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Pathophysiology, pharmacological study of joint disorders and role of nutrition in their the management

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Abstract
Drugs play an important role in the therapy of rheumatoid arthritis (RA). Five classes of drugs are used currently, such as Analgesics, Non-Steroidal Anti-inflammatory drugs (NSAIDs), glucocorticoids, biologic &non-biologic and Disease Modifying anti-rheumatic drugs (DMARDS eg: Methotrexate). Currently, anti-TNF (Anti-Tumor Necrosis Factor) is the commonly used first line drug is abatacept. There is some evidence that tocilizumab is the most effective biologic as a monotherapy agent. The pharmacological treatment of knee osteoarthritis (OA) is a purely symptomatic therapy. Doxycycline is a tetracycline antibiotic that has been shown to induce the inhibition of cartilage matrix metalloproteinases (MMPs) and slow down the progression of structural damage to the affected joint. Hence it has been recommended as a disease-modifying therapy for OA. Regular exercise and stretching can improve flexibility, relieve stiffness, and improve overall physical condition. Physical therapy can help strengthen the muscles around specific joints. Supportive devices, such as braces, splints, and kinesiology tape, can help stay active. In some cases NSAIDS and joint replacement is not suitable, hence using strong pain killers such as codeine, hydrocodone, or oxycodone can help people with OA pain.

Keywords: Biologic, non-biologic, DMARDs, NSAIDS, pain relievers, joint replacement

Introduction

Arthritis

Arthritis is a term often used to mean any disorder that affects joints. Symptoms generally include joint pain and stiffness. Other symptoms may include redness, warmth, swelling, and decreased range of motion of the affected joints. In some types of arthritis, other organs are also affected. Onset can be gradual or sudden.

There are over 100 types of arthritis. The most common forms are osteoarthritis (Degenerative joint disease) and rheumatoid arthritis. Osteoarthritis usually occurs with age and affects the fingers, knees, and hips. Rheumatoid arthritis is an autoimmune disorder that often affects the hands and feet. Other types include gout, lupus, fibromyalgia, and septic arthritis. They are all types of rheumatic disease.

Treatment may include resting the joint and alternating between applying ice and heat. Weight loss and exercise may also be useful. Recommended medications may depend on the form of arthritis. These may include pain medications such as ibuprofen and paracetamol (Acetaminophen). In some circumstances, a joint replacement may be useful.

Osteoarthritis affects more than 3.8% of people, while rheumatoid arthritis affects about 0.24% of people. Gout affects about 1–2% of the Western population at some point in their lives. In Australia about 15% of people are affected by arthritis, while in the United States more than 20% have a type of arthritis. Overall the disease becomes more common with age. Arthritis is a common reason that people miss work and can result in a decreased quality of life. The term is derived from *arthr-* (meaning 'joint') and *-itis* (Meaning 'inflammation'). There are several diseases where joint pain is primary, and is considered the main feature.

Generally when a person has "arthritis" it means that they have one of these diseases, which include:

- Rheumatoid arthritis
- Gout and pseudo-gout
- Osteoarthritis
- Septic arthritis
- Ankylosing spondylitis
- Juvenile idiopathic arthritis
- Still's disease
- Psoriatic arthritis

Epidemiology of Major joint disorders

Arthritis is predominantly a disease of the elderly, but children can also be affected by the disease. Arthritis is more common in women than men at all ages and affects all races, ethnic groups and cultures. In the United States a CDC survey based on data from 2013 to 2015 showed 54.4 million (22.7%) adults had self-reported doctor-diagnosed arthritis, and 23.7 million (43.5% of those with arthritis) had arthritis-attributable activity limitation (AAAL). With an aging population, this number is expected to increase. Adults with co-morbid conditions, such as heart disease, diabetes, and obesity, were seen to have a higher than average prevalence of doctor-diagnosed arthritis (49.3%, 47.1%, and 30.6% respectively).

Disability due to musculoskeletal disorders increased by 45% from 1990 to 2010. Of these, osteoarthritis is the fastest increasing major health condition. Among the many reports on the increased prevalence of musculoskeletal conditions, data from Africa are lacking and underestimated. A systematic review assessed the prevalence of arthritis in Africa and included twenty population-based and seven hospital-based studies. The majority of studies, twelve, were from South Africa. Nine studies were well-conducted, eleven studies were of moderate quality, and seven studies were conducted poorly. The results of the systematic review were as follows:

- **Rheumatoid arthritis:** 0.1% in Algeria (Urban setting); 0.6% in Democratic Republic of Congo (Urban setting); 2.5% and 0.07% in urban and rural settings in South Africa respectively; 0.3% in Egypt (Rural setting), 0.4% in Lesotho (rural setting)
- **Osteoarthritis:** 55.1% in South Africa (urban setting); ranged from 29.5 to 82.7% in South Africans aged 65 years and older
- Knee osteoarthritis has the highest prevalence from all types of osteoarthritis, with 33.1% in rural South Africa.
- **Ankylosing spondylitis:** 0.1% in South Africa (Rural setting)
- **Psoriatic arthritis:** 4.4% in South Africa (Urban setting)
- **Gout:** 0.7% in South Africa (Urban setting)
- **Juvenile idiopathic arthritis:** 0.3% in Egypt (Urban setting)

Rheumatoid Arthritis (RA)

Pathophysiology

Rheumatoid arthritis (RA) primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in joints and other organs where it manifests. The clinical manifestations of disease are primarily inflammation of the synovial membrane and joint damage, and the fibroblast-like synoviocytes play a key role in these pathogenic processes. Three phases of progression of RA are an initiation phase (Due to non-specific inflammation), an amplification phase (Due to T cell activation), and chronic inflammatory phase, with tissue injury resulting from the cytokines, IL-1, TNF-alpha, and IL-6 [17-19].

Non-specific inflammation

Factors allowing an abnormal immune response, once initiated, become permanent and chronic. These factors are genetic disorders which change regulation of the adaptive immune response. Genetic factors interact with environmental risk factors for RA, with cigarette smoking as the most clearly defined risk factor.

Other environmental and hormonal factors may explain higher risks for women, including onset after childbirth and hormonal medications. A possibility for increased susceptibility is that negative feedback mechanisms – which normally maintain tolerance – are overtaken by positive feedback mechanisms for certain antigens, such as IgG Fc bound by rheumatoid factor and citrullinated fibrinogen bound by antibodies to citrullinated peptides (ACPA: Anti citrullinated protein antibody). The relative roles of B-cell produced immune complexes and T cell products in inflammation in RA has continued for 30 years, but neither cell is necessary at the site of inflammation, only auto antibodies to IgGFc, known as rheumatoid factors and ACPA, with ACPA having an 80% specificity for diagnosing RA. As with other autoimmune diseases, people with RA have abnormally glycosylated antibodies, which are believed to promote joint inflammation.

Amplification in the synovium

Once the generalized abnormal immune response has become established, which may take several years before any symptoms occur, plasma cells derived from B lymphocytes produce rheumatoid factors and ACPA of the IgG and IgM classes in large quantities. These activate macrophages through Fc receptor and complement binding, which is part of the intense inflammation in RA. Binding of an auto reactive antibody to the Fc receptors is mediated through the antibody's N-glycans, which are altered to promote inflammation in people with RA. This contributes to local inflammation in a joint, specifically the synovium with edema, vasodilatation and entry of activated T-cells, mainly CD4 in microscopically nodular aggregates and CD8 in microscopically diffuse infiltrates.

Synovial macrophages and dendrite cells function as antigen presenting cells by expressing MHC class II molecules, which establishes the immune reaction in the tissue.

Signs and symptoms

Pain, which can vary in severity, is a common symptom in virtually all types of arthritis. Other symptoms include swelling, joint stiffness, redness, and aching around the joint (s) [1-3]. Arthritic disorders like lupus and rheumatoid arthritis can affect other organs in the body, leading to a variety of symptoms. Symptoms may include:

- Inability to use the hand or walk
- Stiffness in one or more joints
- Rash or itch
- Malaise and fatigue
- Weight loss
- Poor sleep

- Muscle aches and pains
- Tenderness
- Difficulty moving the joint

It is common in advanced arthritis for significant secondary changes to occur. For example, arthritic symptoms might make it difficult for a person to move around and/or exercise, which can lead to secondary effects.

A healthy diet

The comfortable diet suggesting to patients are encouraged to follow a healthy, balanced diet that fosters a healthy weight. It is important to avoid elimination diets and fad nutritional practices and to be cautious of claims of miracle cures.

- Eat a variety of foods
- Balance the food you eat with physical activity, maintain or improve your weight
- Choose a diet with plenty of grain products and vegetables, and fruits
- Choose a diet low in fat, saturated fat and cholesterol
- Choose a diet moderate in sugars
- If you drink alcoholic beverages, do so in moderation

Always encourage patients to eat "real food." This means avoiding processed foods which often contain high levels of preservatives, extra sugar and saturated fats.

Pharmacology of drugs

Drugs used for the treatment of rheumatoid arthritis

Pharmacological Strategies

- There are three general classes of drugs commonly used in the treatment of rheumatoid arthritis: Non-Steroidal Anti-inflammatory agents (NSAIDs), corticosteroids, and Disease Modifying Anti Rheumatic Drugs (DMARDs).
- NSAIDs and corticosteroids have a short onset of action while DMARDs can take several weeks or months to demonstrate a clinical effect.
- DMARDs include methotrexate, sulfasalazine, leflunomide, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, abatacept, rituximab, tocilizumab, anakinra, antimalarials. Other immunomodulators are occasionally used including azathioprine (Imuran) and cyclosporine. Because cartilage damage and bony erosions frequently occur within the first two years of disease, rheumatologists now move aggressively to a DMARD agent early in the course of disease, usually as soon as a diagnosis is confirmed.
- Analgesic drugs are also sometimes helpful in decreasing pain until DMARDs take effect. A summary table of how to monitor drug treatment in rheumatoid arthritis is included.

Non-steroidal Anti-inflammatory Agents (NSAIDs)

The major effect of these agents is to reduce acute inflammation thereby decreasing pain and improving function. All of these drugs also have mild to moderate analgesic properties independent of their anti-inflammatory effect. It is important to note however that these drugs alone do not change the course of the disease of rheumatoid arthritis or prevent joint destruction.

Aspirin is the oldest drug of the non-steroidal class, but because of its high rate of GI toxicity, a narrow window between toxic and anti-inflammatory serum levels and the inconvenience of multiple daily doses, aspirin's use as the initial choice of drug therapy has largely been replaced by other NSAIDs. There are a large number of NSAIDs from which to choose, and at full dosages all are potentially equally effective. Likewise, the toxicities of the currently available NSAIDs are similar. However, there is a great deal of variation in tolerance and response to a particular NSAID. Many different NSAIDS are available, some over the counter including ibuprofen, Nuprin and naproxen and many others are available by prescription including meloxicam, etodolac, nabumetone, sulindac, tolementin, choline magnesium salicylate, diclofenac, Voltaren, Arthrotec, diflusinal, indomethacin, ketoprofen, meloxicam, oxaprozin, and piroxicam.

Longer acting NSAIDs that allow daily or twice daily dosing may improve compliance. The NSAID class also includes drugs known as COX-2 inhibitors that are also effective in controlling inflammation. Only one of these agents is currently available in the United States (Celecoxib) while additional compounds are available in other countries (Etoricoxib, Arcoxia, lumiracoxib, Prexige). These drugs were designed to decrease the gastrointestinal risk of NSAIDS, but concerns of possible increases in cardiovascular risk with these agents has led to the withdrawal of two of these drugs from the market (Rofecoxib, Vioxx, valdecoxib, Bextra) [13-16].

Mode of action

COX inhibitors divide into non-selective Nonsteroidal Anti-inflammatory drugs (NSAIDs), COX-2 selective nonsteroidal anti-inflammatory drugs (c2s NSAIDs), and Aspirin. NSAIDs include ibuprofen, naproxen, ketorolac, and indomethacin. C2s NSAIDs only include celecoxib. Meloxicam and diclofenac are cox-inhibitors that are not categorized. The COX enzyme catalyzes the conversion of arachidonic acid into prostaglandin. It has two known isoforms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). There are over 20 COX inhibitors, and each varies in the amount they inhibit each of the isoforms.

The COX-1 enzyme regulates many cellular processes, including platelet aggregation, kidney afferent arteriole vasodilation, and gastric mucosa acid protection.The COX-2 enzyme is an inducible enzyme and increases during inflammatory processes. It is present in the brain, kidney, bone, and female reproductive system. C2s NSAIDs work by preferentially inhibiting COX-2. Aspirin irreversibly inhibits both COX-1 and COX-2 but, more so, inhibits COX-1 than COX-2 [4-6].

NSAIDs inhibit the generation of prostaglandins by blocking cyclooxygenase enzymes, COX-1 and COX-2. Prostaglandins are mediators of inflammation and pain but also have important roles in maintenance of normal body functions including protection from stomach acid, maintenance of kidney blood flow, and contributing to platelet stickiness and vascular function. COX-2 selective inhibitors selectively block prostaglandins generated via COX-2 which have prominent roles in inflammation.

Dosage: While in some cases, lower doses of NSAIDS are effective, in rheumatoid arthritis and other forms of inflammatory arthritis a higher dose is required to decrease

inflammation. A lower dosage can initially be used if inflammation is mild. If the patient is elderly or if the patient suffers from conditions that increase the risk for toxicity. If a particular preparation is ineffective after a 4-week trial or is not tolerated, then another NSAID can be initiated. No one NSAID has been demonstrated to be better than another for the treatment of rheumatoid arthritis nor have the COX-2 agents been shown to be superior to traditional NSAIDS in terms of effectiveness.

Diagnosis

Diagnosis is made by clinical examination from an appropriate health professional, and may be supported by other tests such as radiology and blood tests, depending on the type of suspected arthritis. All arthritides potentially feature pain. Pain patterns may differ depending on the arthritides and the location. Rheumatoid arthritis is generally worse in the morning and associated with stiffness lasting over 30 minutes. However, in the early stages, patients may have no symptoms after a warm shower. Osteoarthritis, on the other hand, tends to be associated with morning stiffness which eases relatively quickly with movement and exercise. In the aged and children, pain might not be the main presenting feature; the aged patient simply moves less, the infantile patient refuses to use the affected limb.

Blood tests and X-rays of the affected joints often are performed to make the diagnosis. Screening blood tests are indicated if certain arthritides are suspected. These might include: rheumatoid factor, antinuclear factor (ANF), extractable nuclear antigen, and specific antibodies [7].

Osteoarthritis

Osteoarthritis is the most common form of arthritis. It affects humans and other animals, notably dogs, but also occurs in cats and horses. It can affect both the larger and the smaller joints of the body. In humans, this includes the hands, wrists, feet, back, hip, and knee. In dogs, this includes the elbow, hip, stifle (knee), shoulder, and back. The disease is essentially one acquired from daily wear and tear of the joint; however, osteoarthritis can also occur as a result of injury. Osteoarthritis begins in the cartilage and eventually causes the two opposing bones to erode into each other. The condition starts with minor pain during physical activity, but soon the pain can be continuous and even occur while in a state of rest. The pain can be debilitating and prevent one from doing some activities. In dogs, this pain can significantly affect quality of life and may include difficulty going up and down stairs, struggling to get up after lying down, trouble walking on slick floors, being unable to hop in and out of vehicles, difficulty jumping on and off furniture, and behavioral changes (e.g., aggression, difficulty squatting to toilet). Osteoarthritis typically affects the weight-bearing joints, such as the back, knee and hip. Unlike rheumatoid arthritis, osteoarthritis is most commonly a disease of the elderly. The strongest predictor of osteoarthritis is increased age, likely due to the declining ability of chondrocytes to maintain the structural integrity of cartilage. More than 30 percent of women have some degree of osteoarthritis by age 65. Other risk factors for osteoarthritis include prior joint trauma, obesity, and a sedentary lifestyle [9-12].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) treat pain. They also help to prevent painful inflammation and joint damage. They're the top choice of treatment for OA because they're effective and non-sedating. NSAIDs comes in oral and topical forms. There are many options, and some are available over the counter.

Aspirin

Aspirin is an OTC NSAID that treats pain and inflammation. It can help treat your OA symptoms to enhance your quality of life.

Ibuprofen

Ibuprofen (Advil, Motrin, IBU-Tab) is an NSAID available in both OTC and prescription strengths. Taking ibuprofen long term isn't recommended because of the risk of stomach bleeding and heart attack.

Naproxen (Naprosyn) and naproxen sodium (Aleve)

Naproxen (Naprosyn) and naproxen sodium (Aleve) are used to treat OA pain and inflammation.

Naproxen is only available by prescription. Naproxen sodium is available over the counter, and higher doses are also available in prescription forms. Some side effects of naproxen and naproxen sodium include:

- Heartburn
- Stomach pain
- Nausea
- Diarrhea
- Headaches
- Dizziness
- Drowsiness

Diclofenac and diclofenac-misoprostol (Arthrotec)

Diclofenac (Zipsor, Voltaren) is an NSAID that comes in both oral and topical forms. The oral drug Zipsor is available by prescription, while the topical drug Voltaren is available over the counter. The oral drug diclofenac-misoprostol (Arthrotec) combines diclofenac with a drug that protects against stomach ulcers. Diclofenac can cause side effects, which include: stomach pain, diarrhea and nausea.

Other NSAIDs for OA

These prescription NSAIDs are approved to treat the symptoms of OA:

- Celecoxib (Celebrex)
- Diflunisal
- Etodolac
- Fenoprofen (Nalfon)
- Flurbiprofen
- Indomethacin (Indocin)
- Ketoprofen
- Ketorolac
- Meclofenamate
- Mefenamic acid (Ponstel)
- Meloxicam (Mobic)
- Nabumetone
- Oxaprozin (Daypro)
- Piroxicam (Feldene)
- Sulindac
- Tolmetin

Healthy diet required for osteoarthritis

A. Vitamin C

Vitamin C is a vitamin and an antioxidant, body needs it to make cartilage, which protects the bones in the knee joint. It can also help remove free radicals.

- Tropical fruits such as papaya, guava, and pineapple
- Citrus fruits such as oranges and grapefruit
- Cantaloupe
- Strawberries
- Kiwi
- Cruciferous vegetables, such as cauliflower, broccoli, and kale
- Tomatoes

B. Vitamin D and calcium

Some scientists have suggested that vitamin D may help prevent or manage osteoarthritis, but the findings have been mixed.

Vitamin D helps the body absorb calcium. Consuming foods with these nutrients may offer some protection.

Foods that contain vitamin D, calcium, or both include:

- Seafood such as wild-caught salmon, cod, sardines, and shrimp
- Canned fish, such as tuna
- Fortified milk and other dairy products
- Eggs
- Yogurt
- Green leafy vegetables

C. Beta carotene

Beta carotene is another powerful antioxidant. This can identify easily because it gives fruits and vegetables, such as carrots, their bright orange color. Beta carotene is beneficial for skin, eyes, and hair.

Other excellent sources include

Cruciferous vegetables, such as Brussels sprouts, collard greens, mustard greens, and chard, greens, such as romaine lettuce and spinach, sweet potatoes, winter squash, apricots, peppermint leaves, tomatoes and asparagus

D. Omega-3 fatty acids

Some studies trusted Source have suggested that having a higher intake of omega-3 fatty acids compared with omega 6 fatty acids may help prevent osteoarthritis.

Sources of Omega-3 fatty acids include

- Using omega-3 oils, such as olive oil, for cooking and salad dressings
- Eating oily fish twice a week
- Cutting down on red meats and other animal proteins
- Consuming a quarter cup of nuts or seeds a day

Foods that are good sources of omega-3 fatty acids are

- Salmon, either wild, fresh, or canned
- Sardines
- Omega-3-fortified eggs
- Ground flaxseed and flaxseed oil
- Walnuts

Omega-6 fatty acids are present in the sources

- Meat and poultry
- Cereals
- Eggs
- Nuts and seeds
- Some vegetable oils

Gout

Gout is caused by deposition of uric acid crystals in the joints, causing inflammation. There is also an uncommon form of gouty arthritis caused by the formation of rhomboid crystals of calcium pyrophosphate known as pseudogout. In the early stages, the gouty arthritis usually occurs in one joint, but with time, it can occur in many joints and be quite crippling. The joints in gout can often become swollen and lose function. Gouty arthritis can become particularly painful and potentially debilitating when gout cannot successfully be treated. When uric acid levels and gout symptoms cannot be controlled with standard gout medicines that decrease the production of uric acid (e.g., allopurinol) or increase uric acid elimination from the body through the kidneys (e.g., probenecid), this can be referred to as refractory chronic gout [8].

Treatment

There is no known cure for arthritis and rheumatic diseases. Treatment options vary depending on the type of arthritis and include physical therapy, exercise and diet, orthopedic bracing, and oral and topical medications. Joint replacement surgery may be required to repair damage, restore function, or relieve pain.

Physical therapy

In general, studies have shown that physical exercise of the affected joint can noticeably improve long-term pain relief. Furthermore, exercise of the arthritic joint is encouraged to maintain the health of the particular joint and the overall body of the person.

Individuals with arthritis can benefit from both physical and occupational therapy. In arthritis the joints become stiff and the range of movement can be limited. Physical therapy has been shown to significantly improve function, decrease pain, and delay the need for surgical intervention in advanced cases. Exercise prescribed by a physical therapist has been shown to be more effective than medications in treating osteoarthritis of the knee. Exercise often focuses on improving muscle strength, endurance and flexibility. In some cases, exercises may be designed to train balance. Occupational therapy can provide assistance with activities. Assistive technology is a tool used to aid a person's disability by reducing their physical barriers by improving the use of their damaged body part, typically after an amputation. Assistive technology devices can be customized to the patient or bought commercially.

Medications

There are several types of medications that are used for the treatment of arthritis. Treatment typically begins with medications that have the fewest side effects with further medications being added if insufficiently effective.

Depending on the type of arthritis, the medications that are given may be different. For example, the first-line treatment for osteoarthritis is acetaminophen (Paracetamol) while for inflammatory arthritis it involves non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen. Opioids and NSAIDs may be less well tolerated. However, topical NSAIDs may have better safety profiles than oral NSAIDs.

For more severe cases of osteoarthritis, intra-articular corticosteroid injections may also be considered.

The drugs to treat rheumatoid arthritis (RA) range from corticosteroids to monoclonal antibodies given intravenously. Due to the autoimmune nature of RA, treatments may include not only pain medications and anti-inflammatory drugs, but also another category of drugs called disease-modifying antirheumatic drugs (DMARDs). csDMARDs, TNF biologics and tsDMARDs are specific kinds of DMARDs that are recommended for treatment. Treatment with DMARDs is designed to slow down the progression of RA by initiating an adaptive immune response, in part by CD4+ T helper (Th) cells, specifically Th17 cells. Th17 cells are present in higher quantities at the site of bone destruction in joints and produce inflammatory cytokines associated with inflammation, such as interleukin-17 (IL-17).

Surgery

A number of rheum surgical interventions have been incorporated in the treatment of arthritis since the 1950s. Arthroscopic surgery for osteoarthritis of the knee provides no additional benefit to optimized physical and medical therapy.

Adaptive aids

People with hand arthritis can have trouble with simple activities of daily living tasks (ADLs), such as turning a key in a lock or opening jars, as these activities can be cumbersome and painful. There are adaptive aids or assistive devices (ADs) available to help with these tasks, but they are generally more costly than conventional products with the same function. It is now possible to 3-D print adaptive aids, which have been released as open source hardware to reduce patient costs. Adaptive aids can significantly help arthritis patients and the vast majority of those with arthritis need and use them.

Alternative medicine

Further research is required to determine if transcutaneous electrical nerve stimulation (TENS) for knee osteoarthritis is effective for controlling pain.

Low level laser therapy may be considered for relief of pain and stiffness associated with arthritis. Evidence of benefit is tentative.

Pulsed electromagnetic field therapy (PEMFT) has tentative evidence supporting improved functioning but no evidence of improved pain in osteoarthritis. The FDA has not approved PEMFT for the treatment of arthritis. In Canada, PEMF devices are legally licensed by Health Canada for the treatment of pain associated with arthritic conditions.

Conclusion

Now a day's people are not concentrating on their life style, because of busy life or stressful life or conditions may be affecting the several joint and cardiovascular diseases. Proper exercise and maintenance of balanced diet are very important requirements to sustain the life. Hence avoid the stress, maintaining proper balanced diet and continuous exercise will help to overcome the problems of joint diseases.

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