Literature Review

Graftys: HBS and QS injectable Calcium Phosphate bone substitutes –Bone Marrow Lesion Repair

Version 1.2 - 3 December 2014– 37 pages

Report prepared for:

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TABLE OF MODIFICATIONS

N°	Date	Main Modifications	Page
Draft Rev 1.1	21 May 2014	Initial draft	N/A
Rev 1.2	3 December 2014	Incorporation of manufacturer's comments	All

DOCUMENT APPROVAL

Literature Review: Graftys: HBS and QS injectable Calcium Phosphate bone substitutes – BML repair

Version 1.2 – 3 December 2014, 37 pages

	Signature	Date
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1. SUMMARY

This review covers the potential advantages of using injectable calcium phosphate (CaP) - based bone fillers in the repair of bone marrow lesions.

The available literature allows us to assess:

- the use of MRI-visualised bone marrow lesions (BML) as indicators of bone problems
- the potentialities of CaP cement injection to repair BMLs.
- the possible role of underlying bone damage in knee osteoarthritis (KOA)

There are currently no publications on clinical trials sub-chondral bone cement injection, but complications and adverse event rates from case series and studies of procedures using injectable calcium phosphate cements allow baseline risk assessment.

It is concluded that calcium phosphate injectable bone cements are suitable products for the repair of BMLs.

2. INTRODUCTION

Graftys HBS and QS injectable Calcium Phosphate bone substitutes are CE-marked medical devices with indications covering a wide range of orthopaedic and trauma surgery applications in which bone voids need to be filled, or damaged bone needs reinforcement.

Each product is an injectable self-hardening macroporous synthetic calcium phosphate (CaP) bone substitutes, which is strongly osteo-conductive. It comes in a double-compartment mixing syringe which is pre-filled with a powder (calcium phosphate salts and polysaccharide) and with a phosphate-based (Na_2HPO4) aqueous solution. When these two components are mixed in the syringe, an injectable calcium-deficient apatite (CDA) is formed athermally. *In-vivo*, this apatite, which hardens in either 12 minutes (HBS) or 6 minutes (QS), is then resorbed and replaced by bone. HBS and QS are sterile, non-pyrogenic, single-use products.

MedPass International has been asked by the manufacturer to critically review the published literature relating to the use of injectable bone filler in the treatment of knee osteoarthritis:

- To provide the scientific basis of the treatment
- To gather available evidence of efficacy from clinical studies
- To present evidence of likely complication/adverse event rates.

This document contains the results of this review.

It was prepared in compliance with the following guidance:

- MDD 93/42/EEC, the Medical Devices Directive (as amended)
- MEDDEV 2.7.1 December 2009, Clinical Evaluation: a guide for Manufacturers and Notified Bodies

This document refers to two earlier literature reviews:

- Graftys: Calcium Phosphate-based bone fillers. September 2012.
- Graftys: Decompression techniques to improve effectiveness and safety of HBS injectable calcium phosphate bone filler. July 2013.

These cover the safety and efficacy of injectable CaP bone fillers over a wide range of indications, including injection into closed bone spaces, including evidence for the clinical safety and effectiveness of the Graftys injectable fillers based on research involving closely similar products.

2.1. Scope and Methodology

The bibliography (Section 7) contains citations for all the acceptable search output, and other relevant secondary references.

Section 9 contains the search protocol, listing the search terms, the databases searched, and the criteria for sifting results to exclude publications of low evidential value.

Section 10 contains the author's and reviewer's CVs.

2.2. Abbreviations

95%CI	95 per cent confidence interval
BML	bone marrow lesion (synonym for bone marrow oedema)
CaP	Calcium phosphate
CDA	Calcium deficient apatite
CPC	Calcium Phosphate Cement
HA	Hydroxyapatite
KOA	Knee osteoarthritis
MOST	Multi-center Osteoarthritis Study
MRI	Magnetic resonance imaging
N	Sample size
NS	Not statistically significant
PMMA	Poly-methyl methacrylate
SD	Standard Deviation
SE	Standard Error
T2	MRI image weighted towards spin/spin relaxation (by changing echo time)
TKA	Total knee arthroplasty – artificial knee joint implantation

3. INFORMATION FROM MANUFACTURER

3.1. Manufacturer's details

Graftys SA
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4. BACKGROUND

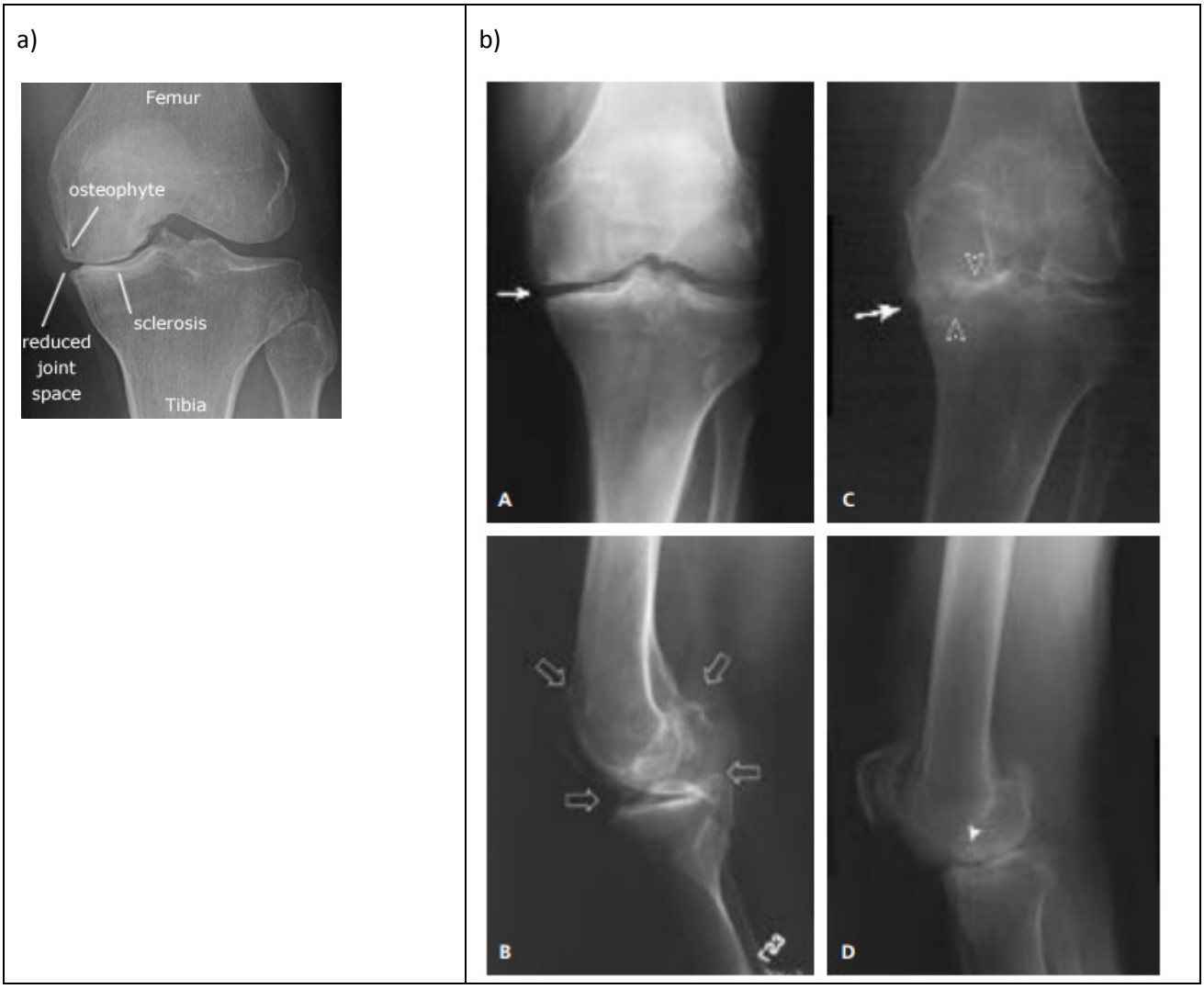


Figure 1a) schematic x-ray image b) from Swagerty 2001.

Osteoarthritis of the knees. (A) Anteroposterior view of the left knee shows medial joint space narrowing (arrow). (B) Lateral view of the left knee shows sclerosis with marked osteophyte formation (arrows). The osteophytes are best seen in this view. (C) Medial joint space narrowing (white arrow) causing a varus deformity of the knee and collapse of the joint space with destruction of the medial cartilage and the subchondral cortex (open arrowheads). (D) Subchondral cysts (solid arrowhead) are noted.

Fig1 shows the changes in an arthritic knee which are visible on a conventional x-ray. The condition involves both loss of cartilage, bone damage, and inappropriate bone regeneration processes, leading to painful knees with restricted movement. (**Swagerty 2001**).

The arthritic changes in the bone involve both sclerosis (stiffening of the bone) of the surface layer, with and degenerative changes below the surface. There is evidence that degenerative bone changes may be linked to bone marrow lesions (Fig. 2) seen on T2-weighted MRI scans (**Sharkey 2012**). Injecting

resorbable bone cement into the BML areas can have beneficial results (**Farr 2013**). Lim 2014 concludes a review article: “therapeutic interventions targeting BMLs have the potential to reduce the burden of knee osteoarthritis”.

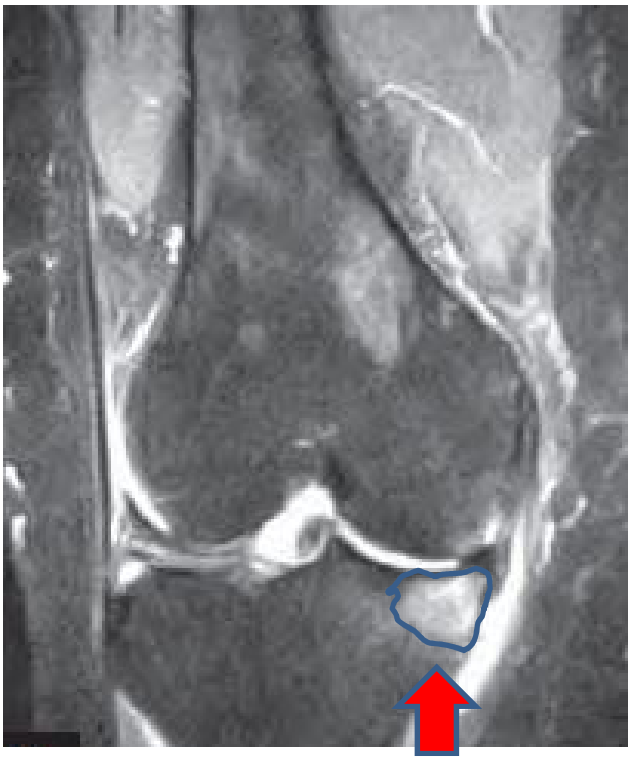


Figure 2 from Sharkey 2012 – an MRI (T2 weighted) scan of an arthritic knee, showing a bone marrow lesion (red arrow, blue outline)

Background levels of adverse events associated with the injection of bone cement into closed bone spaces are covered in accompanying documents.

4.1. Product description (Information from manufacturer)

Graftys HBS and Graftys QS (quickset) are injectable bone fillers. They come in a double-compartment mixing syringe which is pre-filled with a powder (calcium phosphate salts and polysaccharide) and with a phosphate-based (Na2HPO4) aqueous solution.

When these two components are mixed in the syringe, an injectable calcium-deficient apatite is formed athermally. This apatite hardens in-vivo (37°C), in approximately 12 min for Graftys®HBS or 6 min for Graftys®Quickset. The final product provides a bone void filler that resorbs and is replaced with bone during the healing process.The injectable bone cement component is a self-hardening macroporous synthetic calcium phosphate bone substitute.

4.2. Intended Use

This literature review supports a CER evaluating the use of Graftys injectable bone cements in the treatment of BMLs.

4.3. Comparable products

Dorozhin 2011 and Tofighi 2009 review the properties of injectable CaP bone cements. Included is a comparison between Graftys bone cements and the Etex products currently used in Zimmer subchondroplasty procedures (Table xx

Table 1 from Dorozhin 2011 and Tofighi 2009 – HBs, QS and Etex BSM products compared

ETEX (US)	α-BSM®; Embarc; Biobon	Powder: ACP (50%), DCPD (50%); Solution: Un-buffered aqueous saline solution	apatite
	β-BSM®	Composition: could not be found (it has apparently a higher compressive strength and better injectability than α-BSM®)	apatite
	γ-BSM®	Composition: could not be found (putty consistency)	apatite
	OssiPro	Composition: could not be found; the cement is claimed to be macroporous after hardening	apatite
	CarriGen	Composition: synthetic calcium orthophosphate, sodium carboxymethylcellulose, sodium bicarbonate and sodium carbonate	apatite
Graftys (FR)	Graftys® HBS	Powder: mainly β-TCP, ACP, BCP (HA + β-TCP); Solution: phosphate buffered solution	apatite
	Graftys® Quickset	Composition: calcium orthophosphate salts, hydroxypropylmethylcellulose and orthophosphate-based aqueous solution	apatite

a) Etex/Graftys comparison, from Dorozhin 2011

Products	**α-BSM®**	**β-BSM™**
Starting Materials	ACP + DCPD	n-ACP + DCPD
Hydration Media	Physiological Saline	Physiological Saline
Working Time at 25 °C (min)	45-60	10-15
Setting Time at 37 (min)	15-20	3-5
Compressive Strength (MPa)	10-12	28-32
Delivery	Injectable (8-16G)	Injectable (8-16G)
Sterilization	Gamma Rad.	Gamma Rad.
End Product	Carbonated Apatite	Carbonated Apatite

b) Etex product properties, from Tofighi (2009)

5. SUBCHONDRAL BONE REINFORCEMENT– LITERATURE REVIEW

5.1. Natural history of bone marrow lesions

Roemer 2009 and **2010** reports findings for the longitudinal MOST (Multicenter Osteoarthritis study) study – there were 3026 participants with an average age of 63 years – all either with an KOA diagnosis, or considered at risk. 39% had knee symptoms at baseline line, rising to 42% at follow up (2.6 years on average). Average BML incidence at baseline (1025 knees had MRI scans) is shown in Table 2.

Table 2

BML grade (% of knee sub-regions affected)	Average lesions/knee
1 (<25%)	0.65
2 (25-50%)	0.18
3 (≥ 50%)	0.095

There was no pattern of steady increase in BML size over time – at 30-month follow up, 34% of BMLs showed no change, 16% increased, 9% decreased and 9% had disappeared.

Wildi 2010, with data from a randomized controlled trial of two arthritis drugs, demonstrate a steady increase in BML size over 4 consecutive scans at 6-month intervals (Fig. 3).

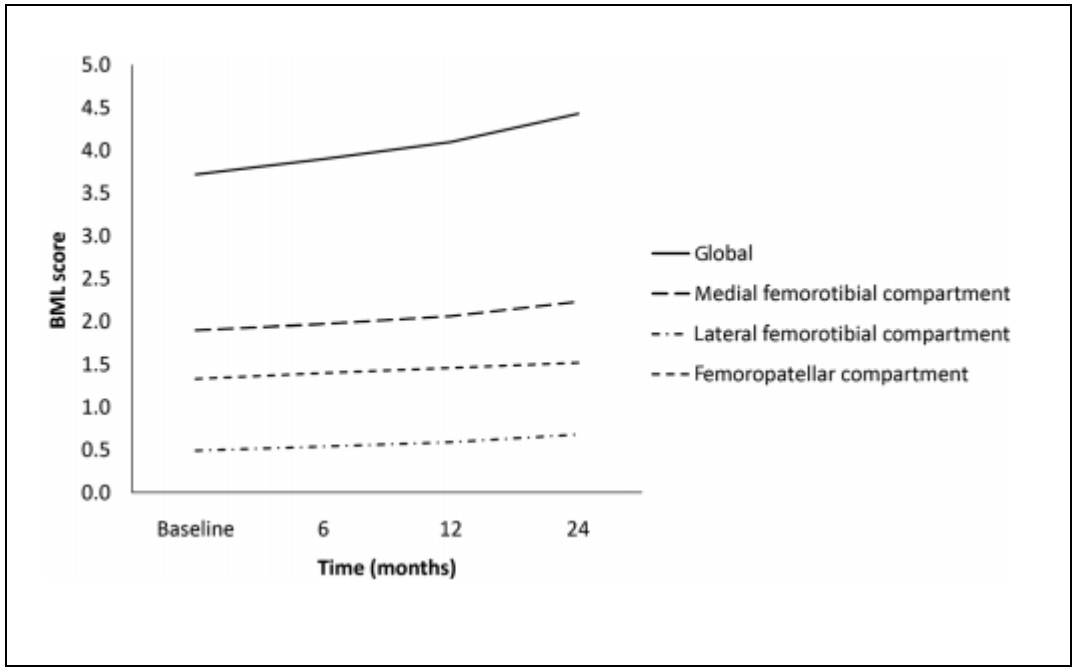


Figure 3 from Wildi 2010 – N=143 All increases are statistically significant

Baranyay 2007 found that 13% of a healthy population (no KOA diagnosis, no knee pain, average age = 58 years) had BMLs. 8% had BMLs which fell into the grade 2 or 3 categories. Similarly **Guymer 2007** found that 13% of a sample of 176 healthy women showed evidence of BMLs.

Berry 2009, with a sample of 148 healthy middle-aged people, found that 46% of the BMLs present at baseline resolved over a 2-year period.

Clearly BMLs are not uncommon in a healthy middle-aged population, but become very frequent in people with KOA.

Ip 2011 demonstrates the increasing frequency of BMLs with diagnostic status, in a sample of 255 subjects, all reporting knee pain:

- No osteoarthritis diagnosis – N=33, 11% had BMLs
- KOA diagnosis – non-radiographic - N= 124, 38% had BMLs
- KOA diagnosis – radiographically confirmed – N=98, 71% had BMLs.

These differences are statistically significant, P<0.001.

5.2. Bone marrow lesions as a target for treatment

Sharkey 2012 provides a narrative in which repetitive joint loading combined with inadequate repair processes produce a chronic bone marrow lesion.

Sharkey et al describe the BML as being underneath a hard brittle sclerotic surface layer (Fig.4). The lesion is the root cause of joint pain – filling the lesion with CaP injectable cement relieves the pain as natural bone replaces the cement.

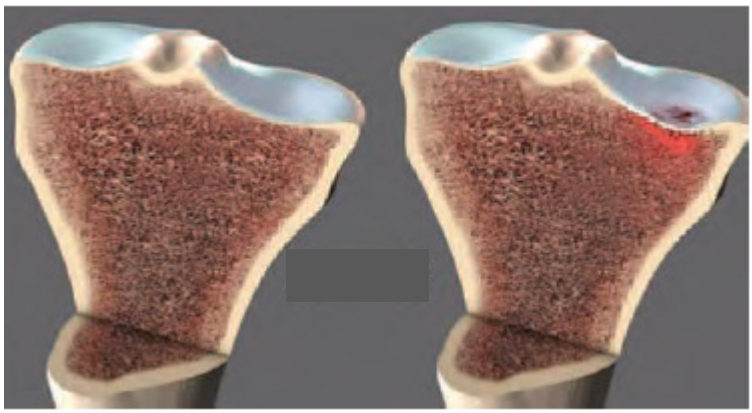


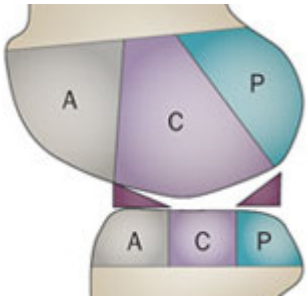
Figure 4 From Sharkey 2012 – schematic drawing, healthy tibia (left) and KOA with BML (right)

Key elements of this theory are tested below.

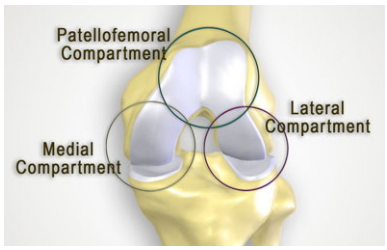
5.2.1. Joint loading and BMLs

Sharkey's theory is supported by **Hayashi 2012** with data from the MOST study, which included a cohort of 3026 patients who either were diagnosed with knee osteoarthritis, or were considered at high risk. Patients were X-rayed and MRI scanned at baseline, and at 30-month follow-up (N=2662). Subchondral BMLs were scored on a 1-3 scale, where 1= <25% of the region, and 3 >50%, involved. No BML scored 0.

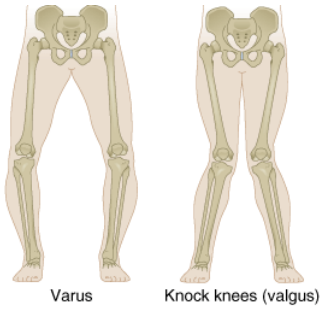
3267 knees showed evidence of malalignment (Fig 5) enabling comparisons between most-loaded and least loaded compartments. At follow-up 26.4% of most-loaded and only 7.3% of least loaded compartments had BML score increases over baseline scores.



a) Subregions – anterior, central, posterior



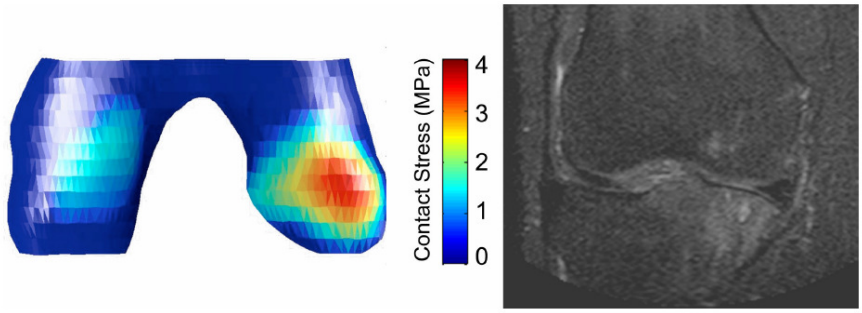
b) Compartments



c) varus and valgus

Figure 5 a) and b) Sub-regions and compartments of the knee. c)– varus and valgus malalignment, showing lateral loading for valgus and medial for varus. (Fauci 2008)

Segal 2012 uses a subsample of people from the MOST study (N=38 knees) to examine the predictive power of a non-invasive assessment of joint loading (MRI -coronal short T1 inversion recovery sequence) at baseline for BML worsening between baseline and 30 month follow up. Fig 6. shows a typical example.



a) b)

Figure 6 (from Segal 2012) a) medial contact stress b) development of region-specific medial tibial and femoral BMLs 30 months later.

Table 3 shows the findings.

Table 3 Data from Segal 2012 – BML development related to joint contact stress

At 30 months, sub-=regions with:	Worsening BMLs (N=52) MPa ±SD	Controls (N=100)
Mean contact stress at baseline	3.6±1.1	1.13±1.7
Peak contact stress at baseline	8.6±2.9	2.78±4.3

This study also found a significant relationship between initial joint contact stress and later cartilage damage.

5.2.2. Histology of BML regions

Sharkey's theory of BML involvement in KOA anticipates degenerative bone changes in the T2 MRI-detected BMLs.

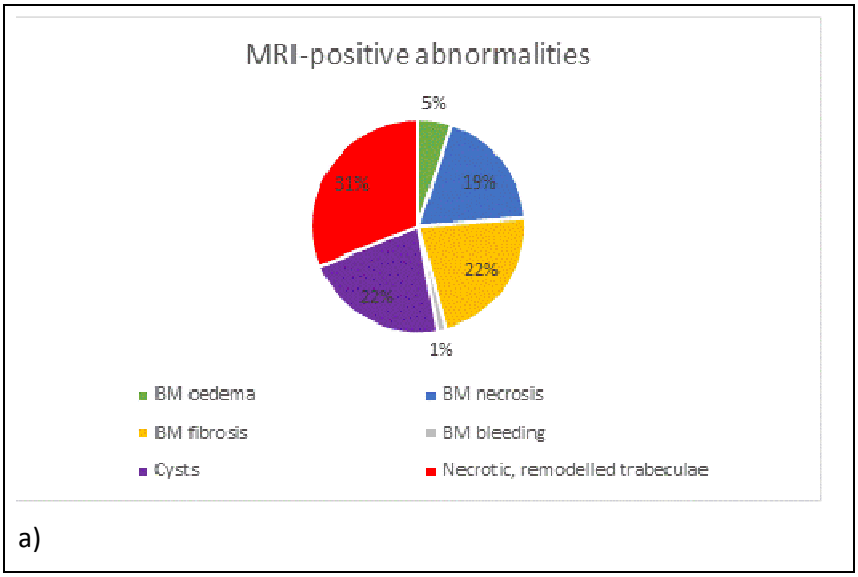
Zanetti 2000 is a small study (N=16) in which patients due for TKA were first subjected to a series of MRI scans to detect BMLs adjacent to the tibial plateau. Bone removed from these patients during the arthroplasty procedure was than examined histologically to correlate histological changes with the MRI images. In each case bone samples both from zones which had normal MRI images and neighbouring MRI-positive (abnormal) regions. Table 4 shows the frequencies of normal and abnormal histological observations for MRI-positive and controls areas of bone, with a large increase in abnormalities in the MRI-positive region.

Table 4 Data for Zanetti 2000

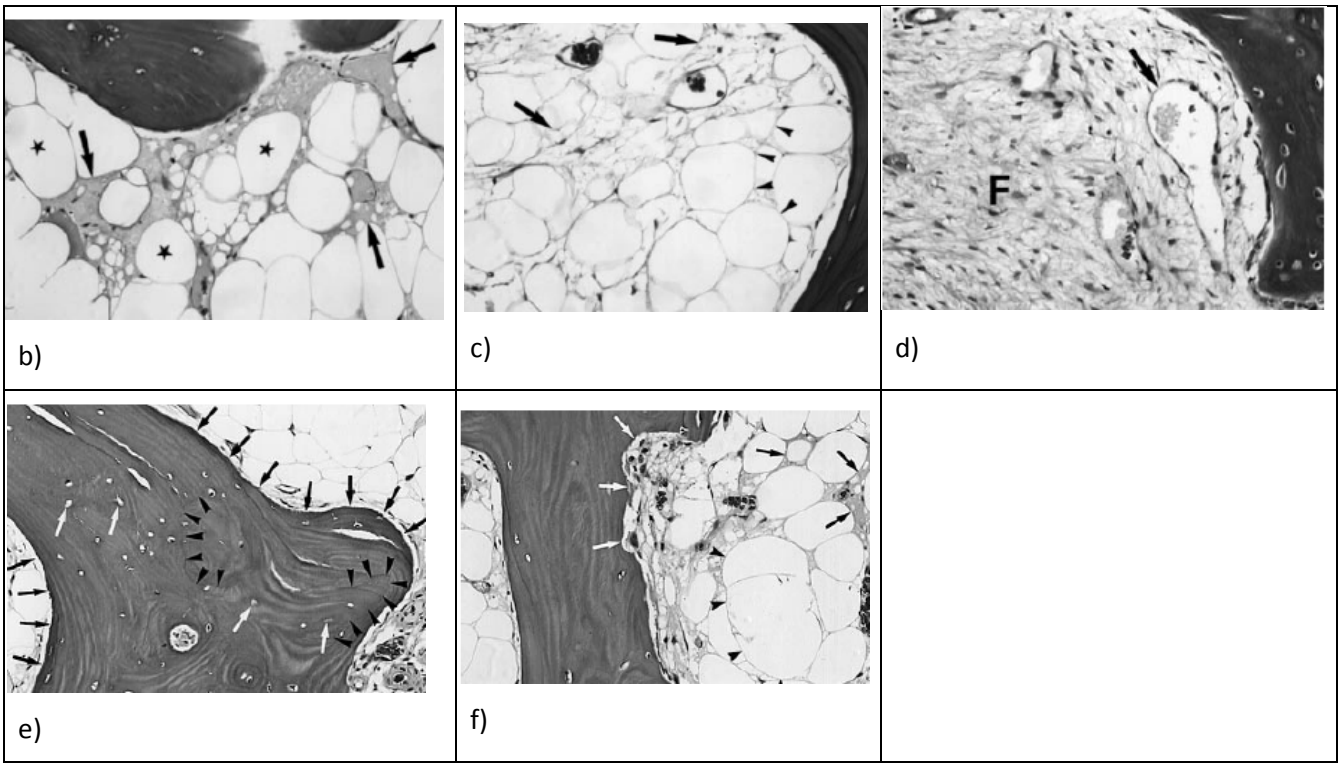
	Histologically normal tissue observations /patient	Histologically abnormal tissue observations/patient
Normal MRI	6.6 (N=26)	1.1 (N=26)
Abnormal MRI	6.3 (N=29)	**7.5** (N=29)

Figure 7a) shows the distribution of the histological abnormalities within the MRI-positive zones – the authors note that oedema is quite rare. Figure 7 b)-g) are typical histologies for the various abnormalities.

MRI assessment for this study was conducted by scanning experts who viewed M1-weighted, M2-weighted and STIR (short tau inversion recovery) images for each patient. Other studies reported in this review have used only T2-weighted images, which Zanetti et al claim underestimate the full extent of the lesions seen on STIR images. In each case abnormalities were only visible on micrographs (x220 magnification).



a)



b) c) d) e) f)

Figure 7 Bone Marrow (BM) and other bone abnormalities in MRI-positive region.

a) incidence, b) BM oedema (swollen fat cells *) c) BM necrosis (foam cells →) d) BM fibrosis (F) e) Trabeculae abnormalities f) Bone resorption (→). From Zanetti 2000.

Kazakia 2013 reports on a recent similar study, in which 18 tibial plateau specimens removed from 12 patients during TKA procedures were examines. 16 of these specimens showed evidence of BMLs (post-operative MRI scans, and 11 had little or no remaining cartilage. Fig 8 shows a typical CT scan with MRI-identified BML overlayed – the authors state "BML trabecular tissue composition had decreased

phosphate and carbonate content. Marrow infiltration by a fibrous collagen network and evidence of increased bone remodeling were present".

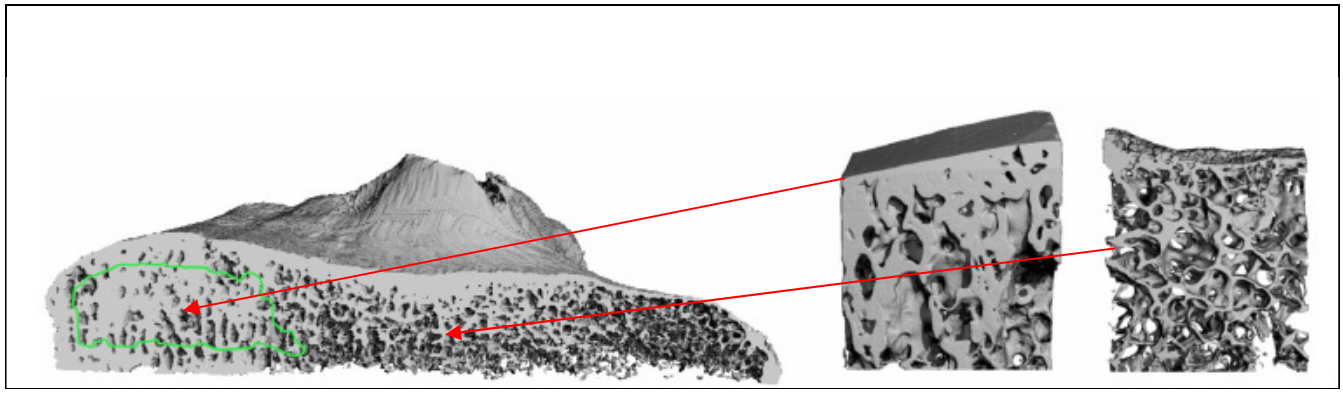


Figure 8 High resolution micro CT scan of tibial plateau, with BML region overlayed (green outline). From Kazakia 2013

5.2.3. Bone attrition and cartilage loss linked to BMLs

Roemer 2010 (section 4.1 has demographic data) shows a strong association between bone attrition (measured radiographically) and BML status: 54% of sub-regions (Fig. 3a) with BMLs showed attrition, which was present only in 4.3% of non-BML subregions. People in this study either had a KOA diagnosis, or were considered "at risk".

Kazakia 2013 (section 4.2.2) includes cartilage data:

T1ρ MRI imaging has been shown to reflect cartilage composition – high signal levels are early indicators of degenerative changes in cartilage (**Borthakur 2012**). Fig 9 shows T1ρ MRI scores for regions immediately above BMLs, and above surrounding healthy bone, for 5 samples. Differences are just statistically significant (p=0.046). This data is from late-stage KOA – the patients had all progressed to knee joint replacement.

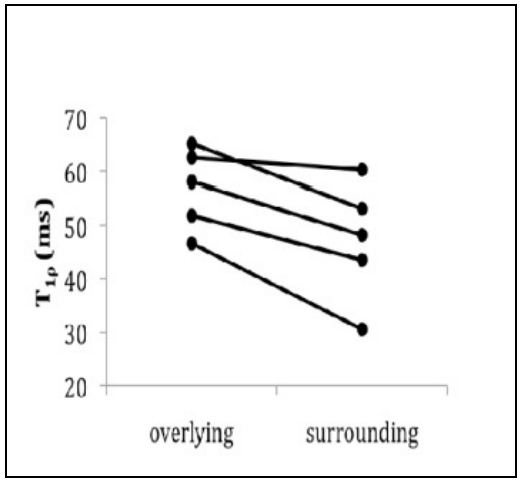


Figure 9 Damage to cartilage overlying a BML – from Kazakia 2013

Hunter 2006 has data from a longitudinal study (N=217) of patients with KOA (mean age 66 years). At baseline 57% of patients had BMLs, and 27% of these BMLs increased in size at 30-month follow-up. A 1-unit increase in BML score was linked to a 1.6 unit increase in cartilage damage score. Cartilage damage was measured on a 1-6 semi-quantitative scale - the Whole-Organ MRI Score, ranging from normal (1) to full-thickness loss (6).

Kothari 2010, in a study of 177 KOA patients with 2-year follow up. Presence of a BML in any knee joint sub-region at baseline was associated with a 4-fold increase in the risk of cartilage damage in that region at follow up, compared with control regions. This odds ratio was greater than those for risk of cartilage loss with either subchondral bone cysts (1.7) or subchondral bone attrition (3.2) present at baseline.

Tanamas 2010 and **2010a** (N=132 patients with KOA) suggest a progressive relationship between cartilage volume loss over a 2-year follow-up period, and both BML and bone cyst presence at baseline – averaging medial and lateral compartments:

Table 5 Data from Tanamas 2010

Status at baseline	**Tibial cartilage volume loss (mm^3 ±95% CI)**
Controls (N=36)	2.62±1.8
BML present (N=21)	6.30 ±2.9
BML and bone cyst present (N=52)	9.26±2.1

These studies also showed an increasing risk of knee joint replacement over a 4-year follow-up period with increasing BML score a baseline (odds ratio =1.57, p=0.03, N=16)

The above studies all demonstrate that BMLs are associated with bone attrition and cartilage loss in patients with, or a risk of, KOA.

Wluka 2008 correlates presence (and size) of BMLs at baseline with cartilage deterioration during the following two years for a group of 271 healthy adults **with no KOA symptoms**. Table 6 shows their findings: there is a weakly statistically significant trend linking large (Grade 2) or very large (Grade 3) BMLs to later cartilage damage.

Table 6 from Wluka 2008 – Large BMLs predict later cartilage damage

	Large BML at baseline			Very large BML at baseline		
	BML (*n*=37)	No BML (*n*=234)	*P*-value[a]	BML (*n*=11)	No BML (*n*=260)	*P*-value[a]
Change in cartilage defects						
Progress/deteriorate	21	89		8	102	
Stable/no change	13	120		3	130	
Regress/improve	3	25	0.04	0	28	0.05

[a]Ordinal regression.

Davies-Tuck 2010 has more findings from the above study, showing that people whose BMLs resolved over the 2-year follow-up period showed reduced annual rates of cartilage loss, when compared with those who developed BMLs.

Table 7 Data from Davies-Tuck 2010 Less cartilage loss when BMLs resolve

BML at baseline	BML at follow-up	N	Medial tibial cartilage volume loss/ year (mm^3±SE)
no	**no**	**201**	**19.5±3.5**
yes	**yes**	**20**	**36.0±8.8**
no	**yes**	**33**	**34.0±9.5**
yes	**no**	**17**	**10.5±11.1**

In summary, there are clearly links between the occurrence of BMLs and the bone and cartilage degenerative changes known to cause KOA symptoms. However evidence for a plausible mechanism by which BMLs could be root causes of these tissue changes is currently lacking.

5.2.4. BML and knee pain

"Snapshot" studies

These reports correlate subjective pain with contemporary MRI-detected BMLs,

Torres 2006 is a study with 143 participants with symptomatic KOA. Fig. 10 shows a strong relation between BML severity and pain scores.

The authors tested a theory that BML only relates to pain scores when there is evidence of bone attrition – Table 8 shows the results, with a strong suggestion that a combination of a large BML and significant bone attrition is needed for a high pain score to result.

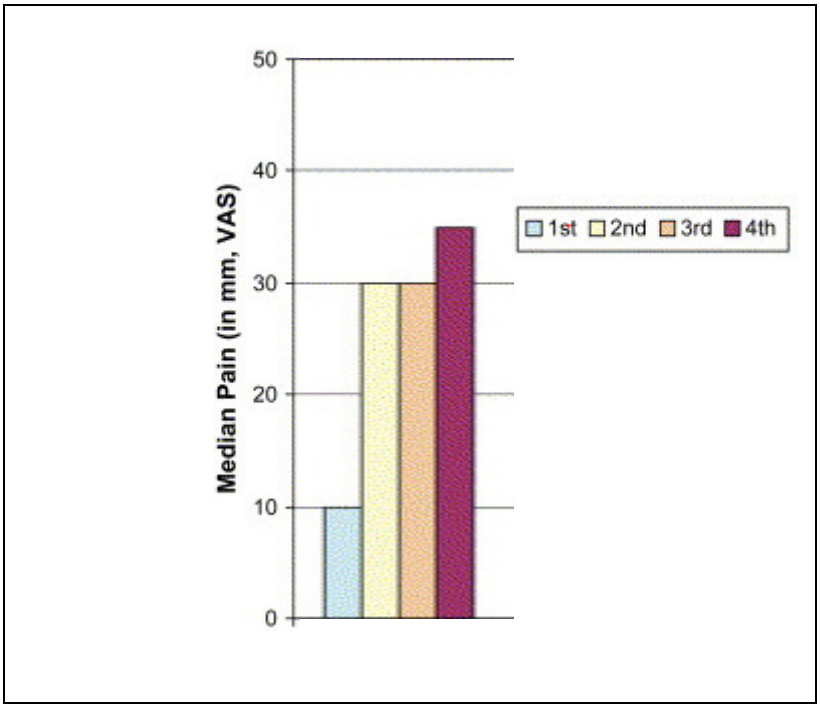


Figure 10 from Torres 2006. Analogue-scale pain scores by BML score quartiles.

Table 8 from Torres 2006 – synergism between BML and bone attrition.

Subarticular bone attrition and bone marrow lesion status (*n* of knees)	Median pain severity (mm)	Difference in median pain (mm) from knees with high attrition and high bone marrow lesion	95% CI of difference
Both high (14)	40.00	(Reference)	–
High attrition only (19)	30.00	−10	−32.43, 12.43
High bone marrow lesion only (13)	15.00	−25	−49.64, −0.36
Neither high (96)	20.00	−20	−38.06, −1.94

Fig 11 shows the data from **Lo 2009**, a study of 160 patients with symptomatic KOA, 91% of whom had BMLs. The authors found a strong correlation between maximum BML grade (see Table 1 above – "0" corresponds to no BMLs) and pain scores. For weight-bearing pain, the relationship is statistically significant ($p<0.001$), and for non-weight-bearing pain (eg pain in bed or at rest) it closely approaches significance ($p=0.06$)

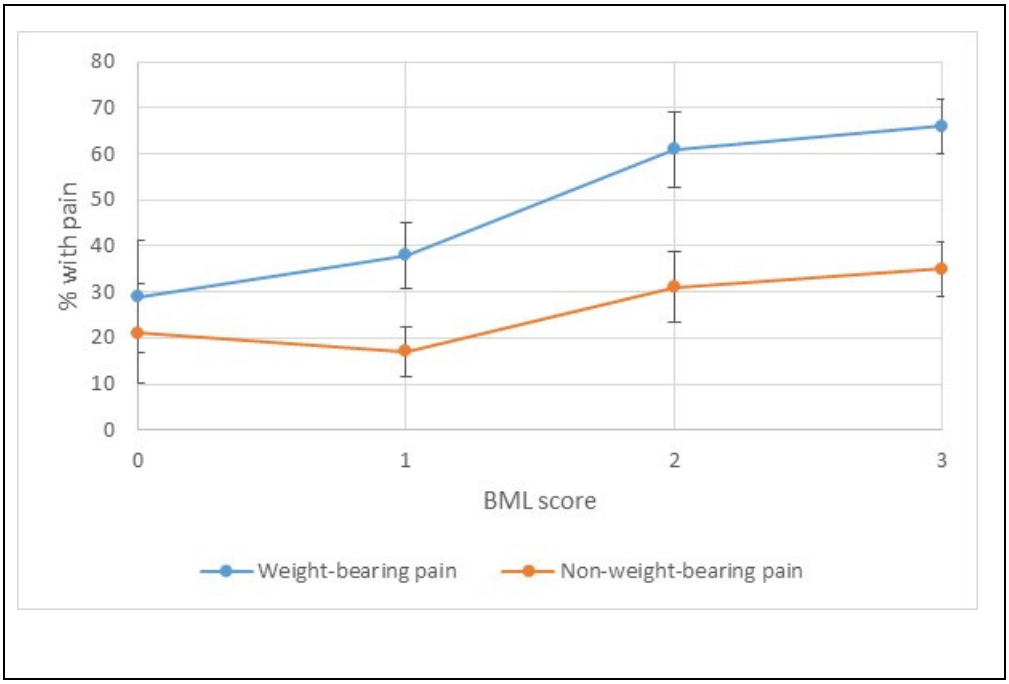


Figure 11 Data from Lo 2009. Incidence of pain increases with maximum BML grade. Bars show standard errors.

This study also found that joint effusion scores (based on hyper-intense MRI signals within the joint capsule) were predictors of pain score, significant for both weight-bearing and non weight-bearing pain.

Wildi 2010, (see section 4.1 above) with a sample of 161 KOA patients, found a mild negative correlation between BML score and pain score (r= -0.13, NS). Changes in BML over the 2-year study period also did not correlate significantly with pain scores.

Ip 2011 has a sample of 255 people with knee pain, of whom 89% have a KOA diagnosis and 47% had BMLs. In this comparatively fit population there were only weak, non-significant correlations between BML data and pain scores, except for a "pain on climbing stairs" scale.

Table 9 summarises data from three studies which just recorded presence/absence data for pain and for BMLs. In each case a contingency table test yields a statisitically significant result.

In summary, the relationship between MBL and pain seems to be significant in populations with moderate to severe KOA, but all studies find substantial minorities with BMLs but no or little pain.

Table 9 "Snapshot" studies of the association of knee pain with BMLs – contingency tables

Study	Patient category	N	Category	(N° with BML) /(Total N° with or without pain)	p-value
Guermazi 2012	No KOA	710	Pain	121/206 (59%)	P=0.03
			No pain	242/489 (49%)	
Javaid 2012	KOA	283 (one painful knee)	Painful Knee	112/283 (40%)	P<0.001
			Other Knee	62/283 (22%)	
Felson 2001	KOA	401	Pain	272/351 (78%)	P<0.001
			No pain	15/50 (30%)	

"Delta" studies

These cover a follow-up period – in general 1-2 years, and focus on the possible link between the change in BML scores between baseline and follow-up, and the change in pain scores over the same period.

Felson 2007 presents data from the MOST study (a prospective epidemiological study), with a subset of 330 subjects. All had no pain at baseline – the case group of 110 patients had knee pain at 15-month follow up, and the control group (N-220) remained pain-free. Table 10 shows the results – the onset of pain went along with an increase in BML score, especially for large BMLs.

Table 10 from Felson 2007 – pain and BML at 15 months follow up

	Control knees, no. (%)	Case knees, no. (%)†
No increase in BML score	161 (73.2)	55 (50.5)
Increase of 1 in BML score	40 (18.2)	24 (22.0)
Increase of ≥2 in BML score	19 (8.6)	30 (27.5)

The contingency table is statistically significant (P<0.001)

Zhang 2011 has a MOST update. For 570 patients with two clinic vists:

Among the knees whose "frequent pain status changed from present to absent, percentage of improvement of BMLs (38.0%) was higher than that of worsening (25.5%)".

Dore 2010 has data from a general population sample (N=395, average age 63 years) 43% of who had BMLs at baseline, and 59% of whom had a radiographic KOA diagnosis. 2.7 year (average) follow-up data were obtained. The association of BML increase and pain score change was only significant for the group who did **not** have a KOA diagnosis at baseline.

Fig 12 shows a scatter plot from **Driban 2013** relating change in BML score and change in pain score over a 2-year period for a sample of 404 people, all with KOA diagnoses. The association is statistically significant (p=0.004), but the scatter is clearly very high.

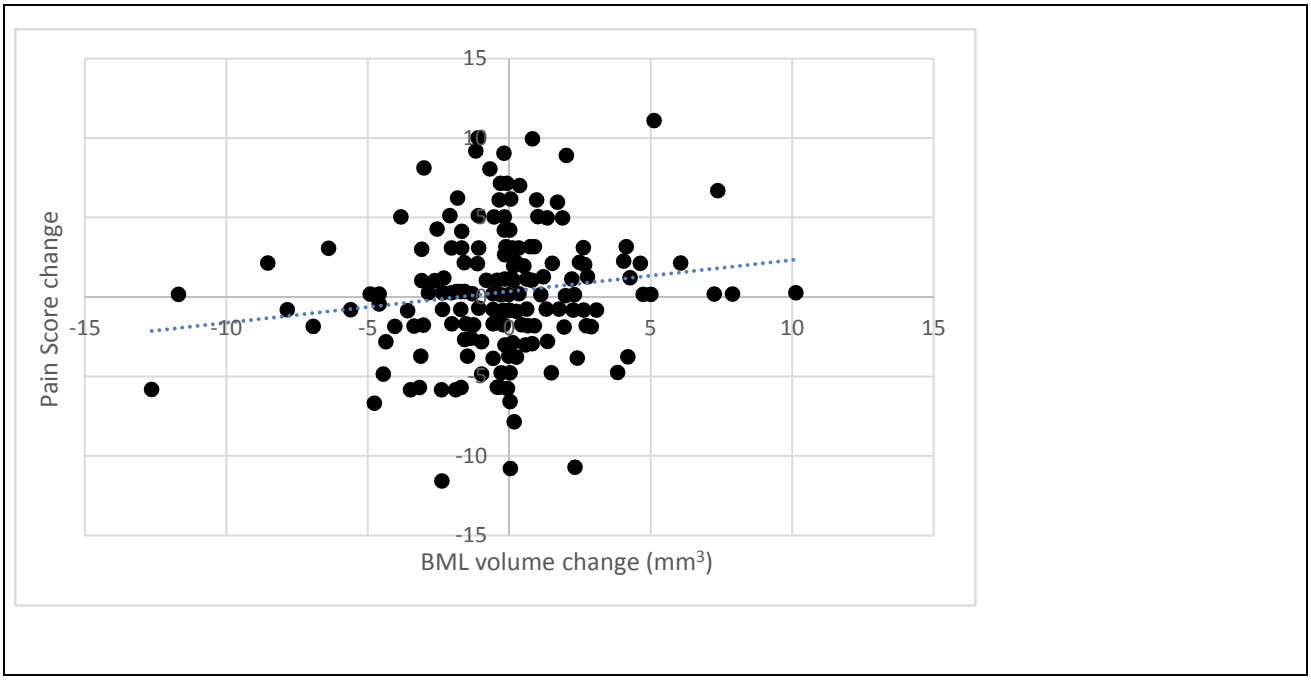


Figure 12 Data from Driban 2013, showing scatter plot ofrelation between BML and pain score changes over a 2-year follow-up period.

5.3. Clinical data for subchondral bone injection

Clinical data for subchondral bone injection procedures is sparse.

Abrams 2013 presents a case study of a patient suffering from osteochondritis dissecans, a childhood disease involving cartilage/bone separation in the knee joint. A BML detected by MRI was filled with CaP bone cement, leading to pain relief.

Cohen 2012 and Sharkey 2012 review the alternative treatments for KOA and presents a justification for subchondroplasty, and present a case report of a 51-year old patient with severe KOA. A BML under the

tibial plateau was successfully injected with bone cement, using the Knee Creations reference frame. At 31-month follow up the patient report an active lifestyle and minimal knee pain.

Farr 2013 provides preliminary results on a case series of 59 patients, average age 56 years. All had suffered knee pain, and undergone pre-operative MRI scans revealing BMLs (37% tibial, 25% femoral, and 37% both). No adverse reaction to the bone cement occurred.

At (average) 15-month follow up, 25% of patients had continuing pain and 15 proceeded to joint repair surgery. For the remaining patients pain and knee function scores were significantly reduced (Fig. 13)

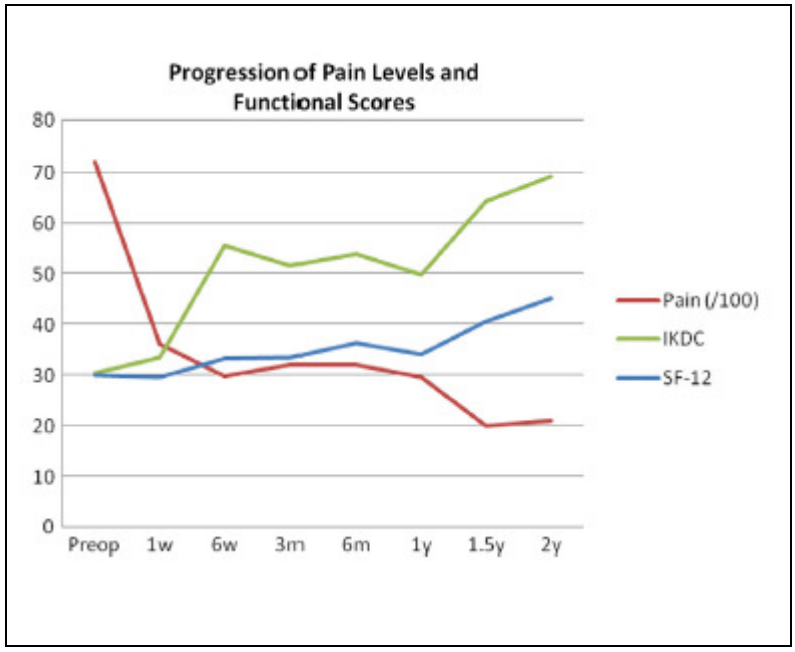


Figure 13 From Farr2013 – data from 59 patients. IKDC: International Knee Documentation Committee, SF-12: Short Form 12 subjective scale.

6. ESTIMATING LIKELY COMPLICATION AND ADVERSE EVENT RATES

Goff 2013 reviews case series studies using CaP cements to treat depressed tibial plateau fractures. CaP cement had the lowest risk of secondary collapse (3.7%, using Norian SRS) as compared to allograft (8.6%), Hydroxy-apatite cement (5.4%) and calcium sulphate cement (11.1%).

Infection rates in the studies reviewed average 3.6%.

Cohen 2012 states that there have been no significant medical complications in the cases reported by Farr above, but note

"Extravasation of the bone substitute into the joint of soft tissue is a potential complication that can be removed during the procedure. There have been no reactions noted from the bone substitute, however, bone substitute which has hardened in the soft tissue can be tender and noted by palpation. This has occurred in a few patients. Patients have reported significant pain postoperatively for up to 72 hours after treatment, more than the typical knee arthroscopy. The formation of a new BML in previously uninvolved compartment has been noted."

No incidence rates are quoted for these complications.

7. CONCLUSION

There is evidence that it is feasible to repair bone marrow lesions by injecting them with CaP cement. Complications and risks associated with this procedure are comparable with the state of the art for other bone repair procedures using injectable cements.

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Zhang Y (2011)	Zhang Y, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, Roemer F, McCulloch C, Felson DT.	Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging.	Arthritis Rheum. 2011 Mar;63(3):691-9. doi: 10.1002/art.30148.

9. GRAFTYS LITERATURE REVIEW METHODOLOGY AND SEARCH PROTOCOL

1. Introduction

Literature searches were conducted by Ruth Long, and reviewed by Stephen Young. CVs of Dr Young and Mrs Long can be found in section 10.

2. Methodology of literature search

An injectable bone cement filler for arthritic knees: search strategy

This search was carried out by Ruth Long, a qualified librarian (MA in librarianship, University of Sheffield, 1998) on 8th May 2014

Scope of search:

-The use of bone void filler in subchondroplasty procedures
- The advantages and disadvantages of subchondroplasty in comparison with other treatments for osteo-arthritis of the knee

The search used the Medline database. Medline covers the whole field of medicine including dentistry, veterinary medicine and medical psychology, clinical medicine, anatomy, pharmacology, toxicology, genetics, microbiology, pathology, environmental health,

occupational medicine, psychology, biomedical technology, health planning and administration, space life science, and many other related subject areas. This database contains over 18 million references to journal articles in life sciences with a concentration on biomedicine.

An additional database, Embase, was not consulted as it is primarily a pharmacological database and its biomedical technology records would duplicate those found in Medline.

Initial search conducted using Medline (via PubMed)

Search	Search Term	Results (number)
1	subchondroplasty [Title/Abstract]	1
2	subchondral [Title/Abstract]	4768
3	bone* [Title/Abstract]	518122
4	filler [Title/Abstract]	4356
5	cement [Title/Abstract]	21436
6	substitute [Title/Abstract]	29828
7	#4 OR #5 OR #6	54948
8	#3 AND #7	10633
9	“bone cements” [MeSH Terms]	8714
10	#8 OR #9	15384
11	calcium [Title/Abstract]	293392
12	tricalcium OR tri-calcium [Title/Abstract]	5049
13	#11 OR #12	296018
14	phosphate* [Title/Abstract]	202894
15	#13 AND #14	29101
16	#1 OR #2	4768
17	#10 OR #15	42585
18	#16 AND #17	155
19	knee [Title/Abstract]	88859
20	#18 AND #19	40
21	marrow [Title/Abstract]	179118
22	lesion* [Title/Abstract]	634482
23	#3 AND #21 AND #22	8283
24	odema OR oedema OR edema	130735

	[Title/abstract]	
25	#3 AND #21 AND #24	1924
26	#23 OR #25	9778
27	#19 AND #26	517
28	osteoarthritis OR osteo-arthritis	55973
29	osteochondral OR osteo-chondral	3961
30	#28 OR #29	59326
31	#27 AND #30	283
32	#20 OR #31	323
33	Limit: abstract available	320
34	Limit: publication in last 10 years	276

These initial results were then hand-searched to eliminate:

- Articles concerning subchondral defects not in the knee
- Review articles
- Editorials and other un-reviewed articles.

75 relevant articles were found.

10. AUTHORS' CVS.

Ruth Long

Address: 13 Barn Street, Crewkerne, Somerset, TA18 8BP
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Email: ruthdavid@btinternet.com

Employment history:

Timetabler King Edward VI Community College May 2007-Date

King Edward VI Community College ('KEVICC') is a large secondary school in South Devon (1900 students and 130 teaching staff based on 4 sites).

- Write and maintain the College timetable
- Research curriculum trends and individual student needs
- Liaise with Vice-Principal and fifteen department heads
- Plan future staffing and rooming needs in an economic manner
- Construct a timetable that produces a balanced use of time for both students and staff
- Modify the timetable during the year as circumstances dictate

Data Co-ordinator King Edward VI Community College 2001-October 2008

- Developed database to track student progress so that under-achievement could be identified and intervention put in place

- Collected assessment data from teaching staff
- Produced termly student progress reports for parents/carers
- Summarised progress of groups of students for teaching staff
- Advised teaching staff on the interpretation of data
- Summarised public examination results
- Produced accurate and timely information for external bodies *eg* termly school census for local authority, numbers studying 6th-form courses for funding agency
- Trained and supported other administrative staff in the use of 'Sims' (school MIS system) so that they could work more efficiently

Senior Assistant Librarian Newton Abbot Library 1998-2000

Newton Abbot Library is a busy full-time public library.

- Assisting all members of the community to access information
- Using reference works (both print and electronic) to research information
- Training members of the public to use ICT resources
- Organising events and visiting schools to promote reading to children
- Training and supervising five library assistants

Qualifications:

MA Librarianship (Information Management), University of Sheffield (included a module on medical information)
BA(Hons) History, University of York (2:1)
Open University 'Using Mathematics' Course (1st year undergraduate level)

ICT Skills:

Excel, Word (fast touch-typist), E-Mail, Internet, school and library database systems

Other interests:

Member of Taunton Wednesday Orchestra
Guide Leader (girls 10-15)

Referees:

Mrs R Hutchinson
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Ashburton Road
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Stephen Young

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Education:
RGS Newcastle and Corpus Christi College Cambridge
A levels – Chemistry Physics Maths (A,A,B respectively)
BA (2.1, Psychology) PhD (Invertebrate Electro-physiology) Cambridge University
Chartered Scientist
Corporate member, Institute of Physics and Engineering in Medicine
Honorary Lecturer, Imperial College, London
Statistical advisor, NRI, Greenwich University

Career:

Head of Department, Clinical Engineering 2003-2008, Royal Brompton and Harefield NHS Trust, which specialises in cardiology and cardiac surgery. Accountable for Clinical Engineering across the trust. Assist users to choose appropriate equipment - manage tendering process. Planning and implementing actions following adverse incidents with medical devices.

Clinical Scientist 1999 -2003 in Clinical Engineering Department, Hammersmith Hospitals NHS Trust. Team leader, near-patient team.

Responsible for training delivery and all user-related medical device management, for implementing Medical Devices Regulations and Dept of Health Controls Assurance standards. Manage technical support provision for ICU's and neonatal unit.

Research collaborator, Chelsea and Westminster Hospital Simulation centre, using Eagle Simulator “plastic patient” to train anaesthetists, and assess their performance in a crisis situation without risk to patients.

Founder member - London teaching Hospitals benchmarking group - have been active in devising performance indexes for medical equipment management.

Technical writer, Medical Devices Agency, Department of Health. 1996-1999 Responsible for background research and drafting Department of Health policy in areas relating to medical device management.

My major project was to research, draft, and manage the production process for "Medical device and equipment management for hospital and community-based organisations."

Other projects included:

- Analyzing data gathered in the evaluation of medical devices, including patient hoists and pressure relief cushions.
- Using the adverse incident database to identify areas in which guidance might be necessary (including electrosurgery and phototherapy) and liaising with clinicians to plan actions needed.
- Developing a dose/response model for the impact of interference from mobile phones and 2-way radios on medical devices.
- Giving presentations to clinical and engineering audiences.
- Devising protocols and analysing data from a study on the potential impact of mobile phones and 2-way radios on implanted pacemakers
- Training users to do calibration checks for aneroid sphygomanometers, launching a routine user management system.

Lecturer in Biology, Imperial College (IC). 1969-1996 This post involved teaching and research over a wide range of topics, including statistics and animal behaviour. I convened courses, and acted as deputy departmental finance director.

While at IC, I developed electronic systems for measuring light and humidity, and for analysis of video signals in three dimensions. I have experience with computer-controlled environmental simulation, and with developing data-logging and analysis software. I have written many scientific papers – publication list attached.

Work at IC directly relevant to clinical science:

- Providing training for medical students at St Mary's in biometry, including data generation, design of experiments, and statistical analysis of data.
- In collaboration with Dr A.C. Easty, Head of Medical Engineering at Toronto Hospital, devising a calibration checking system for medical lasers. This involved two periods of development work and practical testing at Toronto Hospital, and was funded by a Royal Society exchange grant.

APPENDIX 1 : PAPERS NOT INCLUDED, WITH REASONS

Authors	Title	Reference	Reason
Baroud G, Martin PL, Cabana F.	Ex vivo experiments of a new injection cannula for vertebroplasty.	Spine (Phila Pa 1976). 2006 Jan 1;31(1):115-9.	Cannula design for PMMA cement
Baroud G, Steffen T.	A new cannula to ease cement injection during vertebroplasty.	Eur Spine J. 2005 Jun;14(5):474-9. Epub 2005 Jan 26.	Cannula design for PMMA cement
Field RE, Singh PJ, Latif AM, Cronin MD, Matthews DJ.	Five-year prospective clinical and radiological results of a new cannulated cemented polished Tri-Taper femoral stem.	J Bone Joint Surg Br. 2006 Mar;88(3):315-20.	implant
Hunt CH, Kallmes DF, Thielen KR.	A unilateral vertebroplasty approach using a curved injection cannula for directed, site-specific vertebral body filling.	J Vasc Interv Radiol. 2009 Apr;20(4):553-5. doi: 10.1016/j.jvir.2009.01.008. Epub 2009 Feb 26.	Cannula design for PMMA cement
Masala S, Nano G, Mammucari M, Simonetti G.	Kummel disease treatment by unipedicular vertebral augmentation using curved injection cannula.	Cardiovasc Intervent Radiol. 2011 Oct;34(5):1014-20. doi: 10.1007/s00270-010-9985-9. Epub 2010 Sep 22.	Cannula design for PMMA cement
Widmer RP, Ferguson SJ.	A mixed boundary representation to simulate the displacement of a biofluid by a biomaterial in porous media.	J Biomech Eng. 2011 May;133(5):051007. doi: 10.1115/1.4003735.	computer simulation
Cannon CP, Mirza AN, Lin PP, Lewis VO, Yasko AW.	Proximal femoral endoprosthesis for the treatment of metastatic.	Orthopedics. 2008 Apr;31(4):361.	imppnat design
Dhupar S, Iorio R, Healy WL, Dhimitri K.	A comparison of discharge and two-week duplex ultrasound screening protocols for deep venous thrombosis detection following primary total joint arthroplasty.	J Bone Joint Surg Am. 2006 Nov;88(11):2380-5.	Not cement related
Gao H, Liu Z, Xing D, Gong M.	Which is the best alternative for displaced femoral neck fractures in the elderly?: A meta-analysis.	Clin Orthop Relat Res. 2012 Jun;470(6):1782-91. doi: 10.1007/s11999-012-2250-6. Epub 2012 Jan 26.	Not cement related
Hossain M, Andrew JG.	Is there a difference in perioperative mortality between cemented and uncemented implants in hip fracture surgery?	Injury. 2012 Dec;43(12):2161-4. doi: 10.1016/j.injury.2012.08.043. Epub 2012 Sep 20.	not relevant to decompression
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