Transdermal Methotrexate Delivery: A Novel Approach for Rheumatoid Arthritis Treatment

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Abstract- The crippling condition known as rheumatoid arthritis (RA) is linked to a higher risk of osteoporosis and cardiovascular disease. There have been reports of poor nutritional status in RA patients, and some medication regimens, including nonsteroidal anti-inflammatory medications (NSAIDs), that are used to treat RA symptoms may make certain nutrients more necessary and decrease their absorption. This study examines the scientific data supporting the use of nutrition supplements and food in the treatment of RA, whether via symptom relief, slowing the disease's development, or minimizing the need for or adverse effects of NSAIDs. Long-chain n-3 polyunsaturated fatty acid (PUFA) supplementation regularly shows a decrease in NSAID use and an improvement in symptoms. Evidence on antioxidants, zinc, iron, folate, other B vitamins, and other fatty acids.

Patients with rheumatoid arthritis (RA), a chronic inflammatory systemic autoimmune disease, experience differing degrees of joint damage. Age, gender, genetics, and environmental exposure (cigarette smoking, air pollution, and occupational exposure) are risk factors. If left untreated, a number of problems may arise, including rheumatoid vasculitis, elty's syndrome, which necessitates a splenectomy, and irreversible joint degeneration that requires arthroplasty. Since there is no known cure for RA, the objectives of therapy are to lessen discomfort and prevent or delay more damage. Here, we provide a concise overview of the many historical and contemporary approaches to treating rheumatoid arthritis-related problems.

Keyword: Arthroplasty, NSAIDs, Osteoporosis, Rheumatoid arthritis, Splenectomy

INTRODUCTION

An elevated risk of osteoporosis and cardiovascular disease (CVD) is linked to rheumatoid arthritis (RA), a chronic inflammatory, autoimmune disease that causes joint inflammation characterized by swelling, discomfort, functional impairment, and muscle atrophy. Both localized and systemic inflammation are its defining features, and pro-inflammatory cytokines such tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), in terleukin-1b (IL-1b), and acute phase proteins. It is believed that an underlying genetic predisposition that is manipulated in response to an environmental trigger causes RA.

The disease's precise cause or causes, however, remain unknown. In comparison to nonaffected controls, observational studies have shown that patients with RA have poor nutrient status, with lower energy intake from carbohydrates, higher consumption of saturated fat, and poor intake of micronutrients [1] . About 2% of people worldwide have rheumatoid arthritis, which is more frequent in women and usually manifests symptoms in middle life. RA is significant from a public health standpoint because of the related problems of osteoporosis and CVD. Rheumatoid cachexia, which is linked to increased production of the inflammatory cytokines IL-1b and TNF-a, may be a significant risk factor for these consequences. It is characterized by a loss in body cell mass, muscle mass, and strength [2] . The goals of traditional RA therapy, such as corticosteroids, slow-acting anti-rheumatic medications, and nonsteroidal anti-inflammatory medicines (NSAIDs), are to lessen joint inflammation and discomfort, minimize function loss, and halt the progression of joint degeneration. Nevertheless, these therapies are seldom completely successful, and certain pharmaceutical treatments may result in adverse consequences such intestinal hemorrhage and bone loss [3]. Many RA patients thus resort to alternative (self-prescribed) treatments, such as nutritional supplements. Furthermore, several medication treatments used to treat RA symptoms have anti-nutrient effects by raising a nutrient's need and

decreasing its absorption. Research has indicated that nutrition may be important in managing RA, especially in lowering the risk of complications and easing symptoms [4]. This article offers a summary of the scientific data supporting the various ways that diet and/or nutrient supplements can help manage rheumatoid arthritis by reducing symptoms, slowing the disease's progression, or minimizing the need for and adverse effects of concurrent medication. It is not a systematic review. Relationships between certain nutrients in the diet—both in foods and supplements—as well as modifications to the composition of the diet, including elimination diets, were investigated. It draws attention to specific nutrients of interest and might serve as the foundation for further systematic evaluations [5]

With the advent of biological agents and the early and intensive use of traditional disease-modifying antirheumatic drug (DMARD) techniques, the treatment of rheumatoid arthritis (RA) has significantly improved over the past several decades. These days, early RA is treated with patient-specific dosage and medication modifications (tight control) to reach a predetermined level of low disease activity or, more preferable, remission within a certain time frame (treat to goal) . It is generally acknowledged that there is a window of opportunity in the early stages of RA development when receiving adequate therapy can positively impact the disease's long-term course. New remission criteria and new categorization criteria have just been released. Imaging techniques like ultrasonography (US) may be employed for further information in joints clinically suspected of having arthritis, according to the revised categorization criteria . According to several clinical criteria, a significant portion of patients in clinical remission exhibit indications of inflammation on US]. These results suggest that while diagnosing RA or assessing remission in RA, US may have contributed to clinical examination. To do this, we would need to choose which joints the US would assess because it would take a lot of time to evaluate every joint. [6]

Dynamic exercise therapy as a Cochrane review for RA treatment determined that muscular strength and aerobic capacity may be increased by dynamic exercise. At this point, there were no negative impacts on pain or disease activity; nevertheless, it was unknown how exercise affected functional capacity and radiographic advancement, and its impact on cardiovascular outcomes had not been investigated. Only six papers were included in this 2000 Cochrane review6. Numerous researches have examined the impact of various forms of exercise on various outcome measures in RA in the years since this evaluation was conducted.

According to its etiology, osteoarthritis (OA) is a systemic, chronic joint disease that can be classified as primary or secondary. It is characterized by the progressive degeneration of the articular cartilage, which is the end point of OA, as well as alterations in the subchondral bone, meniscus, tendons/ligaments, muscles, and synovium (synovial inflammation) [7] .Age, gender, obesity, mechanical stress, sedentary lifestyle, joint trauma, and patient occupational activities are examples of non-genetic variables that contribute to osteoarthritis (OA), whereas genetic causes include changed gene expression patterns of the cartilage and subchondral bone. It can impact every joint in the body, although it most commonly affects the hand and lower extremity weight-bearing joints, resulting in discomfort and decreased functioning in adults. OA is a prevalent ailment that impairs patients' quality of life and poses a financial and social cost [8]. As people age and become obese, its prevalence rises. More than 70 million people in Europe suffer from knee OA, which has direct expenses of more than 2 billion euros. Although the condition usually progresses slowly, cartilage's inadequate capacity for regeneration eventually results in joint dysfunction. The World Health Organization's (WHO) 2010 Global Burden of Disease Study ranks osteoarthritis (OA) in the hip and knee as the eleventh most common cause of disability. [9]

Non-steroidal anti-inflammatory drugs (NSAIDs), supplements (glucosamine, chondroitin), viscous supplementation, arthroscopic lavage and debridement, combined non-pharmacological and pharmacological modalities, and replacement surgery as a sustainable alternative in certain circumstances are examples of traditional treatments in addition to exercise and weight loss. However, due in large part to the lack of clarity around the disease's pathophysiology, none of these treatments have been able to completely reverse the OA phenotype in patients to far. Although the exact chronology of OA pathology is still up for question, current research has highlighted the subchondral

bone's early pathogenic significance. Together with the articular cartilage, the subchondral bone, which is situated just beneath the layer of calcified cartilage, makes up the osteochondral unit. The cement line is the boundary that divides the calcified cartilage from the subchondral bone plate, whereas the tidemark is the basophilic line on histological sections that divides the hyaline cartilage from the underlying calcified cartilage. In the subchondral bone, there are two components. Together, the cancellous bone and cortical bone plate form the subchondral bone plate, which encloses small intervening areas. A central Haversian canal with nerves and capillaries is surrounded by osteon units that make up the highly mineralized cortical plate. Osteon units use Volkmann canals to exchange information with one another. Rather, only 15% to 25% of the bone volume is mineralized in the trabecular bone modeling medullar cavities. In deeper regions of the subchondral bone, the intervening gaps eventually grow and lengthen to produce the subarticular spongiosa [10]. The architecture, physiology, and mechanics of subchondral cortical and cancellous bone differ, and they react differently in OA. [11]

Types of arthritis:-

One or more joints that are swollen and painful are said to have arthritis. Joint pain and stiffness are the primary symptoms of arthritis, and they usually get worse as people age. Rheumatoid arthritis and osteoarthritis are the two most prevalent forms of arthritis.

1. Juvenile arthritis (JA)

According to the Arthritis Foundation, around 300,000 youngsters in the US suffer with juvenile arthritis (JA). JA is a catch-all name for a variety of juvenile arthritis kinds. Juvenile idiopathic arthritis, formerly known as juvenile rheumatoid arthritis, is the most prevalent kind. These are a class of autoimmune diseases that can affect the joints of youngsters.

JIA starts to occur in children younger than 16 years old. It can cause: muscle and soft tissue to tighten, bones to erode, growth patterns to change, joints to misalign

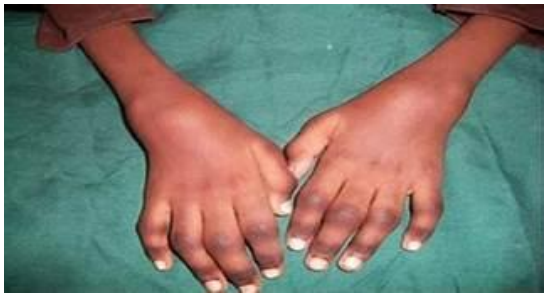


Fig.1 Juvenile arthritis

2. Spondyloarthropathies

The autoimmune diseases known as ankylosing spondylitis (AS) and others target the areas where your tendons and ligaments connect to your bones. Since AS is the most prevalent of these illnesses, your spine will probably be the most impacted. Although it can affect other joints in the body, it mostly affects the spine and pelvis. Peripheral joints like your hands and feet may be affected by other spondyloarthropathies. Bone fusion may happen in AS, which can lead to hip and shoulder problems as well as spinal deformity. The condition ankylosing spondylitis is inherited.

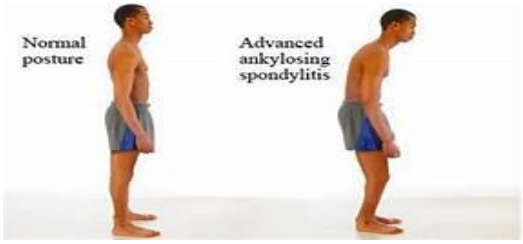


Fig .2 Spondyloarthropathies

3. Lupus Erythematosus

Another autoimmune condition that can impact your body's joints and connective tissue is systemic lupus erythematosus (SLE). Additionally, it may harm other organs including your: skin, lungs, kidney, brain and heart. Women are more likely to have SLE. Swelling and joint discomfort are typical symptoms.

Other signs and symptoms include: chest pain, fatigue, fever, uneasiness, hair loss, mouth sores, facial skin rash, sensitivity to sunlight, swollen lymph nodes.

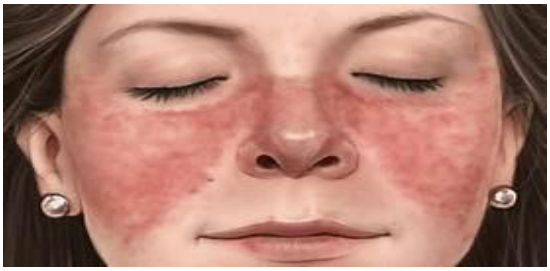


Fig .3 Lupus Erthematosus

4. Gout

Urate crystals build up inside your joints, causing gout, a kind of arthritis. A high blood uric acid level may increase your chance of developing gout. Gout affects an estimated 3.9 percent of American adults, or 5.9 percent of American males and 2 percent of American women, according to a reliable source. Your chance of getting gout might be influenced by your age, nutrition, alcohol consumption, and family history. It can hurt to have gout. Although other joints may be impacted, the most probable joint to be impacted is the one at the base of your big toe. You could feel pain, swelling, and redness in your: Toes, feet, ankles, knees, hands, wrists.

Fig .4 Gout

5. Infectious and reactive arthritis

An infection in one of your joints that results in pain or swelling is known as infectious arthritis. Viruses, parasites, fungus, or bacteria may be the source of the infection. Your joints may get affected after it begins in another area of your body. Fever and chills are common symptoms of this kind of arthritis. When an infection in one area of your body sets off immune system malfunction and inflammation in another joint, you may develop reactive arthritis. The infection usually affects your genital organs, bladder, or gastrointestinal tract. Your doctor may request testing on samples of your blood, urine, and fluid from inside an afflicted joint in order to identify these disorders.

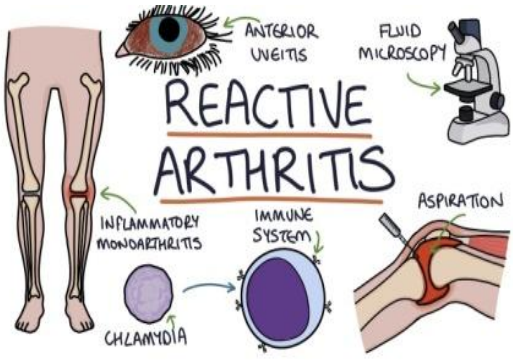


Fig .5 Infections & reactive arthritis

6. Psoriatic arthritis (PsA)

Psoriatic arthritis (PsA) is a painful illness that primarily affects the fingers, although it can also affect other joints. There may also be pitting of the fingernails and pink, sausage-like fingers. Additionally, the illness may spread to your spine, resulting in damage akin to that of ankylosing spondylitis.

Psoriatic arthritis activates the IL-23/Th17 pathway, which releases IL-17, IL-22, and TNF-α. This results in synovial inflammation, enthesitis, osteoclast activation, cartilage breakdown, and abnormal bone growth. Chronic inflammation is driven by dendritic cells, macrophages, and T lymphocytes, which impact the joints and skin. JAK-STAT, NF-κB, and MAPK pathways all have a role in disease progression.

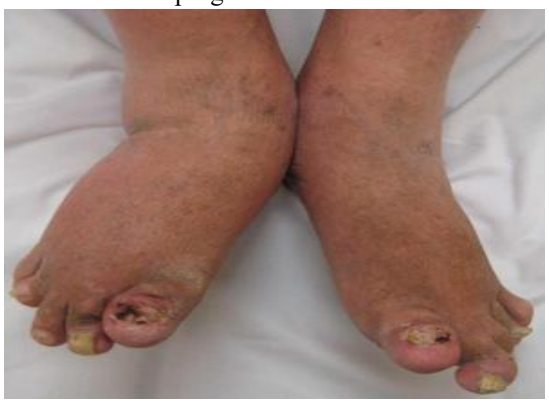


Fig .6 Psoriatic arthritis

7. Rheumatoid arthritis (RA)

One chronic autoimmune disease that mostly affects joints is rheumatoid arthritis (RA). Usually, it causes painful, swollen, and heated joints. After rest, pain and stiffness frequently get worse. The hands and wrist are most frequently affected, and the same joints are usually affected on both sides of the body. Other bodily components such as the skin, eyes, lungs, heart, nerves, and blood may also be impacted by the illness. A low red blood cell count, lung and heart inflammation, and other side effects might arise from this. Low energy and fever are also possible. Symptoms often appear gradually over a period of weeks to months.

Signs and symptoms of rheumatoid arthritis may include:

Tender, warm, swollen joints, stiffness that is usually worse in the mornings and after inactivity, fatigue, fever and loss of appetite

Smaller joints, especially those connecting your fingers to your hands and your toes to your feet, are

typically the first to be affected by early rheumatoid arthritis.

The wrists, knees, ankles, elbows, hips, and shoulders are frequently affected as the illness worsens. Usually, the same joints on both sides of your body experience the same sensations.

Approximately 40% of individuals with rheumatoid arthritis additionally have non-joint symptoms and indicators. Potentially impacted areas include: skin, eyes, lungs, heart, kidneys, salivary glands nerve tissue, bone marrow, blood vessels.

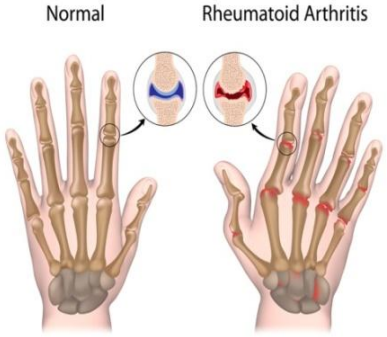
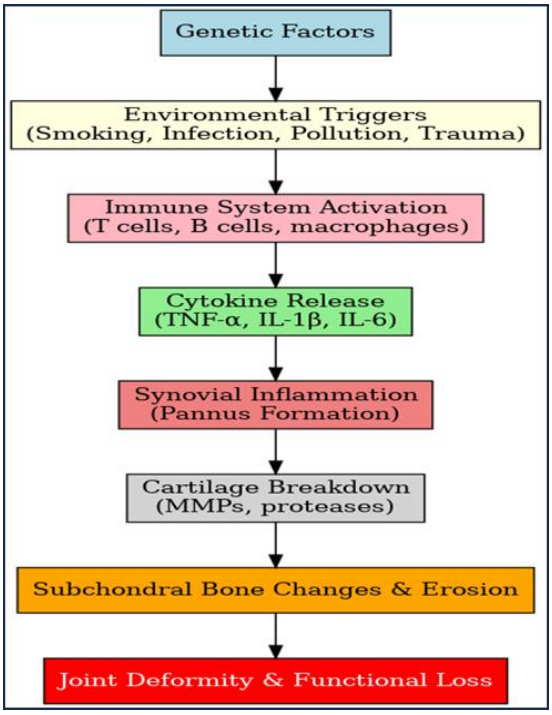


Fig .7 Rheumatoid arthritis

- Factors that may increase your risk of rheumatoid arthritis include:
- Your sex : Women are more likely than men to develop rheumatoid arthritis.
- Age: Rheumatoid arthritis can occur at any age, but it most commonly begins in middle age.
- Family history: If a member of your family has rheumatoid arthritis, you may have an increased risk of the disease.
- Smoking: Cigarette smoking increases your risk of developing rheumatoid arthritis, particularly if you have a genetic predisposition for developing the disease. Smoking also appears to be associated with greater disease severity.
- Excess weight: People who are overweight appear to be at a somewhat higher risk of developing rheumatoid arthritis.



Fig,8 General mechanism of Rheumatoid arthritis

Treatment

Rheumatoid arthritis does not have a treatment. However, clinical research suggests that early initiation of therapy with disease-modifying antirheumatic medicines (DMARDs) increases the likelihood of symptom remission.
The intensity of your symptoms and the length of time you have had rheumatoid arthritis will determine the kinds of drugs your doctor recommends.

NSAIDs. Pain and inflammation can be alleviated by nonsteroidal anti-inflammatory medications (NSAIDs). Ibuprofen (Advil, Motrin IB, and others) and naproxen sodium (Aleve) are examples of over-the-counter NSAIDs. Prescriptions are available for stronger NSAIDs. Kidney damage, cardiac issues, and stomach discomfort are possible side effects.

Steroids. Prednisone and other corticosteroid drugs lessen pain and inflammation while delaying joint deterioration. Diabetes, weight gain, and bone weakening are possible side effects. In order to rapidly alleviate symptoms, doctors frequently administer corticosteroids, which are then tapered off over time.

Conventional DMARDs. These medications can prevent irreversible damage to the joints and other tissues by slowing the course of rheumatoid arthritis.

Leflunomide (Arava), hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), and methotrexate (Trexall, Otrexup, and others) are examples of common DMARDs. Although side effects might vary, serious lung infections and liver damage are possible.

Biological substances. Abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), and tocilizumab (Actemra) are all part of this more recent family of DMARDs, also referred to as biologic response modifiers. Typically, biologic DMARDs work best when combined with a traditional DMARD, such methotrexate. Additionally, this kind of medication raises the danger of infection.

Argeted synthesized DMARDs. If traditional DMARDs and biologics have not worked, baricitinib (Olumiant), tofacitinib (Xeljanz), and upadacitinib (Rinvoq) may be utilized. Increased tofacitinib dosages may raise the risk of cancer, major heart-related events, and pulmonary blood clots.

8. Osteoarthritis (OA)

One kind of degenerative joint illness that arises from the deterioration of joint cartilage and underlying bone is osteoarthritis (OA). Affecting 1 in 7 persons in the US alone, it is thought to be the fourth most common cause of disability worldwide. Joint stiffness and discomfort are the most prevalent symptoms. The symptoms typically worsen gradually over years. Joint swelling, reduced range of motion, and, in cases where the back is impacted, arm and leg paralysis or numbness are possible additional symptoms. The knee and hip joints, the neck and lower back joints, the two joints close to the tips of the fingers, and the joint at the base of the thumbs are the most often affected joints. The symptoms may cause problems at work and in day-to-day activities. Only the joints, not the internal organs, are impacted, in contrast to some other forms of arthritis.

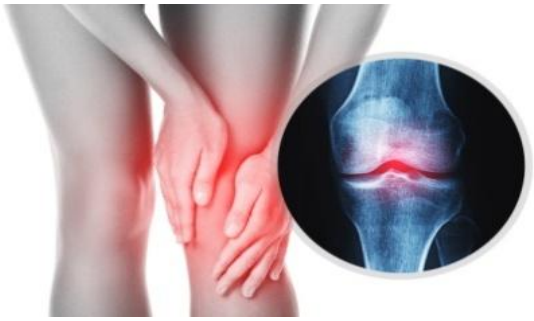


Fig .9 Osteoarthritis

Osteoarthritis symptoms often develop slowly and worsen over time. Signs and symptoms of osteoarthritis include:

1. Pain: Affected joints might hurt during or after movement.
2. Stiffness: Joint stiffness might be most noticeable upon awakening or after being inactive.
3. Tenderness: Your joint might feel tender when you apply light pressure to or near it.
4. Loss of flexibility: You might not be able to move your joint through its full range of motion.
5. Grating sensation: You might feel a grating sensation when you use the joint, and you might hear popping or crackling.
6. Bone spurs: These extra bits of bone, which feel like hard lumps, can form around the affected joint.
7. Swelling: This might be caused by soft tissue inflammation around the joint.

Factors that can increase your risk of osteoarthritis include:

- Older age: The risk of osteoarthritis increases with age.
- Sex: Women are more likely to develop osteoarthritis, though it isn't clear why.
- Obesity: Carrying extra body weight contributes to osteoarthritis in several ways, and the more you weigh, the greater your risk. Increased weight adds stress to weight-bearing joints, such as your hips and knees. Also, fat tissue produces proteins that can cause harmful inflammation in and around your joints.
- Joint injuries. Injuries, such as those that occur when playing sports or from an accident, can increase the risk of osteoarthritis. Even injuries that occurred many years ago and seemingly healed can increase your risk of osteoarthritis.
- Repeated stress on the joint: If your job or a sport you play places repetitive stress on a joint,

that joint might eventually develop osteoarthritis.

- Genetics: Some people inherit a tendency to develop osteoarthritis.
- Bone deformities: Some people are born with malformed joints or defective cartilage
- Certain metabolic diseases: These include diabetes and a condition in which your body has too much iron (hemochromatosis).

Treatment

Although osteoarthritis cannot be cured, there are therapies that can lessen discomfort and improve mobility.

The following drugs can help reduce the pain and other symptoms of osteoarthritis:

Acetaminophen. It has been demonstrated that acetaminophen (found in Tylenol and other brands) helps some osteoarthritis patients with mild to moderate pain.

Nonsteroidal anti-inflammatory drugs (NSAIDs). When used as prescribed, over-the-counter nonsteroidal anti-inflammatory medicines (NSAIDs) such naproxen sodium (Aleve) and ibuprofen (Advil, Motrin IB, and others) usually reduce osteoarthritis pain. NSAIDs have been linked to liver and kidney damage, blood issues, cardiovascular issues, and upset stomachs. When applied to the skin over the afflicted joint, NSAID gels have fewer adverse effects and may be just as effective in reducing pain.

Duloxetine (Cymbalta). This drug is licensed to treat chronic pain, particularly pain from osteoarthritis, and is typically used as an antidepressant.

CONCLUSION

From a fundamental perspective, our understanding of OA as a severe human disease for which there is currently no effective treatment has significantly expanded thanks to the availability of numerous clinically relevant animal models that involve intricate mechanisms involving every joint tissue. The discovery of the mechanisms and mediators behind the development and progression of OA offers hope for the development of modified, innovative clinical therapies in the near future, with a focus on the use of MSCs and tissue engineering techniques to administer safe and efficient therapeutic compounds to patients. [11]

A crippling chronic inflammatory condition, rheumatoid arthritis can lead to both long-term incapacity and joint damage. To avoid major harm and the loss of vital body processes, early diagnosis and management are crucial. By first defining the goals and then putting procedures in place to accomplish and evaluate them, the treating physician should think about following treat-to-target (T2T) recommendations [21]. Better treatment results can also be ensured by early referral to a specialist. We now have a greater knowledge of disease pathways because to developments in molecular medicine, which helps us create medicines that work better.

Both new and improved versions of old therapeutic approaches have been developed. Determining whether patients may respond better to particular drugs is becoming easier with the use of gene array analysis. In order to find the best course of action for a certain patient, this customization will enable faster treatment and reduce the chance of worsening illness, which can be prevented during the trial period. Additionally, gene array analysis is being utilized to identify people who are more susceptible to more severe types of rheumatoid arthritis. It is anticipated that rheumatoid arthritis management techniques would experience significant advancements. [12]

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