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Arthritis and Planning Conception

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Abstract

Arthritis is a form of joint disorder characterized by chronic inflammation in one or more joints that usually results in pain and is often disabling. Rheumatoid arthritis (RA) is a chronic, systemic, debilitating, chronic inflammatory autoimmune disease of synovial joints, which can lead to chronic pain and structural joint damage, as well as other organ involvement, especially if not adequately controlled. The etiology of RA is still unknown. Patients with rheumatoid arthritis have special family planning considerations that require a frank discussion and careful coordination with health care providers. More than 2/3rdof patients experience improvement or even remission of arthritis during gestation. The improvement in RA symptoms can be seen both with changing the eating pattern as well as with inclusion and exclusion of certain food items in the diet.

Osteoarthritis, commonly known as wear and tear arthritis, is a progressive disease of the elderly, but is also found in athletes and young individuals who use their joints more. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is widely used in the evaluation of Hip and Knee Osteoarthritis. Diet and exercise has a major role in alleviating the symptoms of osteoarthritis.

Arthritis- an Overview

The term arthritis is derived from the Greek words "artho" and "itis," meaning joint and inflammation, respectively. Arthritis is a form of joint disorder characterized by chronic inflammation in one or more joints that usually results in pain and is often disabling. Arthritis includes more than 100 different forms: the most common form is osteoarthritis, but other forms include rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases [1-2].

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic, debilitating, chronic inflammatory autoimmune disease of synovial joints, which can lead to chronic pain and structural joint damage, as well as other organ involvement, especially if not adequately controlled. Rheumatoid arthritis affects approximately 1% of the world population [3]. The disease severely impacts quality of life with increased morbidity and reduced life expectancy. Environmental factors blended with abnormal immune reactions and genetic factors are responsible for full expression of the disease. Because it can affect women in their reproductive years, care of pregnant women with RA requires a delicate balance of maintaining disease control while limiting potential toxicity to the fetus and neonate. While most women experience a substantial improvement in disease activity during pregnancy, for some women their RA remains active.

Etiopathogenesis

The etiology of RA is still unknown. The most significant genetic risk factors for rheumatoid arthritis are variations in human leukocyte antigen (HLA) class II genes, especially the HLA-DR1 and HLA-DR4 gene [4] that presumably interact with T cells. The frequency of HLA-DRB1 genes that encode for the so-called shared epitope, an amino acid motif in the third hyper variable chain of the DRβ1 chain, is increased in RA patients [5].The MHC (major histocompatibility complex) associations with RA also provide the clearest demonstration that the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies constitutes a distinct genetic subgroup of RA [6].

The early stages of RA are dominated by activated T cells (30–50% in thesynovia), mainly of the CD4+ T helper type. Failure of regulatory T cells to control autoimmune effector T cells, may contribute to the chronicity of joint inflammation. There is evidence for the dominance of T helper cell type 1 (Th1) cytokines in early stages of RA [7]. Later, T helper cell type 2 (Th2) features emerge. The chronic stage of arthritis is characterized by the presence of macrophages and their products.

The role of B cells in RA pathology has been highlighted by the clinical improvements in RA patients receiving B-cell-depleting therapies such as rituximab, an anti-CD20 antibody [8]. In addition to producing antibodies, pro inflammatory cytokines and chemokines, B cells efficiently act as antigen-presenting cells themselves and thus influence T-cell activation and expansion [9-10].

Other, non genetic factors are also believed to play a role in rheumatoid arthritis. These factors may trigger the condition in people who are at risk, although the mechanism is unclear. Potential triggers include changes in sex hormones (particularly in women), occupational exposure to certain kinds of dust or fibers, and viral or bacterial infections. Long-term smoking is a well-established risk factor for developing rheumatoid arthritis [11]; it is also associated with more severe signs and symptoms in people who have the disease. Early environmental factors such as high birth weight promote chances of development of RA and early start of breast feeding reduces chances of development of RA [12]. An altered intestinal micro biota has thus been implicated in the Etiopathogenesis of RA [13-15].

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Rheumatoid Arthritis and Family Planning

Patients with rheumatoid arthritis have special family planning considerations that require a frank discussion and careful coordination with health care providers. It is now well established through large observational prospective studies that women with RA often experience a spontaneous improvement or stabilization of their disease during pregnancy [16-17] but only to flare postpartum. Ideally, RA should be controlled for 3 to 6 months before attempting pregnancy. Women who have uncontrolled rheumatoid arthritis may be at increased risk of developing complications during pregnancy such as preterm birth and delivering small for their gestational age babies, requiring neonatal intensive unit care after birth.

As RA is a chronic, female-predominant inflammatory disease that may affect women and men during their reproductive years [18], it is found that some women with RA may experience sub fertility with majority facing an unexplained sub fertility or caused, to a lesser extent, by an ovulation [19-22]. It is increasingly being linked with the periconceptional use of NSAIDs [23]. Few authors have related the use of NSAIDs to the occurrence of luteinized unruptured follicle (LUF) syndrome [24-27], wherein ovulation is inhibited without changes in menstrual cycle length and cycle regularity and they may be treated as normal ovulating women. The second issue to be addressed is the limited frequency of intercourse due to painful joints [28]. Embryo implantation is however not compromised in RA patients as is shown by a higher pregnancy rates after IVF and IVF/ICSI (intracytoplasmic sperm injection) treatments in these women when compared to controls [29].

In females where RA is diagnosed before completion of their families, the time to pregnancy exceeds 12 months in as many as 36-42% of cases [30-31] as compared to 10-17% in general population [19,32-33].This longer duration to get pregnant can lead to more damage to the joint.

Preconceptional Counselling

As rheumatoid arthritis is becoming less disabling these days with better treatment modalities, more and more females are choosing to pursue pregnancy. Disease activity may decrease for some, but not for all pregnant women with RA. Preterm birth is more common among women with RA than among healthy women, which may be explained, in part, by disease activity and/or use of certain medications. Family planning consultation with Rheumatologist and Obstetrician before trying for conception is an essential prerequisite and should be done minimum three months prior to planning conception. There can be certain factors that can make conception more difficult. Screening for such factors is important, so also to change certain medications before conception and switching over to safer drugs which are not harmful for the fetus. Few lifestyle factors can negatively impact fertility. This allows to keep arthritis controlled in a way that may be safer for the offspring. Keeping arthritis under control is important since active inflammation can make it more difficult to conceive or increase the risk of negative pregnancy outcomes. Ingestion of any herbal formulas, supplements or vitamins need to be discussed in detail. Medicines should never be stopped on your own as it may worsen the existing condition. In case the health condition is not favourable and pregnancy is not advisable, contraception should be discussed in length. Contraception is safe for women with rheumatoid arthritis.

Changes to the diet, exercise or routine physical activity for weight management, and other lifestyle factors are advised. Its 'important to stay active during pregnancy, inculcating range-of-motion exercises in daily routine to keep the joints flexible. Certain symptoms unique to pregnancy can be seen in rheumatoid arthritis, such as low back pain, fatigue, nausea, swollen ankles, feet or hands.

Postpartum flares are very common. Therefore, visit to a rheumatologist should be a part of the postnatal care.

While discussing the preconception care with a couple, male partner needs to be taken into consideration. In case the male partner is suffering from RA, implications of DMARDs and biologics on male fertility and family planning need to be discussed. Currently, the existing data is very limited and only a few case reports are available on influence of these drugs on the male fertility.

Disease Manifestations

Rheumatoid arthritis is the most common single cause of chronic synovitis, affecting multiple diarthrodial joints in a characteristic distribution, leading to pain, deformities and a reduced quality of life. The disease is two to three times more common in women than in men, which may be related to hormonal factors.

RA is characterized by symmetrical polyarthritis, for example, if joints in the hand are affected, both hands tend to be involved [34] which gets worse after a long rest or on getting out of bed in the morning. The most common signs and symptoms are pain, swelling, and stiffness of the joints. Small joints in the hands and feet are involved most often, although larger joints (such as the shoulders, hips, and knees) may become involved later in the disease. The disease may appear in phases with flare ups and remissions and need not be persistent throughout life in milder cases. Continuous health issues related to disease may be seen in severe cases leading to severe joint damage restricting mobility.

The extra articular manifestations include subcutaneous nodules, lung disease, pericarditis, neuropathy, and vasculitis.The disease can also manifest with other signs and symptoms such as generalised weakness, a low grade fever, weight loss, anemia.Furthermore, patients with RA generally complain of gastrointestinal tract problems particularly dyspepsia (bloating, postprandial fullness, nausea, early satiety, epigastric pain, burning and belching), mucosal ulceration, and altered bowel habits (constipation/diarrhoea) [35].

Effects of Arthritis on Pregnancy

Every pregnancy is unique. More than 2/3rd of patients experience improvement or even remission of arthritis during gestation [36-38]. Most of these patients start seeing an improvement in symptoms by the end of the first trimester with the ease in symptoms sustaining throughout pregnancy.

In few patients where the disease is inadequately controlled, certain symptoms get exaggerated. Joint pain and pressure on joints may increase especially upon climbing the stairs. With weight gain and fluid retention in pregnancy, weight bearing joints like knees, ankles and feet may pain due to this increased pressure. Fluid retention may make the extremities swell but if swelling is severe, the causes may be different and this should be notified. With enlarging

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uterus, the pressure on the back and spine increases which can result in back pain, back muscle spasms, or numbness and tingling in the legs.

The diaphragm is pushed upwards as the pregnancy advances, leading to shortness of breath or at times dizziness. These symptoms should be discussed with both the rheumatologist and the obstetrician. Weight gain in pregnancy should be within the given range for a specific population. Measuring the BMI of the patients helps to allow a particular range of weight gain in pregnancy. Putting on extra kilos further weakens the damaged joints. Eating a balanced diet and keeping an active lifestyle is the key to success. A healthy exercise plan can be drafted for each patient.

As stated earlier, there is aslight increase in prematurity and intrauterine growth restriction in patients with active disease, whereas, in rest of the patients the course of pregnancy and outcome is favourable in RA [39-40].

One should use the same joint protection techniques which were always used to prevent pain and injuries: range-of-motion exercises, good posture, hot or cold packs on sore joints, splints or assistive devices for support, if the need arises, and good sleep habits. Wearing comfortable, supportive footwear prevents slips or falls.

Its also normal during pregnancy to feel irritated, anxious, tired or stressed out. Being pregnant and having a chronic rheumatic disease, with extra medical appointments, tests or concerns, can put a strain on the patient's emotions too. Talking to the doctor and discussing the questions and the concerns, may relax the woman.

An extra care is needed after delivery as relapse is certain in 90% of patients within the first 3 months [38].After delivery, the maternal system adjusts again to then on pregnant state. The postpartum flare of RA could be related to the following:

- Decrease in steroid hormones [41],
- The re-establishment of a Th1-dominated immune response, and
- The unopposed action of pro inflammatory cytokines [42].

Rheumatoid Arthritis Drug Safety in Pregnancy

The desire to start a family adds additional complexity to management decisions preconception, during pregnancy and following delivery, given the lack of safety data and potential teratogenicity of available therapies. Well-established data supporting the safe use of medications in pregnancy and lactation are available for a few medications, while for many others the safety profile is much less certain. It is important to tailor a treatment regimen that stabilises the woman's disease prior to conception, using medications that are safe to continue throughout pregnancy and postpartum. The drugs used for rheumatoid arthritis, in general, are:

- Non-steroidal anti-inflammatory drugs (NSAIDs),
- Glucocorticoids,
- Conventional synthetic DMARDs: methotrexate (MTX), cyclophosphamide,sulfasalazine, leflunomide, antimalarials, azathioprine, colchicine, ciclosporin, tacrolimus, mycophenolate mofetil (MMF),intravenous immunoglobulin (IVIG)
- Targeted syntheticDMARDs: tofacitinib.
- Biologic (biologic response modifier) DMARDs:
  - Tumour necrosis factor inhibitors (TNFi) (adalimumab, certolizumabpegol, etanercept, golimumab and infliximab),
  - The T cell co stimulation inhibitor abatacept,
  - The anti-B cell agents rituximaband belimumab,
  - The interleukin (IL)-6 receptor-blocking monoclonal antibody tocilizumab, and
  - The IL-1 receptor antagonistanakinra.

A European League Against Rheumatism (EULAR) task force [43], on anti rheumatic drugs during pregnancy and lactation, was established to define points to consider on use of anti rheumatic drugs before pregnancy, and during pregnancy and lactation by identifying and critically evaluating recent literature and registry data. EULAR is a multidisciplinary committee consisting of 20 members from 10European countries and the USA. According to this task force, the drugs can be used in the following manner:

Safe in Pregnancy: Hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.

Teratogenic Drugs: methotrexate, mycophenolate mofetil and cyclophosphamide

Limited Safety in Pregnancy: Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone are used only to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters.

Severe, refractory cases: Use of methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered.

Biologic DMARDs: Continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Over the last decade, tumour necrosis factor inhibitors have been used increasingly in the periconceptional treatment of women with RA, and appear to be safe [43] as compared to the earlier reports where the biologics including anti-TNF agents, were recommended to be stopped before pregnancy [44].

The major change in the EULAR consensus paper was the support given to TNFi use in first half of pregnancy. The paper suggested that the difference in placental transfer related to molecule structure and half-life needs to be taken into account when selecting a TNFi for women of fertile age. As a consequence, infliximab and adalimumab may preferentially be stopped at20 weeks, but can be continued throughout pregnancy, if indicated. Etanercept should preferably be stopped at week 30–32 of pregnancy but if needed, can be continued till term.

The safety of certolizumab in using it throughout pregnancy still needs further confirmation by extended published reports. But the current evidence indicates no increased rate of congenital malformations, therefore, certolizumabcan be continued throughout pregnancy, if necessary.

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Sound evidence forfetal/child safety is still lacking for golimumab, abatacept, tocilizumab, rituximab, belimumab and anakinra, but SLR and registry data do not suggest any evidence of harm from these agents when used before conception or in the first trimester.

In nearly 1/3rdto ½ of the cases, pregnancies are unplanned. As the woman gets to know that she is pregnant, it's already the 5-6th week of pregnancy, and organogenesis has already begun. It becomes difficult to manage such cases, especially, in women receiving Teratogenic drugs. Termination of pregnancy or continuation of pregnancy then becomes a major dilemma. Therefore, the women who are planning pregnancy in the near future should be switched over to the safer drugs compatible with pregnancy so that even if they enter pregnancy the drugs need not be changed.

Also the changing of drugs during pregnancy may flare up the disease, which becomes difficult to manage with the growing weight of the fetus. Another point of discussion is the effect of these drugs on the babies. Switching over to drugs that are considered safe in pregnancy should be a part of routine prenatal counselling but at the same time those drugs should not have any long term effects on children after birth. Studies on the long-term effects of drugs administered during pregnancy and/or breast feeding on child health and development are scarce, and often of low quality. The data available for azathioprine, ciclosporin and dexamethasone do not indicate immunosuppression in exposed children or raise special concern in regard to physical or neurological development. By contrast, biologics with extensive placental transfer achieving high serum levels in the child when administered after gestational week 30 might increase the risk of postnatal infection. Children exposed to biologics only before week 22 can receive vaccinations according to standard protocols including live vaccines. Children exposed at the late second and during the third trimester can follow vaccination programmes, but should not receive live vaccines in the first 6 months of life. When available, measurement of child serum levels of the biologic in question could guide the decision for or against a live vaccine.

Inheritance Pattern

The inheritance pattern of rheumatoid arthritis is unclear because many genetic and environmental factors appear to be involved. However, having a close relative with rheumatoid arthritis likely increases a person's risk of developing the condition.

Dietary Interventions in Rheumatoid Arthritis

Several studies advocate the role of altered microbiota in the gut of RA patients being responsible for pathogenesis as well as disease progression [14, 45-46]. Since RA is an inflammatory-destructive joint disease, a dysbiotic intestinal flora, characterized by the loss of beneficial bacteria and a concomitant increase in potentially pathogenic microbes, is associated with chronic inflammatory syndromes [14, 47].Recently, it has been confirmed that the spore-forming probiotic strain Bacillus coagulans may have anti-inflammatory and immune-modulating effects in both animals and humans. On the other hand, the prebiotic insulin also potentially influences immunity by changing the gastrointestinal microbiota composition and fermentation profile [48].

Loss of intestinal microbiota and obesity are important factors, playing a major role in the development and progression of the disease. Both can be corrected to a large extent through diet management [49]. Obese RA patients show a higher degree ofsynovitis even after remission is achieved [50].Obesity may increase RA activity. In a systematic review involving 13 studies on the relationship between serum leptin levels (a protein produced by adipocytes) and rheumatoid arthritis, it was found that plasma leptin level was significantly higher in the RA group than in healthy controls, especially in RA patients of Caucasian, Turkish, or Arab origin [51].

Role of certain Dietary Factors in Preventing Rheumatoid Arthritis

Diet plays a major role in any disease prevention or its progression, if adopted at an appropriate time. The improvement in RA symptoms can be seen both with changing the eating pattern as well as with inclusion and exclusion of certain food items in the diet.

Changing the Eating Pattern

Role of Therapeutic Fasting

Fasting has been practised for thousands of years and is a staple across many different religions and cultures around the globe. Today new varieties of fasting put a new twist on the ancient practice.

Several clinical studies have shown that therapeutic fasting produces anti-inflammatory effects. Fasting leads to an improvement of the symptoms in many patients with rheumatoid arthritis and is regularly used by the applicants for the treatment of rheumatoid arthritis according to various studies.

Fasting alters cellular metabolic pathways and affects immune function through its impact on cell trafficking and proinflammatory cytokine expression. There is a much ongoing debate in literature on Intermittent fasting (IF) and Fasting mimicking diets (FMDs). Popular examples of intermittent fasting are as follows [52-55]:

16/8 fasting diet: This is one of the most popular styles of fasting. Healthy eating is limited to a single 8-hour window every day and abstaining from food for the remaining 16 hours of the day. It is generally considered less restrictive, and more flexible than many other diet plans and can easily fit into just about any lifestyle. There are no strict rules and regulations. It is easy to follow and sustainable in the long term.

Restricting daily food intake may cause weakness, hunger, increased food consumption and weight gain. Animal studies show that intermittent fasting may impact men and women differently and may even interfere with fertility [56].

5:2 fasting diet: Healthy eating for 5 days per week, and limiting calories to between 500 for women and 600 for men for 2 days a week. Intermittent fasting seems to be easier to follow than continuous calorie restriction, at least for some people [57-58].

Also, many studies have shown that different types of intermittent fasting may significantly reduce insulin levels. One study showed that the 5:2 diet caused weight loss similar to regular calorie restriction. Additionally, the diet was very effective at reducing insulin levels and improving insulin sensitivity [59].

Alternate day fasting (ADF): Fasting every other day, and healthy eating during non-fasting days. Studies show that many people find alternate-day fasting much easier to stick to than traditional, everyday

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calorie restriction [60-61]. ADF seems to be particularly effective for weight loss among middle-aged people [62].

The most common version of this diet involves "modified" fasting, where it is allowed to consume 500 calories on fasting days. Research agrees that modified ADF with 500 calories on fasting days is much more tolerable than full fasts on fasting days [63]. Furthermore, combining ADF with endurance exercise may cause twice as much weight loss than ADF alone and six times as much weight loss as endurance exercise alone [64].Studies have shown that ADF doesn't increase compensatory hunger as much as continuous calorie restriction [65-66].Compensatory hunger refers to increased levels of hunger in response to calorie restriction, which cause people to eat more than they need to, when they finally allow themselves to eat.

Warrior Diet: Fasting over a 20-hour window and then eating one large meal during a 4-hour evening window.

One meal a day (OMAD): Fasting for 23 hours and eating daily calories during a1-hour window.

Fasting is an effective treatment for rheumatoid arthritis, but most patients relapse on reintroduction of food. The effect of fasting followed by one year of a vegetarian diet was assessed in a randomised, single-blind controlled trial by Kjeldsen-Kragh et al [67]. Twenty seven patients were allocated to a four-week stay at a health farm. After an initial 7-10 day subtotal fast, they were put on an individually adjusted gluten-free vegan diet for 3·5 months. The food was then gradually changed to a lacto vegetarian diet for the remainder of the study. A control group of 26 patients stayed for four weeks at a convalescent home, but ate an ordinary diet throughout the whole study period. After four weeks at the health farm, the diet group showed a significant improvement in number of tender joints, Ritchie's articular index, and number of swollen joints, pain score, and duration of morning stiffness, grip strength, erythrocyte sedimentation rate, C - reactive protein, white blood cell count, and a health assessment questionnaire score. In the control group, only pain score improved significantly. The benefits in the diet group were still present after one year, and evaluation of the whole course showed significant advantages for the diet group in all measured indices. This dietary regimen seems to be a useful supplement to conventional medical treatment of rheumatoid arthritis.

Mediterranean Diet (MD)

Current knowledge suggests that healthier nutrition by adjusting to a Mediterranean diet and a higher intake of fish is associated with a reduction in inflammatory activity, an increase in physical function, and improvement in RA patients' vitality [68]. Even more, supplementation withomega-3 polyunsaturated fatty acids (omega-3 PUFAs) reduce patients' morning stiffness, painful joints, and NSAIDs consumption. It involves high consumption of olive oil, cereals, fruits, vegetables, fish, and legumes; less red meat; and inclusion of moderate amount of red wine in diet (Cretan MD).

In a study by Matsumoto et al [69], it was found that intake of monounsaturated fatty acids (MUFA) was significantly lower in RA group and the ratio of consumed monounsaturated to saturated fatty acid (MUFA/SFA) significantly differed within the RA group after being sub-classified according to DAS28-ESR.Daily MUFA intake, a component of the Mediterranean diet score, was selected as an independent predictor of remission in the RA group and its intake might suppress disease activity in RA patients.

On the other hand, few studies have not shown any significant benefit with MD. Bloomfield et al [70], pointed out that while many studies have confirmed a beneficial role of the Mediterranean diet in preventing cardiovascular events, cancer and diabetes, no such role in RA has been proven.

Elimination Diet

Studies have shown that consumption of allergenic foods increases pro-inflammatory cytokines that are considered a hallmark of RA [71].An Elimination diet can identify triggers of arthritis pain and can easily be instituted on an outpatient basis.

It is usually started with a simple baseline diet, excluding foods that are more common triggers (mentioned below) and including only those foods not implicated in arthritis such as brown rice, cooked or dried fruits, cooked green, yellow, and orange vegetables, plain or carbonated water, condiments (modest amounts of salt, maple syrup, vanilla extract).

After a few weeks of eating only baseline foods, other foods are added back into the diet one by one and any new symptoms are monitored during these days. If the added foods do not cause any symptoms, those can be continued. A newly added food associated with increased joint pain should be removed from the diet for 1-2 weeks, and then reintroduced to see if the same reaction occurs. This methodical way of adding new foods back in makes it easy to identify which foods cause inflammation and arthritis pain.

There are different types of elimination diets using different methods. For example, certain elimination diets completely avoid all meats including chicken, turkey, fish etc. while others include it.

The most likely triggers found in various Elimination diets are:

Gluten (including all wheat products)
Dairy products
Soy, including edamame, tofu, tempeh, miso, tamari, and many meat substitute products
Corn products (chips, syrups, tortillas)
Any dish containing poultry
Nightshade vegetables, including tomatoes, potatoes, eggplant and peppers
Processed foods
Sugars
Alcohol
Certain meats, including red meat, smoked meats, deli meats and pork.

Elemental Diet

Elemental diet is an hypoallergenic protein-free artificial diet consisting of essential amino acids, glucose, trace elements and vitamins [72]. It is thought to provide complete nutrition and avoids many of the side effects of other drugs used for pain relief in patients with RA [73]. Studies have shown that an antigenic load within the bowel lumen is an important factor in the pathogenesis of rheumatoid arthritis [74], an elemental diet as the sole source of nutrition may be an effective treatment. Elemental diet is given to patients with RA in order to induce a remission and then foods are gradually introduced.

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Where a food is suspected of causing symptoms, it is removed from the diet.

A study by Podas et al [75], has shown that an elemental diet for 2 weeks is as effective as a course of oral prednisolone 15 mg daily in improving subjective clinical parameters. But this study failed to show any significant improvement in swollen joint score.

Vegan and Vegetarian Diets

A diet including intake of only fruits and vegetables, eliminating any animal product or by-products is vegan diet. This has been repeatedly reported to be clinically beneficial for disease remission in RA patients [76-79].Researchers in Norway found that a vegan diet led to reductions in pain, swelling, and morning stiffness, as well as improvements in C-reactive protein [80] and these symptoms were sustained for a long time with removal of meat products from the diet. Another study found significant improvements in RA symptoms with a 4-week vegan diet intervention [81].

Some studies have found that higher intakes of meat [82-83] and elevated serum cholesterol concentrations [84-85]are associated with increased risk of developing this disease.

Inclusion and Exclusion of certain Dietary Factors

There are single dietary factors which have been proven to prevent RA.

Role of Polyunsaturated fatty acids

While n-6 PUFAs have a predominantly pro-inflammatory effect, n-3 PUFAs seem to have anti-inflammatory action. Supplementation with n-3 PUFAs (such as eicosapentaenoic acid and docosahexaeonic acid) has been shown to change favourably the n-6/n-3 fatty acids ratio, reduce inflammation, and alleviate pain, as well as lowering disease activity in rheumatoid arthritis patients. Marine oil is thought to have an analgesic effect in arthritis as a likely consequence of its high content of docosahexaeonic acid (DHA; 22:6 n-3) and eicosapentaenoic acid (EPA; 20:5 n-3) [86-87].

Arachidonic acid (AA; 20:4 n-6), as well as DHA and EPA, are used in the production of lipid mediators (e.g., eicosanoids), which are involved (among other functions) in the regulation of inflammation. However, the mediators produced from DHA and EPA shift the balance toward resolution [88].

Another study has seen a beneficial effect when fish oils were taken with primrose evening oil, containing γ-linolenic acid [89].

Other dietary factors with a beneficial role

Pattison et al [90] confirmed that daily consumption of a glass of freshly squeezed orange juice is inversely correlated with the risk of RA, probably due to the protective action of beta-cryptoxanthin, a natural carotenoid. Similar effect is shown with vegetables like mushroom and spinach.

Both low-sodium [91]and low-magnesium diets seem to have some anti-inflammatory potential. Low-magnesium diet had significant reduction in synovial gene expression of IL-6, RORA and RORC, responsible for the development of Th17 cells [92] in rats and might show similar results in humans.

Dietary factors preventing RA and lowering its activity	Dietary factors promoting RA activity
Bacillus coagulans and/or insulin	Sugary drinks high in fructose
Fish oils rich in omega-3 fatty acids; Olive oil; Borage seed oil	Plant seeds containing lectins
Cereals/ Legumes: Whole oatmeal, whole wheat bread, whole flattened rice, black soybean, black gram	High fat diet
Whole grains: Wheat, rice, oats, corn, rye, barley, millets, sorghum, canary seed	Sweets
Dairy products	
Low sodium and low magnesium diet	
High-methionine diet	
Fruit (oranges, dried plums, grapefruits, grapes, pomegranate, mango, banana, peaches, apples), vegetables (spinach, mushroom, tomatoes, potatoes) and spices rich in polyphenols	
Blueberries , raspberries, cranberries, black elderberries, black berries, strawberries	
Spices: Ginger, turmeric, black pepper, allspice, caraway, bay leaves, cinnamon, licorice, paprika, clove, nutmeg, chilli pepper, bilberry	
Herbs: Sallaki, ashwagandha	
Green tea, cocoa	

Studies suggest that arthritis severity may be alleviated by a high methionine diet [93].A significant reduction was found in serum high-sensitive C-reactive protein (hs-CRP) and disease activity (DAS-28) score in a study involving 40 female patients with a mild to moderate severity of RA who were supplemented for 12 weeks daily with a Selenplus capsule containing 50 μg of selenium, 8 mg of zinc, 400 μg of vitamin A, 125 mg of vitamin C, and 40 mg of vitamin E [94].

Polyphenols and neochlorogenic acid found in dried plums may inhibit TNF-induced formation of osteoclasts by lowering the number of tart rate-resistant acid phosphatase (TRAP) positive cells, responsible for osteoclastogenesis [95]. Similarly, equol, a major soybean isoflavone metabolite, was found to both alleviate the severity of arthritis symptoms and slow down the decline in bone mineral density following collagen induced arthritis [96].

Curcumin has shown to decrease the expression of NF-κB, TNF-α, and IL-1β in the synovial fluid and blood serum [97]. Studies have shown that about 1000 mg/day of curcumin can help in alleviating pain symptoms connected with arthritis [98].Comparable protective effects against RA are seen with ginger [99].

Pomegranate extract and quercetin are not behind in the list of products benefitting RA. A decrease in swollen and tender joints, pain intensity and erythrocyte sedimentation rate (ESR) levels, with reduction in DAS-28 and HAQ, as well as lower hsTNF-α levels were seen with pomegranate and quercetin both [100-101].

Exercises in Rheumatoid Arthritis

People with rheumatoid arthritis can largely benefit from exercise. It helps in relieving pain and joint stiffness, improves joint function and flexibility, increases range of motion, and boost mood. But it is very difficult to stay motivated for exercise especially when patient is in pain. The best exercises are:

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Stretching

Stretching especially in the morning seems to be ideal for these patients. Stretching should be preceded by warming up for 3-5 minutes by simply walking. One should hold each stretch for 10–20 seconds before releasing it and repeat each stretch 2–3 times. Using a yoga strap may help maintain proper form while stretching.

Walking

Walking is a low-impact form of exercise that can help with heart and joint health. It is often sensible to walk slowly initially and then increase the pace when possible. Though it sounds too simple, but walking is one of the easiest and most convenient forms of exercise.

Tai chi and yoga

Both tai chi and yoga combine deep breathing, flowing movements, gentle poses, and meditation. They increase flexibility, balance, and range of motion while also reducing stress.Tai chi (sometimes called "moving meditation") is a traditional Chinese martial art that combines slow and gentle movements with mental focus. This exercise improves muscle function and stiffness and reduces pain and stress levels in patients with RA.

Pilates

Pilates is a low-impact activity that stabilizes the joints and strengthens the muscles around them. Patients suffering from rheumatoid arthritis should avoid using a machine for doing pilates.

Water exercises

According to the Centers for Disease Control and Prevention, water-based exercise can help people with chronic diseases. For people with arthritis, it improves use of affected joints without worsening symptoms [102], as it supports body weight and do not impact heavily on the joints. People with rheumatoid arthritis have more health improvements after participating in hydrotherapy than with other activities [103]. Water-based exercise also improves the use of affected joints, decreases pain, increases flexibility, range of motion, and strength from osteoarthritis [104].

Swimming, water aerobics, and other gentle water exercises can increase flexibility, range of motion, strength, and aerobic conditioning. They can also reduce joint stress and stiffness.

Cycling

Cycling is an excellent, low-impact exercise that's easier on the joints than other aerobic exercises. Riding a stationary bike can be a safe way to get the joints moving and improve cardiovascular fitness. It helps building leg strength and reduces morning stiffness.

Strength training

Strengthening the muscles around the affected joints, using a resistance band, helps in reducing pain and other arthritis associated symptoms.

Hand exercises

Bending the wrists up and down, slowly curling the fingers, spreading the fingers wide on a table, and squeezing a stress ball can help increase strength and flexibility in the hands.

Gardening

Gardening is a good way to alleviate mood. Gardening slowly without overstraining the muscles and joints, serves both the purposes of caring for the plants as well as the joints.

Osteoarthritis

Osteoarthritis (OA) is defined as a heterogeneous group of conditions that lead to joint symptoms and signs associated with a defective articular cartilage and related changes in bone morphology [105].It can occur in almost any joint in the body. Although the usual population associated with the condition is the elderly, who are mostly inactive, athletes and younger individuals are also susceptible.

Osteoarthritis is the most common joint disease and the fastest growing form of disability worldwide [106], causing deterioration of quality of life and reduced participation in social activities. OAis characterised by cartilage loss, subchondralbone changes, synovial inflammation and meniscus degeneration [107]. Treatment options for symptomatic OA are fairly limited and often only provide temporary relief.

Pathogenesis of the Disease

Mechanical injury, hereditary factors and ageing can initiate the pathophysiological processes that lead to OA.Originally; OA was considered a non-inflammatory arthritis while only rheumatoid arthritis was considered inflammatory in nature. The discovery that many soluble mediators such as cytokines or prostaglandins can increase the production of matrix metalloproteinases (MMPs) by chondrocytes led to the first steps of an "inflammatory" theory [108].

Joint swelling is one clinical feature of OA attributed to inflammation and reflecting the presence of synovitis due to thickening of the synovium or to effusion. Recent experimental data have shown that subchondral bone may have a substantial role in the OAprocess, as a mechanical damper, as well as a source of inflammatory mediators implicated in the OApain process and in the degradation of the deep layer of cartilage [109-111].

Why exactly the synovium becomes inflamed in OA remains controversial [112]. Two theories have been proposed:

Theory 1 (Hypertrophic Repair Phase)

In this phase a loss in the glycosaminoglycan will lead to an increase in water content resulting in softening of articular cartilage. Further it leads to alteration in cartilage compressive resistance and osmotic pressure within the tissue [113]. Anabolic activities and production of collagen type II and proteoglycan are intensified. Synovial cells consider fallen cartilage fragments, into the joint, as foreign bodies, thereby producing inflammatory mediators. These mediators can activatechondrocytes present in the superficial layer of the cartilage, resulting in their increased proliferation and cluster formation [114-115]. This leads to metalloproteinase synthesis and, eventually, increase cartilage degradation. The mediators can also induce synovial angiogenesis and increase the synthesis of inflammatory cytokines and matrix metalloproteinases by synovial cells themselves (vicious circle).

Theory 2

Collagen type II fragments from the damaged cartilage surface can

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induce inflammatory responses in the synovial membrane resulting in hyperplasia, lymphocytic infiltration and perivascular lymphoid aggregates [116]. There is an important role for synovial macrophages in MMP-mediated cartilage damage. Therefore, more recently, synovial tissue is involved as a primary trigger of the OA process [117-119]. Synovial inflammation may drive synovial angiogenesis, linked to OA pain, through macrophage activation [120-121].

Further, it is seen that innate immunity may be a driver of the OA process. Synovial fluid from patients with early OA cartilage damage showed:

- Increased fibroblast-like synoviocyte responses to TLR-2 and TLR-4 ligands [122]
- Increased levels of interleukin-15 (IL-15) protein
- Abnormally high expression and activation of complement in human OA joints [123]

Etiology of Osteoarthritis

OA is usually thought to be a progressive disease of the adult and elderly. However, there are several risk factors apart from age that predispose an individual to OA, such as genetics, obesity, joint injury, occupational or recreational activities, gender, and race [124].There are strong associations of OA with obesity and joint injury.

Osteoarthritis, commonly known as wear and tear arthritis, is found in athletes and young individuals who use their joints more. The effect of occupational and recreational activities on the development of OA was evident in a study by Cameron et al [125], where active duty military personnel were found to have significantly higher rates of OA compared to the same age group in the general population.

There is ample evidence that anterior cruciate ligament (ACL) rupture and meniscal tear are two major risks factors for developing early OA [126]. Athletes are more likely to sustain joint injuries compared with the average individual. As a result, there is increased joint instability and altered joint mechanics, even with normal use [127]. This further restricts mobility, induces pain and functional impairment, making them "young patients with old knees".

Joint degeneration occurs in athletes and young individuals through damage to the articular cartilage caused by repetitive impact and loading [128]. Sports that cause direct blunt trauma to joints (such as football, soccer, hockey, lacrosse, and rugby) account for the most impact damage.For contact stressors to cause disruption to normal articular cartilage, a force of 25 MPa or more is required. Activities such as running and jumping, which put mechanical stress on joints, produce force <25 Mpa, and therefore, are less likely to cause any disruption to the cartilage [129].

Smoking, physical inactivity, muscle weakness, leptin, vitamin D deficiency and dietary fatty acid intake [130] also contribute to the pathogenesis of the disease but their role is still controversial and not very well defined, when considered individually.

Clinical Presentation and Diagnosis

Pain is the main presenting symptom of OA but the diagnosis in athletes and sportsperson might get delayed as pain is a part of their everyday routine. Also with a high desire to return to play, athletes at times don't disclose pain or hide the severity of their pain. Few have a high pain threshold and won't complain until ailment gets worsened [131-132].

In the early phases of the disease, pain is related to activity and becomes more constant over time, while in the late stages there is 'background pain' interspersed with unpredictable intense pain [133].

Morning stiffness of the joints is the second most prominent symptom of OA. The stiffness usually involves joints of the fingers, knees, hips, and spine. It usually resolves within an hour of waking up [134]. Crackling or grating sensation, which occurs as a result of the roughness of the surfaces in the joint are other symptoms.

The physical exam focuses on the range of motion (both passive and active), muscle strength, ligament stability, and tenderness of the affected joints [135], crepitus and effusion.

Diagnostic criteria for the OA of knee[136], hand [137] andhip[138].

The diagnosis of the severity of OA is subjective: based on a quality of life questionnaire, physical examination and radiography [135]. The most commonly used quality of life measure is ***Western Ontario McMaster Index (WOMAC)*** although other similar measures such as visual analog scale (VAS) for pain and Lequesne index are also used [139-140].WOMAC Index was developed in 1982 at Western Ontario and McMaster Universities. WOMAC is available in over 65 languages and has been linguistically validated [141-142].

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is widely used in the evaluation of Hip and Knee Osteoarthritis. It is a self-administered questionnaire which takes approximately 12 minutes to complete, and can be taken on paper, over the telephone or computer [143-144]. It consists of 24 items divided into 3 subscales [142]:

Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright

Stiffness (2 items): after first waking and later in the day

Physical Function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties.

The test questions are scored on a scale of 0-4, which correspond to:

- None (0),
- Mild (1),
- Moderate (2),
- Severe (3), and
- Extreme (4).

Plain radiography is usually the initial diagnostic image of choice, although sensitivity is poor, especially in the early stages of OA [145]. Radiographic features of OA include osteophytes, joint space narrowing, subchondral sclerosis, and cysts.

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Diagnostic criteria						
Knee (Presence of knee pain plus at least three others)	Morning stiffness for less than 30 minutes	Crepitus on active knee motion	Older than 50 years of age	Bony enlargement	No palpable warmth	Bony tenderness
Hand(Presence of hand pain and/or stiffness plus at least three others)	Fewer than three swollen metacarpophalangeal joints	Hard enlargement of two or more distal interphalangeal joints	Deformity of at least one of the ten selected joints (second and third distal interphalangeal joints, first carpo metacarpal joints, and second and third proximal interphalangeal joints)	Hard tissue enlargement of two or more of the ten selected joints	-	-
Hip (Presence of hip pain plus at least two others)	Radiographic evidence of femoral or ace tabular osteophytes	Joint space narrowing on radiography	Erythrocyte sedimentation rate of less than 20 mm/h	-	-	-

Many a times the radiological defects are an incidental finding whereas the person is asymptomatic, which often leads to a delay in investigations and by then the pathological process is far advanced[146-147].By the time the first knee joint changes are detected by radiography, more than 10% of the cartilage is already lost [148]. There are many joint tissues not visible by radiographs, including the cartilage, synovium, meniscus, ligaments, capsule and fat pad.

MRI is more sensitive for detecting early structural changes, not only in the bone, but also in all joint tissues, detecting cartilage defects, loss of cartilage volume, subchondral bone changes, bone marrow lesions, synovitis and meniscal tears [149].

Ultrasonography can detect and evaluate both early and late abnormalities in OA involving the hyaline cartilage, synovial membrane, meniscus, joint capsule, bursa and bony cortex. As compared to MRI, it is safe, less expensive and less time consuming. On the other hand, operator-dependency and its inability to assess deeper articular structures due to the acoustic shadowing makes it less widely used [150].Ultrasound can detect synovial hypertrophy, joint effusion and increased vascularity analysed by synovial power Doppler, with a moderate to good intra-observer and inter observer reliability [151].

Management

To identify people at high risk of developing OA, it is important to initiate early interventional treatment in patients with early structural changes, even if they are asymptomatic [152].

Exercise is one of the first and the most recommended tool in the management of OA, which is followed since years [153-154]. Exercises that increase strength, flexibility, and aerobic capacity are likely to be the most effective in lower limb OA [155]. Muscle strengthening exercises are extremely important especially for athletes because these are very helpful in reducing pain.

In the pharmacological management, NSAIDs play a key role in alleviating pain and inflammation and are beneficial in the initial stages of OA. Gastrointestinal upset is a bitter part of NSAIDs, therefore, the athletes with already existing GI problems should be careful [156]. Relief from pain will help in improving the alignment and biomechanical forces in the knee [157]. This is again important to prevent any future musculoskeletal pathologies [158].

Intra articular injection with corticosteroids [159] and viscosupplementation with hyaluronic acid [160] is another modality. Steroids have anti-inflammatory properties and are beneficial for short term relief. Caution should be observed, however, because of the cytotoxicity of steroids to chondrocytes, with or without lidocaine [161].

Hyaluronic acid has anti-inflammatory and analgesic effects, in addition to its viscoelastic properties, making it valuable in the treatment of OA [160].However, the combination of glucosamine and chondroitin sulphate is the most promising. This treatment may be efficacious for pain relief, functional improvement and also result in less joint space narrowing [162-166].

As far as the surgical line of management is concerned, arthroscopy is the first line of management. Radio graphically invisible pathologies such as cartilage defects and meniscal tears can be seen by arthroscopy [167]. Arthroscopy, with its tactile and dynamic capabilities, permits palpation of the joint tissues with a probe, and can easily detect softening, which is the earliest change in the cartilage. One of most widely employed procedures for internal derangement of the knee, the role of arthroscopy in osteoarthritis is still controversial and unproven [168-169].It has very limited role in knee OA and has the potential to even accelerate the disease progression and/or patient's pain.

Other surgical treatments that are considered before total knee arthroplasty (TKA) include high tibial osteotomy (HTO) and unicondylar or partial knee arthroplasty (UKA). Such surgeries are infrequent in young population suffering from OA. These are considered the last resorts in the treatment of OA and are usually performed in elderly.

Dietary Modifications

Thomas et al. performed a literature review of the relevance of dietary interventions to OA management. This group found six modifiable nutritional factors that may be implicated in OA: adiposity/obesity, metabolic syndrome, type 2 diabetes, consumption of long-chain n-3 fatty acids, blood cholesterol levels, and vitamin K intake [170].

Weight reduction: An initial aim of 10% body weight reduction should be included in a first-line approach for obese patients with OA. Overall aim for obese/overweight patients is for BMI within

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the healthy range (18.5–25 kg/m^2). This aim should not be achieved by severely cutting down the calories. Rather it should be achieved by moderate energy restriction without compromising nutrient intake. Input from a dietician would be of immense help especially when mobility is impaired and exercise is limited. Therefore, weight reduction programmes that combine diet and exercise would show a better outcome.

Exercise: The aim of exercise should be to reduce adipose tissue without compromising the muscle mass [171-172]. Exercise schedule should be tailored separately for each patient. Exercise should include aspects of light aerobic exercise, strengthening and flexibility. Few minutes of the exercise schedule should be dedicated to yoga and breathing exercises for overall health of the body.

It appears that for OA patients, exercises involving supervised slow movements or isometric exercises may be efficacious and also have a lower possibility of damage to the joint than other exercises [139,173-177]. Therefore, aquatic exercises, yoga and tai chi should be preferred. Running on treadmills should be avoided.

Alteration in lipid intake: Lipids are stored in the matrix and chondrocytes of articular cartilage and may contribute towards inflammation, cartilage degradation and impaired chondrocyte structure [178].OA joints accumulate high levels of omega-6 (n-6) fatty acids, precursors of pro-inflammatory eicosanoids [179]. On the other hand, dietary intake of omega-3 (n-3) PUFAs generate anti inflammatory mediators (resolvins) [180].Omega-3 fatty acids are a vital component of the diet as they can minimize inflammation and keep the body healthy. It should be borne in mind that the balance of omega-3 and omega-6 in the body plays a role in preventing inflammation. In addition to increasing omega-3 intake, consumption of foods high in omega-6 should be limited. The Western diet has a high ratio of n-6 to n-3 fatty acids, predisposing to inflammation [181].

Increasing long chain n-3 PUFA status to promote an anti-inflammatory effect is best achieved with direct EPA intake alongside decreased LA intake.EPA and DHA are found primarily in oily fish [182].Higher intakes of EPA/DHA, including the proposed anti-inflammatory threshold of >2.7 g/day [183], may be more easily achieved by fish oil supplementation.

Cholesterol Intake

High cholesterol levels are known to increase cytotoxicity [184] in cells leading to higher formation of Arachidonic acid and resulting in more of pro inflammatory mediators [185]. In a normal, healthy joint, cholesterol accumulation does not take place due to the active cholesterol efflux system. The latter gets dysregulated in OA as a result of which, cholesterol gets hoarded in OA cartilage.

Statins have shown promising results in reducing levels of cholesterol. Statins help lower the clinical and radiographic progression of the disease. They help in preventing cartilage degeneration to a certain extent and in reduction of the pro inflammatory cytokines/mediators in joints [186-188].

Studies have shown that dietary changes could result in a 35% reduction in LDL-cholesterol, equivalent to that of a starting dose of statins [189-190]. There are a number of foods that help lowering cholesterol:

Foods rich in Omega 3 fatty acids	Foods rich in Omega 6 fatty acids
Contain EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid)	**Linoleic acid —18:2 (n-6)**
Mackerel	Poultry
Salmon	Eggs
Seabass	Nuts
Cod liver oil	Hulled sesame seeds
Herring	Durum wheat
Oysters	Whole-grain breads
Sardines	Pumpkin seeds
Shrimp	Most vegetable oils including: Grape seed oil Evening primrose oil Borage oil Blackcurrant seed oil Flax or linseed oil Rapeseed or canola oil Hemp oil Soybean oil Cottonseed oil Sunflower seed oil Corn oil Safflower oil Palm oil
Trout	Peanut butter
Anchovies	Avocado oil
Caviar	Walnuts
Seaweed, algae	Tofu
Contain ALA (α Linolenic acid)	Hemp seeds
Flax seeds	Almonds
Chia seeds	Cashews
Walnuts	
Soybeans/Kidney beans	**Arachidonic acid** is found in animal products, like poultry and eggs.
Hemp seeds	
Edamame	
Soybean oil	
Green leafy vegetables	
Linseeds	

High-fibre foods (Oats)

Oatmeal contains soluble fibre, which reduces low-density lipoprotein cholesterol by reducing its absorption in blood. Soluble fibre is also found in such foods as kidney beans, Brussels sprouts, apples and pears.

One serving of a breakfast cereal with oatmeal or oat bran provides 3 to 4 grams of fibre [191]. Adding a banana or berries to it will further enhance the fibre level.

Omega-3 fatty acids (Fatty fish)

Fatty fish has high levels of omega-3 fatty acids, which can reduce triglycerides in the blood. LDL cholesterol levels are not much affected by omega-3 fatty acids. Eating at least two servings of fish a week, preferably by baking or grilling, gives much health benefits.

Almonds and other nuts

Almonds, walnuts and other tree nuts can improve blood cholesterol. A recent study concluded that a diet supplemented with walnuts can lower the risk of heart complications in people with

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history of a heart attack. All nuts are high in calories, so a handful added to a salad or eaten as a snack will do.

Plant Stenols/Sterols

Plant sterols (PSter) (Figure1) and stanols (PStan) (Figure 2), together known as phytosterols (PSS), are cholesterol-like compounds that occur naturally in plant-based foods. Phytosterols interfere with the intestinal absorption of dietary cholesterol by displacing cholesterol from micelles; they also facilitate the excretion of biliary cholesterol in the feces.The LDL-cholesterol lowering effect of phytosterols is summarized in several meta-analyses showing a dose-response relationship with intakes of 1.5 to 3 g/day lowering LDL-C by 7.5% to 12% [192-196].

PSS are efficacious in all foods and food supplements; for optimal efficacy they should be consumed with a (main) meal and twice daily [197].PSS are effective in both healthy and diseased individuals suffering from familial hypercholesterolemia, type-2 diabetes mellitus or Metabolic Syndrome.

Phytosterol Content of FoodsAvocados

Avocados are a potent source of nutrients as well as monounsaturated fatty acids (MUFAs). Research suggests that adding an avocado a day can help improve LDL cholesterol levels in people who are overweight or obese.

Olive oil

In order to lower cholesterol, olive oil should be used in place of other fats in the diet. It can be used in a variety of ways, sautéing vegetables, adding it to a marinade or mixing with vinegar as a salad dressing. Olive oil can be used as a substitute for butter when basting meat or as a dip for bread.

Foods with added plant sterols or stanols

Margarines and orange juice with added plant sterols can help reduce LDL cholesterol. Plant sterols or stanols do not affect levels of triglycerides or of high-density lipoprotein (HDL) cholesterol.

Whey protein

Whey protein, which is found in dairy products, may account for many of the health benefits attributed to dairy. Studies have shown that whey protein given as a supplement lowers both LDL and total cholesterol as well as blood pressure.

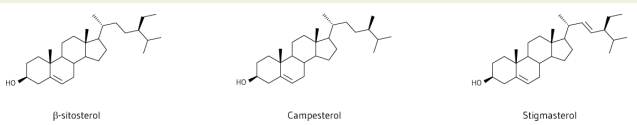

Figure 1: Chemical Structures of Plant-derived Sterols.

Figure 2: Chemical Structures of Plant-derived Stanols.

Food	Serving	Phytosterols (mg)
Rice bran oil	1 tablespoon (14 g)	161
Soybeans, mature seeds, raw	½ cup	149
Peas, green, mature seeds, raw	½ cup	133
Sesame oil	1 tablespoon (14 g)	118
Kidney beans, mature seeds, raw	½ cup	117
Sesame seeds	1 tablespoon (9 g)	64.3
Pistachio nuts	1 ounce (49 kernels)	61
Safflower oil	1 tablespoon (14 g)	60
Lentils, pink or red, mature seeds, raw	½ cup	54
Capers, canned	100 gm	48
Cashew nuts	1 ounce	45
Soybeans, green, cooked, boiled	½ cup	45
Cottonseed oil	1 tablespoon (14 g)	44
Orange, raw	1 fruit	34
Macadamia nuts	1 ounce (10-12 kernels)	33
Asparagus, raw	1 cup	32.2
Almonds, blanched	1 ounce	32
Olive oil	1 tablespoon (14 g)	30
Banana, raw	1 large	24
Brussels sprouts, raw	1 cup	21
Lettuce, green leaf, raw, shredded	1 cup	13.7

Other changes in diet

Getting the full benefit of these foods requires other changes to diet and lifestyle. One of the most beneficial changes is limiting the intake of saturated and trans fats.

Saturated fats, such as those in meat, butter, cheese and other full-fat dairy products, raise total cholesterol. Decreasing the consumption of saturated fats to less than 7 percent of total daily calorie intake can reduce LDL cholesterol by 8 to 10 percent.

Trans fats, sometimes listed on food labels as "partially hydrogenated vegetable oil," are often used in margarines and store-bought cookies, crackers and cakes. Trans fats raise overall cholesterol levels. The Food and Drug Administration has banned the use of partially hydrogenated vegetable oils by Jan. 1, 2021.

Role of Antioxidants

A plausible rationale exists for a role of antioxidants in OA. Reactive oxygen species and reactive nitrogen species may be involved in the pathophysiology of OA, and therefore, suppressing these with antioxidants might delay its onset and progression [198-199].

A free radical is a molecule with an unpaired electron in its outermost orbit [200-201]. In biological systems, a free radical that involves oxygen is termed a reactive oxygen species (ROS) but the term ROS is used loosely for oxidants such as peroxides. Normal physiological processes result in the generation of ROS such as peroxide, superoxide, hydroxyl radical and peroxynitrite. Thus, ROS occur normally in the body at very low concentrations (nanomolar to micromolar). They are a necessary evil since our body needs them for survival but, when in excess, they may have deleterious effects. Our

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body gets rid of the excess ROS using natural antioxidants such as vitamin C (ascorbate), vitamin E, glutathione and various enzymes [200-202]. The term oxidative stress is used as a measure of the overall ROS status. It is the ratio of the amount of peroxide present to that of the antioxidant capacity of the cell. High levels of oxidative stress may damage the cells by oxidising lipids and by altering DNA and protein structure.

The antioxidant vitamins, A, C and E have received the most attention in this context with vitamin C being particularly relevant owing to its requirement for collagen formation [203].Several studies have talked about the use of antioxidant supplements derived from curcumin, avocado, Boswellia and other herbs [204].

Curcumin

Curcumin, a compound with antioxidant properties, was isolated from turmeric about 200 years ago [205]. Curcumin, (diferuloylmethane; 1, 7-bis [4-hydroxy-3- methoxyphenyl]-1,6-heptadiene-3,5-dione) along with its mono and di demethoxy derivatives, collectively called curcuminoids, constitute the major colouring matter and the biologically active constituents of Curcuma longa L. or turmeric. Ayurveda, Unani, Siddha and Chinese medicines recommend turmeric for a wide range of disorders and diseases. Modern science has provided a scientific basis for such uses [206-212].

The properties of curcumin and its potential role in the therapy of several chronic diseases including arthritis, cancer and neuronal disorders have been explored. Curcumin may be efficacious for pain relief and function retention in OA patients. Presently, some of the strongest evidence for the therapeutic efficacy of curcumin (confirmed by meta-analytic analyses of randomized controlled trials) is for the treatment of arthritis, pain and analgesia, and major depressive disorder. In a meta-analysis by Daily et al [98], the systematic review provided scientific evidence that 8–12 weeks of standardized turmeric extracts (typically 1000 mg/day of curcumin) treatment can reduce arthritis symptoms (mainly pain and inflammation-related symptoms) and result in similar improvements of the symptoms as ibuprofen and diclofenac sodium. In another meta-analysis [213], eight RCTs were included and curcuminoids was found to be safe and well tolerated by participants. They were found to significantly reduce pain and the effect was found to be independent of administered dose and duration of treatment with curcuminoids.

But curcumin absorption has been reported to be extremely poor when it is used alone [214-217]. Poor absorption from the gut and avid metabolism in the body is cited as reasons for the lack of systemic availability. While the major portion of ingested curcumin is excreted through the feces unmetabolized, as determined in several animal studies [218], the small portion that is absorbed is extensively converted to its water-soluble metabolites, glucuronides and sulphate, which are then excreted. This seriously limits curcumin to reach targets distant from the gut and exert its beneficial action.

To overcome this problem, numerous methods have been undertaken to increase its bioavailability.These include the use of adjuvants such as piperine, formulating liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complexes, and the use of structural analogs of curcumin such as turmeric oil [219-220]. These efforts have shown some success with an increased blood concentration of curcumin. The study by Shobha et al determined the effect of piperine (inhibits hepatic and intestinal glucuronidation) on the bioavailability of curcumin [217]. A co-administration of curcumin with 20 mg piperine increased its' bioavailability by 20-fold.Curcumin has also been reconstituted with non-curcuminoid components of turmeric into a proprietary preparation termed BCM-95CG or Biocurcumax [221]. Biocurcumax increased the oral bioavailability of curcumin when compared to curcumin alone or curcumin plus lecithin. However, there are no reports using this preparation for OA.

One trial used the combination of roots of Withania somnifera, the stem of Boswellia serrata and rhizomes of Curcuma longa and a zinc complex. There was a significant improvement in pain relief and function [222]. Ainat - a preparation containing devil's claw, turmeric and bromelain also showed a clinically relevant improvement in acute and chronic pain [223].

Avocado/Soybean Unsaponifiable (ASU)

The unsaponifiable fraction from avocado/soybean oils is termed avocado/soybean unsaponifiable. ASU has been tested in the management of OA. ASU contains phytosterols, β-sitosterol, campesterol, and stigmasterol, fat soluble vitamins, triterpene fatty acids and possibly furan fatty acids, but the identity of the active components in it is unknown [224]. Literature provides conflicting results, with few studies showing very good results and a few considering soybean protein alone for benefits in OA.

Boswellia

Resins from trees of Boswellia serrata, and other species of this genus, have been used for arthritis and other diseases in Ayurvedic medicine since ancient times. One of the compounds present in Boswellia, acetyl-keto-beta-boswellic acid (AKBA), is an inhibitor of the lipoxygenase pathway and is suggested to have anti-inflammatory properties [225]. Almost all studies have shown some or the other benefit in OA.

Ayurvedic Preparations

Withania somniferum (ashwagandha) [226], Tinospora cordifolia (Guduchi) [227], Emblica officinalis (or Phyllanthus emblica/amla) and emblicanins A and B [228], Zingiber officinale (Ginger) root are among the other divine herbs used in OA.

Vitamin D and Osteoarthritis

Vitamin D insufficiency is a global nutrition challenge. Once thought to cause solely rickets and decreased bone density, vitamin D deficiency has been associated with several chronic diseases such as multiple sclerosis, type I diabetes, and hypertension [229]. Vitamin D can be obtained through foods such as fatty fish, mushrooms, and vitamin D-fortified products, and through cutaneous synthesis in response to ultraviolet-B exposure. There are plenty of supplements available in the market with different strengths.

The classic role of vitamin D is known to increase calcium absorption through the endocrine pathway. In order for a patient to have adequate and efficient blood calcium levels, both vitamin D and parathyroid hormone must be present at sufficient levels

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and function together [230]. When the levels of blood calcium are low, the parathyroid gland releases parathyroid hormone, causing expression of proteins that leads to an increase in total body calcium levels. In the kidney, parathyroid hormone induces the conversion of 25-hydroxyvitamin D to 1, 25 dihydroxyvitamin D, which ultimately results in an increase in the transcription of genes responsible for calcium absorption [231]. When the parathyroid hormone is removed, vitamin D cannot function properly within the patient, resulting in hypocalcaemia.

However, as more precise methods for calcium absorption measurement have been developed over recent decades, the effect of vitamin D on Ca absorption in adults seems minimal, especially in adults with 25(OH)D levels ≥ 20 nmol/L [232-235] and does not increase calcium absorption in adolescents [236-237]. However, vitamin D supplementation in those with 25(OH) D<50 nmol/L appears to increase bone mass or prevent bone loss in adults [238-239] and positively affect bone mineral augmentation in adolescents [240-241]. Therefore, it is proposed that vitamin D may benefit bone through an autocrine and/or paracrine pathway, especially since circulating 1, 25(OH) 2D, the active vitamin D metabolite, is not associated with 25(OH) D status. Though the mechanism by which vitamin D affects bone is unclear, serum 25(OH) D ≥50 nmol/L is required for optimal bone health.

Vitamin D is thought to reduce inflammation via its effect on T and B lymphocytes, macrophages and dendritic cells [242]. Binding of vitamin D to its receptors in immune cells leads to its activation. This blocks the cellular response to TNF-α and IL-1 and allows for the up regulation of IL-10.

The efficacy of vitamin D in treating or preventing OA is controversial. Some authors have found that vitamin D deficiency increases the risk of patients' developing OA [243-245].Bassiouni et al [246] and Veronese et al [247] both found that serum 25(OH)D levels were significantly decreased in the patients with knee OA and noted that medial meniscal deterioration was seen in patients with low vitamin D levels.

Malas et al [248] found that vitamin D deficiency significantly decreased femoral cartilage thickness in women between 20 and 45 years of age, which was determined by ultrasound.

On the other hand, there were reports which showed no improvement [249-251] with vitamin D supplementation.

Role of Vitamin K

Vitamin K is a group of fat-soluble compounds, with two naturally occurring forms, vitamin K1 (phylloquinones) and vitamin K2 (menaquinones) [252]. Vitamin K1, synthesized by plants and algae, is the form most widely found in the human diet, mainly in green leafy vegetables and oils [253]. Vitamin K2 is predominantly produced by bacteria [254]. The adequate daily intake of vitamin K for adults aged 19 years and older is 120 micrograms (mcg) for men and 90 mcg for women.

The main function of vitamin K is as an enzymatic cofactor for the gamma (γ)-carboxylation of certain calcium-binding proteins, including matrix gla protein (MGP), a vitamin K-dependent (VKD) mineralization inhibitor, expressed in human articular cartilage [255], periostin, gla-rich protein, gas 6 and osteocalcin.

Once carboxylated, MGP inhibits ectopic mineralization by binding calcium crystals, thereby inhibiting calcium crystal growth, and by binding to and inhibiting bone morphogenic protein-2, a protein that induces bone formation [256-258]. In human OA cartilage, MGP is primarily uncarboxylated, (the less functional form), whereas in healthy articular cartilage MGP is primarily carboxylated (functional) [259], suggesting the carboxylation of MGP is relevant to OA. MGP is also detectable in circulation and desphospho-ucMGP [(dp)ucMGP] concentrations increase when vitamin K status is low [260], suggesting circulating (dp)ucMGP may serve as a functional biomarker of vitamin K status for tissues that use MGP.Hence, vitamin K is an important regulator of bone and cartilage mineralization.

Genetic deficiencies of MGP in humans and mice have been linked to skeletal abnormalities, including premature epiphyseal calcification and shortening of long limb bones, reflecting endochondral bone formation [261-264].

A study by Neogi et al [265], suggested that persons with higher vitamin K levels, as measured by plasma phylloquinone, have a significantly lower risk of large osteophytes than do persons with low vitamin K levels, and this finding adds to the understanding of the pathogenesis of osteophytes.

Foods rich in Vitamin K

Food	Amount
Kale, ½ cup cooked	565mcg
Collard greens, ½ cup boiled	530 mcg
Spinach, ½ cup cooked	444mcg
Turnip greens, ½ cup cooked	425 mcg
Brussels sprouts, ½ cup cooked	150 mcg
Broccoli, ½ cup cooked	85 mcg
Asparagus, ½ cup cooked	72 mcg
Lettuce, ½ head of iceberg or 1 cup of romaine	60 mcg
Sauerkraut, ½ cup	56 mcg
Soybeans, ½ cup roasted	43 mcg
Edamame, ½ cup boiled	25 mcg
Pickles, cucumber dill or kosher dill pickle	25 mcg
Pumpkin, ½ cup canned	20 mcg
Pine nuts, per ounce	15 mcg
Blueberries, ½ cup	14 mcg

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