# The Potential Role of Curcumin in Patients with Monoclonal Gammopathy of Undefined Significance—Its Effect on Paraproteinemia and the Urinary N-Telopeptide of Type I Collagen Bone Turnover Marker

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**Abstract**

**Purpose:** To determine the effect of curcumin on plasma cells and osteoclasts in patients with MGUS.

**Experimental Design:** Twenty-six patients with MGUS were recruited into the study and administered 4 grams/day oral curcumin. Blood and urine samples were collected at specified visits after initiating therapy. Full blood count, B2 microglobulin, serum paraprotein, and immunoglobulin electrophoresis (IEPG and EPG) were determined for all patients at each visit. Serum calcium, 25 hydroxyvitamin D3, and bone-specific alkaline phosphatase were determined at baseline only. Urine, as a morning second-void sample, was collected at each visit for urinary N-telopeptide of type I collagen.

**Results:** Our results show that oral curcumin is able to decrease paraprotein load in a select group (i.e., those having a paraprotein level of >20 g/L) of patients with MGUS. Fifty percent (5 of 10) of these patients had a 12% to 30% reduction in their paraprotein levels, while on curcumin therapy. In addition, 27% of patients on curcumin had a >25% decrease in urinary N-telopeptide of type I collagen.

**Conclusion:** Due to the possible progression of MGUS to multiple myeloma, the potential role of curcumin as a therapeutic intervention for MGUS patients warrants further investigation. (Clin Cancer Res 2009;15(18):5917–22)



Plasma cell dyscrasias, most commonly associated with paraproteinaemia, are a diverse group of disorders that includes multiple myeloma, Waldenstrom's macroglobulinaemia, heavy chain disease, monoclonal gammopathy of undefined significance (MGUS), and immunocytic amyloidosis. The incidence of plasma cell dyscrasias is age related, occurring in 1% of persons over age 25 years and 4% of those over age 70 years.

MGUS is the most common of the monoclonal gammopathies. At Mayo Clinic, almost 60% of patients with a monoclonal gammopathy have MGUS (1). MGUS can precede multiple myeloma and is typified by a serum M-protein value of <30 g/L, fewer than 10% plasma cells in the bone marrow, no or a small amount of M protein in the urine, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the plasma-cell proliferative process (1). Myeloma is a progressive neoplastic disease and is characterized by high bone turnover, significant bone loss, and pathologic fractures resulting in significant morbidity and a high mortality. It is also associated with hypercalcemia, anemia, renal damage, and increased susceptibility to bacterial infections.

Fractures are common in myeloma as a result of lytic bone lesions, generalized bone loss, and elevated bone turnover. Although MGUS is largely considered a benign condition, a number of studies show that patients with MGUS are at increased risk of developing fractures even before progression to myeloma (2).

Elevated bone turnover is an independent predictor of fracture risk, and a number of studies have shown elevated bone resorption and/or reduced bone formation among patients with MGUS and myeloma (3, 4). A study by Diamond et al. (5) found that in a small series of 18 MGUS patients, bone density was substantially reduced at the hip and spine compared with young normal values. Melton et al. (2) in a retrospective cohort study found that the risk of vertebral but not peripheral fractures is increased among MGUS patients.

Overall the risk of progression of MGUS to myeloma or related disorder is 1% per year. Although the prevalence of MGUS increases with advancing age, after adjustment for the level of

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**Note:** The potential role of curcumin in patients with MGUS—its effect on paraproteinemia and the urinary N-telopeptide of type I collagen bone turnover marker.

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### Translational Relevance

Monoclonal gammopathy of undefined significance (MGUS) is an untreated, potentially fatal condition. This study shows that curcumin decreases paraprotein load and bone resorption in certain patients with MGUS. Curcumin may thus provide an innovative therapeutic tool to delay or prevent the progression of MGUS to multiple myeloma.

the M-protein, the annual risk of progression to myeloma or a related cancer is not affected by age or the duration of MGUS. Younger patients are more likely to have progression to cancer during their lifetime because they are at risk for longer (6). It is currently not possible to predict the course in any individual patient, and clinically symptomatic myeloma may not evolve for as long as 20 years. Parameters that are currently used to identify those patients at highest risk of developing disease progression are as follows: the size of the M-protein, the type of M-protein with IgA and IgM paraproteins having a higher risk compared with IgG paraproteins, the percentage of bone marrow plasma cells, and an abnormal serum-free light chain ratio.

MGUS occurs in association with a variety of other diseases and currently no treatment is recommended; rather, that patients should be observed for change in clinical and immunochemical status at 4- to 6-month intervals i.e., "watchful waiting." Given the uncertainty of disease progression with MGUS, early intervention with the aim of reducing the paraprotein load and the potential negative effects on the skeleton would provide an innovative therapeutic tool. Curcuma longa or turmeric is a tropical plant native to southern and southeastern tropical Asia. It is a perennial herb belonging to the ginger family. The most active component in turmeric is curcumin (7). Curcumin is a diferuloylmethane present in extracts of the rhizome of the Curcuma longa plant and is the major yellow pigment extracted from turmeric. Turmeric is widely consumed in India and Southeast Asia for a variety of uses, including as a dietary spice, a dietary pigment, and an Indian folk medicine for the treatment of various illnesses. This nonnutritive phytochemical is pharmacologically safe, considering that it has been consumed as a dietary spice, at doses of up to 100 mg/day, for centuries. Recent phase I clinical trials indicate that people can tolerate a dose as high as 8 grams/day with minimal toxicity (8, 9).

A Medline search revealed over 1,500 publications describing various activities of this polyphenol. Numerous reports suggest that curcumin has chemopreventive and chemotherapeutic effects. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, including multiple myeloma cells, through the down-regulation of interleukin-6. Curcumin has also been shown to inhibit osteoclastogenesis and thus reduce bone turnover. Bharti et al. (10) showed that curcumin suppresses proliferation and induces apoptosis in multiple myeloma cells and that curcumin inhibits osteoclastogenesis through the suppression of RANKL signaling (11).

Based on the antimyeloma cell activity and inhibition of osteoclastogenesis exhibited by this polyphenol, we postulated that curcumin will inhibit the action of abnormal plasma cells and affect the activity of osteoclast cells in patients with MGUS. This study offered the opportunity to test a possible preventative strategy with little risk.

## Patients and Methods

***Patients.*** Twenty-six patients with MGUS as defined by Kyle and Rajkumar (1) were randomized into the study between June 2006 and July 2007 at St. George Hospital, Sydney, Australia. Patients were asked to abstain from drugs affecting bone metabolism for at least 3 mo prior and during the study. No patients had evidence of metabolic bone disorder. All the patients were Caucasian ages over 45 y.

Patients were randomized into two groups on a 2:1 randomization: group A patients were given curcumin at the start of the study and were then crossed over to placebo at the end of 3 mo. Group B patients were given placebo initially and then crossed over to curcumin. Seventeen patients (of 26) were assigned to group A (curcumin initially, to cross over to placebo) and 9 (of 26) to group B (placebo initially, to cross over to curcumin). This single-blind, cross-over pilot study was approved by the local ethics committee. Written informed consent was obtained from each patient before enrollment.

***Formulation, dose, and study design.*** One gram "C3" curcuminoid tablets (Allepey finger turmeric) and 1 gram placebo tablets were provided by the Sabinsa Corporation. Each "curcumin" tablet contained 1,000 mg of curcuminoids (900 mg of curcumin, 80 mg of desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin), confirmed by high performance liquid chromatography/mass spectrometry. This formulation is called curcumin. Placebo tablets contained microcrystalline cellulose, dicalcium phosphate, PVPK 30, sodium starch glycolate, and magnesium stearate. Patients consumed two tablets twice daily, i.e., 4 grams/d (this dose has been defined as the dose at which plasma levels of curcumin can be measured and pharmacodynamic effects showed *in vivo*) half an hour before food or 1/2 h after food and were crossed over at 3 mo after initiating therapy. Treatment continued for 6 mo.

***Clinical measurements.*** Blood and urine samples were collected at Baseline (V1), 1 wk (V2), 1 mo (V3), and 3 mo (V4) after initiating therapy. Full blood count, B2 microglobulin, serum paraprotein, and immunoglobulin electrophoresis (IEPG and EPG) were determined for all patients at each visit. Serum calcium, 25 hydroxyvitamin D3, and bone specific alkaline phosphatase (bsALP) were determined at baseline only. Urine, as a morning second-void sample, was collected at each visit for urinary N-telopeptide of type I collagen (uNTx) measurements and samples were protected from light and stored at -80°C.

Serum calcium was measured using standard autoanalyzer methods, serum 25-hydroxyvitamin D3 by RIA (DiaSorin), and bsALP with an immunoenzymatic assay (Metra BAP EIA kit; Quidel Corporation). Serum B2 microglobulin was measured using Beckman instruments (Beckman Instruments). Serum paraprotein and immunoglobulin-electrophoresis was determined by agarose gel (Sebia).

***Measurement of bone resorption.*** Cross-linked N-telopeptides of type 1 collagen, a highly specific marker of osteolyis, was measured using the Vitros Immunodiagnostic System (%CV = 8.5% at 96 nm/mm creatinine and 4.1% at 406 nm/mm creatinine). uNTx was normalized to the level of urinary creatinine. The reference range for uNTx varies according to age, sex, and endocrine function, with a reference interval of 26 to 124 nm/mm creatinine for postmenopausal women and reference interval of 17 to 94 nm/mm creatinine for premenopausal women.

***Statistical evaluation.*** Group values are expressed as the mean ± SEM. Patients were subdivided into two groups according to their baseline serum paraprotein (classified as being either above or below the mean group value) to assess their response to curcumin. Group comparisons were made using unpaired Student's *t* test. Data from different time intervals within groups were compared using ANOVA and paired Student's *t* test. Statistical significance was assigned as $P$ value of $<0.05$.

**Table 1.** Baseline clinical data and serum biochemistry of patients who completed the study

| Patient no. | Group | Age (y) | Sex | Pp type | Para-prot. g/L | B2mic-rogl. mg/L | Hb g/dL | Calcium mmol/L | 25 OH vit D nmol/L | Alk phos mmol/L | uNTx nm/mm cr |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | A | 63 | M | IgGK | 22 | 3.4 | 168 | 2.26 | 103 | 7.1 | 14.1 |
| 2 | B | 74 | F | IgGL | 34 | 2.9 | 115 | 2.27 | 38 | 18.6 | 58.6 |
| 3 | A | 80 | M | IgGK | 15 | 4.2 | 121 | 2.23 | 71 | 11.9 | 45.1 |
| 4 | B | 77 | M | IgMK | 34 | 4.9 | 97 | 2.21 | 132 | 12.7 | 19.5 |
| 6 | B | 57 | M | IgMK | 15 | 2.4 | 138 | 2.17 | 46 | 7 | 33.9 |
| 8 | A | 80 | M | IgGK | 24 | 2.2 | 135 | 2.29 | 35 | 12.2 | 19.1 |
| 9 | A | 64 | M | IgGL | 27 | 2.1 | 136 | 2.31 | 101 | 7 | 9.3 |
| 10 | B | 87 | M | IgGK | 13 | 2.6 | 118 | 2.2 | 108 | 8.3 | 25 |
| 11 | A | 60 | M | IgGL | 24 | 2.6 | 143 | 2.25 | 106 | 8.2 | 37.1 |
| 12 | B | 66 | M | IgGL | 15 | 2.2 | 173 | 2.29 | 48 | 8.3 | 2.4 |
| 13 | B | 55 | F | IgAK | 12 | 3.7 | 117 | 2.23 | 28 | 30.2 | 21.7 |
| 14 | A | 50 | F | IgGL | 11 | 2.3 | 177 | 2.22 | 99 | 59.9 | 29.1 |
| 15 | B | 61 | M | IgGK | 21 | 1.9 | 136 | 2.31 | 46 | 9.7 | 33.3 |
| 16 | A | 69 | F | IgGL | 8 | 2.7 | 127 | 2.18 | 41 | 13.4 | 48.3 |
| 17 | A | 55 | M | IgGL | 36 | 2 | 135 | 2.21 | 85 | 6.7 | 16.3 |
| 18 | A | 70 | F | IgGK | 12 | 2.6 | 100 | 2.34 | 29 | 10.9 | 32 |
| 19 | B | 73 | F | IgAL | 33 | 4.7 | 106 | 2.46 | 74 | 13 | 76 |
| 20 | A | 72 | M | IgGK | 28 | 4.3 | 115 | 2.14 | 67 | 23 | 25.4 |
| 21 | A | 75 | F | IgGL | 30 | 5 | 107 | 2.31 | 51 | 8.1 | 8 |
| 22 | A | 64 | F | IgAK | 8 | 2.2 | 124 | 2.34 | 53 | 8.3 | 18 |
| 23 | A | 60 | M | IgGK | 26 | 2.1 | 127 | 2.29 | 68 | 5.3 | 26.6 |
| 24 | A | 58 | M | IgGL | 8 | 1.8 | 151 | 2.22 | 72 | 12.3 | 21 |
| 25 | B | 60 | M | IgMK | 15 | 1.8 | 155 | 2.15 | 40 | 17.1 | 15.3 |
| 26 | A | 72 | M | IgGK | 14 | 2.8 | 148 | 2.24 | 57 | 9.9 | 20 |
| ***MEAN*** | | 66.8 ± 9.4 | | | 20.2 ± 9.2 | 2.9 ± 1.0 | 132 ± 22.0 | 2.3 ± 0.1 | 66.6 ± 29.0 | 13.7 ± 11.4 | 27.3 ± 16.7 |

## Results

Twenty-six patients were randomized into the study—16 men and 10 women with average age of 68 years. Twenty-four patients completed the study. All patients had a serum M-protein value of <36 g/L, fewer than 10% plasma cells in the bone marrow, no or a small amount of M protein in the urine, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency. Seven (of the 17) patients were given curcumin only during the course of the study. Two patients withdrew from the study before cross-over, as they developed diarrhea and abdominal cramping, which resolved after cessation of treatment.

Baseline clinical data and serum biochemistry of the patients who completed the study are outlined in Table 1. Serum paraprotein concentration ranged from 8 to 36 g/L, with a median value of 20 g/L. Nine of the 26 patients randomized into the study had IgGκ (35%), 9 had IgGλ (35%), 4 had IgMκ (15%), 3 had IgAκ (11%), and 1 had IgAλ (4%) paraproteins. All patients had a normal serum calcium level (mean, 2.62 mmol/L). There were nine patients with Vitamin D deficiency (<50 nmol/L). Two patients had elevated baseline serum bsALP measurements. All patients had elevated baseline B2 microglobulin levels (mean, 2.9 ± 1 mg/L), which remained unchanged throughout the study. All patients had normal baseline uNTx levels (mean of 27 ±16 nmol/mol creatinine) with no patient having a baseline value of >100 nmol/mmol creatinine.

*Effect of oral curcumin on serum paraprotein levels.* Details of the number of patients in each arm and their decreased paraprotein response before cross-over are given in Table 2. Of the 17 patients who were commenced on curcumin, 10 had a baseline serum paraprotein level greater and equal to 20 g/L (mean, 20.2 g/L) and 7 less than 20 g/L. In patients with a serum paraprotein greater and equal to 20 g/L, 50% of these (i.e., 5 patients) had a 12% to 30% decrease in serum paraprotein levels in response to curcumin (Fig. 1). The most significant decrease was seen at V2 ($P < 0.05$ for group comparison between V1 and V2). This decrease remained stable in most patients until they were crossed over to placebo. Two patients then showed a rebound in their serum paraprotein levels. Patients with a baseline serum paraprotein of <20 g/L did not show a response to curcumin, but their serum paraprotein levels remained stable throughout the study period.

**Table 2.** Patient number and response rate in each arm

| | Patients (*n*) | *n* | Responders (%) | Response rate (%) |
|---|---|---|---|---|
| Placebo | 9 | 0 of 9 | 0 | 0 |
| Curcumin (total) | 17 | 5 of 17 | 29 | 12-29% |
| Curcumin (pp >20g/L) | 10 | 5 of 10 | 50 | 12-29% |
| Curcumin (pp < 20g/L) | 7 | 0 of 7 | 0 | 0 |

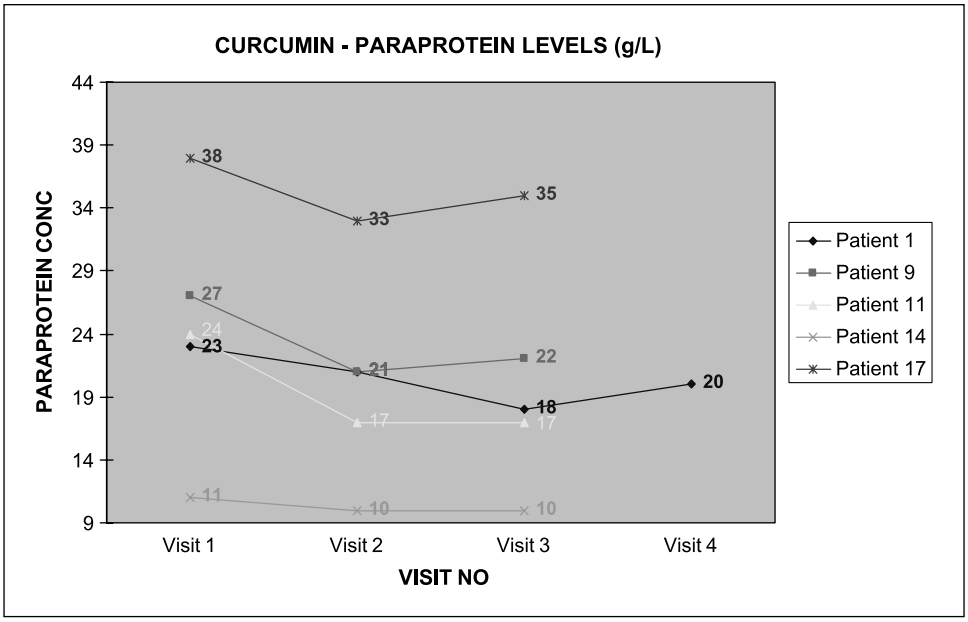


**Fig. 1.** Effect of curcumin on serum paraprotein levels.

*Effect of placebo on serum paraprotein levels.* Nine patients were randomly assigned to receive placebo at baseline. In contrast to a decrease in serum paraprotein seen in patients initiating curcumin therapy, patients receiving placebo showed stable or an increase in their serum paraprotein levels (see Fig. 2). At V4 (i.e., cross-over to curcumin), two patients showed a decrease in their serum paraprotein (12.5% and 15%, respectively).

*Effect of curcumin on uNTx levels.* Although 73% of patients did not show a change in their uNTx levels while taking curcumin or placebo, 27% of patients showed a decrease in their uNTx levels while taking curcumin (Fig. 3). This response was most marked in two patients at cross-over (Fig. 4A and B). Although the difference between the groups (i.e., curcumin versus placebo) did not reach statistical significance, the results do however indicate that certain patients may show a decrease in bone resorption in response to curcumin.

## Discussion

The present study shows that oral curcumin (a known inhibitor of tumorigenesis and osteoclastogenesis) is able to decrease paraprotein load and bone resorption in a select group of patients with MGUS. Fifty percent of patients with a paraprotein >20 g/L responded with a 12% to 30% decrease in their paraprotein levels while taking 4 grams/day curcumin orally. This response was rapid as determined by the reduced paraprotein level measured after 7 days of curcumin therapy. Patients taking placebo had no such decrease in their paraprotein levels. Similar reductions in paraprotein have been seen with conventional antimyeloma therapies such as melphalan and dexamethasone (12). This is the first study, however, assessing the potential therapeutic effect of curcumin in MGUS patients.

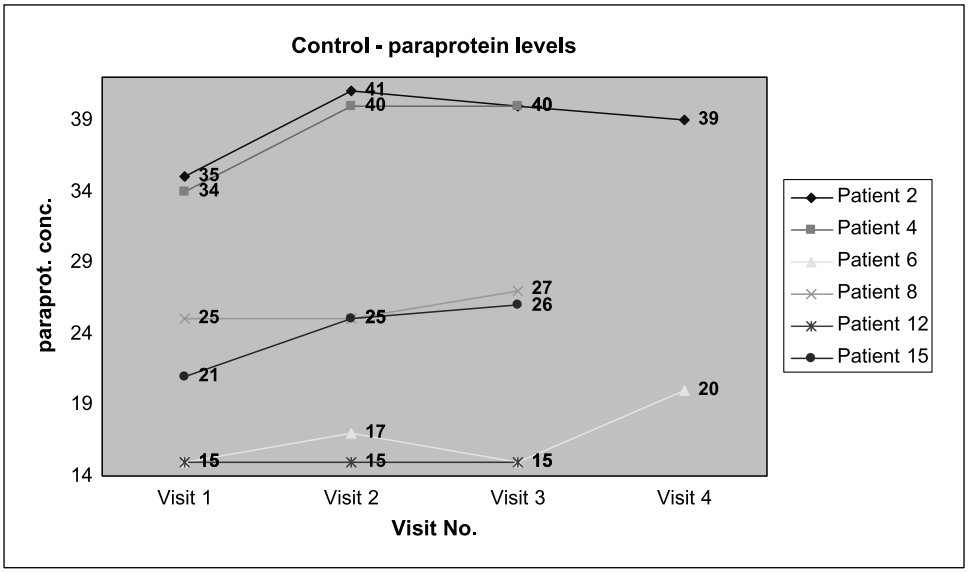


**Fig. 2.** Effect of placebo on serum paraprotein levels.

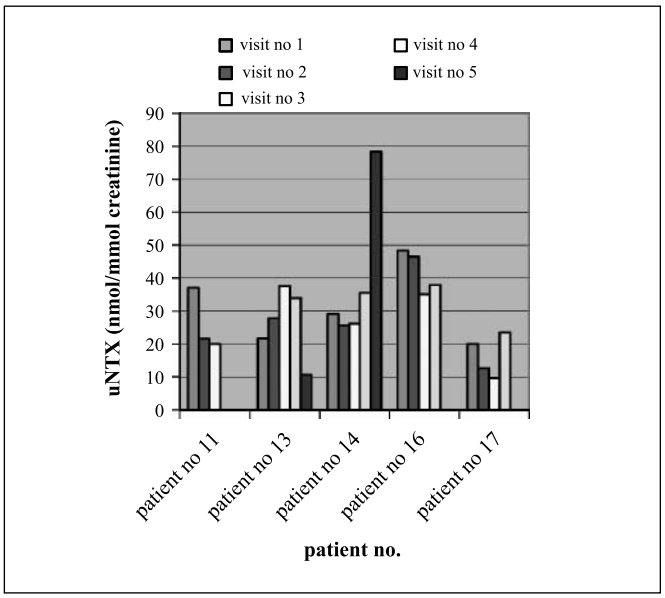


**Fig. 3.** Effect of curcumin on uNTx levels.

We selected to subdivide patients according to the mean baseline group paraprotein level. Our data suggests that only patients with high serum paraprotein values may respond to curcumin. Patients having a paraprotein of <20g/L did not respond to the curcumin. The reason for the response in the high paraprotein group is not known. It is possible this group may have an abnormal plasma cell clone that responds differently to curcumin or its metabolites. *In vitro* studies may help to differentiate a subpopulation of plasma cells that are curcumin responsive.

The partial response rate (i.e., 50-75% decrease in paraprotein concentration) was 0% in both arms. In MGUS patients, the chance of a partial response are low because cell division is very slow. Even in smoldering myeloma, responses take much longer with a drug such as thalidomide compared with relapsed myeloma where cells are dividing more quickly.

A study by Vadhan-Raj (13) found that curcumin downregulates the constitutively active NF-κB in patients with multiple myeloma. This study also showed a reduction in signal transducers and activators of transcription 3 and cyclooxygenase-2 expression. However, no reduction in paraprotein levels was found in these patients. The reason for this may be that these were multiple myeloma patients, although they were asymptomatic, relapsed/refractory, or plateau phase disease. Similarly, a reduction in NF-κB was found *in vitro* by Bharti et al. (10) using myeloma cells.

In multiple myeloma, bone formation is usually suppressed and bone resorption increased, i.e., classic uncoupling of bone biosynthesis. Hence, low bsALP and high uNTx values are expected. Bone turnover in patients with MGUS may be mixed comprising of patients with normal or high bone turnover or a pattern of uncoupling similar to that seen in myeloma. In our study, only two (of 26) patients had raised bsALP. All other patients had normal values indicating normal rates of bone formation.

Bone resorption was determined by uNTx excretion rates. A decrease in uNTx has been shown to occur with antiresorptive treatments (14). A number of studies have found that MGUS patients have raised uNTx levels (15–17) when compared with matched controls. The 26 MGUS patients in this study had a mean uNTx level of 27.3 nmol/mmol creatinine at baseline with no patient having a baseline value above the upper range of normal. Nonetheless, a reduction in uNTx was noted in 7 of 26 patients when given curcumin. This response coincided with the decrease in serum paraprotein. A more detailed study is required to assess the therapeutic role of curcumin in MGUS patients with elevated uNTx values.

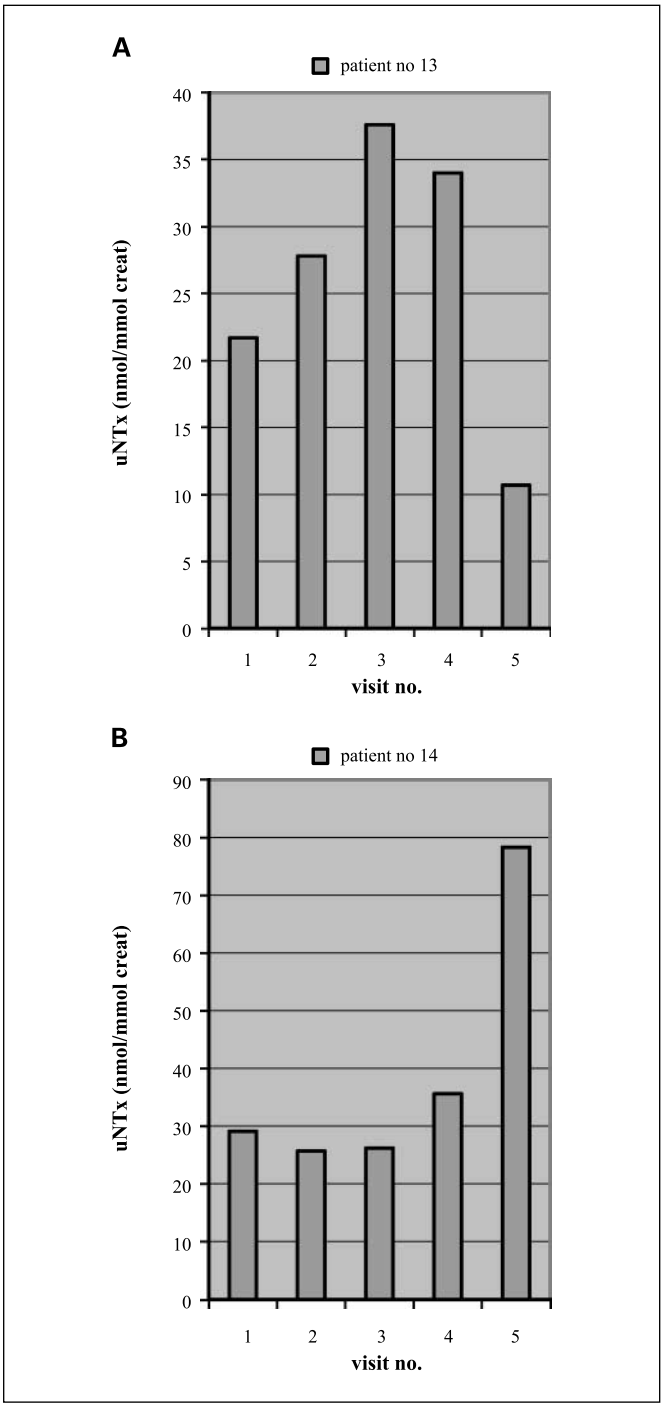


**Fig. 4.** *A,* effect of curcumin on uNTx level at crossover. *B,* effect of curcumin on uNTx level at crossover.

The potential therapeutic benefit of curcumin in plasma cell dyscrasia is not fully understood. Curcumin has been shown to suppress proliferation of a wide variety of tumor cells: to downregulate transcription factors NF-κB, activator protein, and early growth response gene-1; to suppress the expression of cyclooxygenase-2, lipoxygenase, NO synthase, matrix metalloproteinase-9, urokinase-type plasminogen activator, tumor necrosis factor, chemokines, cell surface adhesion molecules, and cyclin D1; to inhibit the expression of growth factor receptors (such as epidermal growth factor receptor and human epidermal growth factor receptor 2); and to inhibit the activity of c-Jun-$NH_2$-kinase, protein tyrosine kinases, and several other protein serine/threonine kinases (7). This polyphenol has antioxidant and anti-inflammatory activity and has been found to suppress tumor initiation, promotion, and metastasis (18). Bharti et al. (10, 11) have shown that RANKL induces osteoclastogenesis through activation of NF-κB (a transcription factor) and treatment with curcumin inhibits both the NF-κB activation and osteoclastogenesis induced by RANKL. We did not evaluate the mechanistic effect of curcumin on paraprotein and uNTx in our cohort.

Our small pilot study suggests that curcumin may decrease both serum paraprotein (in patients with levels of >20 g/L) and uNTx in patients with MGUS. The potential role of curcumin as a therapeutic intervention for MGUS patients warrants further investigation. This has prompted us to commence a double-blind, randomized, control trial using higher dosages of curcumin in a larger cohort of MGUS patients with significant paraproteinaemia.

## Disclosure of Potential Conflicts of Interest

V. Badmaev, employment, Sabinsa Corp.

## Acknowledgments

T. Golombick: designed research, did research, wrote the manuscript.
T. Diamond: designed research, reviewed the manuscript.
L. Browne PhD: analyzed data.

## References

1. Kyle RA, Rajkumar SV. Monoclonal gammopathies of undetermined significance. Best Practice and Research Clinical Haematology 2005;18:689–707.
2. Melton LJ, Rajkumar V, Khosla S, et al. Fracture risk in monoclonal gammopathy of undetermined significance. Br J Haematol 2004;19:25–30.
3. Bataille R, Chappard D, Basle M-F. Quantifiable excess of bone resorption in monoclonal gammopathy is an early symptom of malignancy: a prospective study of 87 bone biopsies. Blood 1996;87:4762–69.
4. Woitge HW, Horn E, Keck AV, et al. Biochemical markers of bone formation in patients with plasma cell dyscrasias and benign osteoporosis. Clin Chem 2001;47:686–93.
5. Diamond T, Levy S, Smith A, et al. Non-invasive markers of bone turnover and plasma cytokines differ in osteoporotic patients with multiple myeloma and monoclonal gammopathies of undetermined significance. Intern Med J 2001;31:272–8.
6. Cook L, Macdonald DHC. Management of paraproteinaemia. Postgrad Med J 2007;83:217–23.
7. Aggarwal BB, Kumar A, Aggarwal MS, Shisodia S. Curcumin derived from turmeric Curcuma longa: a spice for all seasons. Phytopharmaceuticals in Cancer Chemoprevention 2005;349–87.
8. Sharma RA, Euden SA, Platton SL, et al. Phase 1 Clinical Trial of Oral Curcumin: Biomarkers of Systemic Activity and Compliance. Clin Cancer Res 2004;10:6847–54.
9. Lao CD, Ruffin MT, Normolle D, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006;6:10–4.
10. Bharti AC, Donato N, Singh S, Aggarwal BB. Curcumin (Diferuloylmethane) down-regulates the constitutive activation of nuclear factor-κB and $I_κ$Bα kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Blood 2003;101:1053–62.
11. Bharti AC, Takada Y, Aggarwal BB. Curcumin (diferuloylmethane) inhibits receptor activator of NF-KB ligand-induced NF-KB activation in osteoclast precursors and suppresses osteoclastogenesis. J Immunol 2004;172:5940–7.
12. Kyle RA, Rajkumar SV. Multiple Myeloma. N Engl J Med 2004;351:1860–73.
13. Vadhan-Raj S, Weber DM, Wang M, et al. Curcumin downregulates NF-KB and related genes in patients with multiple myeloma: results of a phase 1/11 study. Blood 2007;110:1177a.
14. Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. J Clin Oncol 2005;23:4925–35.
15. Politou M, Terpos E, Angnostopoulos A, et al. Role of receptor activator of nuclear factor-κ B ligand (RANKL), osteoprotegerin and macrophage protein 1-α (MIP-1a) in monoclonal gammopathy of undetermined significance (MGUS). Br J Haematol 2004;126:686–9.
16. Pecherstorfer M, Seibel MJ, Woitge HW, et al. Bone resorption in multiple myeloma and in monoclonal gammopathy of undetermined significance: quantification by urinary pyridinium cross-links of collagen. Blood 1997;90:3743–50.
17. Jacob C, Zavrski I, Heider U, et al. Bone resorption parameters [carboxy-terminal telopeptide of type-1 collagen (ICTP), amino-terminal collagen type-1 telopeptide (NTx), and deoxypyridinoline (Dpd)] in MGUS and multiple myeloma. Eur J Haematol 2002;69:37–42.
18. Kuttan G, Kumar KB, Guruvayoorappan C, Kuttan R. Antitumor, anti-invasion, and antimetastatic effects of curcumin [review]. Adv Exp Med Biol 2007;595:173–84.