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Published in:
Annals of the Rheumatic Diseases

DOI:
[10.1136/ard.61.11.981](https://doi.org/10.1136/ard.61.11.981)

2002

[Link to publication](#)

Citation for published version (APA):
Murphy, E., FitzGerald, O., Saxne, T., & Bresnihan, B. (2002). Increased serum cartilage oligomeric matrix protein levels and decreased patellar bone mineral density in patients with chondromalacia patellae. *Annals of the Rheumatic Diseases*, 61(11), 981-985. <https://doi.org/10.1136/ard.61.11.981>

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EXTENDED REPORT

Increased serum cartilage oligomeric matrix protein levels and decreased patellar bone mineral density in patients with chondromalacia patellae

E Murphy, O FitzGerald, T Saxne, B Bresnihan

Ann Rheum Dis 2002;**61**:981–985

Background: Chondromalacia patellae is a potentially disabling disorder characterised by features of patellar cartilage degradation.

Objective: To evaluate markers of cartilage and bone turnover in patients with chondromalacia patellae.

Methods: 18 patients with chondromalacia patellae were studied. Serum cartilage oligomeric matrix protein (s-COMP) and bone sialoprotein (s-BSP) levels were measured by enzyme linked immunosorbent assay (ELISA) and compared with those of age and sex matched healthy control subjects. Periarticular bone mineral density (BMD) of both knee joints was assessed by dual energy x ray absorptiometry (DXA).

Results: s-COMP levels were significantly raised in all patients with chondromalacia patellae compared with healthy control subjects ($p=0.0001$). s-BSP levels did not differ significantly between the groups ($p=0.41$). BMD of the patella was significantly reduced in patients with chondromalacia patellae compared with the control subjects ($p=0.016$). In patients with bilateral chondromalacia patellae, BMD of the patella was lower in the more symptomatic knee joint ($p=0.005$). Changes in periarticular BMD were localised to the patella and were not present in femoral regions. Neither s-COMP ($p=0.18$) nor s-BSP ($p=0.40$) levels correlated with patellar BMD.

Conclusions: Increased s-COMP levels, reflecting cartilage degradation, and reduced BMD localised to the patella may represent clinically useful markers in the diagnosis and monitoring of patients with chondromalacia patellae. Measures of cartilage degradation did not correlate with loss of patellar bone density, suggesting dissociated pathophysiological mechanisms.

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Accepted 2 May 2002

Chondromalacia patellae is a pathological diagnosis which includes softening and degeneration of patellar articular cartilage. There are four grades of disease severity, ranging from softening and blister-like swelling of the patellar cartilage in grades 1 and 2 respectively to surface irregularity and areas of thinning in grade 3 and ulceration and exposure of subchondral bone in grade 4 disease.¹ The aetiology of chondromalacia patellae is unclear. It has been attributed to predisposing factors such as patellar malalignment and trauma, but many cases are idiopathic. The diagnosis may be confirmed at arthroscopy when changes in cartilage can be directly visualised. However, it is not always thought necessary to carry out an invasive procedure such as arthroscopy to diagnose an often benign and self limiting condition. Recent studies have suggested that radiological techniques including computed tomographic arthrography and magnetic resonance imaging (MRI) may be useful diagnostic modalities.^{2,3}

Measurement of cartilage and bone macromolecules such as cartilage oligomeric matrix protein (COMP) and bone sialoprotein (BSP) in serum and synovial fluid has been suggested as a potential means of monitoring disease processes in both inflammatory and degenerative arthritis.^{4,5} Both are quantifiable by enzyme linked immunosorbent assay (ELISA).^{6,7} BSP is a bone-specific protein, which is enriched in the cartilage-bone interface.^{8,9} COMP was originally identified as a non-collagenous cartilage matrix protein.^{10,11} Subsequently, it has also been found in the meniscus (Mansson *et al*, unpublished), synovial membrane,^{12,13} and loadbearing regions of tendon.^{14,15} Articular cartilage contains the highest amounts of COMP and changes in serum and synovial fluid COMP concentrations correlate with pathophysiological proc-

esses in cartilage.^{5,16} As chondromalacia patellae is primarily a disease of articular cartilage, measurement of COMP levels may provide a means of evaluating the disease process in these patients.

Bone mineral density (BMD) at several skeletal sites can be measured using a number of currently available techniques. We have recently described a novel application of dual energy x ray absorptiometry (DXA) to the measurement of periarticular BMD at the knee joint.¹⁷ This technique has been validated for several regions of interest (ROIs) at the knee, including the patella. This study aimed at evaluating s-COMP levels and quantifying patellar and periarticular knee joint BMD in patients with a clinical diagnosis of chondromalacia patellae. It was observed that patients with chondromalacia patellae had significantly raised s-COMP levels and reduced patellar BMD values in comparison with age and sex matched healthy subjects. Moreover, the loss of patellar bone density was maximal in the more symptomatic knee joints.

PATIENTS AND METHODS

Study subjects

Eighteen patients with a clinical diagnosis of chondromalacia patellae who attended either the rheumatology or orthopaedic clinics at St Vincent's University Hospital, Dublin over a four

Abbreviations: BMD, bone mineral density; BSP, bone sialoprotein; COMP, cartilage oligomeric matrix protein; CV, coefficient of variation; DXA, dual energy x ray absorptiometry; ELISA, enzyme linked immunosorbent assay; MRI, magnetic resonance imaging; OA, osteoarthritis; PA, posteroanterior; ROI, region of interest

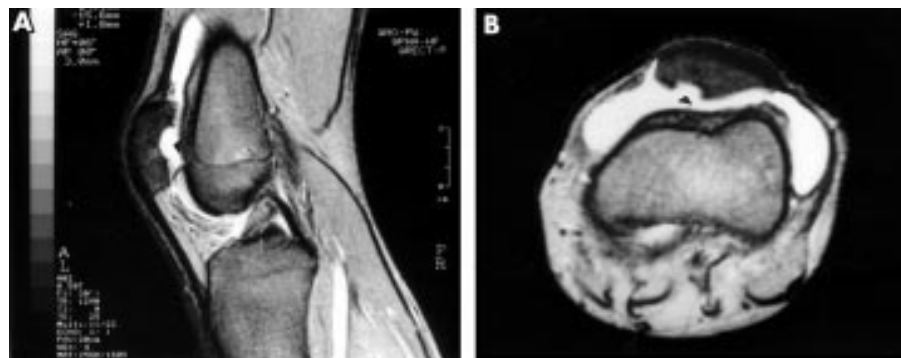


Figure 1 MRI of the knee of a patient with chondromalacia patellae: (A) sagittal T₂ weighted image and (B) axial T₂ weighted image, showing large posterior defect in the patella.

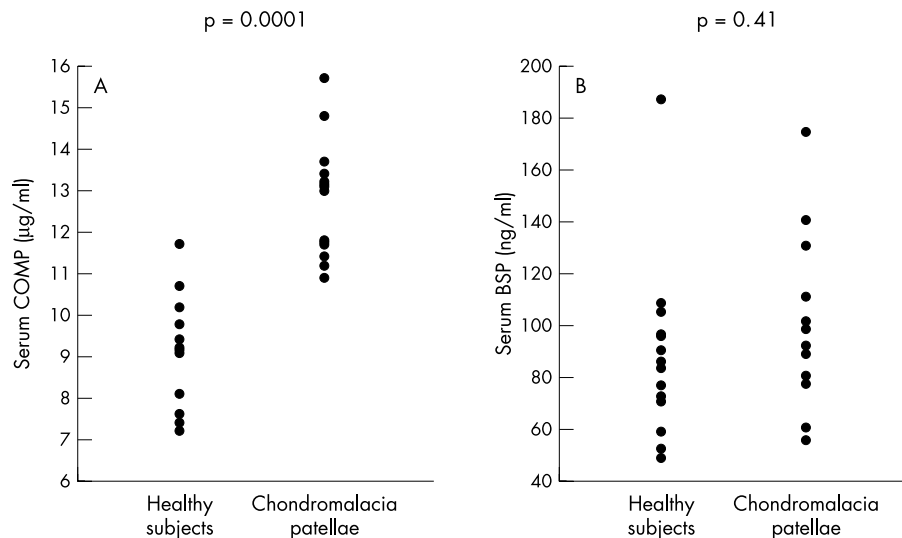


Figure 2 (A) s-COMP and (B) s-BSP levels in patients with chondromalacia patellae and healthy subjects.

year period, were selected for study. The clinical diagnosis of chondromalacia patellae was made according to established criteria.¹⁸ All had persistent unilateral or bilateral anterior knee pain accompanied by patellar crepitus. The pain increased when pressure was applied to the patella or by active quadriceps contraction against resistance. None of the patients had clinical or laboratory features of an inflammatory arthropathy, a congenital or other musculoskeletal disorder, or a history of trauma to the knee which required medical attention. The clinical diagnosis of chondromalacia patellae was confirmed by arthroscopy or MRI examination in some. An age and sex matched control group of healthy subjects with no history of recurring anterior knee pain was selected from hospital staff and relatives of the investigators.

Clinical assessment

Clinical assessment was performed on all patients by a single investigator (EM) and knee radiographs were taken to exclude degenerative or structural abnormalities. Serum samples were obtained from 14 patients and stored in aliquots at -80°C . s-COMP and s-BSP levels were measured by ELISA.^{6,7} Results were compared with those of 14 healthy age and sex matched control subjects.

BMD was measured on all patients using a Hologic 4500 Elite fan-beam bone densitometer. Generalised bone density was determined by a DXA scan of the left hip. Posteroanterior (PA) and lateral DXA scans of both knees were acquired according to a previously established protocol.¹⁷ In brief, the subject was positioned in the supine position for PA scans,

Table 1 Clinical and demographic details of study groups

| | Chondromalacia patellae | Healthy subjects |
|-------------------------------|-------------------------|------------------|
| Total number | 18 | 14 |
| Female | 16 | 14 |
| Mean age (range), years | 26 (15–39) | 24 (21–36) |
| Arthroscopy | 5 | N/A |
| MRI knee | 2 | N/A |
| T score total hip BMD (range) | -0.99 to 1.60 | -1.20 to 1.70 |

N/A, not applicable.

whereas lateral scans of the left and right knees were performed in the left and right lateral positions respectively. Modified thermoplastic leg braces were used as positioning devices to stabilise the joint and improve precision (expressed as percentage coefficient of variation (CV%)). Scans were acquired using the forearm software and analysed by subregion analysis. Precision for measurement of several subregions of interest around the knee joint has previously been described. Results, expressed as CV%, varied, ranging from 1.89% to 2.64% in the femur and from 3.20% to 4.52% in the tibia. The greatest precision was obtained for measurement of patellar bone density. Based on these results, two subregions of interest were selected as being the optimal areas to use for periarticular BMD assessment at the knee—the total patella on the lateral scan (CV%=0.84%) and the distal 4 mm of femur on the PA scan (CV%=2.36%).

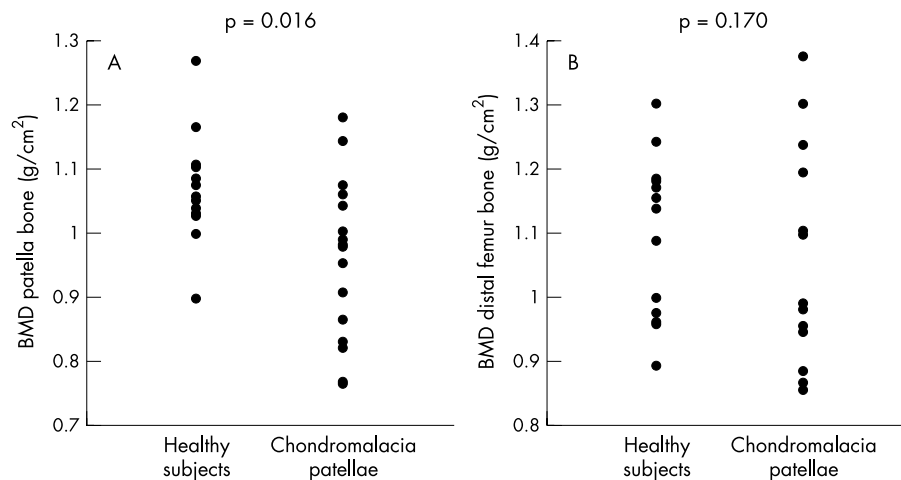


Figure 3 Individual bone density measurements for subregions of interest at the knee joint: (A) patella and (B) distal femur.

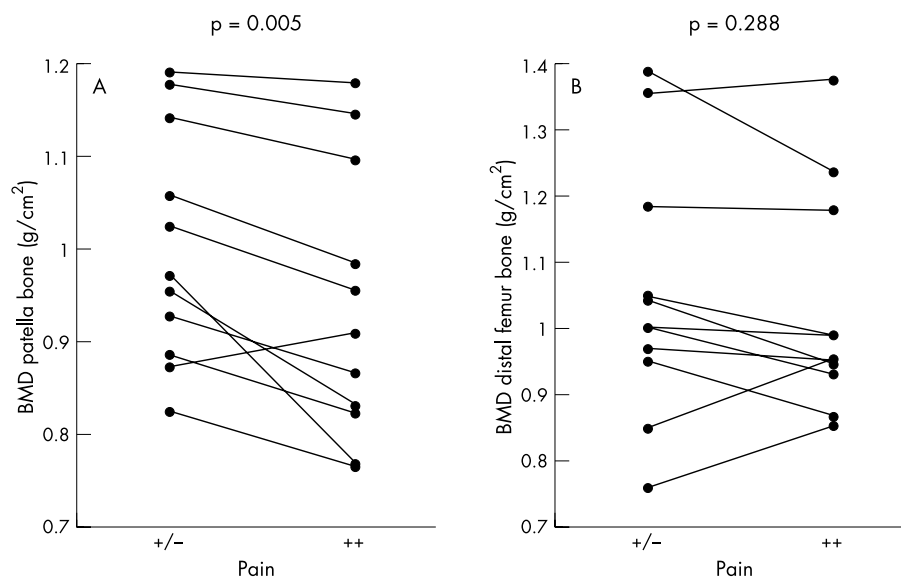


Figure 4 Individual bone density measurements at (A) the patella and (B) the distal femur in patients with asymmetric knee joint symptoms. ++ represents the more painful knee joint, +/- represents the less painful knee joint.

Statistics

Non-parametric statistics were used to determine differences between the two groups in s-COMP levels, s-BSP levels, and bone density measurements (Mann-Whitney U test) and the relationship between bone density of the patella and serum levels of COMP and BSP (Spearman rank correlation). Differences in bone density between symptomatic and asymptomatic knees were determined by a paired *t* test. For patients with asymmetric symptoms ($n=11$), BMD values obtained from the more symptomatic knee were used, whereas mean BMD values were calculated for those with equal bilateral symptoms ($n=5$). Mean knee BMD values were calculated for each of the 14 healthy control subjects.

RESULTS

A total of 18 patients (16 female, two male) with persistent anterior knee pain and a clinical diagnosis of chondromalacia patellae were identified with ages ranging from 15 to 39 years (median age 26.5). The clinical diagnosis of chondromalacia patellae was confirmed by arthroscopy in five patients and MRI examination of the knee in two (table 1 and fig 1). Knee radiographs were normal in all. s-COMP levels were measured in 14 patients and 14 healthy age and sex matched control

subjects. Periarticular BMD at the knee joint was measured in 16 female patients and compared with that of 14 healthy age and sex matched control subjects.

s-COMP levels were significantly higher in the patient group than in the control group ($p=0.0001$). Values ranged from 10.9 $\mu\text{g/ml}$ to 15.7 $\mu\text{g/ml}$ (median 13.05 $\mu\text{g/ml}$) in the patient group and from 7.2 $\mu\text{g/ml}$ to 11.7 $\mu\text{g/ml}$ (median 9.6 $\mu\text{g/ml}$) in the control group. In all matched pairs the s-COMP value was higher in the patient sample. A much wider range of values was seen for s-BSP values, ranging from 56.4 ng/ml to 174.4 ng/ml (median 90.9 ng/ml) in the patient group and from 48.9 ng/ml to 186.7 ng/ml (median 84.8 ng/ml) in the control group. In contrast with s-COMP levels, s-BSP values did not differ significantly between the two study groups ($p=0.41$). Figure 2 illustrates individual values for each of these markers. BMD of the patella did not correlate with either s-COMP ($r_s=-0.48$, $p=0.18$) or s-BSP ($r_s=-0.3$, $p=0.40$) in the patient group.

The two groups also had different bone density of the patella, which ranged from 0.763 g/cm^2 to 1.177 g/cm^2 (median 0.979 g/cm^2) in the patient group and from 0.896 g/cm^2 to 1.266 g/cm^2 (median 1.051 g/cm^2) in the control group. The difference between the two groups was significant with lower values for patellar BMD seen in the patient group ($p=0.016$).

A wide range of values was seen for the BMD of the distal femur in both groups, ranging from 0.853 g/cm² to 1.374 g/cm² (median 0.984 g/cm²) in the patient group and from 0.892 g/cm² to 1.30 g/cm² (median 1.144 g/cm²) in the control group. Bone density of the distal femur did not differ significantly between the two groups ($p=0.170$). Thus, the reduction in BMD in the knee joint was localised to the patella. Figure 3 shows individual BMD measurements of patella and distal femur in the patient and control groups. Total hip BMD, reflecting generalised bone density, did not differ significantly between patients and control subjects ($p=0.68$), with measurements ranging from 0.822 g/cm² to 1.141 g/cm² (T score range from -0.99 to 1.63) in the patient group and from 0.796 g/cm² to 1.154 g/cm² (T score range from -1.20 to 1.70) among healthy subjects.

Of the 16 patients studied, 11 described a difference in the severity of pain between their two knee joints. Figure 4 illustrates the difference in BMD values between the two knee joints in each of these patients. BMD of the patella ranged from 0.763 g/cm² to 1.177 g/cm² (median 0.906 g/cm²) on the more symptomatic side and from 0.823 g/cm² to 1.188 g/cm² (median 0.969 g/cm²) on the less symptomatic or normal side. BMD of the patella was lower on the more symptomatic side in 10/11 patients who described an asymmetric pain pattern ($p=0.005$). However, a similar pattern was not seen for BMD measurements of the distal femur in these 11 patients. BMD of this ROI ranged from 0.853 g/cm² to 1.374 g/cm² (median 0.951 g/cm²) on the more symptomatic side and from 0.759 g/cm² to 1.388 g/cm² (median 1.002 g/cm²) on the less symptomatic side. BMD of the distal femur did not differ significantly between the two sides ($p=0.288$).

DISCUSSION

This study highlights two new observations in patients with chondromalacia patellae. Firstly, s-COMP levels were significantly raised compared with control subjects. There was no difference in s-BSP levels between the two groups. Secondly, BMD of the patella was shown to be reduced in patients with chondromalacia patellae. Of interest, the reduced bone density measurements were localised to the patella, with no significant differences between the groups seen at the distal femur or hip. In patients with asymmetric symptoms, patellar BMD measurements were significantly lower in the more symptomatic knee joints. In contrast, there were no differences in the BMD measurements of the right and left distal femur.

Although not entirely tissue specific, COMP has been identified as a marker of cartilage turnover in serum and synovial fluid.⁵⁻⁶ s-COMP levels have been extensively investigated in osteoarthritis (OA) of the knee joint and have been shown to increase in early disease.¹⁹ In support of this, it has been suggested that in addition to identifying OA, s-COMP levels can reflect disease severity and multiple joint involvement in OA.²⁰ When correlated with bone scan abnormalities in patients with chronic knee pain, both s-COMP and s-BSP levels were shown to be significantly higher in those with bone scan abnormalities. s-COMP, but not s-BSP levels, correlated with the extent of scintigraphic abnormality.²¹ Increased s-COMP has also been identified as a predictor of disease progression in OA of the knee joint, with increasing levels seen in patients who developed radiographic evidence of disease progression at three and five year follow up.¹⁹⁻²² s-COMP has also been shown to be useful in identifying patients with rapidly progressive hip OA.²³

It is generally thought that chondromalacia patellae is a disorder localised to patellar articular cartilage. The significant increase in s-COMP levels in chondromalacia patellae highlights its sensitivity as a marker of pathological processes within cartilage and suggests that measurement of s-COMP may be a useful diagnostic tool in differentiating between

chondromalacia patellae and other causes of anterior knee pain. The observation that s-BSP levels were similar in the two study groups reflects the fact that chondromalacia patellae is primarily a disorder of cartilage as COMP is found predominantly in cartilage and BSP is present only in bone. The lack of correlation between s-COMP levels and BMD is expected as s-COMP is not present in bone. Although BSP is present in bone, the tissue distribution of BSP is predominantly enriched at the cartilage-bone interface. BMD on the other hand estimates the density of the whole bone matrix. Thus, a correlation between s-BSP and BMD would be unlikely. The increased s-COMP levels in chondromalacia patellae might suggest a more diffuse disorder of cartilage. In a previous study it was observed that serum levels of keratan sulphate were increased only in patients with stage 4 chondromalacia patellae, but synovial fluid aggrecan and hyaluronan levels did not differ from control subjects.²⁴ The observations reported in this study are the first to suggest that s-COMP is a molecular marker that could identify patients with chondromalacia patellae. Further follow up is necessary to determine if increasing s-COMP levels might predict the development of knee OA in similar patients.

Focal loss of bone density is associated with several different musculoskeletal disorders, including inflammatory joint disease, radiation therapy, physical inactivity, and musculoskeletal injury. Rapid focal bone loss may follow trauma and may remain for many years after the injury.²⁵ In a previous study that quantified relatively large regions of interest in patients with chronic patellofemoral pain, loss of bone density was demonstrated in the distal femur, proximal tibia, and patella.²⁶ The spine, proximal femur, and calcaneus were unaffected. It was concluded that impaired muscle strength and knee function were important aetiological factors. Other factors, including excess weight, low levels of physical activity, and prolonged symptoms, were identified as independent predictors of reduced bone density in affected knee joints. The exclusive loss of patellar bone density in our study might be partly explained by differences in the ROIs selected, and partly by the shorter duration of symptoms and younger age of the patients. If confirmed, this would suggest that loss of patellar bone density is established early in the course of chondromalacia patellae, and that more extensive loss of bone density in the affected limb develops later as a result of continued impaired use. Limb dominance is unlikely to be a factor in side-to-side differences documented in these patients. While BMD of the arms is on average 2.5% higher in the dominant side in healthy men who have never participated in unilateral activities,²⁷ such a difference does not exist in the legs.²⁸⁻³⁰

In conclusion, chondromalacia patellae is associated with a rise in s-COMP levels and the exclusive loss of patellar bone mineral density. In asymmetric knee pain, the loss of patellar bone density is greater in the more symptomatic knee joint. The observations reported in this study confirm that s-COMP is a highly sensitive marker of increased cartilage turnover.

ACKNOWLEDGEMENTS

Dr Murphy is the Rohan Newman Scholar, University College Dublin.

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