

Relating bone marrow oedema to hs-CRP in knee osteoarthritis

H Bassiouni¹, K Zaki¹, M Elshorbagi², A Mustapha¹, R Tantawi¹, H Ali¹, S Metyas³, DG Arkfeld³

ABSTRACT

Objective: To study the correlation between bone marrow oedema (BME) on knee magnetic resonance imaging (MRI) and plasma high sensitive-CRP (hs-CRP) levels in patients with symptomatic osteoarthritis (OA) of the knee.

Methods: Thirty patients with symptomatic OA of the knee were included and stratified into three equal groups consisting of normal alignment, varus or valgus misalignment of symptomatic knee. Radiographic scoring using Kellgren–Lawrence grading (K–L grade) was performed and an MRI of the knee taken. Intensity of pain was evaluated using a pain visual analogue scale (VAS) and the functional status determined by Lequesne functional index. In addition, hs-CRP was estimated in all patients and in 20 healthy controls.

Results: BME was present in 14 patients (46%) with OA and in none of the controls. Patients with BME had significantly longer disease duration, a higher lequesne score, suggesting greater functional impairment and more advanced radiological changes. A significantly higher number of patients (12/30, 40%) had an elevated hs-CRP than healthy controls (2/20, 10%, $P=0.02$). There was, however, no association between hs-CRP and BME. Patients with varus and valgus deformities harboured BME on the medial and lateral tibiofemoral compartments, respectively.

Conclusion: BME is a feature of advanced OA of the knee and is associated with radiographic progression, a greater functional impairment and longer disease duration. It is, however, not associated with raised hs-CRP levels.

Keywords: Osteoarthritis, bone marrow oedema, high sensitive-CRP, MRI.

INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis, is the leading cause of mobility-related disability in the elderly.¹ The tissue of origin of OA is controversial, though the sub-chondral bone appears in early disease.²

Although OA inherently lacks significant systemic inflammatory response, a low-grade inflammatory response has been suggested by earlier studies.³ Bone marrow lesions (BML), visible using magnetic resonance imaging (MRI), have been recognized as a feature of knee OA and are associated with pain and an increased likelihood of cartilage loss.^{4,5}

Growing evidence suggests that systemic markers of inflammation are associated with the severity of the clinical course of OA.³ Serum CRP has been shown to correlate well with CRP in the synovial fluid of patients with OA.⁴ However, to our knowledge, there is only one study reporting

high sensitivity-CRP (hs-CRP) levels in individuals with OA of the knee and hip undergoing replacement surgery.⁶ Identification of factors that recognize patients at high risk of disease progression might permit a better understanding of the disease process.⁷ Bone marrow oedema (BME) and malalignment have been shown to be associated with disease progression. Patients with varus alignment were shown to be at high risk for subsequent medial compartment progression of knee OA, while those with valgus alignment were reported to be at a high risk of subsequent lateral compartment disease progression.⁶ Cartilage defects, meniscal tears and osteophytes have been strongly related to increasing Kellgren–Lawrence grade (K–L grade).⁸

There are, however, many unanswered questions: Does BME relate to structural progression? Are CRP and BME associated with disease severity, including pain? Does BME reflect an inflammatory process or not?

¹Department of Rheumatology and ²Department of Clinical Pathology, Al-Hussein University Hospital, Azhar University, Cairo, Egypt, ³Department of Rheumatology, USC Keck School of Medicine, Los Angeles, CA, USA.
Correspondence: Prof. Hassan Bassiouni, email: hassanbassiouni@yahoo.com

The objective of the current study was to investigate the association between BME and the sensitive marker of inflammation, hs-CRP, in symptomatic OA of the knee. The roles of BME, joint alignment, structural and radiological severity in OA of the knee were additionally evaluated.

PATIENTS AND METHODS

Thirty patients with symptomatic OA (satisfying the ACR criteria) of the knees were recruited.⁹ Patients were stratified into three equal groups through purposive sampling of 10 each according to knee alignment, namely valgus, neutral and varus deformities. The patients had not sustained any trauma, did not have any cardiovascular ailment or receive intra-articular steroid injections in the knee for at least one year prior to the study. Oral steroid use prior to sampling was not allowed. An informed consent was taken. Twenty controls were included for measurement of hs-CRP.

Pain was measured using a Visual Analogue Scale (VAS) which is a simple assessment tool consisting of a 10 cm line, with 0 on one end representing no pain and 10 on the other representing the worst pain ever experienced, marked by the patient to indicate the severity of pain. The functional status was assessed with the Lequesne functional score which is a 10-question survey given to patients. It has five questions pertaining to pain or discomfort, one question dealing with maximum distance walked, and four questions about activities of daily living. The total questionnaire is scored on a scale from 0 to 24. Lower scores indicate that there is less functional impairment.¹⁰ Mechanical alignment was measured in degrees on a continuous scale with values <0 representing valgus alignment, values =0 representing neutral alignment and values >0 representing varus alignments, read and agreed upon by three study authors.

Radiography

All 30 patients had weight-bearing posterior anterior radiograph of the knee to evaluate the tibiofemoral compartments for further classification by K-L grading (Table 1).¹¹

MRI

The study utilized a Siemens Magnetom Vision 1.5 T superconducting MRI system. T1 and STIR technique sequences were obtained to demonstrate BME.

Hs-CRP

Hs-CRP was estimated by turbidometry technique¹², using kits from Dade Behring (Germany). The cut-off normal value was <0.5 mg/L.

Statistical analysis

Statistical calculations were done using Epi-info software, version 6.04, (WHO, 2001). Student's *t* test was applied for differences between means of two samples; χ^2 tests, Fischer exact test, Yates corrected χ^2 tests for different variables, grades or percentages; $P < 0.05$ was considered significant. The correlation between hs-CRP and VAS variables was determined using Spearman's correlation coefficient.

RESULTS

The patients and controls comprised predominantly females (M:F, patients 24:6, controls 16:4). They were matched with regards to age [mean (\pm SD), patients 54.3 (\pm 4.9) years, controls 53 (\pm 3.1) years]. The mean body mass index (BMI) of the patients was significantly higher than controls [mean (\pm SD), patients 35.6 (\pm 4.2) kg/m², controls 26.7 (\pm 0.97) kg/m², $P = 0.00$].

Patients were classified into two major groups, those with and those without BME. Table 2 compares the levels of hs-CRP, Lequesne index, K-L grading, VAS, BMI and disease duration between the two groups. Patients with BME had longer disease duration [8.7 (+2.6) vs. 5.5 (+3.2) years, $P = 0.006$], with 12/14 (86%) recording the highest lequesne functional score. Grade 4 X-ray changes were significantly higher in patients with BME on MRI (9/14 vs. 1/16, $\chi^2 = 11.3$, $P = 0.001$).

Table 1 The Kellgren and Lawrence classification criteria for knee osteoarthritis

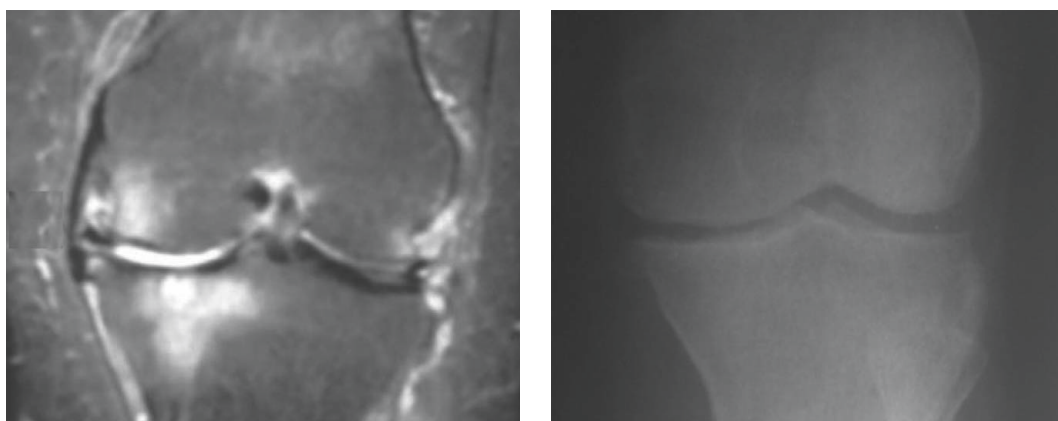
Kellgren & Lawrence grade	Kellgren & Lawrence definition
Grade 1: Doubtful	Minute osteophyte, doubtful significance
Grade 2: Minimal	Definite osteophyte, unimpaired joint space
Grade 3: Moderate	Moderate diminution of joint space
Grade 4: Severe	Joint space greatly impaired with sclerosis of subchondral bone

Table 2 Relation between BME and other factors in the case group

Variables	-ve BME no = 16	+ve BME no = 14	Test of significance	P
Duration (year)	5.53 ± 3.23	8.79 ± 2.67	T = 2.98	0.0058
BMI (%)	30.54 ± 5.41	35.94 ± 3.78	T = 0.71	0.000
Lequesne score > 15	6	12	Yates $\chi^2 = 5.36$	0.007
Hs-CRP < 0.5 (%)	12 (75)	6 (42.9)	Fischer = 2.01	0.1558
≥ 0.5 (%)	4 (25)	8 (57.1)		
X-ray grade 4	2	9	Yates $\chi^2 = 6.23$	0.003
VAS (Mean + SD)	9.21 + 0.80	8.56 + 0.81	T = 2.2	0.03

Table 3 Distribution of BME in relation to alignment of knees

Alignment	Patients with BME on MRI		Location of BME	
	No. = 10	%	Medial tibiofemoral compartment	Lateral tibiofemoral compartment
Varus deformity	7	70	5 (71%)	2 (29%)
Valgus deformity	3	30	1 (33%)	2 (77%)
Neutral alignment	4	40	3 (75%)	1 (25%)

**Figure 1** BMLs of both medial condyles as shown in coronal, fat suppressed T2-weighted magnetic resonance images showing also osteophytes and varying grades of edema, with the corresponding radiography showing narrowing of the medial space in a case of OA of the knee.

Twelve patients (40%) had elevated hs-CRP levels, i.e., >0.5 mg/l in comparison to 2 (10%) in controls ($P=0.02$). However, this was not associated with the presence of BME on MRI. Also, there was no significant association between BME and raised hs-CRP. Higher pain VAS scores were seen in patients with raised hs-CRP vs. those with normal levels (9.58 + 0.51 vs. 8.38 + 0.69, $P=0.00$).

The relationship of BME to alignment is given in Table 3. Patients with varus deformity harboured BME on the medial tibiofemoral compartment (70%) while patients with valgus deformity had BME on the lateral tibiofemoral compartment (77%) (Figure 1). The patients with neutral alignment

showed a predilection to have BME on the medial compartment (40%).

DISCUSSION

There is growing evidence that systemic markers of inflammation are associated with severity or clinical course of OA. Serum CRP, probably the most widely used clinical marker of systemic inflammation, has been shown to correlate well with CRP in synovial fluid in patients with OA or RA.¹³

The present study shows that hs-CRP is elevated in symptomatic knee OA and is suggestive of the fact that OA of the knees may have an inflammatory component. The search for an inflammatory component in OA has been investigated before by measuring immunoglobulins and CRP from serum and synovial fluid. Shine et al. found that CRP was elevated but immunoglobulins, were not. Bassiouni et al., however, found an elevated level of immunoglobulins in primary OA of the knee.^{14,15}

In our study, higher pain VAS scores were observed in patients with raised hs-CRP vs. those with normal levels. This agrees with a previous observation that linked the severity of knee OA pain primarily to the extent of OA.^{16,17}

Also, BME lesions were strongly related to frontal plane malalignment. BME in medial and lateral tibiofemoral compartments was seen in patients with varus and valgus deformities, respectively, as expected. These results are in consonance with Felson et al.⁵

BME is due to mechanical stresses arising out of malalignment that may produce traumatic bone lesions and the wearing of local cartilage evidenced by joint space loss. BME lesions on MRI show surprisingly little oedema on histopathologic examination (HPE). The HPE shows abnormal bone and excessive fibrosis, microfractures, small areas of osteonecrosis and extensive bony remodelling with reversal lines.^{5,18,19} Such remodelling often occurs after fatigue fractures in bone. A recent study by Kesemenli suggested that the BME is the result of microfractures caused by mechanical stresses in malaligned knee which explains a vicious circle of malalignment, BME and pain.²⁰ Hence, BME can be considered as a reflection of existing deterioration of the joint, associated with the disease duration as well as K-L grading score.

In our study, we did not find any significant association between the BME and hs-CRP levels. It could also be explained by the fact that BME is more suggestive of bone microfractures rather than inflammatory oedema.

Our study does have some limitations in the form of small sample size and also has all the associated problems of a cross-sectional study.

CONCLUSION

BME is a feature of advanced knee OA and is associated with radiographic progression, a greater functional impairment and longer disease duration. It is, however, not associated with raised hs-CRP levels. Whether hs-CRP is a marker of disease progression can be answered only by a long-term follow-up study.

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REFERENCES

1. Sun Y, Stürmer T, Günther KP, Brenner H. Inzidenz und Prävalenz der Coxund Gonarthrose in der Allgemeinbevölkerung [Incidence and prevalence of cox- and gonarthrosis in the general population]. *Z Orthop Ihre Grenzgeb* 1997; 135: 184–92.
2. Buckland-Wright C, Lynch JA, Dave B. Early radiographic features in patients with anterior cruciate ligament rupture. *Ann Rheum Dis* 2000; 59: 641–6.
3. Sharif M, Elson CJ, Dieppe PA, Kirwan JR. Elevated serum C-reactive protein levels in osteoarthritis [letter]. *Br J Rheumatol* 1997; 36: 140–1.
4. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* 2001; 134: 541–9.
5. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med* 2003; 139: 330–6.
6. Stürmer T, Brenner H, Koenig W, Günther KP. Severity and extent of osteoarthritis and low grade systemic inflammation as assessed by high sensitivity C reactive protein. *Ann Rheum Dis* 2004; 63: 200–5.
7. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA* 2001; 286: 188–95.
8. Hayes CW, Jamadar DA, Welch GW, Jannausch ML, Lachance LL, Capul DC, Sowers MR. Osteoarthritis of the knee: comparison of MR imaging findings with radiographic severity measurements and pain in middle-aged women. *Radiology* 2005; 237: 998–1007.
9. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; 29: 1039–49.
10. Lequesne M, Méry C, Samson M, Gérard P. Indexes of severity for osteoarthritis of the hip and knee. Validation value in comparison with other assessment tests. *Scand J Rheumatol* 1987 (Suppl 65): 85–8.

11. Kellgren JK, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957; 16: 494–501.
12. Larry, J., Kricka, D. Principles of immunochemical techniques. In: Tietz WW (ed.), *Fundamentals of Clinical Chemistry*, 4th ed. W.B. Saunders: Philadelphia, 1996; 10: 144–69.
13. Kumon Y, Suehiro T, Nishiya K, Hashimoto K, Nakatani K, Sipe JD. Ferritin correlates with C-reactive protein and acute phase serum amyloid A in synovial fluid, but not in serum. *Int J Exp Clin Invest* 1999; 6: 130–5.
14. Shine B, Bourne JT, Begum Baig F, Dacre J, Doyle DV. C reactive protein and immunoglobulin G in synovial fluid and serum in joint disease. *Ann Rheum Dis* 1991; 50: 32–5.
15. Bassiouni M, Bassiouni H, El-Dahan M. Measurement of immunoglobulins G, M and A in idiopathic osteoarthrosis: a suggested explanation for their production. *Ann Saudi Med* 1991; 11.
16. Wluka AE, Hanna F, Davies-Tuck M, Wang Y, Bell RJ, Davis SR, Adams J, Cicuttini FM. Bone marrow lesions predict increase in knee cartilage defects and loss of cartilage volume in middle-aged women without knee pain over 2 years. *Ann Rheum Dis* 2009; 68: 850–5.
17. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. *Arthritis Rheum* 1997; 40: 723–7.
18. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. *Radiology* 2000; 215: 835–40. [PMID: 10831707]
19. Bergman AG, Willen HK, Lindstrand AL, Pettersson HT. Osteoarthritis of the knee: correlation of subchondral MR signal abnormalities with histopathologic and radiographic features. *Skeletal Radiol* 1994; 23: 445–8.
20. Kesemenli, Memisoglu K, Muezzinoglu US. Bone marrow edema seen in MRI of osteoarthritic knees is a microfracture. *Med Hypotheses* 2009; 72(6): 754–5. Epub 2009 Feb 27

ANSWERS TO THE RHEUMATOLOGY QUIZ (page 45)

1d*, 2b, 3d**, 4c, 5b***, 6c†, 7a††, 8b†††, 9c, 10a§

*DILS occurs with profound immunosuppression and resolves rapidly with HAART.

**Stands for: Clinically Significant Upper and Lower GI Events. *J Rheumatol* 2010;37:167–74

***Back pain is worsened by activity and relieved by rest
†this marker has been shown to correlate very closely with the activity of nephritis in SLE

††unlike other MHC class I genes, gene polymorphism is low
†††peripheral arthritis is more common and axial involvement is less severe

§progression often heralded by fever and urinary retention; monophasic course; disease activity high; CSF findings like those of pyogenic meningitis.