Bone mineral metabolism and thyroid replacement therapy in congenital hypothyroid infants and young children


*Clinica Pediatrica III, Istituto Scientifico H San Raffaele, Università degli Studi di Milano and **Istituto di Biometria e Statistica Medica, Università degli Studi di Milano, Milano, Italy

ABSTRACT. Impairment of calcium metabolism and low bone density have been found in hypothyroid adults. We investigated the effect of thyroid replacement therapy on calcium metabolism and bone mineralization in congenital hypothyroid (CH) infants and children. One hundred and 16 Caucasian CH consecutive patients were studied and were grouped according to their age: 23 patients at diagnosis, 20 at 3 mo, 24 at 6 mo, 25 at 12 mo and 24 at 36 mo. Thyroid replacement therapy was started at an initial dose of 6-8 Ilg/kg/day of L-thyroxine, and then decreased progressively. Calcium, phosphorus, magnesium, alkaline phosphatase (AP), parathyroid hormone (PTH) and osteocalcin (BGP) were measured as calcium metabolism indices. Bone mineral content (BMC) was measured at the mid-portion of the right radius AP, PTH and BGP concentrations were significantly higher in subjects at 3 mo of age (p<0.05). This rise coincided with the end of the period of maximum dosage of L-thyroxine. Mild asymptomatic hypercalcemia was observed in 20 patients. All the other indices did not differ between age groups. BMC values and BMC annual increment were not different from those calculated for age-matched controls. We found that L-thyroxine replacement therapy does not alter bone mineralization of CH infants and children. Only a transitory increase of osteoblastic function was observed after the first few months of therapy.

INTRODUCTION

Lack of thyroid hormones lowers bone turnover (1). Although overt disorders of calcium metabolism are not often seen in adult hypothyroid patients, negative calcium balance (1), hypocalcemia (2) and osteopenia (3) have been reported. To the contrary, hyperthyroidism, both endogenous or exogenous, increases remodeling activity in both cancellous and cortical bone (1, 4-6). The elevated bone turnover shows a prevalence of the resorption rate and leads to osteopenia and osteoporosis in hyperthyroid adults (7-10). Several investigators have also reported alterations of calcium metabolism, such as hypercalcemia (11-14), hyperphosphatemia (2,11,13-15) and increased alkaline phosphatase and osteocalcin concentrations (16-19). Congenital hypothyroidism (CH) is a relatively frequent finding in newborns. Neonatal screening programs enable pediatricians to precociously identify CH newborns and to begin the replacement therapy early in life, to ensure normal development of the central nervous system and appropriate skeletal growth. To maintain euthyroid state, thyroxine dosage must be carefully monitored: this is now possible with the new generation of sensitive TSH assays. Accidental episodes of under- or overtreatment are therefore discovered through TSH (20) and free thyroxine measurements. Several studies reported a direct relationship between subclinical hyperthyroidism, as a result of overzealous replacement therapy, and reduced bone density (21-24) or calcium metabolism alterations in hypothyroid adults (25, 26). Although data on bone mineralization in CH children are very scarce (1, 6), there are evidences of hypercalcemia during the first 6 months of treatment (27).

The aim of the present study was to evaluate the bone mineralization and calcium metabolism in a large number of CH infants and children detected by neonatal screening. For this purpose we measured the bone mineral content and we studied several biochemical indexes of thyroid function and...
calcium metabolism in 5 groups of CH patients of different ages.

SUBJECTS AND METHODS

Subjects

Eligible for the study were all the newborns either positive at the neonatal screening for CH or diagnosed after clinical evaluation and thyroid function tests. Excluded from the study were all the subjects who presented bone abnormalities or metabolic disorders, as well as premature or small for gestational age newborns.

One hundred and sixteen Caucasian CH patients were enrolled in the study (81 girls and 35 boys). Twenty three were studied at diagnosis (age range 2-7 weeks), 20 at 3 months, 24 at 6 months, 25 at 12 months and 24 at 36 months of age. Treatment with L-thyroxine was started immediately after baseline evaluation at an initial dose of 6-8 μg/kg body weight given orally once daily. All patients during the first year of life received rickets prophylaxis with 400-1200 IU of vitamin D daily. On the basis of thyroid imaging studies, the patients were divided into 4 groups: 56 patients were athyreotic and 58 had evidence of residual thyroid tissue: 51 ectopic and 7 hypoplastic glands. The remaining 2 patients had familial dyshormonogenesis.

As a control group for bone mineral content determinations we studied 98 healthy Caucasian infants and children aged 0.02 to 3.50 years (40 girls and 58 boys). All subjects were in good health and appropriately physically active for their age; their weight, length and height values were within the third and ninety-seventh percentiles for age. Candidates were excluded if they had a history of chronic illness, if they had one or more fractures, or if they had taken regularly any medication, hormone or calcium supplement. All infants and children received 400-1200 IU/day of vitamin D during the first year of life.

Informed consent was obtained from all the parents and legal guardians of the patients and control subjects. The study was performed in accordance to the Declaration of Helsinki, as modified in 1983.

Methods

Thyroid function was monitored through free triiodothyronine (FT3), free thyroxine (FT4) and TSH determinations. FT3 was measured with a specific radioimmunoassay (RIA) (FT3 Solid Phase Component System; Becton Dickinson & Co., Orangeburg, NY) which has a sensitivity of 0.09 pmol/L; intraassay and interassay variations were 3.6% and 6.6%, respectively. A RIA was also employed for FT4 determinations (Becton Dickinson & Co., Orangeburg, NY); sensitivity of the assay was 0.58 pmol/L, while intraassay and interassay variations were 3.9% and 6.3%, respectively. Measurements of TSH were carried out with a sensitive immunometric procedure (Enzymun-test® TSH, Boehringer Mannheim Immunodiagnostics, Germany). Intra- and interassay variations were less than 6%. Sensitivity of the assay was 0.03 mU/L.

Total calcium, phosphorus, alkaline phosphatase (AP) and magnesium were measured with standard methods. Ionized calcium (iCa) was measured with an automated procedure, employing