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Glucosamine for osteoarthritis: magic, hype, or confusion?

It's probably safe—but there's no good evidence that it works

People with joint pain, including those with osteoarthritis, are consuming large quantities of glucosamine as a result of a huge volume of recent media coverage on its possible value. Reviews and leading articles in medical journals have variously labelled it a magical new treatment,[1] criticised the "hype,"[2] or, more commonly, been non-committal.[3] Perhaps we are just confused.

Glucosamine is a sugar, a sulphated aminomonosaccharide, one of the constituents of the disaccharide units present in articular cartilage proteoglycans. In vitro work has shown that it can alter chondrocyte metabolism, and this is the rationale usually given for its use in osteoarthritis.[4] However, it is unclear whether oral glucosamine can reach chondrocytes in vivo,[3] and in addition to the oral compound (the commonly available form), injectables and local preparations have been subjected to clinical trial.[5–8] The most appropriate dose and route of administration remain unknown. We do not even seem to know how to classify it: is it a drug, a food supplement, a nutriceutical, or a complementary therapy?

Osteoarthritis is a heterogeneous and poorly understood condition. It is a common, age related cause of pain and physical disability in older people. In clinical practice any regional joint pain in an older person may be labelled as due to osteoarthritis, a concept reinforced by the almost ubiquitous radiographic changes.[9] However, the origin of pain caused by osteoarthritis is unclear, and regional joint pain in older people is often due to periarticular lesions or referred pain rather than articular problems.[10] Recent work also confirms that there is little relation between the severity of the radiographic changes and the severity of symptoms.[11]

There is confusion about what we are trying to do when we treat people with osteoarthritis, epitomised by the glucosamine literature. A reasonable objective is the reduction of pain, stiffness, and other symptoms that arise from a joint as a result of osteoarthritis, with the plausible goal of a secondary reduction in disability. But why should we expect an agent that affects articular cartilage to have any effect on symptoms? There are no nerves in articular cartilage.[10] In addition, examination of the glucosamine literature shows that investigators have used several different patient related outcome measures, often mixing up different domains of outcome. An agent that affects cartilage might conceivably affect the radiographic changes of osteoarthritis, but why should we want to try to alter the radiographic changes when there is no relation between their severity and the clinical expression of the disease?[11]

Nevertheless, a race is on among pharmaceutical companies to find agents that do alter the radiographic progression of osteoarthritis, in the belief that this will be followed by proof that this results in less long term morbidity and fewer joint replacements. That concept remains to be proved, though a recent report in the *Lancet* suggests that glucosamine and its makers may have won the race.[5]

So how good is the evidence that glucosamine alters either the symptomatic expression of osteoarthritis or its radiographic progression? Actually, not very good. Indeed, something amusing seems to be happening as a result of our evidence based approach to new therapies. Glucosamine may become the first agent about which we have more published systematic reviews, editorials, meta-analyses, and comments than we do primary research papers. Our literature search identified nine reviews (and many editorials and comments), but only 24 primary studies (three of which were on combined therapies that included glucosamine). Other overviews, including a Cochrane systematic review, are in the pipeline. Perhaps we could have got away with examining other peoples' reviews, but we have studied most of the trial publications as well.

We agree with McAlindon et al[12] and Delafuente,[13] who complain that most of the primary studies are poor and most of the trials too small. To be fair, the reviews and meta-analyses are dominated by trials done several years ago, many of which were particularly poor, and the quality of more recent studies is clearly better. But we have two additional concerns about the existing evidence. Firstly, much of the research is sponsored by companies making glucosamine. Company sponsorship affects the likelihood of positive results in trials of non-steroidal anti-inflammatory drugs,[14 15] and the same bias will probably exist with glucosamine. We identified 12 trials with clear involvement by a company producing the product: all these trials gave positive results. Nine other studies reported positive findings but we could not ascertain the source of funding. Conversely, of the three trials that reported a negative effect, only one reported commercial funding. Secondly, most reviews have not been able to take account of the possible effects of publication or language bias.[12 16 17] So, though much of the research points to glucosamine being a safe and effective treatment for osteoarthritis, problems with bias and quality mean that these results must be treated with caution.

We conclude that there is more confusion and hype than magic about glucosamine. The rationale for its use is unclear, the best dose and route of administra-

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tion unknown, and the published trials do not allow any conclusion about its efficacy (let alone its effectiveness or cost effectiveness). In its defence it does seem to be very safe—and any safe, effective compound used for osteoarthritis could do much good, even if the effect size is small. However, given the confusion we cannot recommend its wholesale use. We need large clinical trials, without company interference.

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Twenty years of AIDS, and no end in sight

A BMJ theme issue will refocus attention on this catastrophic epidemic

A Martian researcher is sent to earth. His mission is to assess a pandemic sweeping the southern hemisphere. On returning to Mars he files his report: "Human beings are undergoing one of the greatest catastrophes in recorded history. The epidemic rages far beyond their control and is steadily gaining momentum. Widespread misery, the devastation of communities, and death outpace the inconsequential expenditures of governments in denial. Nothing stands in its way."

All this began without fanfare. In 1981 the *Morbidity and Mortality Weekly Report* published a small case series of five gay men in Los Angeles who had *Pneumocystis carinii*—a rare form of pneumonia usually found in people with immune dysfunction.[1] Since then, the disease has left 23 million dead; it will have killed 55 million by 2010. Africa suffers most of the disease burden. India is next in line.

Why did the Martian's report fail to mention the United Nations Secretary General's call for a $10bn (£7bn) global health and AIDS fund?[2] Because the international response has been feeble. President Bush has pledged only $200m, when a donation of $2.5bn would have been consistent with his country's wealth.[3] Worse, as the southern pandemic spirals out of control, northern development assistance has fallen to its lowest level in 20 years.[4]

Drug company discounting of various medications is largely immaterial since the most heavily indebted countries still cannot afford them. And heterosexual transmission rates, and thus incidence, will probably remain high in many southern regions with or without medications.

The HIV tragedy in the south must be foremost on every country's agenda. The *BMJ* wants to help by publishing a theme issue in January 2002 on "Global voices on the HIV catastrophe." By focusing on the south, we aim to boost international and cross-cultural understanding and cooperation. We want to stimulate inquiry, attract high quality research, and collect outstanding educational materials to improve clinical practice among all people infected or affected by HIV.

Among other topics, the issue will include the long term care of AIDS orphans, influencing the social status of women, reducing mother-to-child transmission, the opportunities and pitfalls of an HIV vaccine, and prospects for an effective response by the global health community. We welcome your manuscripts for any section of the journal, but particularly research papers on the HIV epidemic in the developing world. The closing date for submissions is 1 August 2001; please email them to papers@bmj.com.

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