CASE REPORT

Osteoporosis Secondary to Levothyroxine

J.L. Mather, C.D. Bayliff, L.M. Brownscombe

INTRODUCTION

Excessive thyroid replacement has been associated with osteoporosis.[1-7] We report a case of a patient who was receiving excessive thyroid replacement which may have contributed to an osteoporotic fracture.

CASE

A 67 year-old female was admitted to hospital with a chief complaint of left hip pain and inability to bear weight on her left leg following a recent fall. Her past medical history included cancer of the lung, a brain tumour, a seizure disorder, and left hip hemiarthroplasty. The patient had a history of excessive alcohol intake.

Her medications at home included phenytoin 250 mg po daily, levothyroxine 0.15 mg po daily, salbutamol 200 mcg four times daily as needed, and ipratropium bromide 40 mcg four times daily as needed. The patient was reported to be allergic to penicillin.

Physical examination was remarkable for pain and tenderness over the trochanter of the left hip. Routine biochemistries were unremarkable other than a slightly elevated alkaline phosphatase value. An X-ray of the left hip indicated a subcapital fracture.

The patient was taken to the operating room and had a Richard's screw fixation of the left hip. Postoperatively she was prescribed dimenhydrinate, morphine, salbutaml, ipratropium, Tylenol #3®, and levothyroxine 0.15 mg po daily. During her course in hospital, thyroid function tests were ordered. The results indicated suppressed thyroid-stimulating hormone (TSH) of less than 0.10 mU/L (N 0.30-5.80). The free thyroxine index (FTI) was 0.55 (N 0.23-0.72) while T4 total was 129 nmol/L (N69-168). Subsequently, due to the suppressed TSH, the patient's levothyroxine dose was decreased to 0.1 mg po daily and soon thereafter she was discharged. One month later, thyroid function tests revealed that the TSH was still suppressed (<0.10 mU/L) and the dose of levothyroxine was decreased to 0.075 mg po daily.

DISCUSSION

Several factors may have contributed to this patient's risk of hip fracture including malnutrition secondary to poor oral intake and excessive use of alcohol, metastatic disease associated with the lung cancer, long-term phenytoin leading to osteomalacia and levothyroxine. While there was no evidence of metastatic cancer, poor oral intake likely contributed to the event. As well, an elevated alkaline phosphatase value of 135 U/L (N30-115) would suggest that phenytoin may also have contributed.[8] Finally, there is substantial recent information that levothyroxine particularly in supraphysiologic doses may have contributed to the risk of fracture.[1-7]

Ross et al[1] measured bone density in 28 premenopausal females who were receiving suppressive doses of levothyroxine. The average free thyroxine index (FTI) was above normal and 75% had an undetectable TSH concentration. The mean dosage of levothyroxine (T4) was 0.171 mg/day. Twelve women who had been taking replacement for greater than ten years had a 9% decrease in cortical bone density compared with control subjects.

Paul et al[2] compared long-term levothyroxine therapy (>5 years) on the bone mass in premenopausal women with a control group. The mean dosage was 0.175 mg/day. The treated group had a free thyroxine index significantly higher and a significantly lower serum TSH

J.L Mather, B.Sc.Phm. is currently a Staff Pharmacist at Kingston General Hospital, Kingston, Ontario. At the time of writing, J.L. Mather was a Pharmacy Resident at Victoria Hospital, London, Ontario.
C.D. Bayliff, Pharm. D. is Clinical Co-ordinator of Pharmacy Services, Victoria Hospital.
L.M. Brownscombe, MD, FRCPC is a member of the Department of Medicine, Victoria Hospital.
Address correspondence to: J.L. Mather, Pharmacy Department, Kingston General Hospital, 76 Stuart Street, Kingston, Ontario K7L 2V7

concentration than the control group. The results showed femoral trochanter bone density was 10.1% lower and femoral neck bone density was 12.8% lower in the treated group compared to the control group. The greatest effects on bone density were in women over 35 years of age.

Aldin et al[3] determined bone mass density in 19 women treated with levothyroxine for five or more years at an average dose of 0.120 mg/day. Thirteen of 19 subjects had a low TSH and 16/19 had normal T4. Subjects who had no past history of hyperthyroidism had an 11% decrease in bone mass density in the spine and 4 - 10% decrease in the hip, both of which were not statistically significant compared to the controls. However, 7 of 19 who had a history of hyperthyroidism in the past had a 16.29% decrease in hip density which was statistically significant. Compared to other studies, the average daily dose was lower and the majority of patients had a normal T4 level which may have obscured any relationship between dose and bone density in the entire group.

Greenspan et al[4] studied the impact of long-term levothyroxine therapy on skeletal integrity when the FTI was maintained within a physiologic range. Twenty-eight premenopausal and 28 postmenopausal women were studied. In both groups, approximately 80% of patients had a FTI in the normal range when their bone density was measured, however, 82% of postmenopausal and 61% of premenopausal women's TSH was less than 0.4 μU/mL(N0.4-4.8). The results showed in the premenopausal women a statistically significant decrease of 6.7% in vertebral trabecular bone density, and a 5.1% decrease in femoral bone density compared to controls. The decrease in the bone density of the spine of 3.1% was not statistically significant.

In postmenopausal women there was a 0.2% decrease in vertebral trabecular bone density, a 1% decrease in integral bone density, and a statistically significant 6.2% decrease in femoral neck bone density. Greenspan et al[4] concluded that bone density loss is less if the FTI is maintained in physiologic range as the losses in this study were less than in previous studies.[1-3,5,7]

To date, no long term studies maintaining both the TSH and FTI in the normal range have been performed but in view of the fact that many of the patients with a normal FTI had a suppressed TSH, close attention to TSH would seem prudent.

In conclusion, it would appear that long-term levothyroxine therapy, particularly in excess, would increase the risk of fracture and periodic evaluation of thyroid function tests should be undertaken. As well, attention to other risk factors may minimize the risk of osteoporotic fracture.

REFERENCES

1. Ross DS, Neer RM, Ridgway EC, et al. Subclinical hyperthyroidism and reduced bone density as a possible result of prolonged suppression of the pituitary-thyroid axis with l-thyroxine. *Am J Med* 1987;82:1167-70.
2. Paul TL, Kerrigan J, Kelly AM, et al. Long term l-thyroxine therapy is associated with decreased hip bone density in premenopausal women. *JAMA* 1988;259:3137-41.
3. Aldin EV, Mauer AH, Marks AD, et al. Bone mineral density in postmenopausal women treated with l-thyroxine. *Am J Med* 1991;90:360-6.
4. Greenspan SL, Greenspan FS, Resnick NM, et al. Skeletal integrity in premenopausal and postmenopausal women receiving long term l-thyroxine therapy. *Am J Med* 1991;91:5-14.
5. Fallon MD, Perry HM, Bergfeld M, et al. Exogenous hyperthyroidism with osteoporosis. *Arch Intern Med* 1983;143:442-4.
6. Ross DS, Ardisson LJ, Samuel R, et al. Serum osteocalcin in patients taking l-thyroxine who have subclinical hyperthyroidism. *J Clin Endocrinol Metab* 1991;72:507-9.
7. Coindre JM, David JP, Riviere L, et al. Bone loss in hypothyroidism with hormone replacement. *Arch Intern Med* 1986;146:48-53.
8. Sotaniemi EA, Hakkarainen HK, Puranen JA, et al. Radiologic bone changes and hypocalcemia with anticonvulsant therapy in epilepsy. *Ann Intern Med* 1972;77:389-94.