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# Does Long-term Administration of Tamoxifen Affect Bone Mineral Density?

A.J. Neal, K. Evans and P.J. Hoskin

**A retrospective study was performed to determine whether the long-term (5 years or more) administration of tamoxifen is detrimental to bone mineral density (BMD). 19 patients taking adjuvant tamoxifen for breast cancer were paired with 19 controls comparable in age, time since menopause and performance status. BMD was measured at the femoral neck, lumbar spine and total body by dual energy X-ray absorptiometry (DEXA). There was no detrimental effect on BMD at any site. There was a trend towards an increase in BMD at the femoral neck. There were minor decreases in the serum calcium, phosphate and alkaline phosphatase.**
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## INTRODUCTION

TAMOXIFEN IS widely used in the treatment of breast cancer both as systemic adjuvant therapy and for the treatment of metastatic disease. As an adjuvant agent, there is convincing evidence [1] that tamoxifen prolongs both disease-free survival and overall survival. The optimum duration of treatment is yet to be defined, and so there is a tendency for patients to remain on tamoxifen indefinitely or until disease progression. There is also increasing interest in using tamoxifen for the treatment of benign conditions such as mastalgia [2] and as a chemopreventative agent in women at high risk of breast cancer [3], which will inevitably lead to its use in a much larger number of healthy women. The potential long-term toxicities of tamoxifen must, therefore, be explored and the risks defined. Evidence to date suggests a favourable toxicity profile. Up to 2 years of treatment has not been associated with any detrimental effect on bone mineral density (BMD). This study was designed to assess the skeletal effect of tamoxifen when taken for 5 years or more.

## PATIENTS AND METHODS

Females who had taken tamoxifen 20–40 mg daily as adjuvant systemic therapy for 5 years or more were identified from patients routinely followed up in our clinic. Patients were excluded if there was any evidence of active locoregional disease, past history of distant metastases, radiological evidence of osteoporosis prior to starting tamoxifen or a World Health Organisation (WHO) performance score greater than 0 (i.e. able to carry out all normal activity without restriction). Each tamoxifen patient was then paired with a control who had also had breast cancer diagnosed at least 5 years earlier but had not received any adjuvant systemic therapy. Pairs were matched for age to within 5 years, and time since menopause to within 3 years.

In all, 19 pairs of patients aged 45–84 years (median 62) were recruited. 36 of the 38 patients were postmenopausal. All underwent dual energy X-ray absorptiometry (DEXA) using a Lunar DPX scanner to record BMD of the lumbar spine (L2–L4), femoral neck and total skeleton. Of the patients taking tamoxifen, 10 had received 20 mg daily and 9 had received 40 mg daily. Duration of tamoxifen prior to DEXA scan was between 60 and 140 months (median 75). Blood was taken for measurement of serum calcium (corrected for an albumin of 40 g/l), serum phosphate and alkaline phosphatase.

## RESULTS

BMDs were available for 18 pairs of patients at each location. There was a trend towards a higher BMD at each site in the women receiving tamoxifen, particularly in the femoral neck. This effect appeared to be most pronounced in those receiving 20 mg daily rather than 40 mg. In no group was the difference statistically significant (Table 1). Values for serum calcium, phosphate and alkaline phosphatase were available for all 38 patients. There was a small, statistically significant decrease in serum calcium and alkaline phosphatase (Table 2).

## DISCUSSION

Oestrogen withdrawal is implicated in the osteoporosis that occurs with ageing [4, 5]. Oestrogen receptors have been identified on osteoblasts [6], and thus it is possible for an anti-oestrogen such as tamoxifen to induce bone mineral loss. This could result in an increased susceptibility to fractures of the vertebrae, distal radius and femoral neck. However, evidence from animal studies suggests that tamoxifen has a partial agonist activity on the skeleton and actually helps to maintain BMD [7, 8]. DEXA is a safe, rapid and non-invasive means of estimating BMD. Lumbar spine BMD measurements are representative of trabecular bone, while those of the femoral neck are representative of cortical bone. The oesteoporosis seen with ageing is reflected predominantly by a decline in the former [9].

These results confirm those from other studies which have shown no reduction in BMD with adjuvant tamoxifen [10–18]. A large randomised double-blind placebo-controlled prospective study showed that 2 years of tamoxifen caused an increase in lumbar BMD of 0.61% per year vs. a decrease of 1% per year in the controls ($P < 0.001$), and that there was no difference between the groups with respect to radial BMD [19]. There are reports of tamoxifen causing a decrease in alkaline phosphatase [19] and serum calcium [20] but as in this study, these changes are small and unlikely to be of any clinical significance. Our results indicate that there was a trend towards tamoxifen increasing BMD, particularly at the femoral neck which, in terms of

Correspondence to A.J. Neal at the Royal Marsden Hospital, Sutton, Surrey, U.K.
K. Evans is at the Royal London Hospital Trust, Whitechapel, London E1 1BB and P.J. Hoskin is at the Mount Vernon Hospital, Northwood, Middlesex, U.K.
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*Table 1. Mean bone mineral densities (BMD) according to treatment*

| | Mean lumbar BMD ($g/cm^2$) | Mean femoral BMD ($g/cm^2$) | Mean total body BMD ($g/cm^2$) |
|---|---|---|---|
| All tamoxifen patients | | | |
| ($n$ = 18) | 1.081 | 0.934 | 1.078 |
| All controls | | | |
| ($n$ = 18) | 1.065 | 0.877 | 1.057 |
| $P$ value* | > 0.1 | > 0.1 | > 0.1 |
| 95% CI | −0.045–0.094 | −0.047–0.165 | −0.036–0.07 |
| Tamoxifen 20 mg daily | | | |
| ($n$ = 10) | 1.059 | 0.894 | 1.075 |
| Controls | | | |
| ($n$ = 10) | 1.028 | 0.838 | 1.034 |
| $P$ value* | > 0.1 | > 0.1 | > 0.1 |
| 95% CI | −0.007–0.115 | −0.026–0.136 | −0.038–0.107 |
| Tamoxifen 40 mg daily | | | |
| ($n$ = 8) | 1.104 | 0.984 | 1081 |
| Controls | | | |
| ($n$ = 8) | 1.100 | 0.921 | 1.087 |
| $P$ value* | > 0.1 | > 0.1 | > 0.1 |
| 95% CI | −0.109–0.165 | −0.19–0.316 | −0.202–0.001 |

*Two-tailed value. CI, confidence interval.

*Table 2. Mean serum biochemistry indices according to treatment*

| | Calcium (mmol/l) | Phosphate (mmol/l) | Alkaline phosphate (U/l) |
|---|---|---|---|
| All tamoxifen patients | | | |
| ($n$ = 19) | 2.30 | 1.10 | 63.7 |
| All controls | | | |
| ($n$ = 19) | 2.39 | 1.20 | 76.2 |
| $P$ value* | < 0.05 > 0.01 | < 0.1 > 0.05 | < 0.05 > 0.01 |
| 95% CI | −0.16–−0.02 | −0.21–0.01 | −21.5–−3.1 |
| Tamoxifen 20 mg daily | | | |
| ($n$ = 10) | 2.30 | 1.12 | 60.1 |
| Controls | | | |
| ($n$ = 10) | 2.40 | 1.21 | 76.9 |
| $P$ value* | < 0.1 > 0.05 | > 0.1 | < 0.01 > 0.001 |
| 95% CI | −0.21–0.01 | −0.23–0.05 | −26.3–−7.3 |
| Tamoxifen 40 mg daily | | | |
| ($n$ = 9) | 2.29 | 1.07 | 67.7 |
| Controls | | | |
| ($n$ = 9) | 2.38 | 1.19 | 75.4 |
| $P$ value* | < 0.1 > 0.05 | > 0.1 | > 0.1 |
| 95% CI | −0.19–0.03 | −0.30–0.07 | −25.6–11 |

*Two-tailed value. CI, confidence interval.

morbidity from osteoporosis, is the most critical site of bone loss, although this trend did not reach statistical significance in any group.

While our results offer further reassurance to those concerned about the long-term effects of tamoxifen on the skeleton, a large prospective study is required looking specifically at premenopausal women.

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# Insulin-like Growth Factor (IGF)-I, -II and IGF Binding Protein-2 (IGFBP-2) in the Plasma of Children with Wilms' Tumour

**Walter Zumkeller, Juerg Schwander, Christopher D. Mitchell, David J. Morrell, Paul N. Schofield and Michael A. Preece**

**Insulin-like growth factors (IGF)-I, -II and IGF binding protein-2 (IGFBP-2) have been measured in plasma of children with Wilms' tumour. The mean levels for total serum IGF-I and -II were not significantly altered in Wilms' tumour as compared with normal control plasma. However, the chromatographic profiles for IGF-I and -II in these groups were different with regard to the presence of IGF binding proteins and high molecular weight forms of IGFs; the high molecular weight form (9–15 kD) of IGF-II was significantly reduced in Wilms' tumour. Levels of IGFBP-2 were substantially elevated in serum from Wilms' tumour patients (1025 ± 112 ng/ml compared with 416 ± 44 ng/ml in controls), and inversely correlated with the levels of high molecular weight forms of IGF-II. We suggest that IGFBP-2 measurements might be of value as a marker for monitoring this type of tumour, either as an adjunct to diagnosis or surveillance of tumour growth during therapy.**
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## INTRODUCTION

INSULIN-LIKE growth factors (IGF)-I and -II are growth-promoting polypeptides involved in a variety of physiological and pathological processes of the kidney [1]. In circulation, they are associated with specific binding proteins (IGFBP) which both extend their half-life and modulate their actions. The synthesis of these binding proteins is under a complex, as yet poorly understood, system of regulation [2].

The expression of IGFs depends upon the state of tissue differentiation and undergoes dynamic changes during fetal development [1]. IGF-II mRNA has been found to be highly expressed in embryonic tissues [3–5] and in a number of embryonal tumours [6–8], including nephroblastoma (Wilms' tumour, WT) [9–11], pheochromocytoma [11] and hepatoblastoma [8].

During embryonic development, IGFBP-2 expression is