions remained still unclear, such as the effect of these therapies on fracture risk.
Study Design: We performed a systematic search of the published studies from January 1975 through January 2012 on the effects of hormonal contraceptives on bone metabolism. We analyzed the overall effect on bone mineral density (BMD) and on fracture risk of combined oral contraceptives (COCs), progestogen-only contraceptives, transdermal contraceptives and vaginal ring.
Results: COC therapy does not seem to exert any significant effect on BMD in the general population. In adolescents, the effects of COCs on BMD seem to be mainly determined by estrogen dose. The use of COCs in perimenopausal women seems to reduce bone demineralization and may significantly increase BMD even at a 20-mcg dose. Use of depot medroxyprogesterone acetate is associated with a decrease in BMD, although this decrease seems to be partially reversible after discontinuation. Data on other progestogen-only contraceptives, transdermal patch and vaginal ring are still limited, although it seems that these contraceptive methods do not exert any influence on BMD.
Conclusions: Hormonal contraceptives do not seem to exert any significant effect on bone in the general population. However, other randomized controlled trials are needed to evaluate the effects on fracture risk since the data available are derived from studies having the effects on BMD as the primary end point, and BMD may not accurately reflect the real fracture risk.

Keywords: Contraceptives; Bone mineral density; Fracture risk

1. Introduction

Estrogens are major determinants of bone mass, affecting the acquisition of peak bone mass during adolescence and young adult age and modulating bone mineral density (BMD) and the risk of osteoporosis later in life [1–3]. As revealed by in vitro and in vivo studies, estrogens are also important factors in the regulation of bone tissue metabolism [2]. These effects are of utmost importance, in particular during adolescence and after the menopause. Indeed, estrogens are very important for acquiring an adequate peak bone mass during youth, and the fall of their circulating levels during the postmenopausal period induces a fast resorption of bone tissue. Both these actions concur in determining the risk of developing osteoporosis and bone fractures.

Today, the use of combined or progestogen-only contraceptives for long periods is a worldwide habit, with millions of hormonal contraceptive users. Hormonal contraceptives induce a reduction of estrogen and a suppression of progesterone endogenous production by the ovaries. In these women, circulating levels of sex steroids are mainly determined by the dosages present in the contraceptive formulation. If the formulation of the contraceptive is insufficient to grant adequate sex steroid levels, bone tissue metabolism might be affected. This holds particularly true during adolescence, when the hypothalamus–pituitary–ovary axis is not completely mature, and during the perimenopausal period, when circulating levels of estrogens and progesterone may be reduced.

In the last decades, the modification of sexual habits among teenagers and the increase of sexual activity in the late 40s induced a significant increase of hormonal

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contraception use in these ages [4]. The particular hormonal profiles of adolescents and perimenopausal women may expose hormonal contraceptive users of these age periods to modifications of bone metabolism that may respectively prevent the peak bone mass to be reached or induce an early bone loss, finally leading to an increased risk of developing osteoporosis.

In this review, we will briefly analyze the effects of sex steroids on bone formation and resorption via osteoblast and osteoclast activity and discuss in vivo studies on animal models evaluating the impact of sex hormones on bone. Furthermore, a systematic review of the data present in the literature dealing with the effect of different hormonal contraceptive formulations on BMD and fracture risk will be performed.

2. Methods

In the first part of this review, the effects of sex hormones on bone metabolism in vitro on animal and human tissues and in vivo on animals are discussed.

In the second part of the review, we performed a systematic search of the published studies on the effects of hormonal contraceptives on bone metabolism in humans.

We searched for all studies published from January 1975 through January 2012 that report on BMD or fracture outcomes by use of hormonal contraceptives. The following search strategy was executed using the keywords "contraceptives" or "oral contraceptives" or "contraceptive patch" or "contraceptive devices" or "contraceptive ring" or "progestogen only contraception" or "injectable contraceptives" in combination with "bone mineral density" or "bone mineral content" or "bone turnover" or "osteoporosis" or "fracture risk" and searching the following database: PubMed, Embase, Science Citation Index and Cochrane Database of Systematic Reviews.

The search results were then limited to studies in humans but were not limited by language. Reference lists from these articles were hand searched to identify additional articles.

Two authors (G.A.T. and V.G.) independently scrutinized abstracts and retrieved full articles of all citations that were likely to meet the predefined criteria. At the first screening, titles were investigated in order to discard duplicated and to exclude nonrelevant studies. The remaining studies were screened reading the abstracts and included if data on the effects of hormonal contraceptives on BMD values or fracture risk were reported. Studies on women with specific circumstances (e.g., those with anorexia nervosa and endurance athletes) were excluded because of the peculiarity of the subjects studied. We also excluded studies of women who had conditions or diseases known to affect BMD, such as hyperthyroidism, anorexia and premature menopause. The included studies, along with uncertain items, underwent a third screen, during which full articles were collected and read. During this phase, study design, number of patients and the effect of confounding variables to assess the risk of any study bias were evaluated. All case reports or analyses not reporting the consequences were excluded. Any discrepancy between the screening results was discussed by all the authors, and consensus was reached.

Data extraction was conducted by two reviewers (C.D.C. and V.G.) independently. The data extracted were inputted in an Excel spreadsheet. These included the study design, number of patients and main outcome measure.

Because studies were heterogeneous with regard to age of participants, site and method of BMD measurement and length of follow-up, we did not compute summary estimates. Studies analyzed were divided into three categories: studies about combined oral contraceptives (COCs), studies about progestogen-only contraception and studies about transdermal contraceptives and vaginal ring. For each category, we analyzed the overall effect of the contraceptive on BMD on fracture risk.

3. Bone tissue composition and the process of bone formation and readsorption

The skeleton is a metabolically active organ undergoing a continuous process of remodeling throughout life. This remodeling is necessary both to maintain the structural integrity of the skeleton and for the metabolic function of calcium and phosphorus storage [5]. The bone remodeling cycle involves an intricate series of sequential steps with a highly complex regulation in which a pivotal role is played by sex steroids. The first step in bone formation is the deposition of mineralized tissue at specific sites, generally preceded by a cartilage analogue. The lengthening of bone involves an orderly sequence of replacement of cartilage by bone, called *endochondral* bone formation. Another mechanism of bone formation in which bone is formed independently of cartilage is the *membranous* bone formation, which takes place particularly in the flat bones, such as those of the skull. However, also in this case, bone formation takes place adjacent to a cartilage template. Bone remodeling begins early in fetal life and depends on the interactions of two cell lines, the mesenchymal osteoblastic and the hematopoietic osteoclastic. The activation stage involves the interaction of osteoclast and osteoblast precursor cells (Fig. 1). This process leads to the differentiation, migration and fusion of the large multinucleated osteoclasts [6]. The differentiation pathway for osteoclasts is illustrated in Fig. 2. These cells attach to the mineralized bone surface and initiate resorption through the secretion of hydrogen ions and lysosomal enzymes, particularly cathepsin K, which can degrade all the components of bone matrix. The attachment of osteoclasts to bone may require specific changes in the so-called *lining cells* on the bone surface, which can release proteolytic enzymes to uncover a mineralized surface [7]. Osteoclastic resorption produces irregular scalloped cavities on the trabecular bone surface, called Howship lacunae, or