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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Trends in rheumatic disease: Update on new diagnostic and treatment strategies

ABSTRACT

Advances in our understanding of the pathophysiology of rheumatic and immunologic diseases have led to improved therapies, such as tumor necrosis factor inhibitors and bisphosphonates. These drugs can not only alleviate symptoms but also alter the course of the disease. However, they also have significant potential side effects, which mandate, more than ever, correct diagnosis and vigilant monitoring for toxicity.

KEY POINTS

Rheumatic manifestations may be the first hint of hepatitis C infection.

Joint damage can be slowed or prevented if rheumatoid arthritis is treated aggressively.

Combining a nonselective generic NSAID with a proton-pump inhibitor may be more cost-effective under some circumstances than switching to a COX-2-selective NSAID.

Gastrointestinal intolerance to bisphosphonates is less likely when patients follow medication instructions, so clinicians must educate patients. Changing dosing schedules or bisphosphonates may also reduce intolerance.

Nonpharmacologic therapies such as rest, orthotics, and exercise are useful in osteoarthritis; acetaminophen should be the first-line pain reliever.

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NEW MEDICATIONS and a deeper understanding of the pathophysiology of rheumatic disease have greatly improved the treatment possibilities. In this article, I will discuss current trends in rheumatology that can affect how primary care physicians diagnose and manage these potentially complex diseases. To illustrate several of these trends, I will present heuristic but real case scenarios.

CASE 1: PURPURA AND ARTHRITIS

A 36-year-old woman presents with a 12-week history of symmetrical synovitis of the small joints of her hands, wrists, elbows, and knees, along with significant fatigue. She reports morning stiffness in these joints that lasts more than 2 hours every day. Her erythrocyte sedimentation rate (ESR) is 46 mm/hour; her rheumatoid factor (RF) and antinuclear antibody (ANA) tests are positive; she is mildly anemic (hemoglobin 11.4 g/dL); and her platelet count is 524 × 10^9/L. The painful joints are mildly swollen and tender to palpation.

After receiving a diagnosis of rheumatoid arthritis, she is started on a nonsteroidal anti-inflammatory drug (NSAID) and hydroxychloroquine. She feels slightly better, but after 1 week she develops profuse nonthrombocytopenic purpura on her legs and feet.

1 What should you do?

- ❑ Switch to a COX-2-selective NSAID, which will have no antiplatelet effect
- ❑ Switch to a COX-2-selective NSAID, and add prednisone in a low dosage
- ❑ Order a test for antineutrophil cytoplasmic antibody (ANCA)

- ❑ Discontinue the NSAID and start methotrexate with low-dose prednisone
- ❑ Order additional tests for infectious or rheumatic diseases

Rheumatoid arthritis is a diagnosis of exclusion, so the diagnosis should not be made quickly or with certainty when patients have symptoms consistent with other diseases. This patient's symptoms are compatible with rheumatoid arthritis, but also suggest the possibility of a wide variety of other diseases. The differential diagnosis for symmetrical polyarthritis of the small and large joints with purpura includes rheumatoid arthritis with cryoglobulinemia, a drug reaction, Sjögren syndrome with nonvasculitic purpura, a primary vasculitic syndrome, lupus, a paraneoplastic process, and infection.

Therefore, the best option would be to order additional tests.

The ANCA test is useful in supporting the diagnosis of systemic Wegener granulomatosis (anti-PR3). It is not very specific, so it should be used only to support diagnoses made on the basis of other findings. Some patients with rheumatoid arthritis may have positive ANCA results. This patient's condition, although consistent with Wegener granulomatosis or microscopic polyangiitis, is not typical enough of these diseases to be confirmed by a positive ANCA alone. Thus, neither a negative nor a positive test would be useful.

Hepatitis C is a 'stealth' infection

This patient previously had normal transaminase levels, but serologic testing revealed hepatitis C RNA with cryoglobulinemia. The diagnosis was changed from rheumatoid arthritis to hepatitis C with associated polyarthritis and cryoglobulinemic purpura.

Recognize the rheumatic manifestations of hepatitis C

Hepatitis is a "stealth" infection. About 40% of patients have no identified risk factors, and rheumatic manifestations may be the first hint of the disease.

One of these manifestations is RF-positive polyarthritis, which may mimic early rheumatoid arthritis. In one study,[1] 303 patients with a diagnosis of rheumatoid arthritis were screened for hepatitis C, and 23 (8%) actually had hepatitis C. This frequency was much higher than was found in a sample of blood donors (about 1%) or a random control sample (about 3%).

Most cases of cryoglobulinemia that were once considered essential or idiopathic are now recognized as a complication of hepatitis C. Vasculitis, with or without cryoglobulinemia and frequently associated with neuropathy, may be associated with hepatitis C, as is membranoproliferative glomerulonephritis.

Hepatitis C may be associated with a Sjögren-like syndrome of sicca syndrome and mild parotid gland enlargement. Patients are usually negative for anti-Ro seroantibody but are sometimes positive for both RF and anti-Ro, a situation that illustrates the limitations of using autoantibodies to make the diagnosis of a rheumatologic disease.

Other extrahepatic manifestations of hepatitis C include corneal ulcers, thyroiditis, porphyria cutanea tarda, and perhaps lichen planus.[2–4]

CASE 2: POLYARTHRITIS, FATIGUE, AND PERIARTICULAR OSTEOPENIA

A 24-year-old woman reports an 8-month history of progressive polyarticular arthritis of the metacarpophalangeal joints, metatarsophalangeal joints, proximal interphalangeal joints, knees, and wrists. Tests for parvovirus and hepatitis C are negative. She feels mild fatigue and morning stiffness in her hands and knees that lasts about 90 minutes. Her ESR is 55 mm/hour, hemoglobin level 11.5 mg/dL, and RF markedly elevated. Radiography of her hands shows periarticular osteopenia.

2 What is the best treatment option?

- ❑ Begin a standard NSAID in anti-inflammatory doses, and if there is no response after 3 weeks, add methotrexate in escalating doses
- ❑ Begin a COX-2-selective NSAID in anti-inflammatory doses, and if there is no response after 3 weeks, add methotrexate in escalating doses
- ❑ Begin methotrexate at 10 mg/week
- ❑ Begin prednisone 40 mg daily tapered

over 8 weeks, with a weekly 10 mg dose of methotrexate

- ❑ Begin simultaneous treatment with methotrexate 10 mg weekly, hydroxychloroquine 200 mg twice a day, and sulfasalazine 500 mg twice a day.

Treat rheumatoid arthritis aggressively to prevent joint damage

This patient has established rheumatoid arthritis with demineralization. Both radiographic and functional measures show that articular and periarticular damage caused by rheumatoid arthritis begins early in the course of the disease and is cumulative.

Most rheumatologists strongly recommend aggressive initial therapy, perhaps including combination therapy, rather than symptomatic therapy such as NSAIDs, which do nothing to reverse the disease process. NSAIDs can be added if necessary to augment pain control. An appropriate course of action for this woman would be to begin methotrexate (MTX), with or without hydroxychloroquine and sulfa salazine. Weekly MTX is generally started with daily folic acid (1 mg) to decrease some of the MTX side effects.

Medications that demonstrably alter the course of the disease include MTX, sulfasalazine, leflunomide and tumor necrosis factor (TNF) inhibitors (etanercept and infliximab). Gold and prednisone may also have disease-modifying effects, but the results with these agents are more controversial.

Treatment strategies. Two therapeutic strategies that are popular today are the "step up" and the "step down" approaches. In step up therapy, the initial regimen is designed to treat symptoms and prevent the progression of rheumatoid arthritis. It may include MTX, sulfasalazine, or even combination therapy using lower doses of disease-modifying medications. Therapies are then added on or doses increased fairly rapidly to gain disease control.

In step-down therapy, an aggressive combination regimen is started as soon as rheumatoid arthritis is diagnosed. After the disease responds and symptoms quiet or disappear, the doses are gradually reduced and some therapies may be discontinued, until a minimum level needed to eradicate symptoms is reached. There is no consensus yet about whether step-up or step-down is better, but both seem superior to the older "pyramid" strategy, in which medication was very slowly escalated above the level needed to control symptoms.

Predicting rapid progression of rheumatoid arthritis

Some clinicians are hesitant to begin aggressive treatment because the progression of rheumatoid arthritis is variable. Although it is not possible to predict with certainty which patients will have aggressive disease, there are several risk factors that should be considered red flags for aggressive disease: RF-positive status, early nodulosis, early knee involvement, and early erosions. Persistently elevated acute-phase markers may also be an indicator of progression. In addition, certain major histocompatibility complex loci and T-cell receptor polymorphisms seem to identify groups of patients likely to have the worst disease, but this information is not yet available to the clinician.

Regardless of these possible predictors, a trend now is to assume that most patients with rheumatoid arthritis will have progressive disease, and to treat them aggressively as soon as disease is diagnosed. If rheumatoid arthritis is undertreated, it will often progress inexorably, though at varying rates.

Autoantibodies are not totally specific for any rheumatologic disease

Relieving pain and maintaining function

In addition to retarding damage, therapy should also be directed at relieving symptoms and maintaining function. Frequently, especially early in the course of the disease, effective disease-modifying anti-inflammatory drugs (DMARDs) alone are sufficient. However, some patients may still be uncomfortable enough to require pain therapy. Pain is common in patients who have already experienced damage to joints and periarticular structures and in patients who must perform mechanically stressful tasks using their arthritic joints.

One option for these patients is to combine an analgesic with the baseline immunosuppressant therapy. If active inflammation is not the problem, analgesics other than NSAIDs are appropriate.

If pain is mechanical in origin, orthotics or surgery may be necessary; foot orthotics are often underused. Inflammatory pain can be treated with low-dose steroids more effectively than with NSAIDs, although the potential side effects of low-dose prednisone (≤ 7.5 mg daily) must be weighed against the cost and potential side effects of NSAIDs. Many patients with rheumatoid arthritis have pain that stems from superimposed pain syndromes such as fibromyalgia. These patients should be counseled to begin slowly progressive aerobic exercise regimens and to take measures to improve the quality of sleep such as over-the-counter sleeping pills, prescription sleep aids, or psychological therapy. Patients should be counselled regarding joint protection techniques; physical and occupational therapy evaluations are often extremely beneficial.

Joint stiffness is common in rheumatoid arthritis and should be relieved by treating the inflammatory component of the disease.

Neuropathies, if compressive, can be treated with splints, treating the synovitis, or surgery. Vasculitic neuropathies, however, require intensified immunosuppressive therapy, such as cyclophosphamide.

Foot orthotics are underused in rheumatoid arthritis

Monitor for effect and toxicity

It is critical to monitor all rheumatoid arthritis patients to follow the effects of their drug regimens and to detect any drug toxicity. Outcomes of treatment should be documented both radiographically and functionally. However, radiographic measures do not always correlate precisely with functional measures, so the primary emphasis in the clinic should be on functional outcomes.

Methotrexate and leflunomide can damage the liver and suppress bone marrow function. Glucocorticoids are linked to osteoporosis, glucose intolerance, and glaucoma. Sulfasalazine is linked to occasionally severe leukopenia. TNF antagonists are linked to infections and rarely to demyelination, which may lead the patient to report mysterious dysesthesias. Some patients with rheumatoid arthritis who experience demyelination when treated with TNF antagonists may actually have occult multiple sclerosis.[5–10]

Better-designed clinical trials give more precise information

The treatment of rheumatoid arthritis today has improved in part because of better-designed, more informative clinical trials. These trials emphasize radiographic and functional outcomes, not just patient-reported symptoms.

In addition, they have attempted to distinguish mere statistical significance from clinically relevant effects by using validated composite outcome measures such as the American College of Rheumatology (ACR) index. This index is a combination measure calculated from variables such as the number of painful joints, the number of swollen joints, the C-reactive protein level, and scores on validated disability questionnaires. Recent clinical trials[5–7] have used this index and reported the percentage of patients who experienced a 20% improvement in ACR, a 50% improvement, and a 70% improvement (known as ACR 20, ACR 50, and ACR 70, respectively). Thus, the reader can determine how many patients experienced a clinically meaningful composite improvement (perhaps a 50% or a 70% improvement), rather than merely seeing improvement in group means.

CASE 3: SYSTEMIC LUPUS AND CHILDBIRTH

A 42-year-old woman with systemic lupus erythematosus (SLE) previously well controlled with hydroxychloroquine presents with pain and continuous fatigue 2 months after the birth of a healthy child. She describes increasing joint pain and stiffness of her back, neck, elbows, and hands, with fatigue and trouble sleeping. Fatigue was an initial characteristic of her lupus, and she is concerned that she may be experiencing a postpartum flare.

Her ESR is 32 mm/hour, her ANA is high-titer, and her IgG antiphospholipid antibody test is positive, but only moderately elevated. She is afebrile and has tender, nonswollen joints particularly in the fingers and knees, along with bilateral trochanteric bursitis, gluteal tenderness, lateral epicondylitis, costochondritis, and pes anserine bursitis. Her chronic Raynaud syndrome is unchanged, as is her livedo reticularis.

Her urinalysis is normal, her hemoglobin level is 12.9 mg/dL, and her white blood cell count is 3.9×10^9/L (unchanged from her baseline mild leukopenia).

3 What should you do?

- ❑ Increase the prednisone dosage to 20 mg daily and observe while tracking C3 levels
- ❑ Add methotrexate 7.5 mg weekly with folic acid
- ❑ Add a tricyclic antidepressant and prescribe aerobic exercise
- ❑ Suggest over-the-counter dehydroepiandrosterone (DHEA) and melatonin
- ❑ Initiate warfarin therapy to maintain the international normalized ratio (INR) between 2.5 and 3.

Postpartum flares of lupus are not uncommon, but in this case, there are no firm signs of active lupus, and so the patient's syndrome of clinical pain and fatigue is most likely postpartum fibromyalgia, perhaps exacerbated by lack of sleep.

Generalized pain syndromes may be superimposed

People with the chronic stress associated with chronic disease frequently have myofascial pain or fatigue syndromes. These pain syndromes are not necessarily associated with any increase in disease activity but may be strongly associated with disability and a worsening quality of life. It has been estimated that more than 20% of patients with SLE have fibromyalgia, and this prevalence is probably similar in other chronic diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease.

Fibromyalgia symptoms often include fatigue, myalgias, paresthesias, impaired cognition, and headache. These symptoms can mimic lupus activity, and the two conditions may at times be difficult to distinguish. As a result, both physicians and patients probably confuse the two frequently. A detailed examination may help distinguish fibromyalgia from lupus by identifying additional myofascial tender points. Patients undergoing corticosteroid withdrawal may also exhibit features of fibromyalgia.

Chronic fatigue syndrome shares many of the characteristics of fibromyalgia, although with less prominent pain. There are no diagnostic tests for either condition, and nonspecific tests such as Epstein-Barr titers and ANA levels are more likely to lead to the wrong decision than the right one. Talking with and examining the patient is far more helpful than indiscriminate laboratory testing. Hypothyroidism and hepatitis C infection should be excluded.

Other problems that may be superimposed on rheumatic and immunologic disease include depression, particularly in patients with a history of physical or sexual abuse, autoimmune thyroid disease, and, rarely, autonomic dysfunction.

Generalized myofascial pain syndromes should be treated with symptomatic therapy. Prednisone and narcotics should be avoided. In the case described above, education about fibromyalgia, a low-dose tricyclic antidepressant to resolve her sleep cycle disturbance, and aerobic exercise would probably be the most helpful. Some patients find it preferable to use health-store supplements such as DHEA and melatonin for pain and sleep disorders. In the present case, despite the livedo reticularis and the antiphospholipid antibodies, there is no compelling clinical reason to use anticoagulation therapy.[11–15]

Many patients with chronic inflammatory diseases also have myofascial pain syndromes

CASE 4: RHEUMATOID ARTHRITIS, NSAIDs, AND HEME-POSITIVE STOOLS

A 66-year-old man with a 10-year history of rheumatoid arthritis, controlled with sulindac and methotrexate, is found to have asymptomatic heme-positive stools. His hemoglobin level is 10.6 mg/dL, down from 11.3 mg/dL when checked 4 months ago. For years, he has had chronic dyspepsia whenever taking NSAIDs, but he tries to take them regularly. Esophagogastroduodenoscopy shows several nonbleeding, punctate gastric erosions but no ulcers. His vital signs are no different from usual; he does not exhibit orthostatic hypotension; and his reticulocyte count is 1.8%.

4 What should you do?

- ❑ Change to a COX-2-selective NSAID
- ❑ Discontinue the NSAID and add low-

dose prednisone (≤ 5 mg/day)

- ❑ Discontinue the NSAID, start either a COX-2-selective NSAID or low-dose prednisone, and also perform colonoscopy
- ❑ Discontinue methotrexate and sulindac, and add low-dose prednisone

Recognize the benefits and hazards of NSAIDs

The best option is to discontinue or change the NSAID, which is a potential cause of gastrointestinal bleeding, but also to perform colonoscopy to exclude alternative sources of the bleeding. In this case, a right-sided adenocarcinoma was discovered and removed in a potentially curative resection. Do not assume that an NSAID is the cause of bleeding unless a clear source of bleeding in the upper gastrointestinal tract is identified!

COX-2-selective NSAIDs are safer, but not more effective

Don't attribute bleeding to NSAIDs if the bleeding source is not clear

The COX-2-selective NSAIDs have wrongly been perceived as "super-aspirins." This is inaccurate and fails to acknowledge the limitations of these drugs.

The COX-2-selective NSAIDs are not more effective than ordinary NSAIDs, they are not the primary treatment for rheumatoid arthritis, and they do not eliminate the chance of NSAID-associated dyspepsia. Unlike aspirin and most traditional NSAIDs, they have no antiplatelet effect, so they are not cardioprotective. Furthermore, there is some evidence that the COX-2-selective NSAIDs, like their nonselective counterparts, may actually slow the rate of ulcer healing.

In clinical trials COX-2 selective NSAIDS reduced the risk of developing significant upper gastrointestinal complications in the first place. However, the risk of GI bleeding from nonselective NSAIDs is low—an annual incidence of 1% to 3%—and the COX-2-selective NSAIDs are costly. Therefore, it may be best to reserve these drugs for patients at high risk for GI complications (bleeding ulcers, GI bleeding, or ulcer perforations), such as the elderly, patients with rheumatoid arthritis, patients with cardiovascular diseases, patients on low-dose aspirin, and patients on warfarin. For the latter group, the INR should be carefully monitored throughout the course of therapy.

The COX-2-selective NSAIDs may alter the INR, particularly in patients being maintained at a higher level of anticoagulation. If patients require proton-pump inhibitor therapy, there is no proven benefit to using a costly selective COX-2 NSAID. A generic NSAID with a proton-pump inhibitor is likely to be just as safe and much cheaper, although this has not been demonstrated in clinical trials.

CASE 5: OSTEOPOROSIS AND INTOLERANCE TO ALENDRONATE

A 64-year-old woman with osteoporosis was recently diagnosed with dermatomyositis, and a deep vein thrombosis developed during immobilization after her muscle biopsy. Long-term steroid therapy is anticipated. She has a family history of osteoporosis and a mother and sister who died of breast cancer.

However, she has previously refused to take alendronate (which was prescribed at 10 mg per day, along with calcium and vitamin D) because she had been warned by her pharmacist that it would cause stomach upset and ulcers. She experienced dyspepsia after taking the first pill.

5 What should you do?

- ❑ Increase the dosage of calcium to 2 g/day with vitamin D
- ❑ Prescribe nasal calcitonin with calcium and vitamin D
- ❑ Switch to risedronate 5 mg/day
- ❑ Switch to alendronate 70 mg/week
- ❑ Add a selective estrogen receptor modulator (SERM)

This patient is at extremely high risk for complications of osteoporosis. Some patients who are intolerant of alendronate may be more comfortable with risedronate. Alternately, a once-a-week dose of alendronate is more likely to be tolerated.

Education about how to take the medication and reassurance that clinically significant complications are uncommon should reduce gastrointestinal intolerance. Intravenous bisphosphonate regimens, although costly, are

also available for patients with malabsorption or true GI intolerance.[16,17]

Treat osteoporosis aggressively

There is an increasing awareness that osteoporosis is common and should be routinely screened for, particularly in perimenopausal women and in high-risk younger patients (those with a strong family history of osteoporosis, a history of steroid use, or malabsorption. Older people with fractures and anybody with atypical fractures should also be screened. In addition, keep in mind that men also get osteoporosis.

Aggressive therapy is indicated for patients at high risk. Calcium and vitamin D are required baseline therapy, but are insufficient by themselves. Bisphosphonates are more effective than calcitonin. SERMs are also effective, but relatively contraindicated in patients with a history of thromboembolic disease. Behavioral changes to reduce the risk of falling also help.

Bone densitometry provides a reasonable, though not precise, surrogate marker of fracture risk.

CASE 6: ARM CRAMPS IN POLYMYALGIA RHEUMATICA

A 64-year-old woman telephones on a Friday afternoon to report 2 weeks of progressive bilateral cramping pain in her forearms when she uses the vacuum cleaner. She has a long-standing diagnosis of polymyalgia rheumatica. About a year and a half ago, she began treatment with prednisone for polymyalgia rheumatica and carpal tunnel syndrome (10 mg daily for 8 months, now tapered to 2.5 mg daily). She no longer has morning stiffness, dysesthesias, or joint swelling. In addition to prednisone, she takes calcium and estrogen, as well as enalapril and hydrochlorothiazide for chronic hypertension that had been difficult to control.

You increase her prednisone to 15 mg daily and order blood studies. She calls as instructed the next week but feels no better. Her ESR is 24 mm/hr, hemoglobin 12.8 mg/dL, and creatinine 1.6 mg/dL. Her blood pressure is 94/60 mm Hg. She has no synovitis, and her neurologic examination is normal.

6 What is your main concern?

- ❑ A flare of her polymyalgia rheumatica
- ❑ A paraneoplastic syndrome
- ❑ Atherosclerotic cardiovascular disease
- ❑ Inflammatory vascular disease

Because this woman is reporting symptoms that suggest claudication of her upper extremities, it would be important to investigate possible inflammatory vascular disease.

Despite her history of difficult-to-control hypertension, she has low blood pressure now, suggesting that she may have stenotic lesions in her upper arms, producing arm claudication and artificially lowering the blood pressure reading.

Because polymyalgia rheumatica can be associated with large-vessel arteritis, this is a strong diagnostic possibility. The normal ESR should probably be discounted, as the ESR is not sensitive enough to detect all flares in polymyalgia rheumatica or giant cell arteritis, particularly when obtained from an outpatient.

Temporal arteritis is associated with aortitis and stenoses

Patients with polymyalgia rheumatica or giant cell arteritis must be examined and questioned routinely about symptoms because they are at high risk for aortitis, aortic aneurysms, and aortic branch stenoses.

This patient had bilateral subclavian bruits. Vascular MRI revealed bilateral subclavian stenosis, probable left renal artery stenosis, and aortitis (edema of the aortic wall). At angiography she was found to have left renal artery stenosis and a cerebral arterial pressure of 150/80 mm Hg. She was treated with prednisone 60 mg by mouth daily.

To limit bisphosphonate intolerance, teach patients how to take these drugs

IN OSTEOARTHRITIS, TRY NONPHARMACOLOGIC THERAPY

New guidelines for the treatment of osteoarthritis continue to emphasize the value of nonpharmacologic therapies. Some of these include weight loss for overweight patients, judicious use of rest and orthotics, aerobic exercise, and directed active physical therapy

(not just passive massage or heat).

Some patients prefer NSAID therapy, and objective measures may show that some patients respond better to NSAIDs than to acetaminophen or nonpharmacologic measures. However, NSAIDs carry risks, and the selective COX-2 inhibitors, which are safer, are much more expensive. Therefore, it is reasonable to use acetaminophen as the initial therapy but to monitor the patient's response and consider trying single-blind "n of 1" trials with alternative medications.

Acetaminophen can be started at up to 4 g daily in patients who do not drink significant amounts of alcohol and do not have liver disease. It can be supplemented with other analgesics or even NSAIDs as needed.

A recent study[18] of patients with osteoarthritis of the knee showed that treatment with pharmaceutical grade glucosamine sulfate was clinically effective (ie, it improved function) and reduced the rate of knee joint space narrowing. The therapy had no significant side effects. This study is promising, but awaits independent confirmation. In addition, it is not clear whether results from the pharmaceutical grade preparation could be applied to over-the-counter preparations of glucosamine. Some concerns have been expressed regarding the technique used for the knee radiographs. Nonetheless, this does fit with older studies, which suggested an analgesic effect of glucosamine. This does not imply that glucosamine can "cure" arthritis.

Studies suggest an analgesic effect of glucosamine

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