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The effect of thyroid stimulating hormone suppressive therapy on bone geometry in the hip area of patients with differentiated thyroid carcinoma

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ABSTRACT

Subclinical hyperthyroidism has been reported to increase the fracture risk. However, the effect of thyroid stimulating hormone (TSH) suppressive therapy on bone geometry in the hip area of patients with differentiated thyroid carcinoma (DTC) is still unclear. The aim of this study was to investigate the effect of TSH suppression on bone geometry in the hip area of pre- and postmenopausal women with DTC.

We conducted a retrospective cohort study including 99 women with DTC (25 pre- and 74 postmenopausal) who had received TSH suppressive therapy for at least 3 years and 297 control subjects (75 and 222, respectively) matched for sex and age. Bone mineral density (BMD) in the spine and hip area and bone geometry at the femoral neck measured by dual energy X-ray absorptiometry (DXA) were compared between patients and controls. The association between thyroid hormone and bone parameters was investigated. All analyses of bone parameters were adjusted for age, body mass index, and serum calcium levels.

In premenopausal subjects, TSH suppressive therapy was not associated with poor bone parameters. In postmenopausal subjects, patients with DTC undergoing TSH suppression showed lower cross-sectional moment of inertia (CSMI), cross-sectional area, and section modulus and thinner cortical thickness at the femoral neck than those of control subjects, whereas their femoral neck BMD was comparable with controls. Total hip BMD was lower in postmenopausal patients than in controls. CSMI and section modulus at the femoral neck were independently associated with serum free T4 levels in postmenopausal patients. The difference in femoral neck bone geometry between patients and controls was only apparent in postmenopausal DTC patients with free T4 >1.79 ng/dL (23.04 pmol/l), and not in those with free T4 levels ≤1.79 ng/dL (23.04 pmol/l).

TSH suppression in postmenopausal DTC patients was associated with decreased bone strength by altering bone geometry rather than BMD in the hip area, especially the femoral neck. This alteration in bone quality was observed only in patients with free T4 levels above the upper normal limit.

1. Introduction

Differentiated thyroid carcinoma (DTC) is the most frequent endocrine cancer and its incidence has increased by over 4% every decade for the last 30 years [1]. In patients with DTC, thyroid stimulating hormone (TSH) suppressive therapy using exogenous levothyroxine after an initial surgical treatment is recommended because it inhibits further growth of any residual neoplastic tissue [1,2]. However, there is growing interest in the potential harmful effects of long-term TSH suppressive therapy because of the prolonged patient survival rate after the initial treatment of DTC [1]. In particular, increased fracture and cardiovascular risks caused by exogenous subclinical thyrotoxicosis have been reported [1,3–6]. Therefore, the potential benefits and potential risks of TSH suppression should be considered carefully, especially in elderly patients.

It is well established that an excess of thyroid hormone results in skeletal toxicity. Triiodothyronine is an important regulator of osteoblast differentiation and stimulates osteoclasts, resulting in increased bone turnover [7]. In addition, TSH has a direct protective effect on bones, which enhances osteoblast differentiation and stimulates osteoprotegerin to attenuate bone resorption [8–10]. Therefore, lowering the TSH levels in patients with DTC might result in bone loss from a direct effect of thyroid hormones or from failure to maintain the protective effect of TSH [11]. Several recent studies and meta-analyses have reported that

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subclinical hyperthyroidism or suppression of TSH by levothyroxine treatment increased the risk of fracture [4,12,13]. However, it remains uncertain whether decreased bone mass mediates the adverse effect of low TSH levels on the risk of fractures, and there have been conflicting results of the effect of subclinical hyperthyroidism on bone mineral density (BMD) [12,14–17].

Bone strength is determined by composite aspects of bone mass, measured as BMD, and bone quality, measured from the structural geometry of cross-sections of long bones. In the hip area, parameters of bone geometry are associated with fracture risk independently of BMD [18–20] and most previous studies have reported that suppressed TSH levels were associated with hip fractures [12,13]. From these considerations, TSH suppressive therapy can be supposed to have more adverse and prompt effects on bone geometry than on BMD in the hip area. In this study, we included 25 premenopausal and 74 postmenopausal women with DTC who had maintained TSH suppressive therapy for over 3 years after thyroidectomy. Their BMD in multiple sites and bone geometry in the proximal femur were measured using DXA and compared with those of sex- and age-matched control subjects.

2. Methods

2.1. Subjects

A total of 128 women aged 20 years or older who were diagnosed with DTC or who had started a follow-up of DTC in Seoul National University Bundang Hospital from October 2003 to July 2011 were eligible. They had maintained TSH suppressive therapy with levothyroxine for longer than 3 years following thyroidectomy with or without radioactive iodine (^{131}I) therapy and their DXA data after 3 years or longer of TSH suppression therapy were available. We also recruited control subjects of three times as many as the number of patients who were matched for sex and age at the time when DXA was performed. These control subjects were recruited from subjects who had a health checkup in the Health Promotion Center of Seoul National University Bundang Hospital from January 2009 to December 2013. The exclusion criteria for the patient and control groups were as follows: 1) subjects who have histories of exposure to bisphosphonate, oral contraceptives, menopausal hormone therapy, selective estrogen-receptor modulators, diuretics, lithium, or corticosteroids; 2) those with active secondary malignancies; 3) those who have histories of liver or renal diseases, hyperthyroidism, hyper- or hypoparathyroidism, malabsorption syndrome, or rheumatic diseases. This study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of the Seoul National University Bundang Hospital.

2.2. Treatment and follow-up

All patients with DTC underwent treatment according to Korean Thyroid Association (KTA) guidelines for the long-term management of DTC [21]. The KTA guidelines recommended a similar degree of TSH suppression with the American Thyroid Association guidelines [2] according to the risk-group stratification. According to the KTA guidelines for the long-term management of DTC, serum TSH levels below 0.1 mIU/L are recommended in patients with persistent disease; serum TSH levels of 0.1–0.5 mIU/L are recommended for patients free of disease but who originally presented with high-risk disease; and a lower normal range (0.3–2.0 mIU/L) of serum TSH is recommended even for those patients at low risk for recurrence [21].

2.3. Anthropometric and biochemical parameters

We measured the height and weight of subjects in light clothing and without shoes to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated by determining the ratio between weight and the square of the height (expressed in kg/m^2). Serum levels of creatinine, calcium (corrected for albumin binding), and phosphate were also measured by automated standard laboratory methods (Hitachi 747; Hitachi, Tokyo, Japan). Serum 25 hydroxyvitamin D (25OHD) concentrations were measured using Diels–Alder derivatization and ultrahigh performance liquid chromatography–tandem mass spectrometry (Waters, Milford, MA, USA). Concentrations of serum free thyroxine (T4) and TSH were measured by immunoradiometric assays (free T4, DiaSorin S.p.A, Saluggia, Italy; TSH, CIS Bio International, Gif-sur-Yvette, France). Free T4 had an analytical sensitivity of 0.05 ng/dl. TSH had the analytical sensitivity of 0.04 mU/L and the functional assay sensitivity of 0.07 mU/L. The reference ranges of free T4 and TSH were 0.89–1.79 ng/dL and 0.3–4.0 mIU/L, respectively.

2.4. Assessment of bone mineral density and proximal hip geometry

BMD at the lumbar spine, femoral neck and total hip was assessed using Lunar Prodigy enCORE 8.8 DXA scanner (software version 10.50.086, GE Medical Systems, Madison, WI, USA) according to the manufacturer's protocol. This DXA scanner uses PA projections ant the detector is located above the patient. Femur neck scans were further analyzed for geometric bone structure properties using the hip structure analysis (HSA) program included in the Prodigy enCORE software of Lunar, as described [22,23]. The HSA program automatically set the region of interest, defined as the narrow neck (NN), traversing the narrowest width of the femoral neck. In addition to hip axis length (in mm), femoral neck width (in mm), and neck shaft angle (in degrees), the HSA program yielded data for cross-sectional area (CSA in mm^2), cross-sectional moment of inertia (CSMI in mm^4), mean cortical thickness (in mm), section modulus (in mm^3), and buckling ratio at the NN. CSA was defined as the total surface area of bone in a cross-sectional slice, excluding all the spaces occupied by marrow or other soft tissues. CSMI is the index of structural rigidity and reflects the distribution of mass about the center of a structural element. Stress within a cross-section subjected to bending is inversely related to the CSMI. Section modulus is an indicator of bending strength for maximum bending stress and is derived by dividing CSMI by the maximum bending stress in a cross-section. Buckling ratio is the ratio of the outer radius to the wall thickness, and higher buckling ratio means thin-walled structure which can be folded easily [22,23]. BMDs were measured in the lumbar vertebrae (L1–L4) and in the proximal femur (neck, trochanter, ward, and total) using the Prodigy enCORE software.

2.5. Data analysis

Values with normal distributions are expressed as the mean ± SD, and values with non-normal distribution are expressed as the median and (interquartile range). A Generalized Estimating Equation (GEE) analysis was used for the comparison of parameters between the patient and their sex- and age-matched control groups. Linear regression analysis was used to estimate multiple correlations between bone parameters and other factors. All statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Data with a p-value <0.05 were considered significant.

3. Results

3.1. Subject characteristics in the patient and control groups

Among the eligible 128 patients with DTC, 24 patients with histories of exposure to medications that might affect bone metabolism and 5 patients with active secondary malignancies (three with breast cancer, one with colon cancer, and one with non-small cell lung cancer) were excluded. Finally, 99 patients with DTC (mean age 57.4 ± 9.6 years) and 297 control subjects were included in this study. All 99 patients had no evidence of persistent disease; low-risk and intermediate-risk diseases, as defined by the KTA guidelines [21,23], were present in 42