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XVI CONGRESSO NAZIONALE

Siena 9 - 10 ottobre

UP - TO - DATE NELL'OSTEOPOROSI E NELLE MALATTIE DELL'APPARATO MUSCOLO SCHELETRICO

PRESIDENTE GISMO
Ranuccio Nuti

PRESIDENTI CONGRESSO
Bruno Frediani - Stefano Gonnelli

GISMO

GISMO odv

II Sessione Malattie dell'apparato Muscolo Scheletrico Moderatori:
C.Cisari, L.Pietrogrande

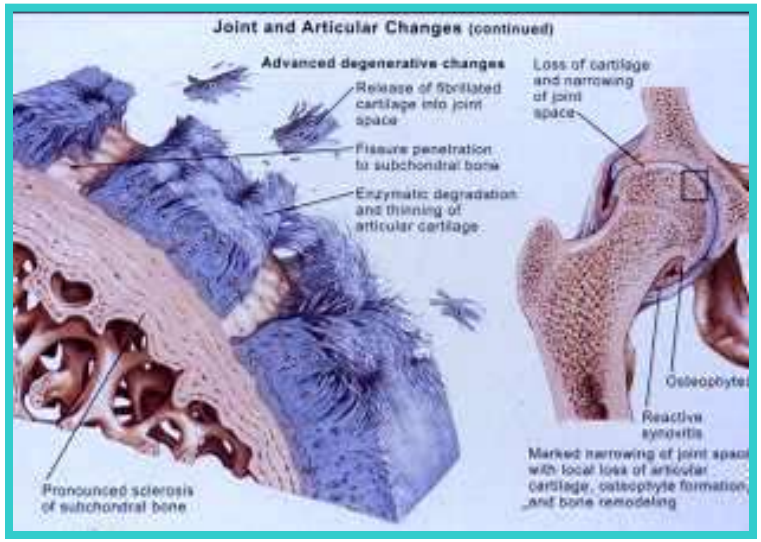
16.30 Sarcopenia: criteri diagnostici e implicazioni scheletriche
P. D'Amelio
16.50 La salute dell'osso periprotesico.
L.Molfetta

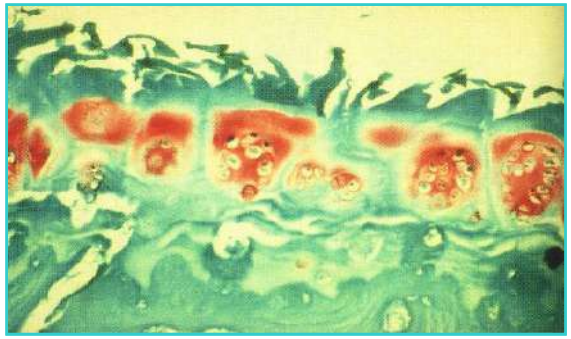
17.10 L'osso subcondrale come target terapeutico nell'artrosi
N. Malavolta

Osteoartrosi

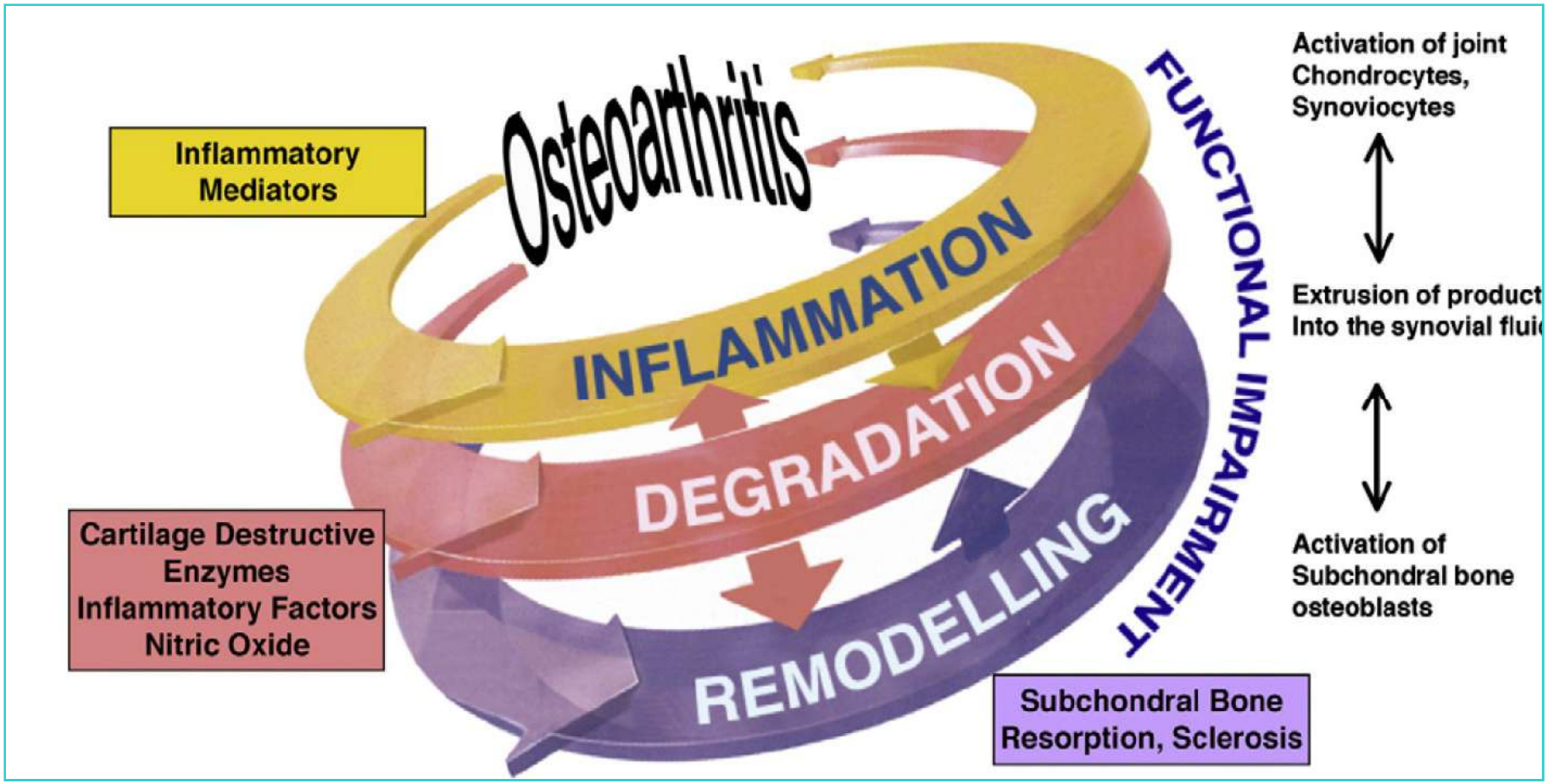
In passato considerata un disordine primario della cartilagine articolare, oggi rappresenta "*the failure of the joint*" dove tutte le strutture articolari sono coinvolte, inclusa la cartilagine calcificata, l'osso subcondrale corticale e trabecolare, la sinovia e i tessuti della capsula articolare

Goldring MB, Ann NY Acad Sci 2010; 1192: 230-237



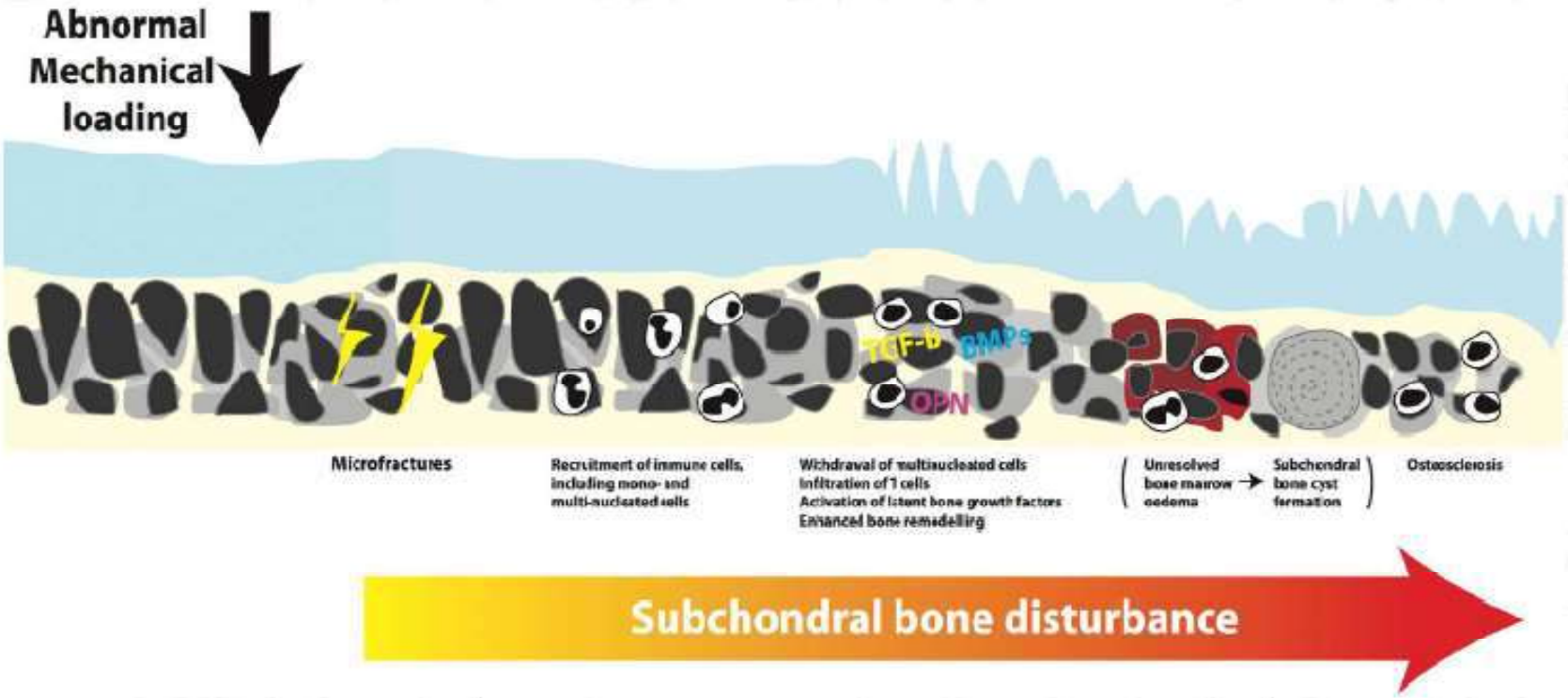


Fissurazioni della cartilagine articolare



Martel-Pelletier J. Osteoarthritis and Cartilage 2010; 18: S7-S11

Proposed contribution of immune cells to subchondral bone disturbance in PT-OA



Weber A. et al., Prog Biophys Mol Biol. 2017

In the situation of abnormal mechanical loading, subchondral bone may develop bone marrow oedema, also known as “bone bruising” or “bone marrow lesion”(BML) Link et al 2003

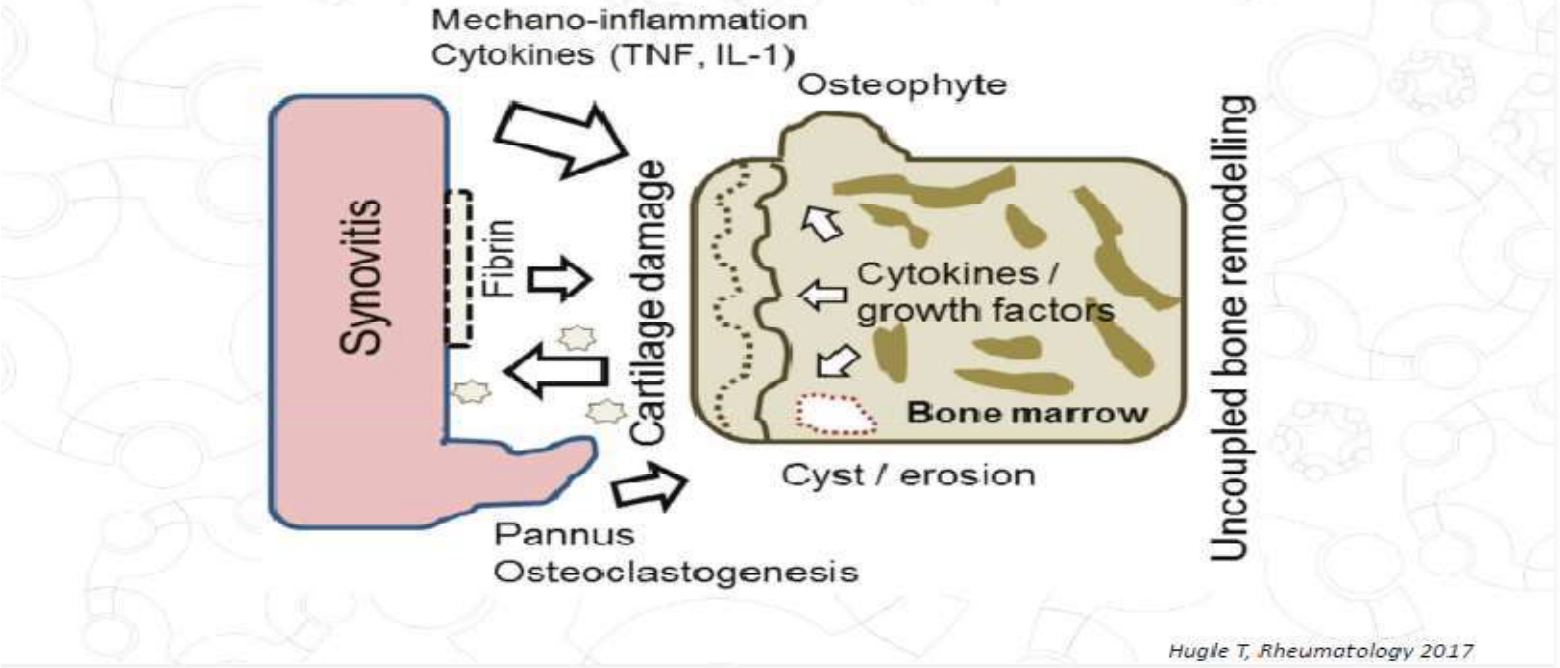
And BML ……

- Is an early MRI diagnostic feature of OA closely correlated with severity of pain….. (Carotti et al., 2017)

- Is useful in predicting the rate of cartilage loss in knee OA patients….. (Tanamas et al., 2010b; Felson et al., 2007;Hunter et al., 2006)

- Histomorphologically, the presence of BML is associated with perfusion abnormalities, e.g. increased vascular permeability and ischemia….. (Lee et al., 2009; Aaron et al., 2007), Formation of fibro-vascular tissue and under-mineralised sclerotic bone…. (Hunter et al., 2009; Shabestari et al., 2016)

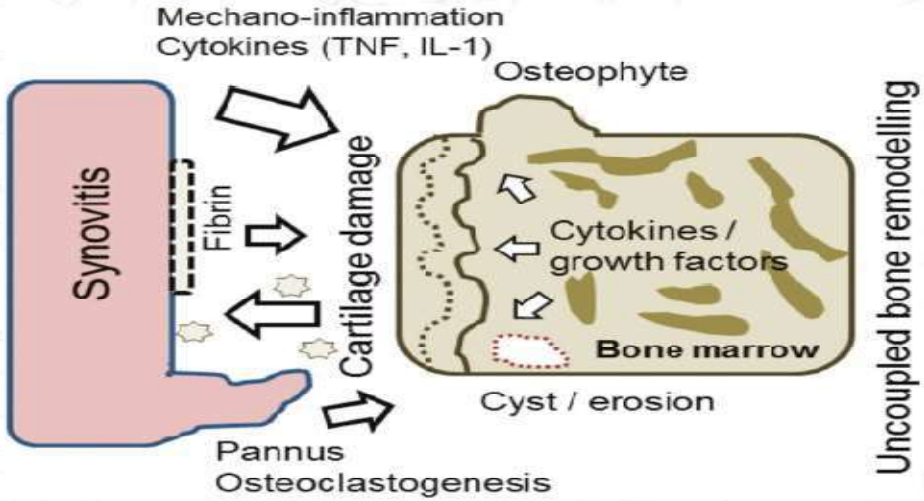
Schematic illustration of the interaction between synovial tissue, cartilage and subchondral bone in OA



It has been unequivocally demonstrated that both synovitis and BMLs occur and coexist before the development of radiographic OA (Roemer FW, et al. Arthritis Rheumatol 2015)

BMLs typically develop subjacent to areas of cartilage loss (Kothari A, et al . Arthritis Care Res , 2010)

Schematic illustration of the interaction between synovial tissue, cartilage and subchondral bone in OA

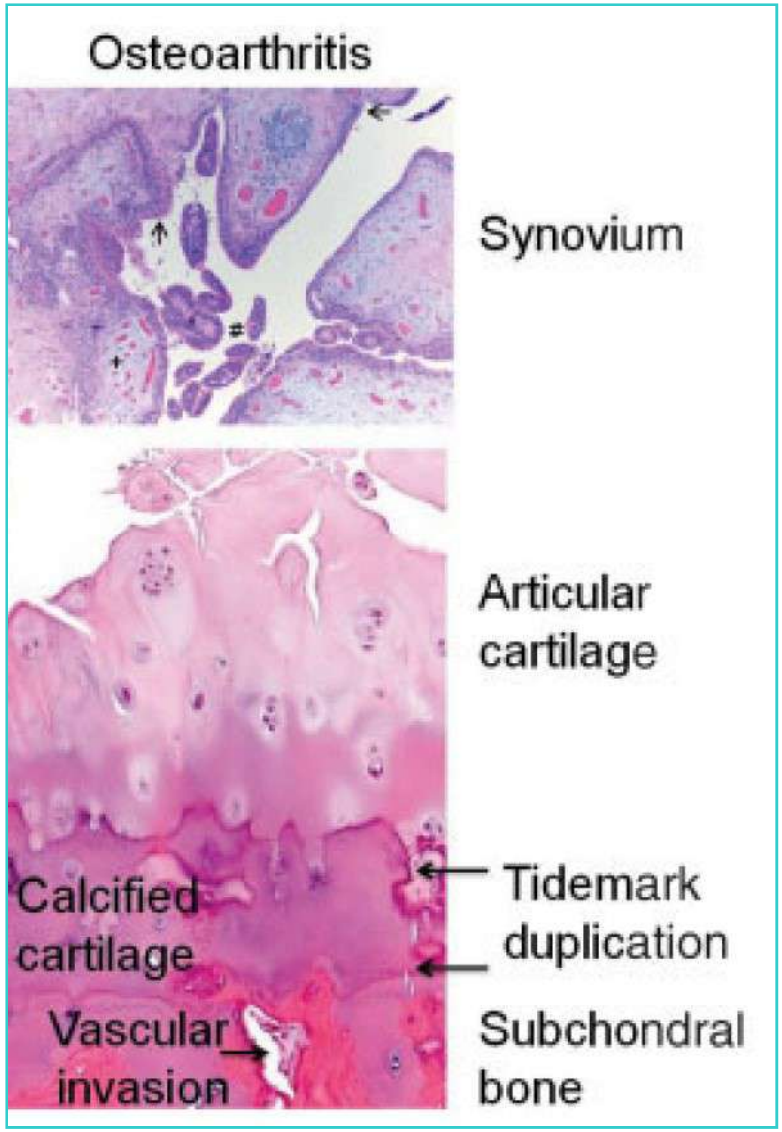


Hugle T, Rheumatology 2017

Rheumatology key messages

- Both synovitis and subchondral bone remodelling are actively involved in OA and often precede cartilage damage.
- In OA, synovitis triggers osteoclastogenesis, pannus formation and increases adherence of synovial tissue to cartilage.
- Chronic mechanical impairment in combination with metabolic dysregulation is a common trigger of subchondral bone changes and osteophytosis.

Periarticular bone changes in OA



The advancement and duplication of the **tidemark**, a line of demarcation between the hyaline articular cartilage and calcified cartilage, is associated with vascular invasion of the calcified cartilage from the subchondral bone and contribute to overall thinning of the articular cartilage

Trabecular bone thickening leads to bone sclerosis, which in turn causes decreased shock absorbency and cartilage damage

High bone turnover increases the release of various cytokine from subchondral bone, which can lead to cartilage degeneration

Goldring MB, Ann NY Acad Sci 2010; 1192: 230-237

Chiba K, Osteoarthritis and Cartilage 2011; 19: 180-185

Best Pract Res Clin Rheumatol. 2010 February ; 24(1): 51–70. doi:10.1016/j.berh.2009.08.004.

Targeting subchondral bone for treating osteoarthritis: what is the evidence?

Steeve Kwan Tat, PhD, Daniel Lajeunesse, PhD, Jean-Pierre Pelletier, MD, and **Johanne Martel-Pelletier, PhD***
Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, 1560 Sherbrooke Street East, Montreal, Quebec H2L 4M1, Canada

Practice Points

1 Subchondral bone remodelling in OA

Alterations in subchondral bone activity occur early in the OA process

Early subchondral bone activity is resorptive

Although subchondral bone sclerosis is considered a hallmark of OA, it appears to occur at a later stage of the disease

Subchondral bone sclerosis is due to an increase in material density, and not mineral density

2 Cross-talk between subchondral bone and cartilage

There is strong evidence of a diffusion of molecules/factors from the subchondral bone to the articular cartilage

This diffusion possibly occurs through the clefts and channels in the tidemark seen early in OA as well as through microcracks in the articular cartilage

3 Markers of OA

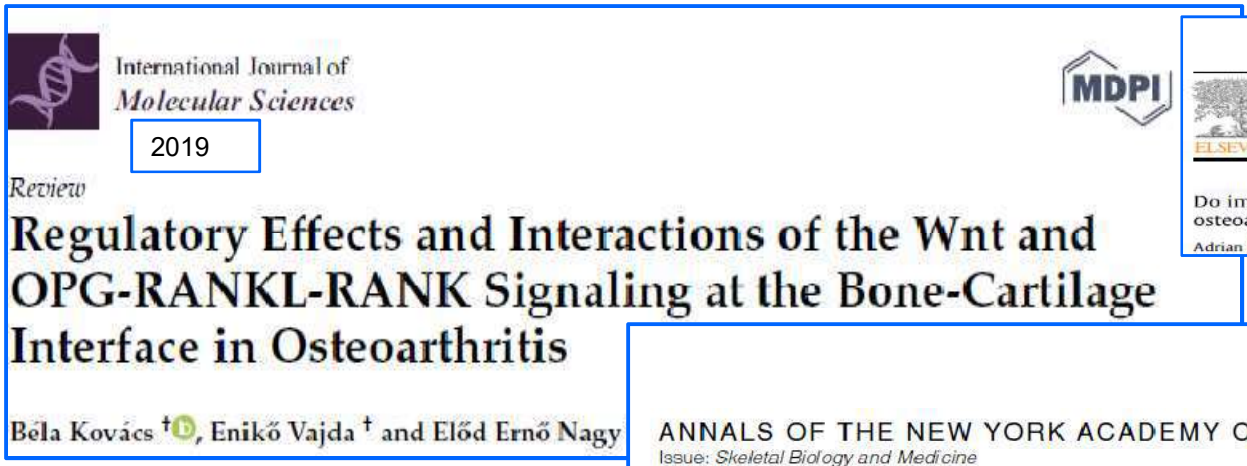
Individual biomarkers are not very informative on their own of the disease process or of early disease

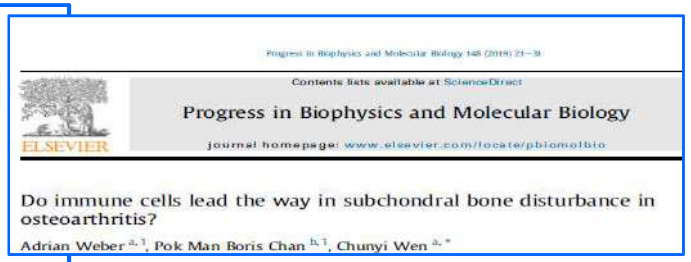
Clusters of markers are suggested to better correlate with disease progression and also could identify early disease

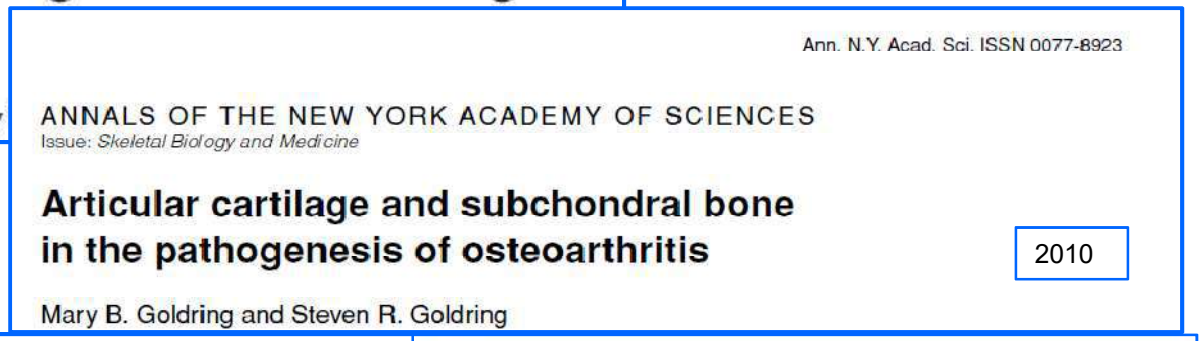
Imaging technology, such as MRI, is useful for assessing not only disease progression but also early events (BMLs)

Subchondral bone changes in OA are not only the result of cartilage attrition, but also the cause of cartilage attrition

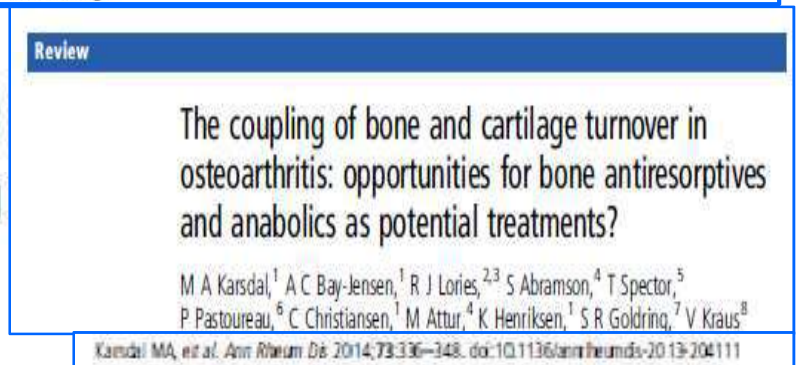
Chiba K, Osteoarthritis and Cartilage 2011; 19: 180-185


International Journal of
Molecular Sciences
2019
MDPI
Review
Regulatory Effects and Interactions of the Wnt and OPG-RANKL-RANK Signaling at the Bone-Cartilage Interface in Osteoarthritis
Béla Kovács, Enikő Vajda and Előd Ernő Nagy


Progress in Biophysics and Molecular Biology
ELSEVIER
Do immune cells lead the way in subchondral bone disturbance in osteoarthritis?
Adrian Weber, Pok Man Boris Chan, Chunyi Wen


Ann. N.Y. Acad. Sci. ISSN 0077-8923
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Skeletal Biology and Medicine
Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis
2010
Mary B. Goldring and Steven R. Goldring


Li et al. Arthritis Research & Therapy 2013, 15:223
http://arthritis-research.com/content/15/6/223
arthritis research&therapy
REVIEW
Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes
Guangyi Li, Jimin Yin, Junjie Gao, Tak S Cheng, Nathan J Pavlos, Changqing Zhang and Ming H Zheng


Review
The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments?
M A Karsdal, A C Bay-Jensen, R J Lories, S Abramson, T Spector, P Pastoureau, C Christiansen, M Attur, K Henriksen, S R Goldring, V Kraus
Karsdal MA, et al. Ann Rheum Dis 2014;73:336–348. doi:10.1136/annrheumdis-2013-204111


RHEUMATOLOGY
Original article
Intravenous neridronate in the treatment of acute painful knee osteoarthritis: a randomized controlled study
Massimo Varenna, Francesca Zucchi, Simonetta Failoni, Andrea Becciolini and Massimo Berruto


PLOS ONE
2017
RESEARCH ARTICLE
Subchondral bone histology and grading in osteoarthritis
Olli-Matti Aho, Mikko Finnilä, Jerome Thevenot, Simo Saarakkala, Petri Lehenkari

Subchondral Bone Remodelling

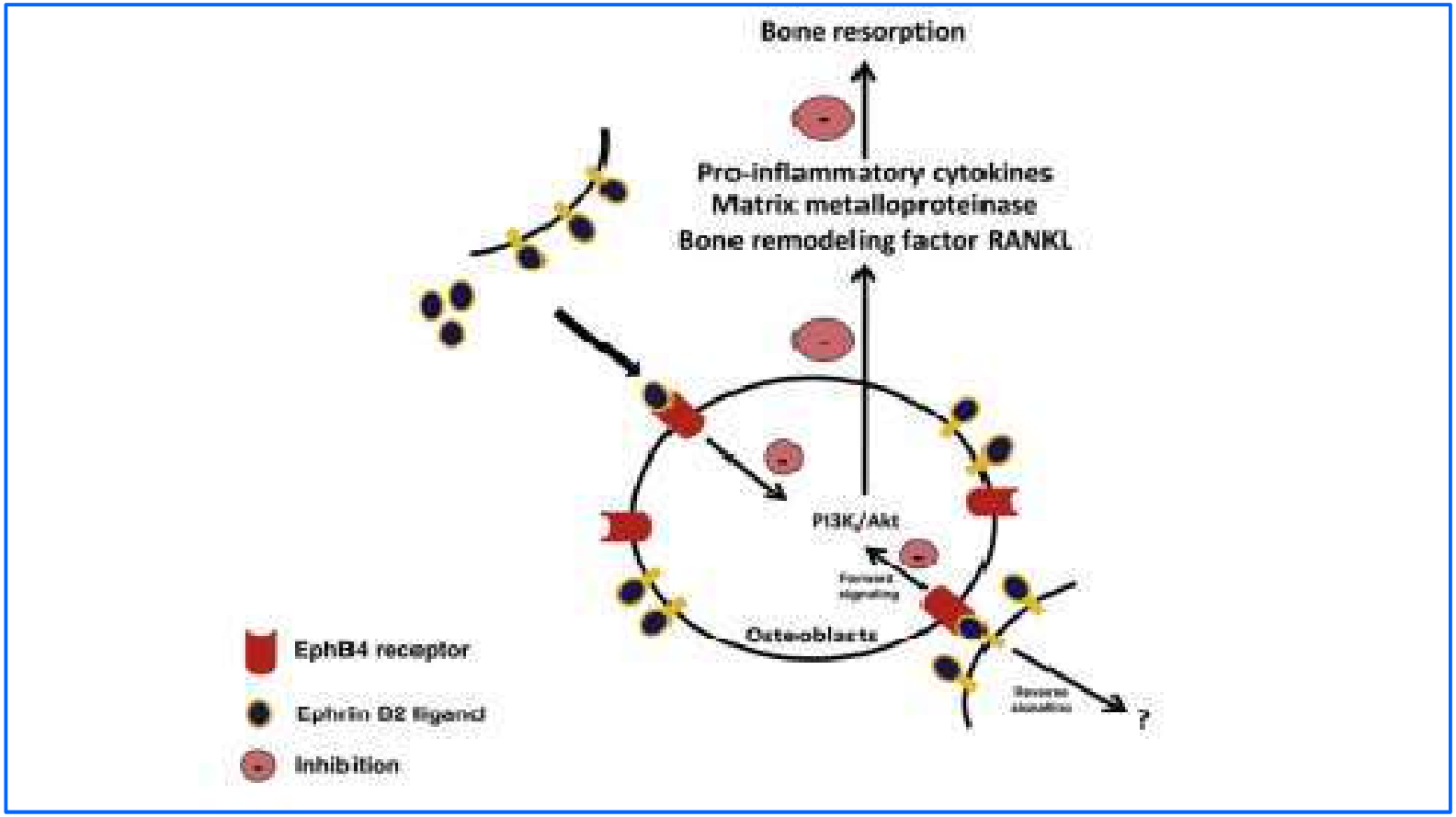
Early phase of OA: subchondral bone resorption

Sebbene la sclerosi ossea sia considerata un segno distintivo (Hallmark) dell'OA, gli indici di riassorbimento osseo subcondrale sono stati trovati in pazienti con OA del ginocchio progressiva

Tat SK et al, Best Pract Res Clin Rheumatol 51-70, 2010

Le caratteristiche precoci di riassorbimento osseo osservate nei pazienti con OA sono state valutate in un sottogruppo di pazienti con OA del ginocchio misurando i marcatori del riassorbimento osseo NTX e CTX in tre diversi momenti: i pazienti con OA progressiva del ginocchio hanno mostrato un maggior riassorbimento osseo rispetto a quelli con artrosi non progressiva

Bettica P et al, Arthritis Rheumatol 178-84, 2002



Interaction between the EphB4 receptor and ephrin B2 ligand leads to both a forward and a reverse signaling. The signal through the EphB4 receptor is considered a forward signal whereas the reverse signaling is through the ephrin B2 ligand. In OA subchondral bone osteoblasts, the activation of EphB4 receptor by ephrin B2 results in a decreased activation of PI3K/Akt which, in turn, inhibits some pro-inflammatory cytokines and matrix metalloproteinases as well as RANKL, all of which are involved in the remodeling process of the OA subchondral bone [81].

Best Pract Res Clin Rheumatol. 2010 February ; 24(1): 51–70. doi:10.1016/j.berh.2009.08.004.

Targeting subchondral bone for treating osteoarthritis: what is the evidence?

Steeve Kwan Tat, PhD, Daniel Lajeunesse, PhD, Jean-Pierre Pelletier, MD, and **Johanne Martel-Pelletier, PhD***
Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, 1560 Sherbrooke Street East, Montreal, Quebec H2L 4M1, Canada

Research agenda

Therapeutic agents targeting bone remodelling

The promise of agents targeting bone remodelling in the treatment of OA has created an urgent need for clinical trials in humans

With the recognition of early changes in subchondral bone during the OA process, patients with less advanced disease could be enrolled in standardised clinical trials instead of those at later stages

L’osso subcondrale come bersaglio terapeutico nell’OA

Sebbene il ruolo preciso nell’OA rimanga indefinito, le modifiche dell’osso subcondrale avvengono in modo parallelo alla progressione dell’OA

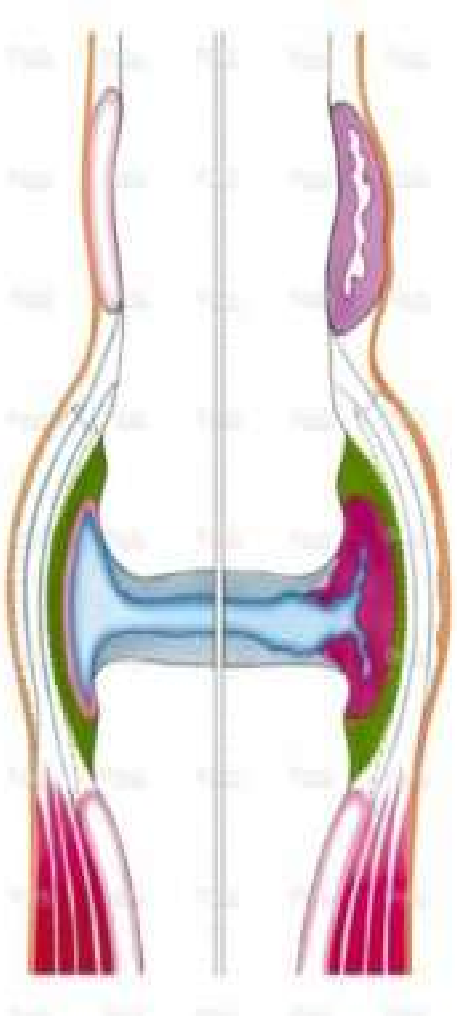
Il compartimento subcondrale potrebbe rappresentare pertanto un target per rallentare o prevenire la progressione della malattia

In alcuni modelli animali è stato osservato che i ***bifosfonati*** (farmaci in grado di inibire il riassorbimento osseo) sono in grado di inibire il riassorbimento dell’osso subcondrale e lo sviluppo dell’OA

Altri studi hanno dimostrato che la ***calcitonina*** (ormone in grado di inibire l’attività degli osteoclasti) e l’***osteoprotegerina*** (fattore di inibizione dell’osteoclastogenesi) riducono l’agressività della malattia

Questi effetti non sono stati tuttavia confermati negli studi clinici condotti in pazienti con OA e rimangono controversi

Ulteriori studi saranno quindi necessari per stabilire se l’osso subcondrale possa rappresentare un potenziale bersaglio nel trattamento dell’OA



- I cambiamenti e il rimodellamento dell'osso sono la conseguenza dell'alterata espressione di geni che regolano l'attività delle cellule dell'osso, ovvero gli osteoclasti, gli osteoblasti e gli osteociti

- Data l'evidenza di una importante comunicazione tra la cartilagine articolare e l'osso sottostante, l'alterazione dei processi che avvengono a livello dell'osso subcondrale può riflettersi nel tessuto cartilagineo e quindi giustificare la scelta dell'osso subcondrale nel trattamento dell'OA

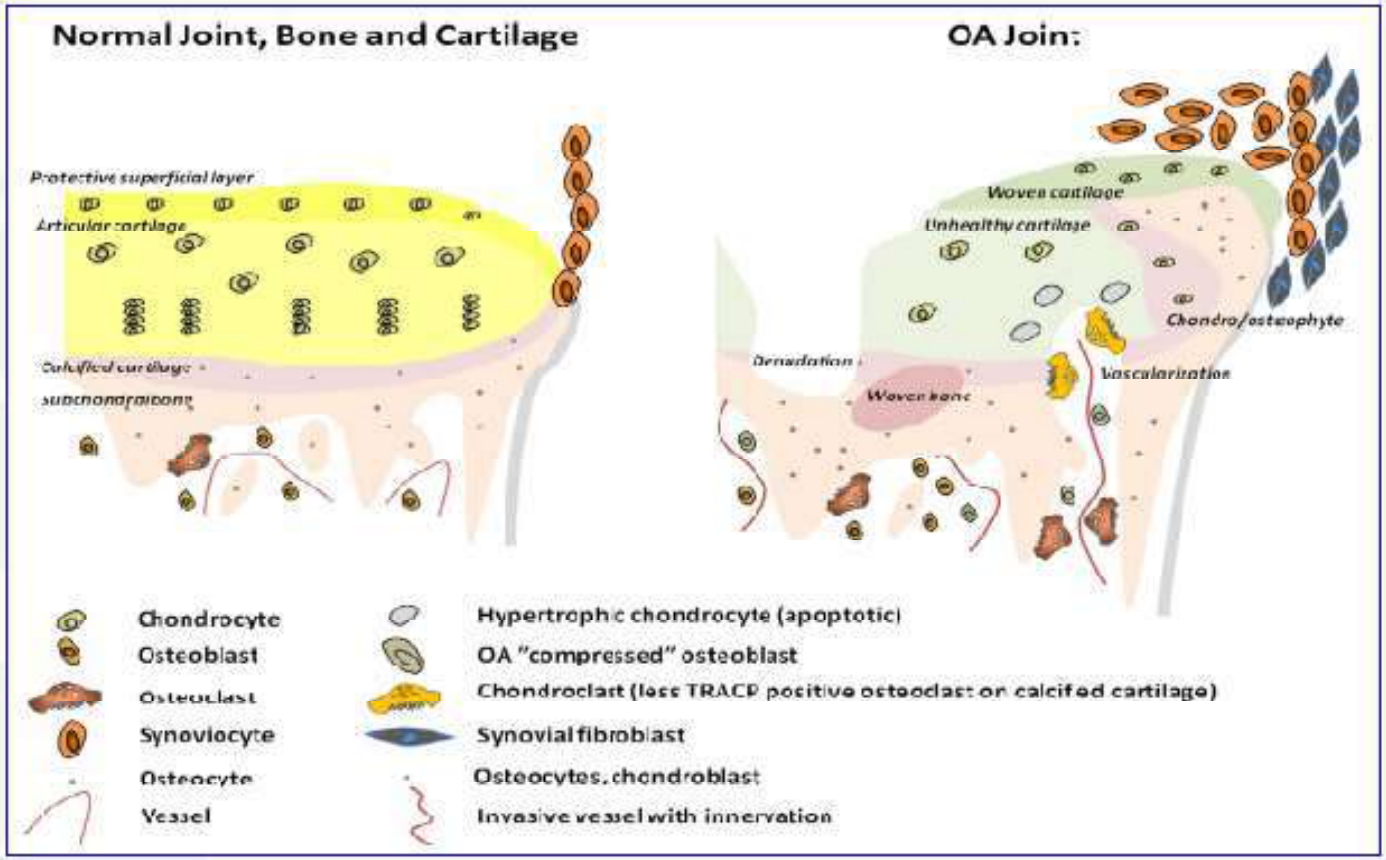
Gli interventi che riducono il turnover osseo possono avere effetti positivi sulla progressione di OA?

DMOADs: BISPHOSPHONATES

Review

The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments?

Karsdal MA, *et al. Ann Rheum Dis* 2014;**73**:336–348.



Perche' trattare l'osso subcondrale?

Bone Remodeling

Calcitonina

In studi preclinici e' stato documentato in grado di indurre inibizione dell'attivita' delle MMP e la degradazione cartilaginea sia in vitro che in vivo
Potrebbe avere anche un effetto sull'inibitore dei recettori toll-like che rilascia citochine e mediatori infiammatori

Karsdal MA et al, Ann NY Acad Sci 2007 1117:181

Studi pilota con Calcitonina di salmone comparata con due dosi di calcitonina di salmone con il carrier un 5-CNAC contro placebo non ha dimostrato significative differenze sullo score del dolore
Tuttavia, un notevole miglioramento e' stato osservato nel punteggio della funzione tra i pazienti che ricevevano calcitonina

Manicourt DH, et al, Arthritis Rheum 2006; 54:3205

Tuttavia i risultati di due studi clinici di fase III sulla calcitonina orale di salmone non sono riusciti a fornire alcun beneficio clinico riproducibile nei pazienti con OA sintomatica del ginocchio

Karsdal MA et al, Osteoartthritis Cartilage 2015; 23:532

Bisphosphonates

The have the potential to retard subchondral bone remodeling.
Patients with progressive OA have been found to have higher urinary levels of C-terminal telopeptide of type II collagen (CTX-II), a marker of cartilage degradation

Bingham CO 3rd, et al Arthritis Rheum 2006; 54:3494

Bisphosphonates can also exert a slight immunomodulating effect via the inhibition of proinflammatory cytokines, with etidronate in vitro, showing some inhibitory effect on MMPs when they bind to human cartilage


Editorial

Bisphosphonates for osteoarthritis prevention: "Holy Grail" or not?

Kenneth G Saag

Saag KG Ann Rheum Dis 2008 67: 1358

The use of bisphosphonate in OA has yield mixed results

In the Knee OA Structural Arthritis (KOSTAR) study, 2483 patients with medial compartment Knee OA, from North America and the European Union, were given risedronate or placebo and followed for two years

The risedronate –treated groups did not show significant improvements in signs and symptoms of OA compared with placebo, and there was no significant reduction in radiographic progression

Bingham CO 3rd, et al Arthritis Rheum 2006; 54:3494

Research article

Open Access

Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]

Tim D Spector[1], Philip G Conaghan[2], J Christopher Buckland-Wright[3], Patrick Garnero[4], Gary A Cline[5], John F Beary[5], David J Valent[5] and Joan M Meyer[5]

The British study of risedronate in structure and symptoms of knee osteoarthritis (BRISK) trial was a randomized control trial of patients with mild to moderate OA of the medial compartment of the knee

Patients (284) were randomized to once daily risedronate (5 or 15 mg) or placebo. Those who recived 15 mg of risedronate showed improvement in the WOMAC index, significant improvement in the patients global assessment, and decreased used of walking aids

Spector TD et al: Arthritis Res Ther 2005; 7 R625

DMOADs: BISPHOSPHONATES

In mice and rabbit

Bone 66 (2014) 163–170

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Inhibited osteoclastic bone resorption through alendronate treatment in rats reduces severe osteoarthritis progression

M. Siebelt [a,*], J.H. Waarsing [a], H.C. Groen [b], C. Müller [c], S.J. Koelewijn [b], E. de Blois [b], J.A.N. Verhaar [a], M. de Jong [b,e], H. Weinans [d,f]

Highlights

- Alendronate (ALN) treatment was applied in a rat model for severe osteoarthritis.
- OA induction through both papain injections and running exercise
- ALN protects against loss of cartilage matrix.
- Synovial macrophages are less activated with ALN treatment.
- ALN treatment did not reduce sclerosis development.

Chondroprotective Effect of High-Dose Zoledronic Acid: An Experimental Study in a Rabbit Model of Osteoarthritis

Kalliopi Lampropoulou-Adamidou,[1,2] Ismene Dontas,[1] Ioannis P. Stathopoulos,[1,2] Lubna Khaldi,[1,3] Pavlos Lelovas,[1] John Vlamis,[2] Ioannis K. Triantafillopoulos,[1] Nikolaos A. Papaioannou[1]

J Orthop Res 32:1646–1651, 2014.

In conclusion, zoledronic acid, in a high-dose regimen, was proved to be chondroprotective in a well-established animal model of OA.

DMOADs: BISPHOSPHONATES

In humans

OPEN ACCESS Freely available online

PLOS | ONE

Are Bisphosphonates Effective in the Treatment of Osteoarthritis Pain? A Meta-Analysis and Systematic Review

Alison J. Davis[1], Toby O. Smith[2], Caroline B. Hing[3], Nidhi Sofat[1]*

1 Department of Rheumatology, Division of Biomedical Sciences, St George's, University of London, London, United Kingdom, 2 Faculty of Medicine and Health Sciences, University of East Anglia Norwich, United Kingdom, 3 Department of Orthopaedics St George's Hospital, London, United Kingdom

2013

Results: Our searches found 13/297 eligible studies, which included a total of 3832 participants. The trials recruited participants with OA of the hand (n = 1), knee (n = 8), knee and spine (n = 3), or hip (n = 1). Our meta-analysis of the two largest knee studies using risedronate 15 mg showed odds ratios favouring placebo interventions for the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain (1.73), WOMAC function (2.03), and WOMAC stiffness (1.82). However, 8 trials (61.5%) reported that bisphosphonates improve pain assessed by VAS scores and 2 (38.5%) reported significant improvement in WOMAC pain scores compared to control groups.

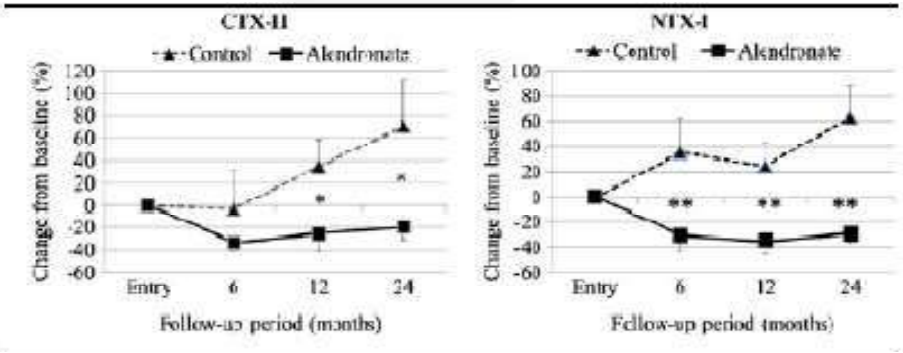
Conclusions: There is limited evidence that bisphosphonates are effective in the treatment of OA pain.

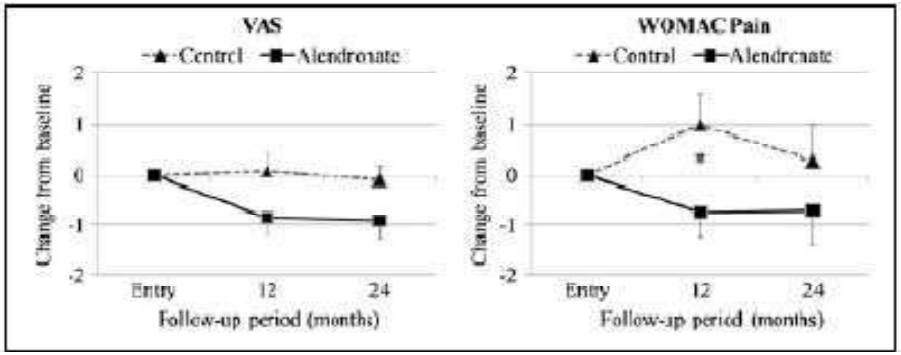
Clin Rheumatol (2013) 32:1759–1765
DOI 10.1007/s10067-013-2238-8

ORIGINAL ARTICLE

Alendronate treatment for hip osteoarthritis: prospective randomized 2-year trial

Takashi Nishii · Satoru Tamura · Toshiyuki Shiomi · Hideki Yoshikawa · Nobuhiko Sugano





Clin Rheumatol (2013) 32:1759–1766
DOI 10.1007/s10067-013-2338-8

ORIGINAL ARTICLE

Alendronate treatment for hip osteoarthritis: prospective randomized 2-year trial

Takashi Nishii · Satoru Tamura · Toshiyuki Shiomi · Hideki Yoshikawa · Nobuhiko Sugano

In a hip OA study with alendronate versus placebo, significant improvements in WOMAC pain score were seen with alendronate, but there were no significant differences in structural OA progression

Nishii T, Clin Rheumatol 2013; 32:1759

EXTENDED REPORT

Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial

Laura Louise Laslett,[1] Dawn A Doré,[1] Stephen J Quinn,[2] Philippa Boon,[1] Emma Ryan,[1] Tania Maree Winzenberg,[1] Graeme Jones[1]

May be of potential promise with the initial trial of a single infusion of zoledronic acid compared with placebo, showing a significant reduction in areal bone marrow lesion size at six months with an ongoing trend after 12 months. A significant reduction in Visual Analogue Scale pain score was also seen at six months, which was not sustained by 12 months

Laslett LL, et al Ann Rheum Dis 2012; 71:1322

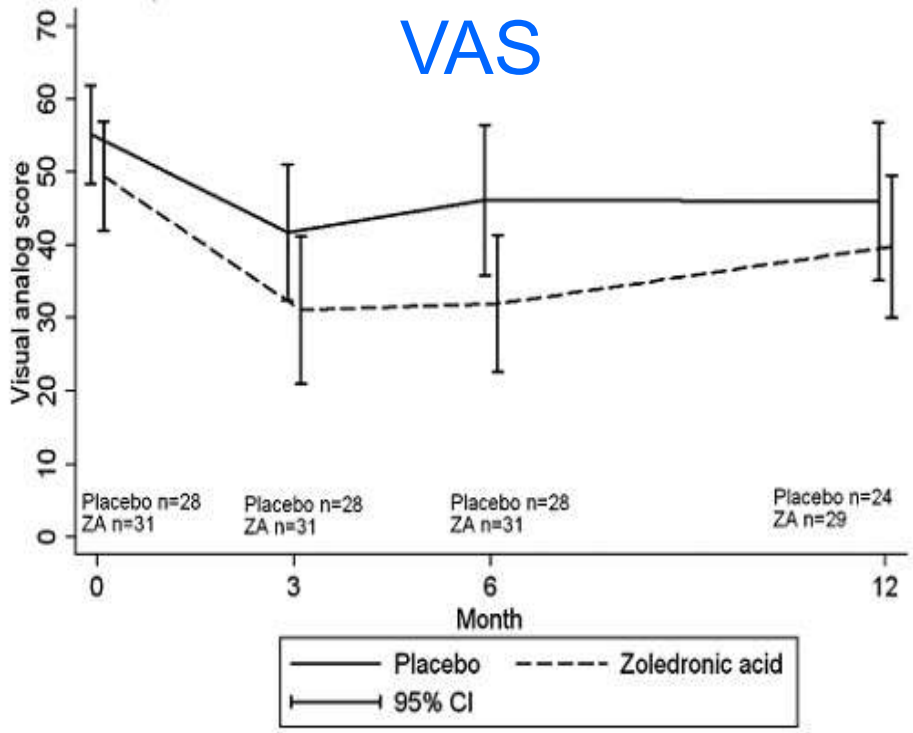
Ann Rheum Dis 2012;**71**:1322–1328.

EXTENDED REPORT

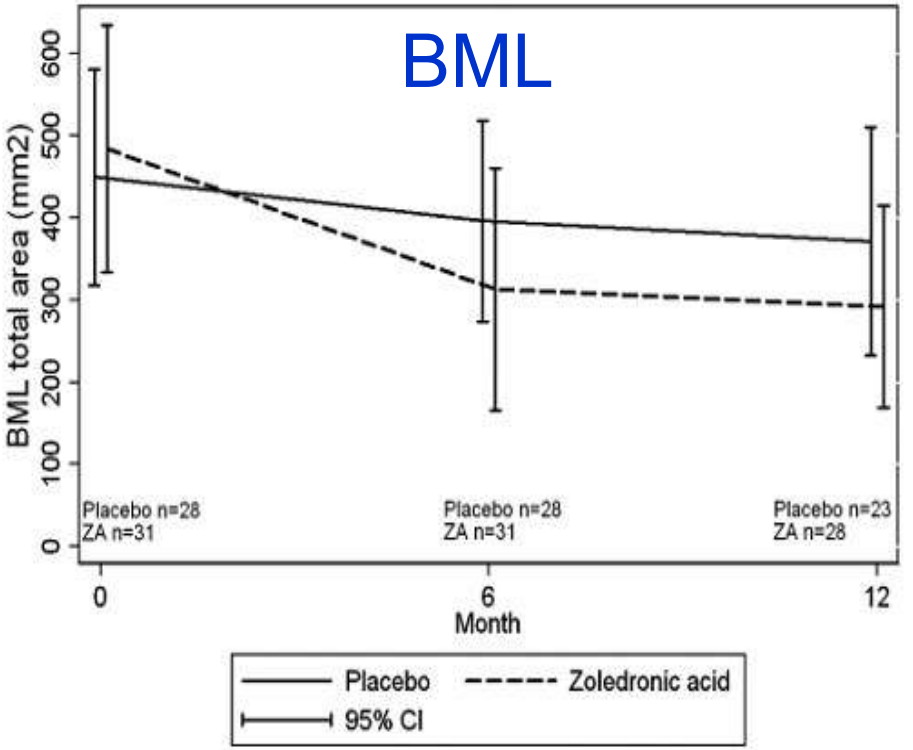
Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial

Laura Louise Laslett,[1] Dawn A Doré,[1] Stephen J Quinn,[2] Philippa Boon,[1] Emma Ryan,[1] Tania Maree Winzenberg,[1] Graeme Jones[1]

VAS



BML



JAMA | Original Investigation

Effect of Intravenous Zoledronic Acid on Tibiofemoral Cartilage Volume Among Patients With Knee Osteoarthritis With Bone Marrow Lesions

A Randomized Clinical Trial

Guoqi Cai, MMedSci; Dawn Aitken, PhD; Laura L. Laslett, PhD; Jean-Pierre Pelletier, PhD; Johanne Martel-Pelletier, PhD; Catherine Hill, PhD; Lyn March, PhD; Anita E. Wluka, PhD; Yuanyuan Wang, PhD; Benny Antony, PhD; Leigh Blizzard, PhD; Tania Winzenberg, PhD; Flavia Cicuttini, PhD; Graeme Jones, PhD

223 patients with Knee OA found that yearly zoledronic infusions compared with placebo did not result in statistically significant differences in cartilage volume loss over the two years follow-up period

Bone marrow lesion size was not significantly changed in either group and no significant between-group differences were observed over 24months

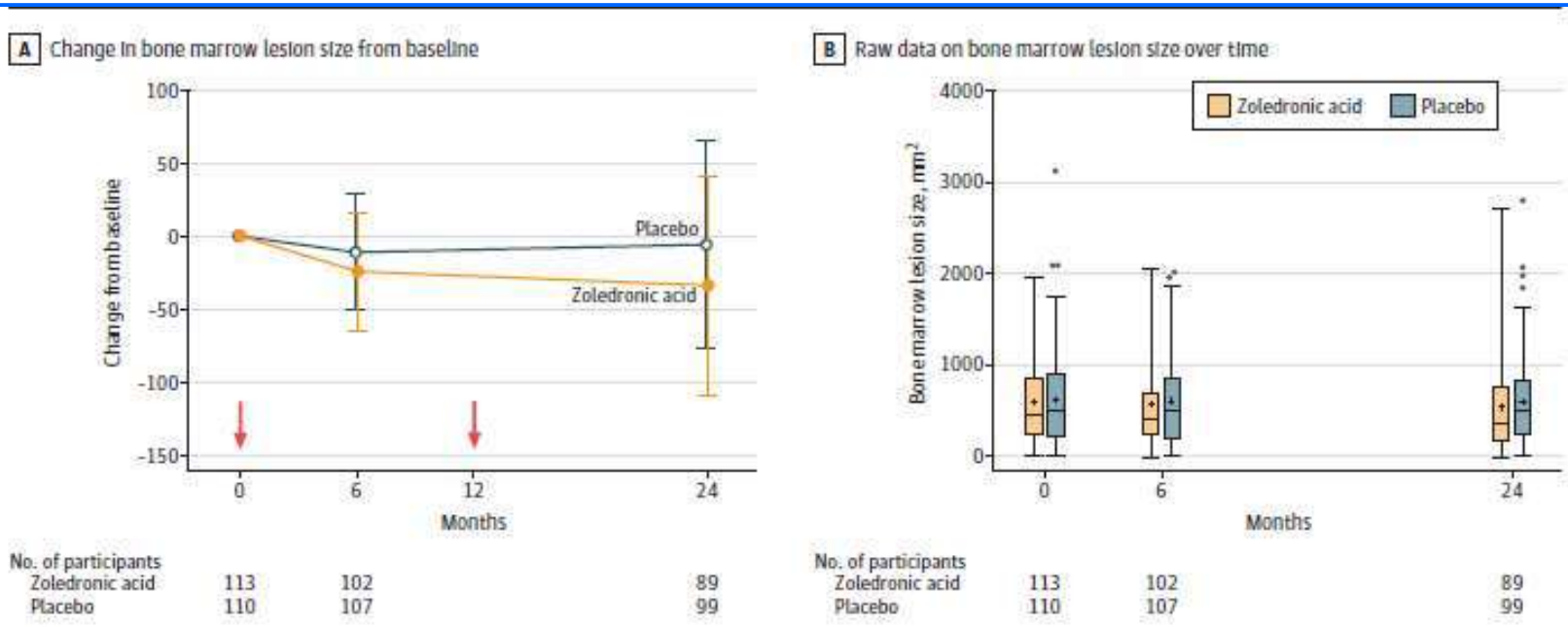
Cai G, et al JAMA 2020 323:1456

JAMA | Original Investigation

Effect of Intravenous Zoledronic Acid on Tibiofemoral Cartilage Volume Among Patients With Knee Osteoarthritis With Bone Marrow Lesions

A Randomized Clinical Trial

Guoqi Cai, MMedSci; Dawn Aitken, PhD; Laura L. Laslett, PhD; Jean-Pierre Pelletier, PhD; Johanne Martel-Pelletier, PhD; Catherine Hill, PhD; Lyn March, PhD; Anita E. Wluka, PhD; Yuanyuan Wang, PhD; Benny Antony, PhD; Leigh Blizzard, PhD; Tania Winzenberg, PhD; Flavia Cicuttini, PhD; Graeme Jones, PhD



Cai G, et al JAMA 2020 323:1456

Neridronate stimulated osteoblasts to produce osteocalcin in an OA model, providing yet another potential pathway for bisphosphonate activity in OA

Corrado A et al Clin Rheumatol 2005, 24 527-34

RHEUMATOLOGY

Rheumatology 2015;54:1826–1832
doi:10.1093/rheumatology/kev123
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Original article

Intravenous neridronate in the treatment of acute painful knee osteoarthritis: a randomized controlled study

Massimo Varenna[1], Francesca Zucchi[1], Simonetta Failoni[2], Andrea Becciolini[3] and Massimo Berruto[4]

TABLE 2 Clinical characteristics of patients with painful knee OA 50 days after treatment (T2) with neridronate or placebo

	Neridronate (n = 31)	Difference from baseline, mean (%)	Placebo (n = 25)	Difference from baseline, mean (%)	P-value[a]
VAS score	9.4 (10.8)*	−81.9 (22.7)	50.1 (16.9)	−14.2 (37.2)	0.001
WOMAC score	58 (58)*	−73.1 (30.9)	228 (162)	15.3 (108.8)	0.001
SF-36 physical component	51.1 (8.7)*	47.5 (51.8)	39.3 (19.1)	26.4 (68.6)	0.01
SF-36 mental component	62.5 (11.1)**	13.8 (29.5)	58.3 (13.8)	6.7 (39.1)	0.2
McGill	3.7 (4.6)*	−57.2 (71.6)	15.6 (10.8)	36.3 (136.8)	0.001
WORMS	3.7 (4.2)**	−41.1 (102.6)	7.1 (3.6)	23.7 (90.3)	0.002

Values are given as mean (S.D.). [a]Mann–Whitney U test (neridronate group vs placebo group). *P = 0.001; **P = 0.01 vs baseline values (Wilcoxon signed rank test). SF-36: 36-Item Short Form Health Survey; VAS: visual analogue scale; WORMS: whole-organ MRI score.

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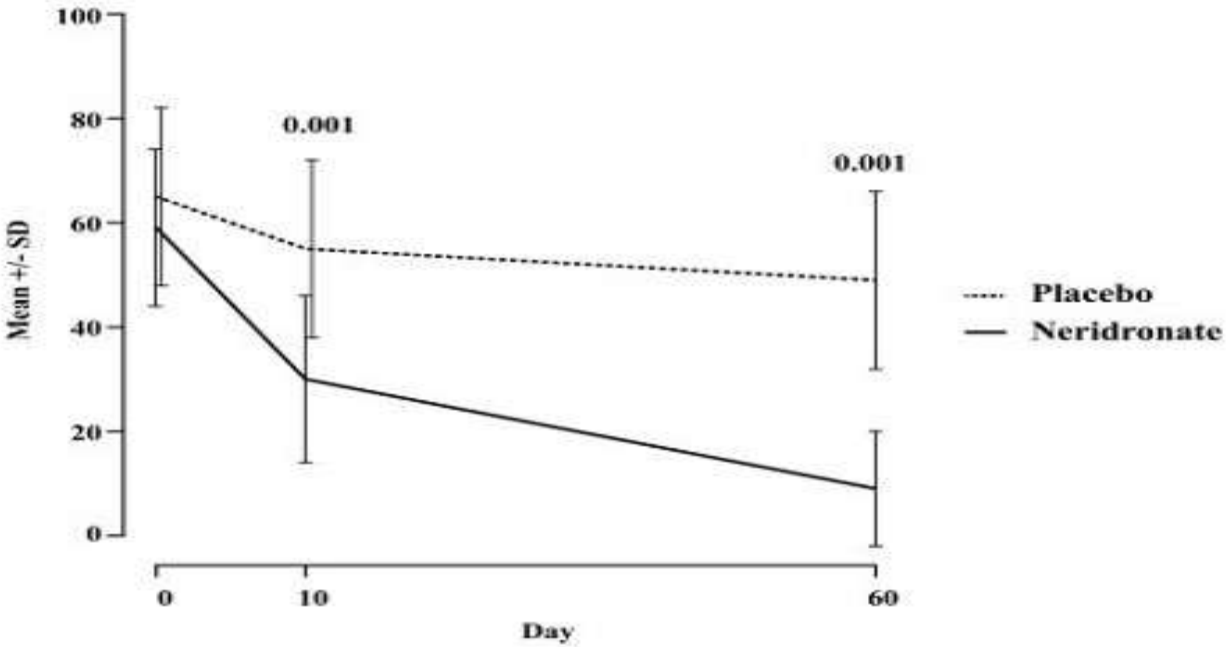
FIG. 2 Pain trend at baseline and after neridronate treatment or placebo



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Rheumatology key messages

- Intravenous infusion of neridronate provides clinically relevant pain benefit in acute painful knee OA.
- Bone marrow lesion size in knee OA patients decreased significantly after i.v. neridronate treatment.
- Long-term pain and functional improvements were found in knee OA patients after i.v. neridronate treatment.

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https://doi.org/10.1007/s40268-020-00294-4

ORIGINAL RESEARCH ARTICLE

Intramuscular Clodronate in Long-Term Treatment of Symptomatic Knee Osteoarthritis: A Randomized Controlled Study

Bruno Frediani[1] · Carmela Toscano[1] · Paolo Falsetti[1] · Antonella Nicosia[1] · Serena Pierguidi[1] · Alberto Migliore[2] · Stefano Giannotti[3] · Luca Cantarini[1] · Edoardo Conticini[1]

Abstract

Background and Objective Clodronate is a nitrogen-free bisphosphonate that is widely and effectively used in the treatment of many osteo-metabolic disorders. The objective of our study was to evaluate the effectiveness of clodronate in reducing pain and bone marrow edema in knee osteoarthritis.

Methods In total, 74 patients were included in the study. Group 1 received intramuscular clodronate 200 mg daily for 15 days and then once weekly for the next 11.5 months; group 2 received intramuscular clodronate 200 mg daily for 15 days and then once weekly for the next 2.5 months. Visual analog scale (VAS) scores were recorded at baseline (T0) and after 30 days (T1), 3 months (T2), 6 months (T3), 9 months (T4), and 12 months (end of study; T5). We also evaluated functional status and use of paracetamol (T0, T1, T2, T3, T4, and T5) and changes in Whole Organ Magnetic Resonance Imaging Score (WORMS; T0, T2, and T5).

Results Both groups had a statistically significant reduction in VAS score until 3 months. Group 1 then experienced further VAS reductions, whereas VAS scores for group 2 progressively increased. Pain, stiffness, and physical function also showed the same trend, as did bone marrow edema extension, which was evaluated with WORMS.

Conclusion Our study indicates that intramuscular administration of a therapeutic dose of clodronate followed by a maintenance dose is effective in the management of symptomatic knee osteoarthritis, improving functional outcomes and reducing pain and bone marrow edema. Prolonged treatment increases the long-term efficacy of clodronate compared with the shorter schedule.

74 Patients were randomized to receive Clodronate 200 mg i.m :

group 1 *clodronate 200 mg i.m./daily for 15 days and after 1 injection weekly for the following 11,5 months;*

group 2 *clodronate 200 mg i.m./daily for 15 days and after 1 injection weekly for the following 2,5 months*

All patients can take paracetamolo at maximum dosage of 3000 mg/die; patients had to draft an analgesics diary

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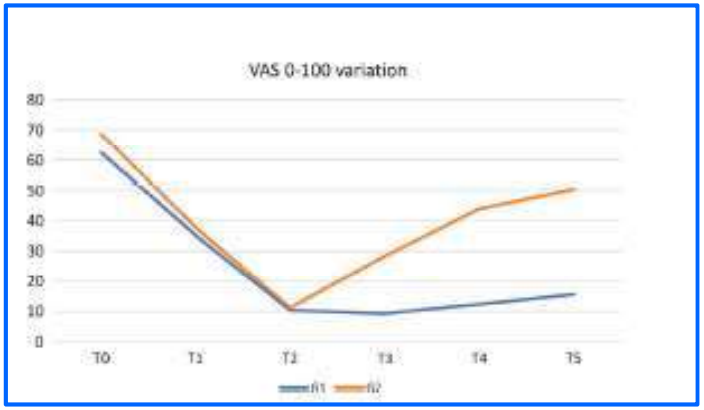
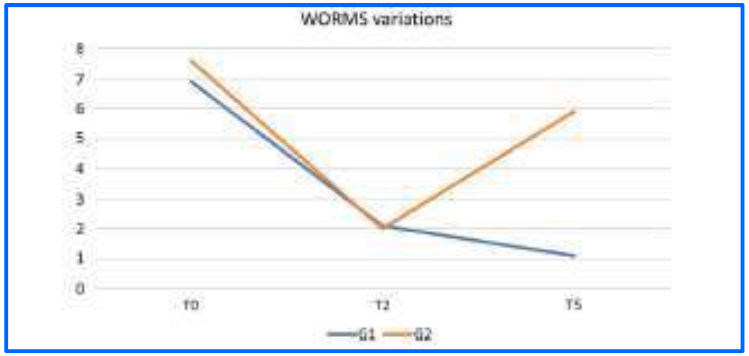
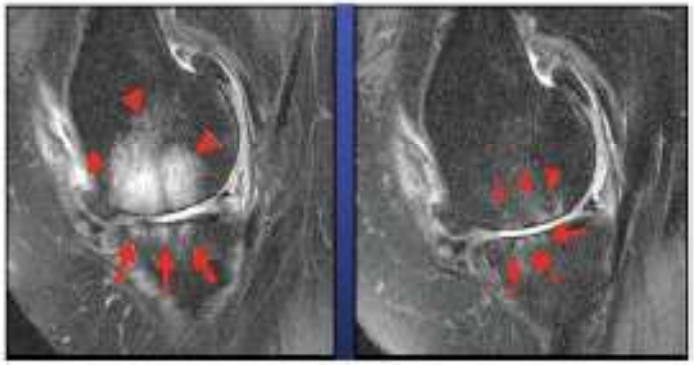


VAS variation (%); VAS visual analog scale



Worms variation (%) WORMS Whole Organ Magnetic Resonance Imaging Score



MRI before and after clodronate Therapy T2 (3 months). MRI magnetic resonance imaging

Fig. 3 MRI before and after clodronate therapy (T2 [3 months]). *MRI* magnetic resonance imaging

Key Points

Intramuscular clodronate is well-tolerated and effective for the management of symptomatic knee osteoarthritis.

The efficacy of clodronate is directly proportional to the treatment duration.

SCHEMI TERAPEUTICI i.v., i.m. nelle BMLs

BMLs nell' OA:

- NERIDRONATO 100 mg x 4 in 10 gg poi 1 i.v. al mese o ogni 2 mesi o 2 i.m. al mese
- CLODRONATO 600-900 mg X 3 in 10 gg poi ogni 3 mesi Oppure 200 mg i.m. a settimana

In conclusione:

L’osso subcondrale come target terapeutico nella OA ha delle solide motivazioni per essere preso in considerazione

La presenza di remodeling e di BMLs costituisce il presupposto razionale per l’utilizzo di farmaci antiriassorbitivi dell’osso

Evidenze scientifiche hanno maggiore forza per studi in vitro e sull’animale

Dati clinici sull’uomo sono meno concordanti per le diverse molecole (alendronato, residronato, neridronato, clodronato, zoledronato),

Gli studi clinici devono essere ulteriormente rafforzati e implementati perche’ tali molecole rappresentano una importante risorsa per il trattamento dell’ AO soprattutto nella fase Early

Il nuovo fascino di una Vecchia Signora

Grazie per l'Attenzione!