Casual Friday Series

Getting a Grip on RA

A Biogenetix Clinical Presentation

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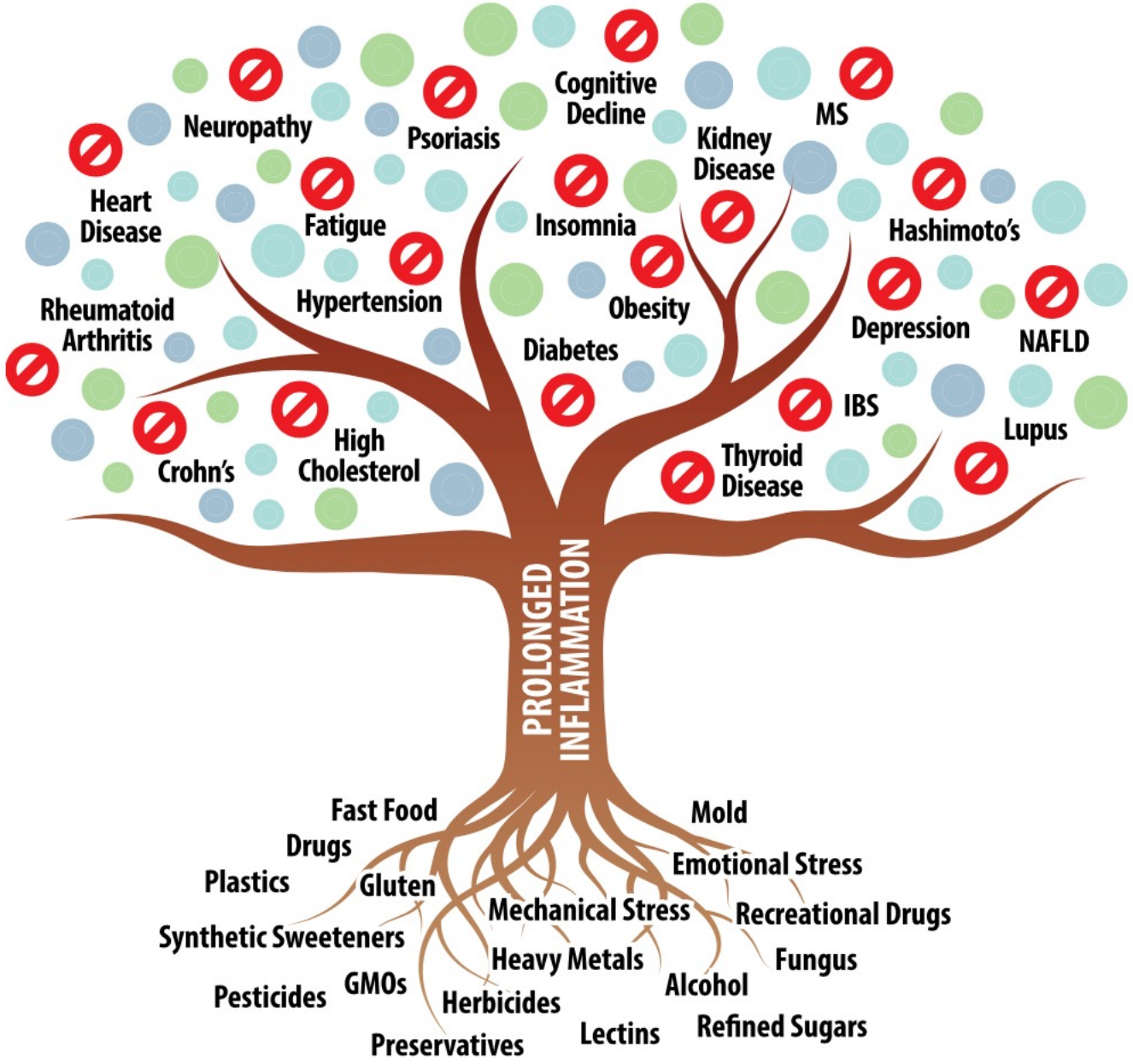
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*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Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
PROLONGED INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
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Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Lectins
Refined Sugars
Preservatives

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Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement. It is a chronic inflammatory disorder of unknown etiology that primarily involves synovial joints. It typically starts in small peripheral joints, is often symmetric, and progresses to involve proximal joints if left untreated.[1] Joint inflammation over time leads to the destruction of the joint with cartilage and bone erosion. RA with a symptom duration of fewer than six months is defined as early RA, and when the symptoms have been present for more than six months, it is defined as established RA.[1]

There is no pathognomonic laboratory test for rheumatoid arthritis, which makes the diagnosis of this disease challenging. An astute and comprehensive clinical approach is required to make the diagnosis and prevent debilitating joint damage.[1] The treatment of patients with rheumatoid arthritis requires both pharmacological and non-pharmacological therapy. Today, the standard of care is early treatment with disease-modifying anti-rheumatic drugs. Despite treatment, many patients progress to disability and suffer significant morbidity over time. A comprehensive pharmacological and non-pharmacological support (physical therapy, counseling, and patient education) is required to improve clinical outcomes.

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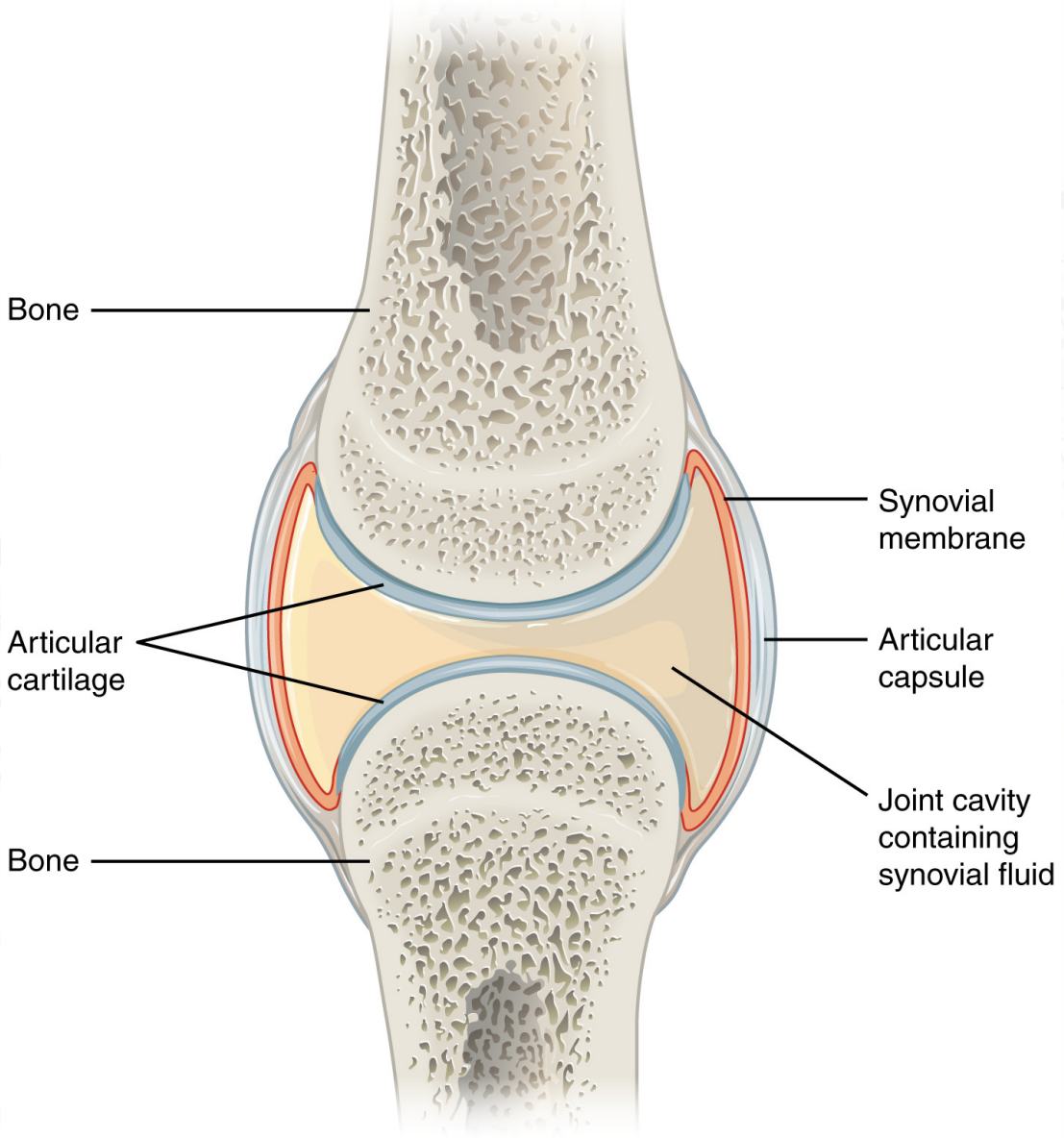

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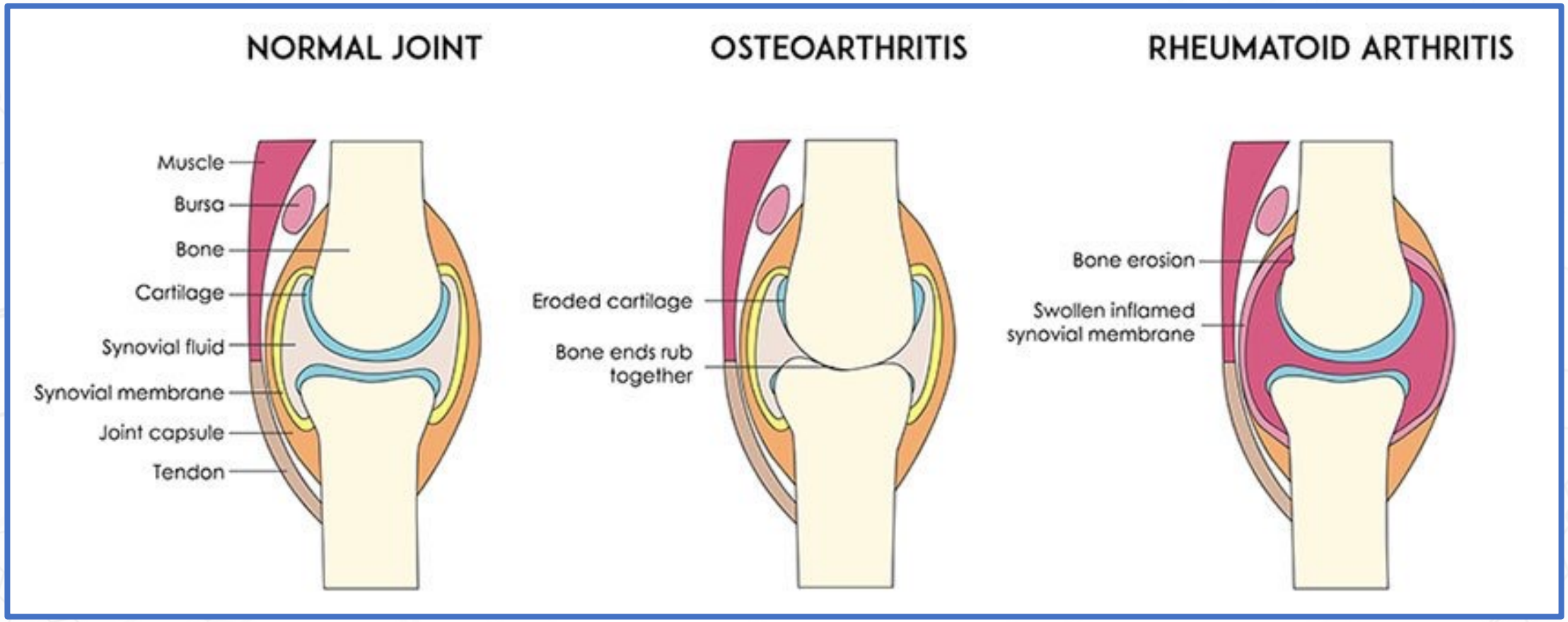

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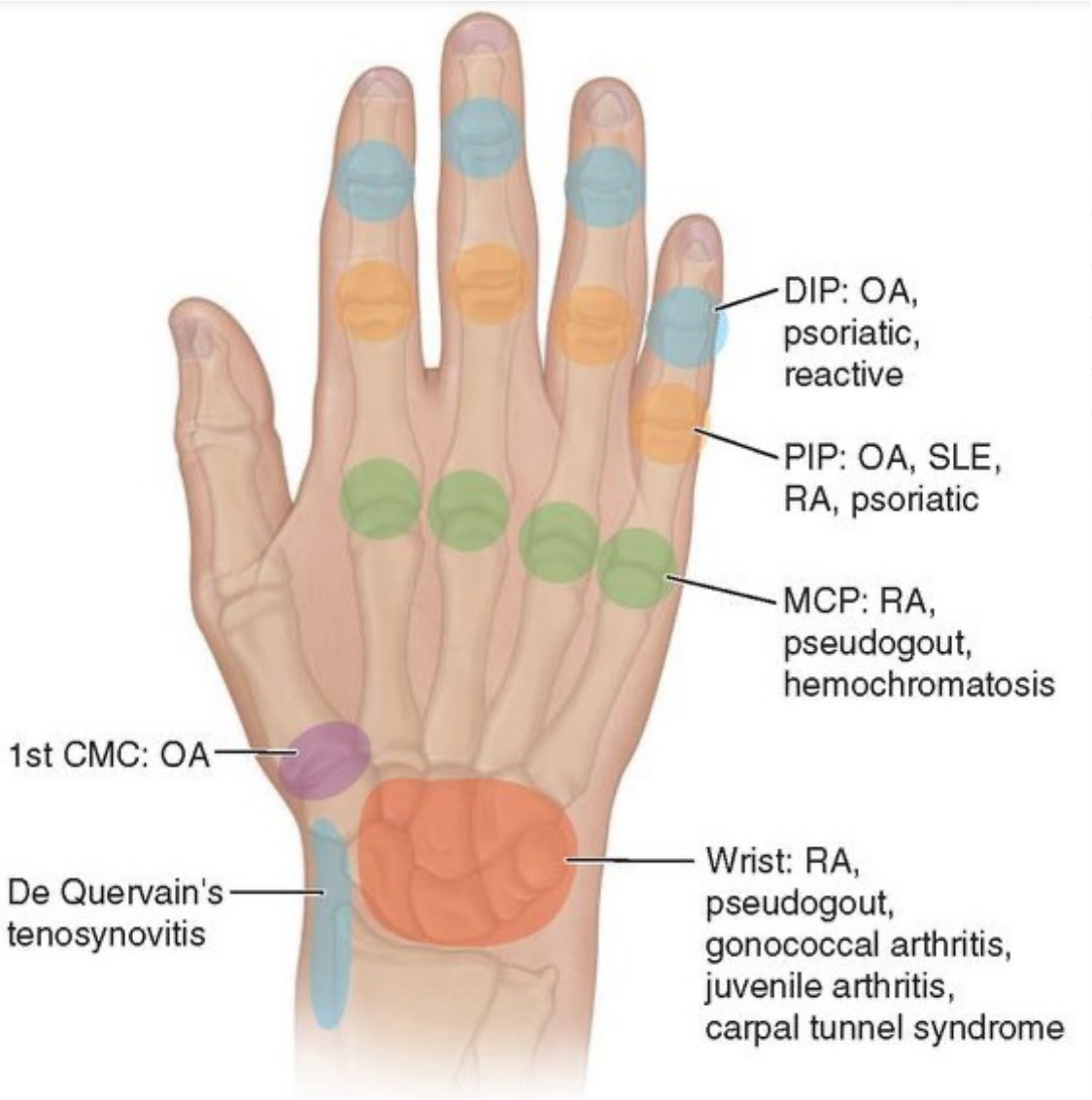
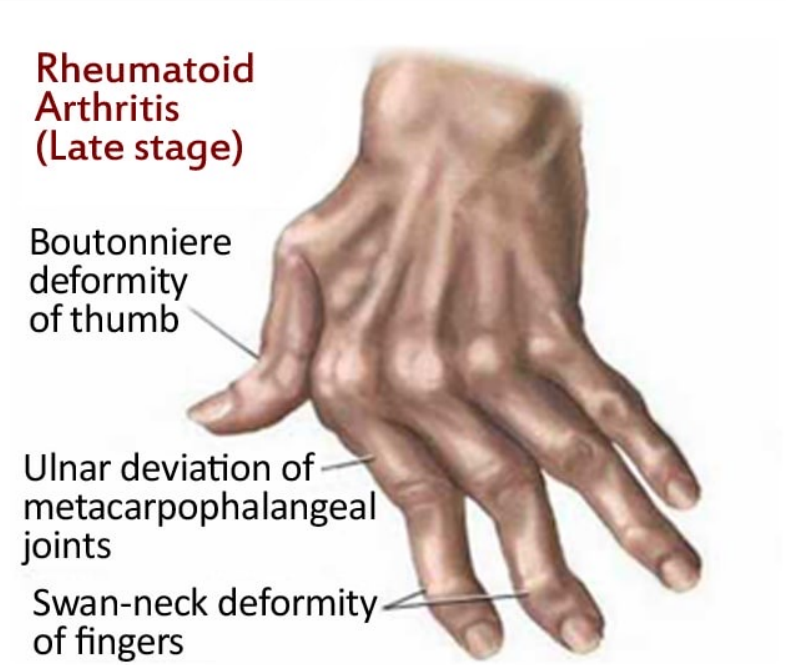
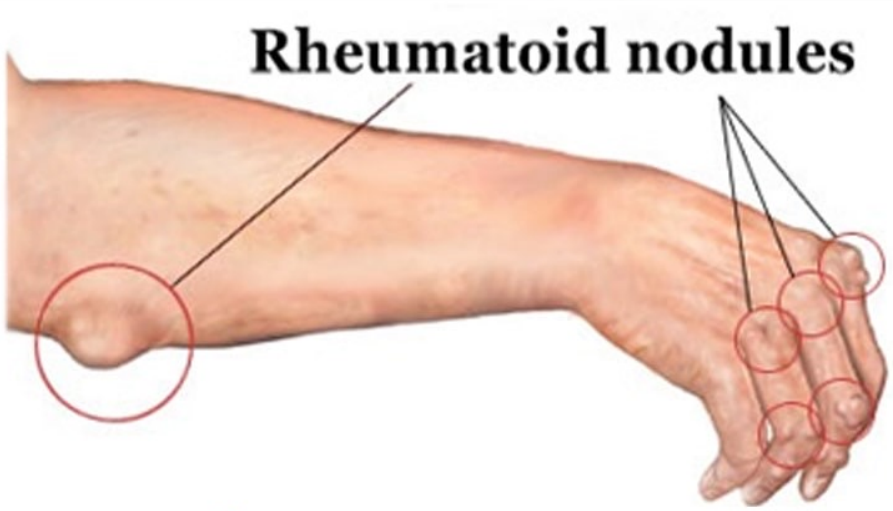
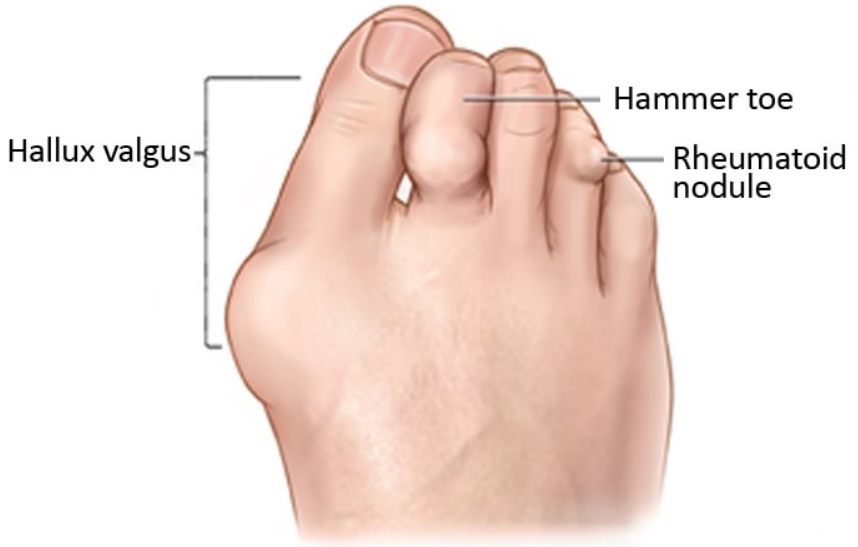
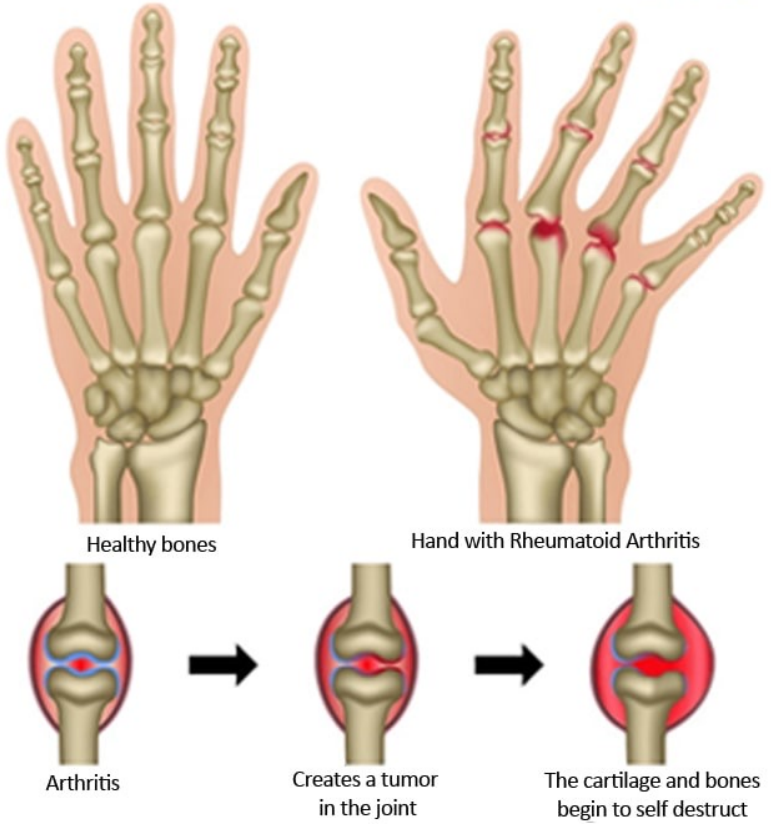

DIP: OA, psoriatic, reactive
PIP: OA, SLE, RA, psoriatic
MCP: RA, pseudogout, hemochromatosis
1st CMC: OA
De Quervain's tenosynovitis
Wrist: RA, pseudogout, gonococcal arthritis, juvenile arthritis, carpal tunnel syndrome









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The etiology of RA remains unknown.[2] It is thought to result from the interaction between patients' genotype and environment. In a nationwide study of 91 monozygotic (MZ) and 112 dizygotic (DZ) twin pairs in the United Kingdom, the overall MZ concordance rate was 15% and 5% among dizygotic twins.[3] The heritability of rheumatoid arthritis is approximately 40% to 65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis.[2] The risk of developing rheumatoid arthritis has been associated with HLA-DRB1 alleles: HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10. These HLA-DRB1 alleles contain a stretch of conserved five amino acid sequences and the shared epitope (SE) in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA.[4][5]

The term epigenetics refers to heritable changes without altering the DNA sequence. These changes may be present in chromatin or the DNA. These include DNA methylation, histone modification, and non-coding RNA-mediated regulation. RA-FLS (fibroblast-like synoviocytes) overexpress tyrosine phosphatase SHP-2, coded by gene PTPN11 compared to synoviocytes from osteoarthritis (OA) patients, promoting the invasive nature of RA-FLS. The enhancer region of the PTPN11 intron contained two hypermethylated sites, resulting in abnormal epigenetic regulation of the gene and alteration of function of RA-FLS.[7]

Cigarette smoking is the strongest environmental risk factor associated with rheumatoid arthritis. Studies have shown in ACPA (anti-citrullinated protein antibody) positive individuals; there is an interaction between genes and smoking that increases the risk of RA.[8]

Changes in the composition and function of the intestinal microbiome have been related to rheumatoid arthritis as well. The composition of the gut microbiome becomes altered in patients with rheumatoid arthritis (dysbiosis), where rheumatoid arthritis patients have decreased gut microbiome diversity compared with healthy individuals. There is an increase in these genera: *Actinobacteria, Collinsella, Eggerthalla, Faecalibacterium*. *Collinsella* alters gut mucosal permeability and has been related to increased rheumatoid arthritis disease severity.[8]

Among modifiable risk factors, cigarette smoking has the strongest association with RA.[15] Diet and nutrition have been shown to play a significant role as environmental triggers for RA. The typical 'western' diet that is rich, high in caloric content, and low in fiber increases the risk of RA.[16] Consumption of long-chain omega-3 polyunsaturated fatty acids is associated with a reduced risk of RA.[16]

Obesity is another well-established risk factor for RA. There is a 30% increase in the risk of RA for patients with a body mass index (BMI) of greater than 30 kg/m^2 and a 15% increased risk for those with a BMI of 25 to 29.9 kg/m^2.[17]

There is significant literature regarding the association of RA in patients with chronic mucosal or periodontal disease. However, no clear, consistent link has been identified in well-established studies. There is evidence that mucosal injury from occupational exposures and environmental pollutants can increase the risk of RA.[18][19]

Epigenetics:

Study of changes in the DNA that do not involve changes in the DNA sequence.

Rheumatoid arthritis patients contain antibodies to citrullinated proteins. Citrulline is an amino acid generated by post-translational modification of arginyl residues by peptidyl arginine deaminases. These antibodies are called anti-citrullinated protein antibodies (ACPA). ACPA can be IgG, IgM, or IgA isotypes. ACPA can bind citrullinated residues on self-proteins like vimentin, fibronectin, fibrinogen, histones, and type 2 collagen.[8] The binding of antibodies to proteins leads to complement activation. The presence of antibodies in rheumatoid arthritis is referred to as seropositive RA. ACPA can be present in the serum up to 10 years before the onset of clinical symptoms. With time the concentration of ACPA and serum cytokine level increases.[20][8]

The synovium in rheumatoid arthritis is infiltrated by immune cells, which include innate immune cells (monocytes, dendritic cells, mast cells) and adaptive immune cells (Th1 (T-helper 1), Th17 (T-helper 17), B cells, and plasma cells). Cytokines and chemokines like tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-monocyte colony-stimulating factors activate endothelial cells and attract immune cells within the synovial compartment. [8] The fibroblast in the rheumatoid synovium changes to an invasive phenotype. Fibroblast and inflammatory cells lead to osteoclast generation resulting in bone erosion, the hallmark feature of rheumatoid arthritis.[21]

The mechanism behind environment-triggered RA is thought to be due to the repeated activation of innate immunity. Cigarette smoking induces peptidyl arginine deiminase (PAD) expression in alveolar macrophages, which leads to the conversion of arginine to citrulline in the airway.[22] This process creates a "neoantigen" that activates an immune response and leads to the formation of anti-citrullinated protein antibodies (ACPAs).[22]

Due to the varied clinical presentation and lack of universal pathognomonic testing for RA, diagnosing the disease can be challenging. Traditionally the presence of at least four of the following criteria for at least six weeks would classify the patient as having RA. These criteria were: morning stiffness, arthritis of three or more joints, arthritis of the hands, symmetric arthritis, elevated acute phase reactants, elevated rheumatoid factor, and radiologic evidence of RA. These criteria separated inflammatory from non-inflammatory arthritis but were not very specific for RA. It was also not sensitive for early-stage RA, which was a significant drawback.[38] With the development of serologic markers, the diagnostic criteria were redefined. The 2010 American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) diagnostic criteria for RA are outlined below. It includes four different domains, which are as follows:

2010 ACR/EULAR Diagnostic Criteria for RA [39]

- Number and site of involved joints
  - 2 to 10 large joints = 1 point (shoulders, elbows, hips, knees, and ankles)
  - 1 to 3 small joints = 2 points (metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists)
  - 4 to 10 small joints = 3 points
  - Greater than 10 joints (including at least 1 small joint) = 5 points
- Serological testing for rheumatoid factor or anti-citrullinated peptide/protein antibody
  - Low positive = 2 points
  - High positive = 3 points
- Elevated acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) = 1 point
- Symptom duration at least six weeks = 1 point

A total score of greater than or equal to 6 classifies the patient as having RA. It is important to note that joint involvement refers to any swollen or tender joint on examination. Imaging studies may also be used to determine the presence of synovitis/joint involvement. The 2010 ACR/EALAR criteria excluded distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints from this criteria. Also, this criteria may only be applied to those patients where the joint involvement is not better explained by other inflammatory diseases, such as systemic lupus erythematosus or psoriasis. Specific testing must be obtained to rule out these diseases. The new criteria were noted to better predict the probability of RA, have the same sensitivity as the previous criteria for the diagnosis of RA and have a higher specificity as well as higher negative predictive value.[38]

Differential Diagnosis

- Systemic lupus erythematosus
- Chronic Lyme disease
- Osteoarthritis
- Septic arthritis
- Psoriatic arthritis
- Sjogren syndrome
- Sarcoidosis

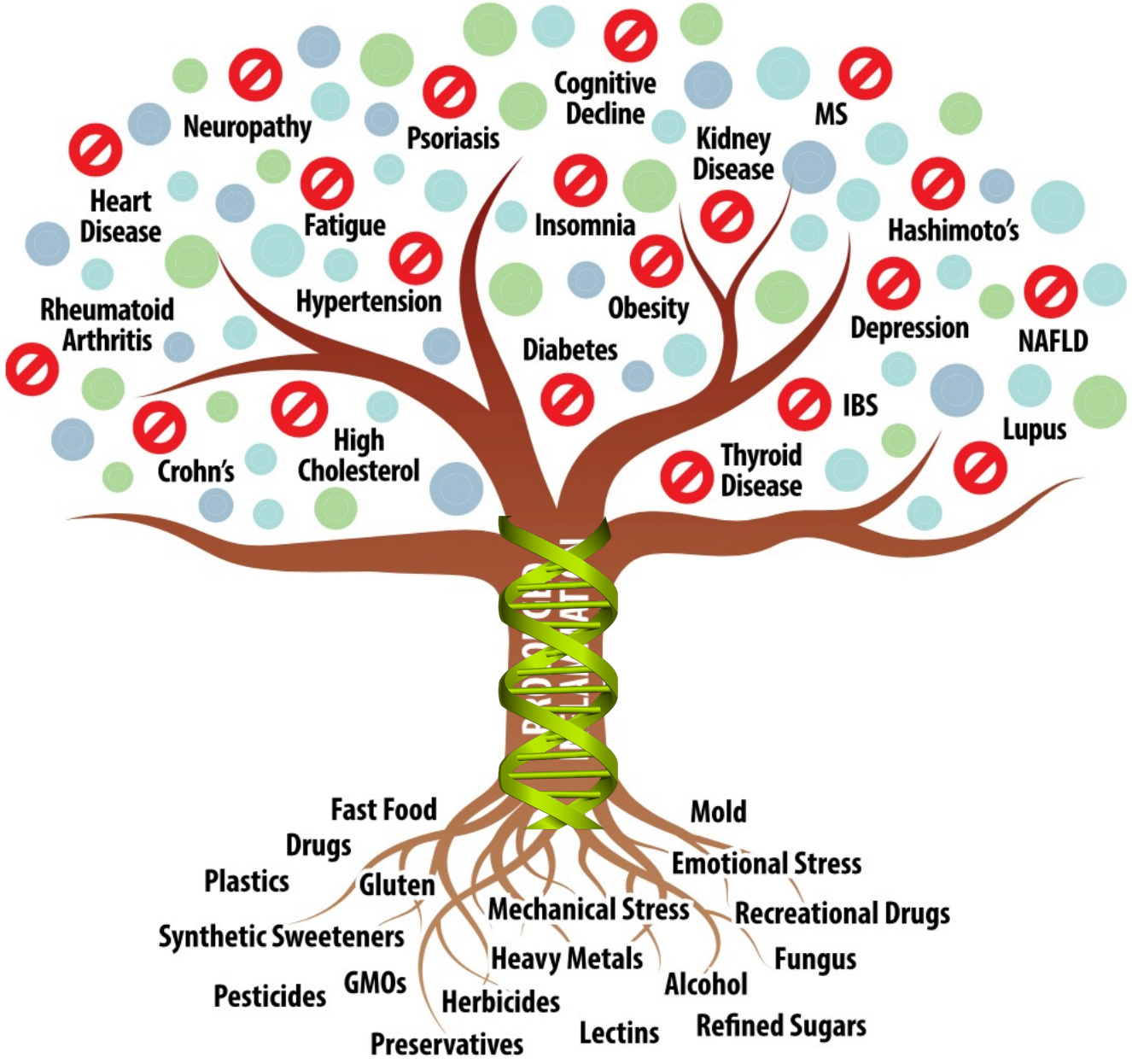
Stages of RA as Defined by the ACR: [42]

Stage 1: No destructive changes on x-rays

Stage 2: Presence of x-ray evidence of periarticular osteoporosis, subchondral bone destruction but no joint deformity

Stage 3: X-ray evidence of cartilage and bone destruction in addition to joint deformity and periarticular osteoporosis

Stage 4: Presence of bony or fibrous ankylosis along with stage 3 features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High Cholesterol
Lupus
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Lectins
Refined Sugars
Preservatives

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Managing Rheumatoid Arthritis with Dietary Interventions

Shweta Khanna,[1] Kumar Sagar Jaiswal,[1] and Bhawna Gupta[1,*]

Self-help by means of dietary interventions can help in management of various disorders including rheumatoid arthritis (RA), a debilitating autoimmune disease. Dietary interventions necessitate a widespread appeal for both patients as well as clinicians due to factors including affordability, accessibility, and presence of scientific evidences that demonstrate substantial benefits in reducing disease symptoms such as pain, joint stiffness, swelling, tenderness and associated disability with disease progression. However, there is still an uncertainty among the community about the therapeutic benefits of dietary manipulations for RA. In the present review, we provide an account of different diets and their possible molecular mechanism of actions inducing observed therapeutic benefits for remission and management of RA. We further indicate food that can be a potential aggravating factor for the disease or may help in symptomatic relief. We thereafter summarize and thereby discuss various diets and food which help in reducing levels of inflammatory cytokines in RA patients that may play an effective role in management of RA following proper patient awareness. We thus would like to promote diet management as a tool that can both supplement and complement present treatment strategies for a better patient health and recovery.

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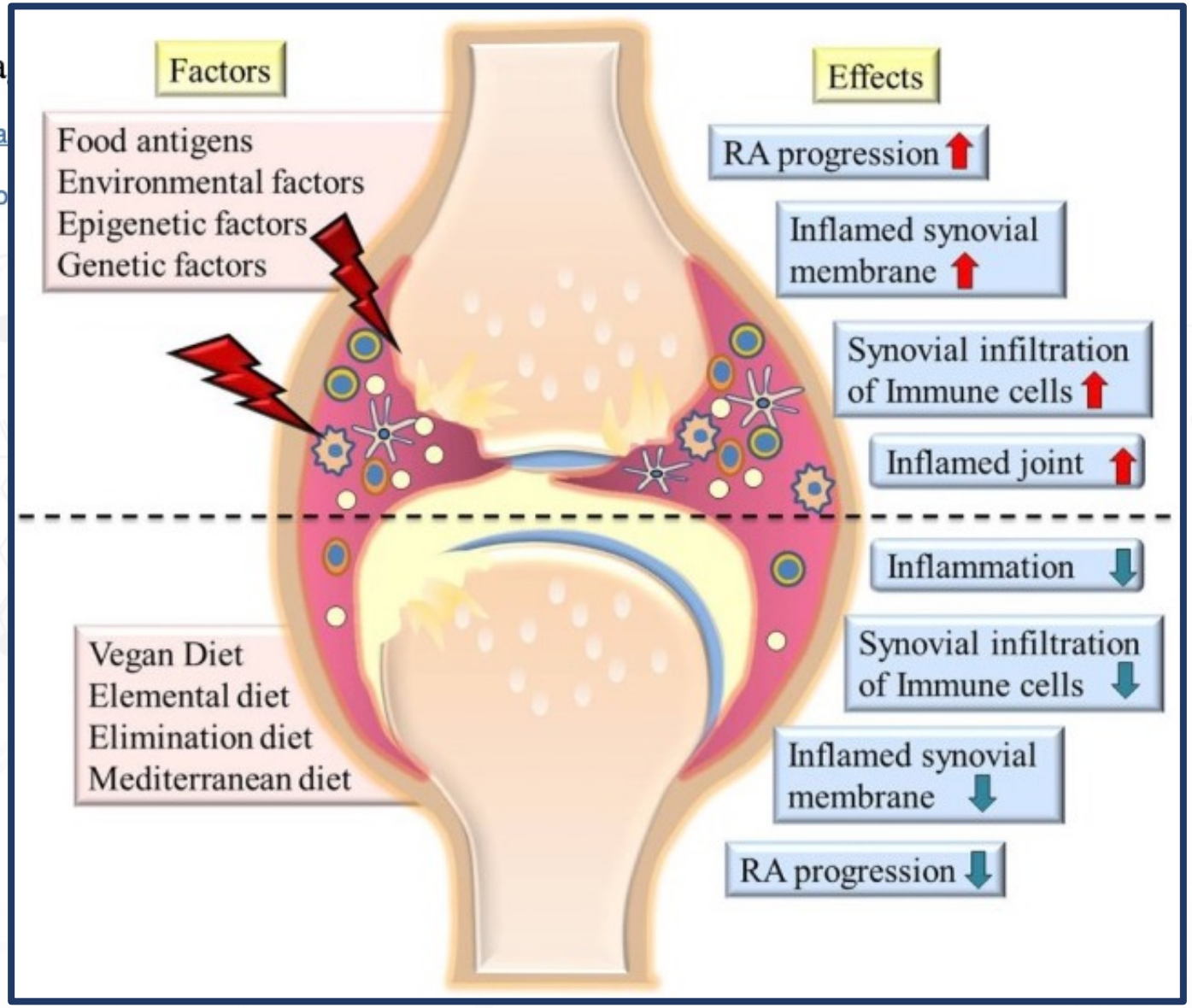

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Most of the staple food consumed all over the world are comprised of dietary fibers and whole grains. A definitive explanation for dietary fibers can be put as remnants of food not digested in small intestine, which then moves to large intestine and gets fermented by the microflora and induces several health promoting effects (92). Insoluble fibers such as cellulose and lignin are found in fruits, vegetables, and whole grains; and soluble fibers include pectin, guar gum, and mucilage (93). Earlier studies have found an inverse relationship between intake of dietary fiber and inflammatory biomarkers such as plasma fibrinogen, hs-CRP, TNF-α, IL-6 levels which are indicators of RA (94). However, contradictory reports were published as well by Hu and the group (95).

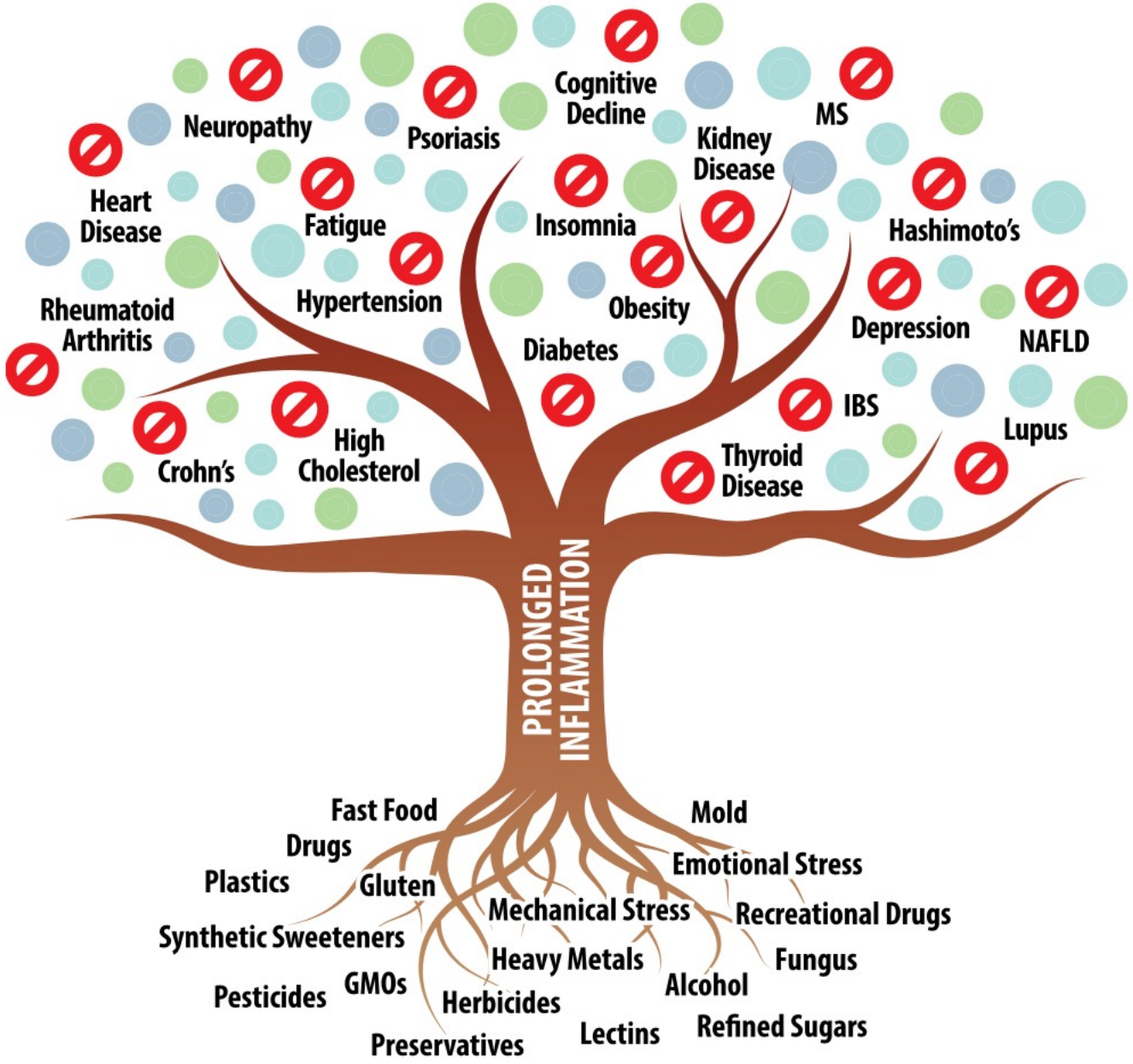
Even if no conclusive evidences are found about the role of dietary fibers and whole grains in RA, Food and Drug Administration (FDA) has approved their health promoting claims (98). As per Dietary Reference Intakes recommendations, daily consumption of dietary fibers within the limit of 14 g per 1,000 kcal intake or 25 and 38 g for an adult women and men, respectively (93) has health benefits.

3 FM questions:

1. What are you currently doing with your lifestyle?
2. Is therapy designed to protect your lifestyle?

OR

3. Is therapy designed to chop the disease down?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