

I'm Dr. Bob Arnot, a physician, a journalist who has covered osteoarthritis for 20 years for three different networks, an author who has written a book on OA called BEATING WEAR AND TEAR (Simon and Schuster 2003) and a patient who suffers from severe OA of the right hip and moderate of both knees. I'm a traditional physician and take only a small handful of supplements...fish oil, SamE and a Glucosamine/Chondroitin formula. In researching a book last year on OA, I took a careful look at Glucosamine/Chondroitin and the idea of prevention. In the news media we look not just at the sheer volume of data but at the one landmark study which changes the way medicine is practiced.

One of the most prominent studies was released in 2001. (Lourdes, Belgium): I'd like to review this study in brief, the citation: *Lancet* 2001; 357: 251-56.

Methods: 212 patients with knee osteoarthritis were randomly assigned 1500 mg sulphate oral glucosamine or placebo once daily for 3 years. Weightbearing, anteroposterior radiographs of each knee in full extension were taken at enrollment and after 1 and 3 years. Mean joint-space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum joint-space width was measured by visual inspection with a magnifying lens. Symptoms were scored by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index.

Findings: The 106 patients on placebo had a progressive joint-space narrowing, with a mean joint-space loss after 3 years of -0.31 mm (95% CI -0.48 to -0.13). There was no significant joint-space loss in the 106 patients on glucosamine sulphate: -0.06 mm (-0.22 to 0.09). Similar results were reported with minimum joint-space narrowing. As assessed by WOMAC scores, symptoms worsened slightly in patients on placebo compared with the improvement observed after treatment with glucosamine sulphate. There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups.

On the basis of this study, physicians I have canvassed at Johns Hopkins, Harvard and Stanford regularly recommend this to their patients as do I. As part of a regular program of strength and flexibility training, I began taking a Glucosamine/Chondroitin combination. I went from taking 16 Advil a day to none. I had not been able to ski, play tennis, run or hike. I have returned to all of those activities. I selected this product from a website that rated the quality of these products.

The biggest question before this panel today, is whether there is a biological marker for OA. I would argue strongly that the loss of cartilage is as good a biological marker as the gold standard markers of cholesterol or bone density.. The FDA in its tentative conclusions states Biomarkers are parameters from which the presence or risk of a disease can be inferred rather than being a measure of the disease itself. In conducting a health claim review, FDA does not rely on a change in a biomarker as a measurement of the effect of a dietary factor on a disease unless there is evidence that altering the parameter can affect the risk of developing that diseases or health related condition. This is the case with serum cholesterol in that high levels are generally accepted as a predictor of risk for coronary heart

disease. I'd argue strongly that preventing a bad event is prevention. In fact I can't think of a more obvious one than slowing or stopping the loss of articular cartilage. Decreased numbers of Heart attacks, the necessity for bypass surgery or PCTA serve as the events which measure the effectiveness of cholesterol lowering drugs. The key point is that bone on bone pain and the need for joint replacement that comes with the inexorable loss of cartilage is about as good as it gets when it comes to clinical events. I was supposed to have a hip replacement four years ago and have avoided that to date. I no longer take NSAIDS for pain.

The biggest problem area here appears to be at what point the patient is diagnosed with OA, since the FDA would argue that the Lancet study involves patients with disease rather than healthy individuals whose disease was prevented. Yet patients with high cholesterol can have dozens of hot, vulnerable plaques in their coronary arteries and yet have no symptoms and carry no diagnosis of Coronary Artery Disease. Still if their cholesterol is lowered because they are gauged to be at risk, and they do not suffer a bad event, the cholesterol lowering medication is judged to have prevented disease... even though they have not been diagnosed as heart disease patients. The same logic should apply here. Here's why.

The key with OA (osteoarthritis) is that x-ray changes PRECEED the clinical diagnosis and precede the onset of symptoms. Most people over 60 have disease on X-ray, and about one-third have actual symptoms. That means that the majority of individuals with x-ray changes and proven cartilage loss are not formally diagnosed with Osteoarthritis. So any treatment in this group would appear to prevent events. The great difficulty has been that the Millions of Americans are losing cartilage year in year out... yet are not diagnosed with osteoarthritis. This is a steady progressive loss that will result in many bad events... There are beneficial changes in the surrogate endpoints for the disease... less loss of cartilage, without dispute, delays the onset of a bad event...and the need for joint replacement surgery.

The biggest difficulty is the point at which a diagnosis can actually be made. Presumably, any events which are avoided before the patient has diagnosed disease, would constitute real prevention. To be clear, there is first a period of pure mechanical destruction of cartilage. I call this wear and tear. The British call this Arthrosis. Eric L Raidin MD... Prof Emeritus Tufts University says "Arthritis is a joint problem primarily from metabolic or inflammatory cause." That means that there is a transformation from a mechanical process to a chemical process.. Were is the dividing line between mechanical damage and chemical destruction? Simply stated, no clinician can measure that point. So, since x-ray changes are evident in the vast majority of older Americans well in advance of symptoms, this group would be an enormous population in which true prevention could be undertaken.

RISK BENEFIT: In any analysis of evidence based medicine, the risk benefit ratio is absolutely key. Let's first look at what happens with standard pain relievers. In a study by Rush Presbyterian St Luke's Medical Center, 53 subjects with symptomatic radiographic evidence of wear and tear arthritis of the knee were studied. They took acetaminophen relieving their pain. When gait was analyzed, those with

decreased knee pain tended to increase the load on the degenerated portion of their knee... loading the worn and torn cartilage with forces high enough to do further damage to the joint. Bottom line, traditional pain relievers may accelerate the destruction of cartilage.

Glucosamine/Chondroitin are called "**Incredibly safe compared to NSAIDS**" by Tim McAlindino of the BU Arthritis Center.

How safe? There are over 16500 deaths per year from NSAIDS. Many of those individuals who are taking NSAIDS, such as ibuprofen or aspirin, for arthritis. There have been none attributed to GC products that I am aware of.

AS you consider what the worst is that can happen with the use of Glucosamine/Chondroitin for the prevention of OA... it is that fewer patients will die from the catastrophic effects off NSAIDS. There are no reported deaths from Glucosamine/Chondroitin. The best is that the loss of cartilage is prevented. What physician wants to bet against GC, given the risk of developing OA and the complications of its treatment.

Who should take preventive GC?: The field of osteoarthritis prevention is virtually nonexistent. Knee OA can be as disabling as any cardiovascular disease except stroke yet there is nothing being offer in terms of prevention. GC is a great first step at the point of sale to educate consumers about what they can do. Who is at risk?

-Osteoarthritis affects an estimated 20.7 million Americans, mostly after age 45

-Women are more commonly affected than men

-Those with Joint injuries due to sports, work related activity or accidents.

-Those with faulty biomechanics due to a Pistol Grip Hip, knock need condition, bow leggedness, cavus foot, hypermobile foot, past ACL injuries.

OA is a disease that every American will get if they live long enough, yet there is no prevention of any kind at present. This results in billions of dollars in disability and the loss of thousands of lives.