ORIGINAL ARTICLE

Evaluation of urinary N-telopeptide of type I collagen measurements in the management of osteoporosis in clinical practice

I. Baxter · A. Rogers · R. Eastell · N. Peel

Abstract

Summary We measured urinary N-telopeptide of type I collagen (U-NTX) to monitor response to bisphosphonates for osteoporosis. Decrease in U-NTX was associated with increase in spine bone density. A lesser response in U-NTX was more likely in those with secondary osteoporosis or with poor compliance. U-NTX may be a useful early indicator of treatment non-compliance or secondary osteoporosis.

Introduction This study aims to determine the utility of the bone resorption marker, U-NTX, in the clinical setting, to monitor the response to bisphosphonate therapy (alendronate and risedronate) for osteoporosis.

Methods A retrospective evaluation of data collected as part of the bone turnover marker monitoring service in the Metabolic Bone Centre, Sheffield, UK. Treatment compliance, underlying causes of osteoporosis, change in U-NTX/creatinine (Cr) at 4 months and change in spine and hip bone mineral density (BMD) by dual-energy X-ray absorptiometry were recorded. Treatment response was defined as either a change in U-NTX/Cr greater than a pre-defined least significant change (LSC) of

54 % or to within the lower half of a pre-defined pre-menopausal reference interval (≤30 nM BCE/mmol Cr).

Results A greater decrease in U-NTX/Cr at 4 months was associated with a greater increase in spine BMD at 18 months ($r=-0.33$; $P<0.0001$, Pearson's correlation). The mean U-NTX/Cr at 4 months was higher in patients with secondary osteoporosis compared with those with primary osteoporosis ($P<0.01$, ANOVA). A lesser response in U-NTX/Cr increased the likelihood of secondary osteoporosis or poor treatment compliance ($P=0.04$, Fisher's exact test). A lack of response in U-NTX/Cr to within the lower half of the reference interval was a better indicator of secondary osteoporosis and treatment non-compliance than a change in U-NTX/Cr greater than LSC.

Conclusions Treatment monitoring using U-NTX/Cr has a place in clinical practice for the early identification of non-compliance or presence of secondary osteoporosis.

Keywords Biochemical markers of bone turnover · Bisphosphonate · Dual-energy X-ray absorptiometry · Monitoring · Osteoporosis

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Introduction

Ensuring that patients adhere and persist with their medication is a major challenge with any long-term therapy. Up to 50 % of patients taking a bisphosphonate will have stopped taking their medications at 1 year, and many of these patients stop within the first 3 months [1]. Monitoring patients improves adherence and persistence with therapy which ultimately results in increased treatment effectiveness and reduced risk of fracture [2]. We have previously shown that monitoring patients in nurse-led clinics at 3-, 6- and 9-month intervals improved adherence to treatment by 57 % compared with no monitoring [3].

Response to osteoporosis therapies may be monitored objectively by examining either change in bone mineral

density (BMD) or in biochemical bone turnover marker (BTM). Change in lumbar spine BMD is the method most commonly used to identify response to treatment; however, this approach has drawbacks. Firstly, the change in BMD is small compared with the precision error of the measurement, which means that changes in an individual patient can only be reliably detected after 2 years of treatment. Secondly, lumbar spine BMD measurements become increasingly un-reliable with ageing and this approach cannot be interpreted reliably in a proportion of patients. BTMs, on the other hand, may have some advantages over BMD in that they show a significant response within weeks of beginning medication. The 'signal-to-noise' ratio is also more favour-able than that of dual-energy X-ray absorptiometry (DXA) measurements [4, 5]

The largest decreases in BTMs are observed with urinary N- and serum C-terminal telopeptides of type I collagen (U-NTX and S-CTX) [6]. These markers of bone resorption are also more strongly associated with BMD response than other markers and are the most widely used in clinical practice. Bone resorption markers also show a more rapid response (within 1 month) than bone formation markers where the change becomes significant between 3 and 9 months after commencing treatment. The choice of marker in clinical practice needs to be made on pragmatic grounds. U-NTX may be the preferred marker in the clinic setting as unlike S-CTX, it is not as sensitive to circadian changes and is not affected by food intake [7]. Patients may be asked to collect second morning void urine samples at home and bring these to their hospital appointment. This avoids the requirement for patients to attend fasting and means that they may have clinic appointments at any time of day.

In clinical practice, there are two possible approaches to estimate what constitutes a treatment response using BTM: (1) a target of the lower half of the pre-menopausal reference interval or (2) a change greater than the 'least significant change' (LSC) [8].

The first approach requires the establishment of a robust reference interval. A reference interval is best estimated in women with a mature skeleton who have not yet reached menopause. We have developed a reference interval locally from a group of 153 healthy pre-menopausal women between the ages of 35–45 years [8]. We determined this age range to be the most suitable as BTM reach a nadir during this period.

We have previously estimated that that the LSC for urinary N-telopeptide of type I collagen corrected for creatinine (U-NTX/creatinine (Cr)) is 54 %, i.e. 95 % of repeat measure-ments will not exceed 54 % change [1].

The most common drugs currently used for the treatment of osteoporosis are the oral bisphosphonates (such as alendronate and risedronate). Response to bisphosphonate therapy is gen-erally good but can be variable. Currently, if a response to treatment is not detected, we would act by (1) checking for good compliance and (2) investigating for secondary osteo-porosis or (3) considering a change in treatment.

Secondary osteoporosis is common and may be due to the direct pathophysiology of a disease such as primary hyperparathyroidism or indirectly from conditions causing periods of immobilisation such as multiple sclerosis [9]. Glucocorticoid treatment may also lead to osteoporosis by its action on osteoblast activity and by decreasing calcium absorption [10, 11].

In this study, we examined data collected from patients in the clinical setting. The aims of the study were to determine (a) the proportion of patients with a response in U-NTX/Cr to bisphosphonate treatment at 4 months, (b) the association between change in U-NTX/Cr at 4 months and change in BMD at 18 months, (c) the causes and outcome of non-response, e.g. presence of poor compliance or secondary osteoporosis and (d) the proportion of clinical patients in whom BMD by DXA results are uninterpretable.

Subjects and methods

Study design

This was a retrospective evaluation of the BTM monitoring service in Sheffield, UK. Study subjects were 200 patients who attended the Metabolic Bone Centre (MBC), Northern General Hospital, Sheffield, between 1st April 2004 and 31st October 2009.

Approximately 650 patients/month attend the MBC for evaluation of fracture risk. Most patients are referred by the general practitioner (GP) or from the orthopaedic fracture clinic. A small number are referred by other secondary care departments. Patients undergo a clinical evaluation which includes completion of a baseline questionnaire, assessment of BMD by DXA and spinal radiographs if necessary. Around 85 % of patients are referred back to their GP with management advice and the remainder, with more severe or complicated osteoporosis, return to the physician-led clinics for further investigation and treatment. This group includes patients with vertebral fractures, those with low BMD for age (Z-score below −2) and those with unexplained bone loss. Patients treated in the physician-led clinics are routine-ly monitored using BTM. Subjects for this analysis were identified through a database held by the MBC. We identi-fied 200 subjects who met the inclusion/exclusion criteria and were included in this analysis.

The study subject inclusion criteria were: no previous treatment for osteoporosis (excluding calcium and vitamin D or oestrogen replacement therapy); osteoporosis or osteo-penia requiring treatment; patients who were about to com-mence either alendronate or risedronate therapy; patients with a baseline U-NTX/Cr measured after 31st March

2004 (after the introduction of triplicate pooled urine samples into the clinical service); and a follow-up BMD by DXA scan by 1st November 2009.

The study subject exclusion criteria were: previous bisphosphonate treatment; the current use of an osteoporosis treatment; absence of a baseline measurement; measurements that were carried out in laboratories other than the Clinical Chemistry laboratory at the Northern General Hospital, Sheffield; and absence of a follow-up BMD by DXA scan.

As part of the usual clinical monitoring procedure for the MBC, urine samples for measurement of U-NTX/Cr are collected at several time points as follows:

– Before attending the clinic (when patients attend for investigation for underlying causes of osteoporosis)
– At the first physician clinic visit
– At the nurse clinic after 4 months on treatment
– At the nurse clinic after 7 months on treatment (if the response to treatment at 4 months is poor).

With the exception of the first pre-clinic measurement, all U-NTX/Cr measurements were performed on a pooled sample of three second morning void samples collected between 0900 and 1100 hours as we have previously found this approach to reduce variability by between 20 and 61 % [12].

The U-NTX measurements were carried out in the NHS Clinical Chemistry laboratory at the Northern General Hospital, Sheffield. Measurements of U-NTX and Cr were performed using the Ortho-Clinical Diagnostics, Vitros ECi autoanalyser (Johnson & Johnson, New Brunswick, NJ). The measurement is expressed as a ratio of U-NTX to Cr. The intra-assay coefficient of variation (CV) for this assay was between 1.1 and 6.7 %, and the inter-assay CV was between 3.8 and 6.1 %.

A value for LSC of 54 % was derived from previously published data [1] using the formula: $LSC = 1.96 \times \sqrt{2} \times CV$, where CV is the CV calculated from the standard deviation of the measurement divided by the population mean. The target response of the lower half of the pre-menopausal reference interval ($\leq$30 nMBCE/mmol Cr) was derived from previously published data from women living in Sheffield [8].

BMD measurements were performed by DXA (Hologic Discovery A or C, Bedford, MA) at the lumbar spine and hip. Serial measurements for each patient were performed using the same densitometer. Instrument stability was monitored using daily measurements of a semi-anthropomorphic hydroxyapatite phantom. A value for LSC for change in BMD of 4.5 % was derived from previously published data [13]. All DXA spine and hip scans were scrutinised before being regarded as being of sufficient quality for inclusion in the analysis. DXA scans were considered to be unsuitable for this analysis according to the criteria presented in Table 1.

Table 1 Criteria for excluding patients with uninterpretable dual-energy X-ray absorptiometry (DXA) scans

Criteria for spine DXA	Criteria for hip DXA
Overlying artefacts in the scan field	Overlying artefacts in scan field
Large change in weight between scans (>10 % or >5 kg)	Large change in weight between scans (>10 % or >5 kg)
Poor replication of positioning	Poor replication of positioning
Incorrect vertebrae scanned	Severe abduction/adduction of the hip
More than 2 prevalent fractures in the scan field	Severe change in abduction/adduction of the hip
Severe scoliosis	Incorrect hip measured at follow-up
Extensive diffuse idiopathic skeletal hyperostosis	Bilateral hip replacement

Treatment compliance was established qualitatively at the monitoring visit by asking the patient an open question to describe how they were taking their medication. Further direct questioning was used to define the nature and extent of sub-optimal compliance and enable the nurse practitioner to form a clinical judgement of whether there was a problem with compliance likely to affect the clinical response to treatment. Poor compliance was defined as (1) failing to take treatment on a weekly basis, which included patients who had stopped treatment altogether and those who missed more than 1 tablet/month and (2) taking treatment incorrectly, which included patients who had not fasted prior to taking their bisphosphonate, those who took their tablet with a beverage other than tap water and those who took calcium-containing supplements shortly after the bisphosphonate.

Statistical methods

Statistical analyses were performed using SPSS v16.0 (SPSS Inc, Chicago, IL) and GraphPad Prism (GraphPad Software Inc, La Jolla, CA). Log transformation or non-parametric testing was used for analysis of skewed data. Association between change in U-NTX/Cr and change in BMD was assessed by Pearson's correlation after log transformation of the U-NTX/Cr data. The association between treatment compliance and U-NTX/Cr response was assessed by Fisher's exact test. The association between diagnosis and U-NTX/Cr response was assessed by Chi-square test. Unpaired t tests were used to compare unpaired data. A P value of less than 0.05 was considered to be significant.

Results

The demographics of the 200 participating subjects are shown in Table 2. We identified 161 women and 39 men

Table 2 Baseline characteristics of study participants attending clinic for a baseline and 4-month follow-up visit

	All	Women	Men
Total number	200	161	39
Age (mean (range) years)	68 (32–91)	69 (50 to 91)	66 (32–86)
BMI (mean (range) kg/m^2)	26 (14–47)	26 (17 to 41)	25 (14–47)
Years since menopause (mean (range) years)	–	22 (1 to 48)	–
Number (%) with primary osteoporosis	130 (65 %)	110 (68 %)	20 (51 %)
Number (%) with secondary osteoporosis	40 (20 %)	26 (16 %)	14 (36 %)
Number (%) with glucocorticoid-induced osteoporosis	30 (15 %)	25 (16 %)	5 (13 %)
Number (%) receiving risedronate	124 (62 %)	98 (61 %)	26 (67 %)
Number (%) receiving alendronate	76 (38 %)	63 (39 %)	13 (33 %)

who met the inclusion/exclusion criteria. The age of the men (66; range, 32–86 years) was lower than that of the women (69; range, 50–91 years), but this was not statistically significant ($P=0.08$, unpaired t test). Four patients were changed to alternative intravenous bisphosphonate therapies at 4 months due to poor compliance or side effects of oral therapy. These patients were not included in the BMD analysis.

Secondary osteoporosis was identified in 35 % of patients (15 % due to glucocorticoid use and 20 % due to other causes). Causes other than glucocorticoid use included coeliac disease (either poorly controlled or undiagnosed), rheumatoid arthritis, primary and secondary hyperparathyroidism and the use of medications such as phenytoin. Seven patients were diagnosed with primary hyperparathyroidism: two patients underwent surgery between the 4- and 18-month follow-up visits, one received surgery before attending the clinic, one patient declined surgery and the remainder were treated conservatively. Baseline U-NTX/Cr was higher in patients with an underlying cause of osteoporosis other than glucocorticoid use compared with those with primary osteoporosis (60.8 vs. 46.1 nM BCE/mmol Cr; $P<0.01$, ANOVA).

Response in U-NTX/Cr to bisphosphonate treatment at 4 months

Using the target of the lower half of the reference interval, after 4 months of alendronate or risedronate therapy, 81 % of patients could be classified as 'responders'. Using a U-NTX/Cr response of greater than LSC as the target response, 53 % could be classified as responders; 45 % of patients met both criteria for response whilst seven patients (3.5 %) showed no response.

Uninterpretable BMD by DXA results

Spine DXA scans were uninterpretable in 28 (14 %) of the 200 patients. Reasons included presence of severe scoliosis, vertebral fractures, extensive degenerative changes, change in weight between scans and incorrect positioning. Hip DXA

scans were either not done or were not interpretable in seven (3.5 %) due to the presence of total hip replacement, increase in weight or poor positioning.

Association between change in U-NTX/Cr at 4 months and change in BMD at 18 months

Figure 1 shows the relationship between change in spine BMD at 18 months and change in U-NTX/Cr at 4 months in response to risedronate or alendronate. There was a significant inverse correlation between change in spine BMD and change in U-NTX/Cr ($r=-0.33$; $P<0.0001$, Pearson's correlation). In addition, 70 % of patients with a decrease in U-NTX/Cr
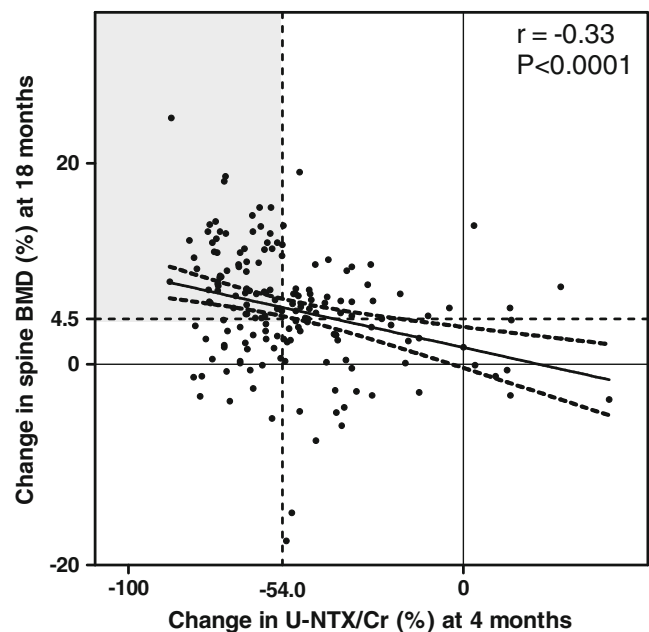

Fig. 1 The relationship between change in U-NTX/Cr at 4 months with change in spine BMD at 18 months. The *vertical broken line* shows the least significant change for U-NTX/Cr (54 %) and the *horizontal broken line* shows the least significant change for spine BMD (4.5 %). The number of patients responding by U-NTX/Cr change was 105 (52.5 %); the number by BMD change was 100 (50 %). The *upper left shaded area* shows the number of patients who responded by both U-NTX/Cr and spine BMD (64, 32 %)

of >54 % subsequently had an increase in spine BMD of greater than 4.5 %. Patients meeting both criteria (i.e. U-NTX/Cr of >54 % and U-NTX/Cr of ≤30 nM BCE/mmol Cr) had a greater percentage increase in spine BMD than those meeting one or no response criteria (+7.00±0.57 vs. +3.86± 0.64 %; $P=0.0003$).

There was no significant association between change in U-NTX/Cr and change in hip BMD. This is not surprising in light of the fact that the magnitude of change in response to treatment with anti-resorptive agents is typically smaller at the hip in comparison to the spine [14] and that BMD measurement at the hip is somewhat less precise than that at the spine [11]. Furthermore, patients meeting both criteria for U-NTX/Cr response did not have a significantly greater increase in hip BMD (data not shown).

Causes and outcome of non-response

When we examined the impact of the initial diagnosis, we observed no difference in the percentage of patients who responded to therapy using the LSC criterion (primary osteoporosis, 54 %; secondary osteoporosis, 50 %; and glucocorticoid-induced osteoporosis (GIOP), 57 %). U-NTX/Cr was greater than 30 nM BCE/mmol Cr after 4 months bisphosphonate treatment in 33 % of patients with secondary osteoporosis. This compared with 15 % of patients with primary disease and 20 % of patients with GIOP ($P=0.04$, Chi-square test) (Table 3). The mean U-NTX/Cr at 4 months was higher in patients with secondary osteoporosis compared with primary osteoporosis. However, mean U-NTX/Cr at 4 months in patients with GIOP was not different to primary or secondary osteoporosis (Fig. 2).

On the basis of the 4-month assessment, 23 patients were given further advice about the correct way to take treatment and/or correction of reversible underlying causes such as additional vitamin D supplementation. They were reviewed again after a further 3 months. At the 7-month review, 13 of 23 had a U-NTX/Cr of <30 nM BCE/mmol Cr and 9 of 23 had a change in U-NTX/Cr which exceeded the LSC in comparison to the pre-treatment level. Eight patients showed response by both criteria, six responded by one

criterion and nine were complete non-responders. Management at that stage depended on the individual circumstances and involved, for example, surgical intervention for primary hyperparathyroidism; continued use of first-line treatment for compliant patients with an underlying cause of their osteoporosis; and change in treatment for persistent non-compliers.

Impact of fracture on monitoring response

There were 23 patients who had sustained a fracture in the year prior to baseline. They had higher baseline U-NTX/Cr in comparison to those without fracture (68 vs. 47 nM BCE/mmol Cr; $P<0.001$) but at 4 months there was no significant difference in the proportion of responders between those with and without fracture (proportion of <30 nM BCE/mmol Cr, 74 vs. 82 %; mean decrease in U-NTX, 59 vs. 49 %). Four patients experienced an incident fracture between their baseline measurement and the 4-month measurement (three of digits and one vertebral). All four of these patients were classified as responders at 4 months by both criteria.

Compliance

Poor compliance was observed in 22 (11 %) of our patients. Patients assessed as having poor compliance had a higher U-NTX/Cr at the 4-month follow-up visit than those who had good compliance (27.2 vs. 22.5 nM BCE/mmol Cr; $P=0.05$). The proportion of patients with poor compliance who were defined as responders was lower than the proportion among patients who had good compliance (proportion of <30 nM BCE/mmol Cr, 64 vs. 83 % ($P=0.04$); proportion with U-NTX change greater than LSC, 36 vs. 54 % ($P=0.01$), Fisher's exact test) (Table 4).

Discussion

The overall aim of this study was to determine the usefulness of bisphosphonate treatment monitoring using U-NTX/Cr in the clinical setting. There has been only one previous report describing the utility of BTM in clinical practice.

Table 3 U-NTX at 4 months and percentage change in U-NTX in primary, secondary and glucocorticoid-induced osteoporosis patients

	Diagnosis			
	Primary osteoporosis	Secondary osteoporosis	Glucocorticoid-induced osteoporosis	Total
U-NTX of ≤30 nM BCE/mmol Cr at 4 m*	111	27	24	162
U-NTX of ≥30 nM BCE/mmol Cr at 4 m*	19	13	6	38
Change in U-NTX at 4 m>LSC (54 %)	69	19	17	105
Change in U-NTX at 4 m<LSC (54 %)	61	21	13	95

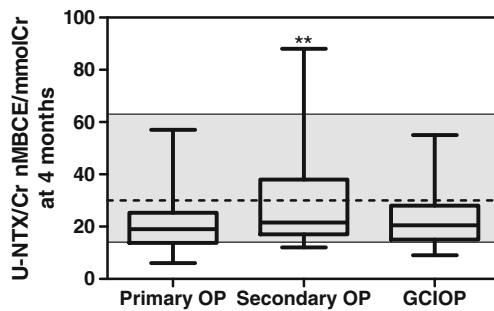*$P=0.04$, Chi-square test

Fig. 2 Box and whisker plots to show the absolute values of U-NTX/Cr at 4 months. There was a significant difference in U-NTX/Cr between patients with primary and secondary osteoporosis (**P<0.01). The shaded area shows the pre-menopausal reference interval; the geometric mean is indicated with a dotted line

Eekman et al. [15] observed that 81 % of a small cohort of 31 patients commencing osteoporosis treatment had a decrease greater than the LSC in both S-CTX and S-PINP at 3 months. In a further cross-sectional evaluation of 95 patients (including the 31 in the prospective analysis), they observed that levels of S-CTX and S-PINP after 3 months of bisphosphonate treatment were below the pre-menopausal mean in 95 % of their cohort. Our study adds to this clinical evaluation by showing data for another BTM in a larger cohort of patients. This has enabled us to examine the impact of underlying causes and poor compliance in more detail and to evaluate the relationship of the change in BTM to the change in BMD.

We found that about one half of patients (53 %) had a decrease in response to bisphosphonate greater than the LSC of 54 % after 4 months of treatment. This is similar to the data presented in the fosamax actonel comparison trial (FACT) [14]. In the FACT study, a lower LSC of 40 % was used for U-NTX/Cr, and the follow-up period was 12 months; 67 % of alendronate-treated patients and 49 % of risedronate-treated patients were responders. Given the different duration and the smaller LSC, these response rates may be regarded as being similar to ours. In this study, a greater proportion of patients (81 %) had values for U-NTX/Cr in the lower half of the reference range after 4 months compared with those having a response greater

Table 4 U-NTX at 4 months and change in U-NTX in compliant and non-compliant participants

	Compliance		
	Good	Poor	Total
U-NTX of ≤30 nM BCE/mmol Cr at 4 m*	148	14	162
U-NTX of ≥30 nM BCE/mmol Cr at 4 m*	30	8	38
Change in U-NTX at 4 m>LSC (54 %)**	97	8	105
Change in U-NTX at 4 m<LSC (54 %)**	81	14	95

Poor compliance was defined as either failing to take treatment on a weekly basis or taking it incorrectly

*P=0.04; **P=0.01, Fisher's exact test

than LSC after 4 months. The higher proportion of patients exceeding LSC and with 3-month values below the pre-menopausal mean in Eekman's analysis is likely to be explained by the use of serum-based markers with a smaller CV [15]

We found that the U-NTX/Cr response to alendronate and risedronate at 4 months was weakly associated with change in spine BMD (but not total hip BMD) at 18 months ($r=-0.33$). A previous study reported the 6-month change in U-NTX/Cr in response to alendronate was related to change in total hip BMD ($r=-0.34$) but not spine BMD over 3 years [16]. The finding of only modest association between changes in BMD and changes in BTM is not surprising in view of the considerable variability in both types of measurement which are being used as a surrogate for the outcome of interest, namely change in fracture risk, which cannot be determined directly.

In this study, secondary osteoporosis was associated with higher U-NTX/Cr at follow-up which is a novel observation. The causes of secondary osteoporosis included primary hyperparathyroidism, and bisphosphonates do reduce bone turnover in these patients [17]. In one randomised controlled trial of alendronate in patients with primary hyperparathyroidism, the mean urinary NTX/Cr ranged between 30 and 50 nmol BCE/mmol Cr higher than that found in patients with primary osteoporosis treated with alendronate [14]. However, in another major clinical trial of alendronate in patients with primary hyperparathyroidism, U-NTX/Cr decreased by a mean value of 66 % [18]. In this study, we observed a significant difference in U-NTX/Cr at 4 months between patients with primary and various causes of secondary osteoporosis (21.2 vs. 28.5 nMBCE/mmol Cr; $P<0.05$).

The occurrence of a fracture in the months prior to commencement of treatment or between the time of the baseline and monitoring measurements might be anticipated to increase or decrease the apparent BTM response to treatment, respectively. However, in this evaluation, we did not find a significant effect of fracture. Those patients with fracture within a year before treatment did have higher baseline BTM values, and there was a trend for a greater mean decrease in U-NTX between baseline and 4 months but this did not result in a higher proportion of patients being classified as responders. Furthermore, the occurrence of fractures between the baseline and 4-month measurements did not lead to a diagnosis of non-response. Fracture is however an important consideration in the interpretation of BTM measurements and fracture of a large bone might be expected to impair the ability to monitor that individual using BTM.

Treatment compliance is an important issue when considering the effects of long-term therapies. In this study, poor compliance was associated with higher U-NTX/Cr after 4 months of therapy. We have previously reported that poor compliance with raloxifene (assessed by electronic caps) is associated with poorer NTX response to treatment over 12 months [3]. Our data suggest that the target of the

lower half of the reference interval appears to be a better indicator of treatment compliance than use of LSC.

As we were evaluating retrospective data collected in the clinical setting rather than from a controlled research study, certain limitations of these data should be acknowledged. Our patient population consisted of both men and women but the thresholds for LSC and references intervals were derived from studies of women alone. However, our aim was to determine the usefulness of monitoring with U-NTX/Cr in the clinical setting using the available background reference data, and as yet there are no data for change in U-NTX/Cr and change in fracture risk in men. We observed a lesser response in U-NTX/Cr in those patients who went on to have a lesser response in BMD. This association may have been underestimated as a poor response in U-NTX at 4 months led to further intervention and possible improved response in BMD.

In summary, in this clinical evaluation, we have shown that measurements of U-NTX/Cr in patients treated with alendronate or risedronate may be a useful early indicator of the presence of underlying causes of osteoporosis or poor compliance. In the evaluation of treatment response, it may be helpful to consider whether the U-NTX/Cr value lies within the lower half of the pre-menopausal reference interval and also whether there has been a change in U-NTX/Cr greater than the LSC.

Conflicts of interest None.

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