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On The COVER

A Novel Approach In The Treatment of Arthritis

Suprising new discoveries reveal the underlying cause of age-related cartilage breakdown and what can be done about it

Osteoarthritis & Rheumatoid Arthritis

What's the difference?

Can arthritis be prevented or cured?

New research is shedding light on old, natural remedies and opening up new treatment possibilities.

by Karin Granstrom Jordan, M.D.

Arthritis is all too well known by most of us as a source of discomfort and pain. There are different forms of arthritis, however, with distinctive symptoms and prognosis.

Osteoarthritis is the most common form. It is the kind that seems to come with the wear-and-tear process of aging, affecting approximately 70-80% of the population over age 50. The onset is marked by morning stiffness, crackling joints and perhaps some pain. As it gets worse it causes discomfort, pain and disability in varying degrees for millions of people. It also causes an enormous consumption of painkillers and anti-inflammatory drugs that many times have undesirable long-term effects. Does it have to be this bad?

Modern medicine does not have much to offer for these chronic conditions, only symptomatic, temporary relief. Painkillers and the so called NSAIDs, non-steroidal anti-inflammatory drugs, are effective in reducing symptoms quickly but often cause serious side effects such as ulcers and gastrointestinal bleeding, and do not stop the progression of the disease. In the long run they have actually proven to worsen the condition by accelerating joint destruction.

The last few years of research, however, have brought some hope to this dismal picture. Old herbal remedies such as ginger, nettle and willow bark, as well as fish oils and the already well known cartilage constituents glucosamine sulphate and chondroitin sulphate, are about to revolutionize the treatment of arthritis. These substances not only give symptomatic relief but actually intervene at the root of the problem and help the body to rebuild functioning joints.

Osteoarthritis

Osteoarthritis(OA)/arthrosis is a disease mainly characterized by degenerative processes of the articular cartilage, but changes also involve the synovial membrane and the bone next to the cartilage. It is a gradual decay that most often affects the weight bearing joints (knees, hips and spinal joints) and the joints of the hand. A breakdown of the cartilage matrix leads to cracks and ulcers and a thinning of the cartilage with a loss of shock absorption. The underlying bone starts to thicken as a response to the increasing stress and bone spurs are formed. In the advanced phases of osteoarthritis, an inflammatory reaction in the synovial membrane can be seen. This severe degeneration causes pain, swelling, deformation and reduced range of motion.

Traditionally osteoarthritis has been connected to aging, obesity and repeated mechanical joint stress. Predisposing factors such as trauma or inherited abnormalities are also known to trigger degenerative changes and cause secondary osteoarthritis at even younger ages. New research is beginning to shed light on how osteoarthritis develops at the cellular and molecular levels.

Evidence is accumulating that the culprits may be factors called cytokines together with enzymes that break down the collagen matrix. Cytokines are proteins that carry messages between cells and regulate immunity and inflammation. Two cytokines, tumor necrosis



factor alpha (TNF-a) and interleukin one beta (IL-1b), play an essential role in the cartilage destruction and inflammation process (Feldman et al., 1996). They have been found in elevated levels in both the synovial membrane, the synovial fluid and the cartilage of osteoarthritis patients. In animal models it was shown that inhibition of TNF-a results in decreased inflammation, while inhibition of IL-1b effectively prevents cartilage destruction (Plows D et al., 1995).

TNF-a has proven to be an even more important factor in rheumatoid arthritis (RA), where it is a key factor in promoting inflammation and damage to cartilage and bone (Bertolini et al, 1986; Saklatvala J, 1986).

Rheumatoid arthritis

Unlike osteoarthritis, RA is a so-called autoimmune disease, characterized by chronic inflammation and thickening of the synovial lining in addition to cartilage destruction. In autoimmune diseases the immune system attacks body tissues as if they were foreign invaders. As in most other chronic inflammatory diseases, the etiology and pathogenesis of RA is poorly understood. Contributing factors are thought to include food allergies, leaky gut syndrome, hereditary factors and microbes.

RA affects approximately 3% of the population, striking women three times as often as men. The typical onset is at the age of 20-40. The clinical picture varies from mild chronic joint inflammation with occasional flare-ups to painfully deformed joints. The disease is often accompanied by low-grade fever, weight loss and a general feeling of sickness and soreness.

Biochemical mechanisms

The destruction of cartilage and bone in both OA and RA is currently believed to be due mainly to the action of matrix enzymes (metalloproteinases), which include collagenases and stromelysins (Birkedal-Hansen H et al., 1993; Hill et al., 1994). These enzymes are under the control of cytokines such as IL-1b and TNF-a, which are known to be highly activated in rheumatoid arthritis. Some of the enzymes have pro-inflammatory characteristics and some have anti-inflammatory properties. The varying balance between these forces probably accounts for the variation in disease activity as it flares up and subsides.

Inflammation is a living tissue response to mechanical, chemical and immunological challenge. It is characterized by high levels of arachidonic acid metabolites, which are metabolized along two different enzymatic pathways: cyclooxygenase and lipoxygenase, leading to prostaglandin PGE2 and leukotriene LTB4, which are the most prominent metabolites and important mediators of inflammation (Srivastava KC et al., 1992). They play a crucial role in arthritis by causing resorption of bone, stimulating the secretion of collagenase and inhibiting the formation of proteoglycans.

Data from many studies confirm the important role of TNF-a in regulating production of both inflammatory and anti-inflammatory mediators in RA. Because of the demonstrated excess of pro-inflammatory cytokines, such as TNF-a, it was hypothesized that a blockade of TNF-a should be beneficial. Several experimental as well as clinical studies have been conducted with anti-TNF-a antibody. (Paulus HE et al., 1990). The results have confirmed that TNF-a is a good therapeutic target in RA.

A placebo-controlled trial by Feldman et al. (1997), provided the first convincing evidence that blockade of a specific cytokine could be effective treatment in human autoimmune or inflammatory diseases. Interesting results with TNF-a blockade have also been achieved in trials conducted on Crohn's disease, sepsis and HIV/AIDS.

The effectiveness and reproducibility of short-term anti-TNF-a antibody therapy, which has severe limitations, has stimulated the development of more convenient and practical alternatives to this kind of therapy. Interestingly enough, the leaf of the common nettle plant has recently been shown to lower TNF-a levels.

Nettle Leaf (Urtica Dioica)

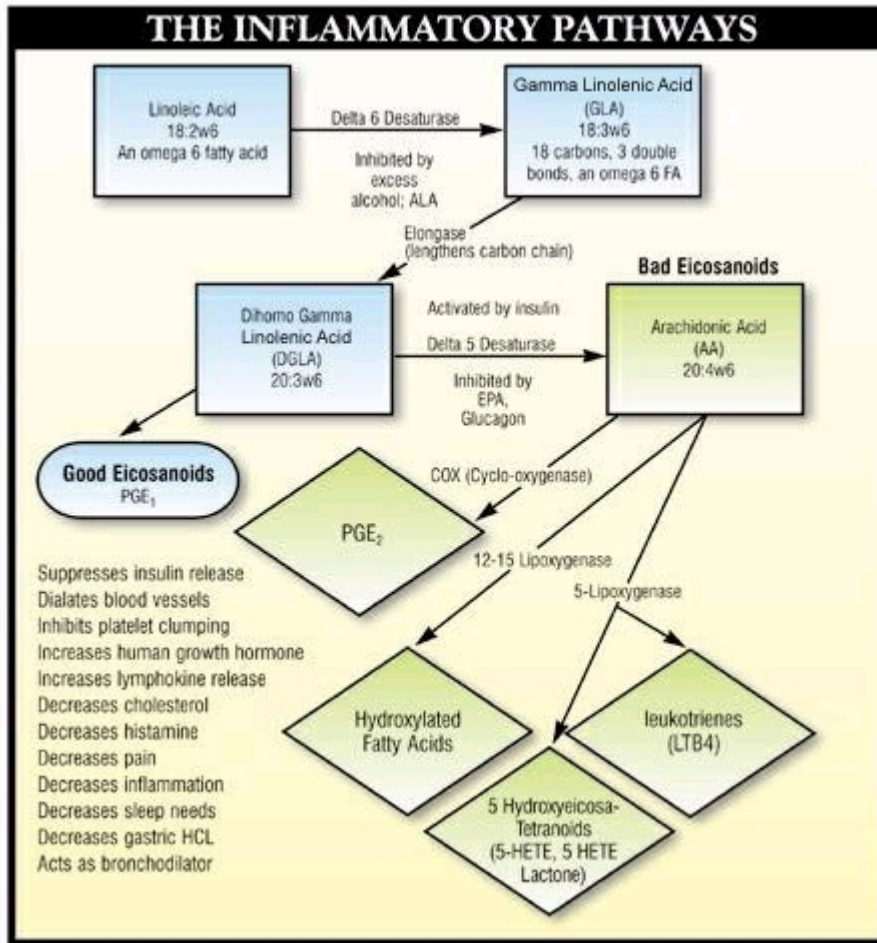
Nettle leaf is an herb that has a long tradition of use as an adjuvant remedy in the treatment of arthritis in Germany. Nettle leaf extract has recently been found to contain a variety of active compounds, such as cyclooxygenase and lipoxygenase inhibitors and substances that affect cytokine secretion (Obertreis et al., 1996; Teucher et al., 1996).

Not only does nettle leaf reduce TNF-a levels, as mentioned above, but it has recently been demonstrated that it does so by potently inhibiting the genetic transcription factor that activates TNF-a and IL-1b in synovial tissue (Riehemann K et al., 1999). This proinflammatory transcription factor, known as nuclear factor kappa beta (NF-kb), is known to be elevated in chronic inflammatory diseases and is essential to activation of TNF-a. Nettle is thought to work by preventing degradation of the natural inhibitor of NF-kb in the body. It has also been shown that TNF-a activates NF-kb in synovial cells, leading to the suggestion that a cycle of cross-activation between TNF-a and NF-kb may sustain and amplify the disease process in rheumatoid arthritis (Jue DM et al., 1999).

A study on healthy volunteers showed the anti-inflammatory potential of nettle (Obertreis B, 1998). Lipopolysaccharide was used to stimulate and increase the secretion of proinflammatory cytokines. When nettle extract was given simultaneously in a dose dependent manner, TNF-a and IL-1b concentration was significantly reduced.

Another study conducted on forty patients suffering from acute arthritis compared the effects of 200 mg of a NSAID (diclofenac) with

50 mg of the NSAID in combination with 50 g of stewed nettle leaf per day (Chrubasik S et al., 1997). Total joint scores improved significantly in both groups by approximately 70%. The nettle leaf extract clearly enhanced the anti-inflammatory effect of the NSAID. The addition of nettle extract made possible a 75% dose reduction of the NSAID, while still retaining the same anti-inflammatory effect with reduced side effects.



Ginger

Ginger (*Zingiber officinale*) is mostly known to us in the West as a spice and a flavor. In China, however, it has been used for thousands of years for medicinal purposes, such as nausea, stomachache, rheumatism and toothache. Modern research has found ginger to be a powerful anti-oxidant and to have strong anti-inflammatory effects.

The pharmacologically active components of the ginger root are thought to be aromatic ketones known as gingerols. These have been shown in experimental studies to inhibit both the cyclooxygenase and lipoxygenase pathways and the production of prostaglandins, thromboxane and leukotrienes (Kiuchi F et al., 1992; Srivastava KC, 1986; Flynn DL et al., 1986), just as the NSAIDs do. No significant side effects have been reported.

Ginger oil is obtained by steam distillation of dried ginger root. In an experimental study on rats (Sharma JN et al., 1997), arthritis was induced in the knee and paw by injection of bacilli, leading to inflammation. One group of rats was also given ginger oil by mouth for 28 days starting the day before the injection. The rats given ginger oil had less than half the knee and paw inflammation compared to the controls.

Glucosamine sulfate

Among the natural therapies for osteoarthritis glucosamine sulfate is probably the best known. It is extensively used as a drug for osteoarthritis in Europe, and it has been readily available in health food stores in the United States in recent years.

Glucosamine is a naturally occurring substance in the body, synthesized in the chondrocytes. In osteoarthritis this synthesis is defective and insufficient and supplementation with glucosamine has proven to be useful. The body uses supplemented glucosamine to synthesize the proteoglycans and the water-binding glycosaminoglycans (GAGs) in the cartilage matrix. In addition to providing raw material, the presence of glucosamine seems to stimulate the chondrocytes in their production of these substances. Glucosamine also inhibits certain enzymes, which destroy the cartilage, e.g. collagenase and phospholipase. By blocking pathogenic mechanisms that lead to articular degeneration, glucosamine delays the progression of the disease and relieves symptoms even for weeks after termination of the treatment (Qiu GX et al., 1998).

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