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Invited Review

Rheumatoid arthritis treatment: Is exercise a game changer?

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ABSTRACT

It is known that physical activity and exercise have many effects on patients with rheumatoid arthritis, such as reducing pain, stiffness, and fatigue and having positive effects on the development of complications related to the disease. However, despite all this information, the level of exercise and physical activity in patients with rheumatoid arthritis is lower than in healthy individuals. This may be due to reasons such as thinking that the disease will worsen, not having enough information about exercises, and not being supported enough by healthcare professionals and family in this regard. This review summarized the basic effects of exercises and recommended exercise programs.

Keywords: Non-pharmacological treatment, physical activity, rheumatoid arthritis.

Rheumatoid arthritis (RA), which is encountered at a frequency of 3.6% in females and 1.7% in males, has a prevalence of 0.24% worldwide.[1] Studies have reported that only physical activity/exercise can reduce the global impact of the disease and increase the quality of life.[2]

Rheumatoid arthritis is an autoimmune inflammatory disease.[3] Pathological immune processes cause joint damage and pain, and systemic inflammation paves the way for many secondary complications. These complications include changes in body composition, such as rheumatoid cachexia with increased fatty infiltration in the muscles, decreased functional capacity, cognitive dysfunction, fatigue, depression, cardiovascular issues, such as hypertension and dyslipidemia, and secondary osteoarthritis.[3] In a review conducted by Coskun Benlidayi,[4] it was reported that cardiovascular involvement in RA reduces 10-year life expectancy, and the premature death rate is 35-50%. Cardiovascular diseases are responsible for 40% of the deaths in patients with RA.[4] Exercise has a positive effect on the cardiovascular system in many different ways, such as regulating vascular functions, autonomic system, lipid profile, reducing systemic inflammation, and increasing muscle function.[4]

It has been shown that leptin levels, which are thought to play a role in the pathogenesis of the disease and are correlated with its severity, are significantly reduced by a resistance exercise program.[5] Therefore, the exercise program has become an integral part of the treatment program.[5] In the systematic review of clinical practice guidelines by Conley et al.,[6] it was stated that general exercise therapy, hydrokinesiotherapy, and joint-specific exercise programs are strongly recommended in the guidelines.

The World Health Organization reported that all adults should have a healthy and balanced diet and that physical activity is a basic need for health. These recommendations are important for the whole society, particularly for those with musculoskeletal system diseases and rheumatological diseases. However, there is no consensus on specific activity recommendations for rheumatological diseases.[7] In a study conducted in the Netherlands, a significant improvement in physical functions and quality of life was found in a 52-week exercise program applied to patients with RA who were severely limited in their daily living activities and compared it to usual care.[8] The results demonstrated that exercise can contribute to functional status and quality of life at every stage and that it is never too late

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to start exercise.[8] Exercise therapy has been shown to provide the most benefit in older, more inflamed, and less fit patients, likely because the disease is more active in those who live more sedentary lives.[2]

RHEUMATOID ARTHRITIS AND EXERCISE

Rheumatoid arthritis is a disease that usually starts in the hands and affects only the joints of the hands for a while. There may be a decrease in bone density, muscle strength, and functional capacity. Attention should be paid to stiffness, swelling, and limitation in the hand joints.[9] Muscle loss and inactivity are the main causes of mortality and morbidity.[9]

The evidence regarding the place of exercise in the treatment of RA has increased over the years, and exercise has the strongest evidence among supportive treatments. This data has enabled it to be included in treatment algorithms.[10] In the 2022 American College of Rheumatology guideline, recommendations regarding exercise and physical activity were conveyed.[11] These recommendations can be grouped into six sections and are discussed below.[11]

First, we strongly recommend consistent engagement in exercise over no exercise. Regular exercise improves physical function and reduces pain. Aerobic, resistance, aquatic, and mind-body exercises should be recommended. The duration, frequency, and intensity of the exercises can be shaped according to the characteristics of the patient. There is no clear recommendation on this subject. National guidelines should be established.

Second, we conditionally recommend consistent engagement in aerobic exercise over no exercise. Aerobic exercise has a positive effect on physical function, but moderate evidence has not shown an effect on pain. The recommendation should be considered according to the patient's physical condition, comorbidities, access to treatment, and cost.

Third, we conditionally recommend consistent engagement in aquatic exercise over no exercise. Its effect on physical function, such as aerobic exercise, has been shown, but its effect on pain is not clear. Patient preference, cost, and accessibility should be considered.

Fourth, we conditionally recommend consistent engagement in resistance exercise over no exercise. Its effect on physical function and pain has been shown with low- to very low-level evidence. It is recommended to work under control according to the patient's comorbidities, physical condition, and joint damage.

Fifth, we conditionally recommend consistent engagement in mind-body exercise over no exercise. The effects of exercises such as yoga, tai chi, and qigong on physical function have been shown with low- to very low-level evidence.

Finally, for patients with hand involvement, we conditionally recommend hand therapy over no hand therapy exercises. Low-level evidence has shown an effect on function and pain. It should be recommended by an experienced specialist according to the patient's needs.

Mechanism of exercise

The mechanism of action of exercise in RA can be explained by its effects on the immune system, inflammation, matrix metalloproteases (MMPs), oxidative stress, and epigenetic adaptation.[12]

It is known that short-term exercise increases the leukocyte count by two to three times, and when exercise is prolonged (0.5 to 3 h), the leukocyte count can increase up to five times. Although it is known that an increase in the leukocyte count is negative for inflammation/infection, particularly after endurance exercises, the leukocyte count reaches a value 30 to 50% lower than the preexercise value in 6 to 24 h. This value is clinically significant, and neutrophils and lymphocytes stimulated by exercise increase effector/cytotoxic function.[12] In a recent study investigating the effect of exercise in patients with stable RA, it was shown that the neutrophil migration toward chemokines (CXCL-8) increased, and proinflammatory monocytes (CD14+/CD16+) decreased in the circulation after exercise.[12] Since it is known that there is dysfunction in neutrophil migration and an increase in proinflammatory monocytes in RA, it was thought that exercise may affect this mechanism.[12] Most studies on the effect of exercise on inflammation are conducted on interleukin (IL)-6, which is a proinflammatory cytokine. However, IL-6 released from the muscle tissue is called a myokine and is anti-inflammatory. It is possible that exercise has an acute effect through myokine release.[12]

Matrix metalloproteinases are a zinc-dependent protease group that breaks down extracellular matrix elements such as collagen, gelatin, casein, and elastin. Studies conducted on different disease groups, healthy individuals, and sedentary individuals have shown that exercise reduces MMPs. Preclinical studies and a

clinical study have shown that exercise reduces MMP-1 and MMP-13 in RA patients.[12,13] However, studies should be conducted on its effect on MMP-3.[12]

Oxidative stress is an important risk factor in the onset and progression of the disease in RA patients. Animal and human studies have shown that exercise can reduce oxidative stress and increase antioxidant mechanisms, but the results are controversial.[12]

Animal studies have shown that hypoxic treadmill exercise reduces joint destruction to a greater extent than nonhypoxic exercise and prevents slow-twitch muscle atrophy and fibrosis.[14-16]

The effect of exercise on epigenetic mechanisms in patients with RA has been investigated in a small number of studies and the results are controversial.[17-20]

Patterson et al.[21] evaluated the effects of physical activity with actigraphy and performed RNA sequencing in 35 patients with RA. In this study, they compared low and high physical activity levels and gene expression in age-, sex-, and race-matched patients. Activity levels were grouped as 1.1 h of physical activity per day and 4.3 h of physical activity per day. Patients with RA in the high physical activity tertile showed a dose-dependent suppression of several signaling pathways associated with RA development, compared to those in the low physical activity tertile. These pathways included CD40, STAT3, TREM-1, IL-17A, IL-8, TLR (toll-like receptor), and IFN (interferon) signaling. Analysis of upstream cytokine activation suggested lower activity of TNF-α (tumor necrosis factor-alpha) and IFN, alongside enhanced erythropoietin activation, in the group with the highest physical activity levels.

The mechanisms by which physical activity reduces inflammation and inflammatory gene expression in RA can be explained through the desensitization of the hypothalamic-pituitary-adrenal axis, which is specific to certain stimuli. Regular physical activity improves the regulation of cortisol production, which is often inadequate due to chronic cytokine-driven inflammation in individuals with RA. It has been shown that even 15 min of low-intensity exercise in individuals who have not exercised before produces significant amounts of cortisol.[22] Physical activity also increases monocyte sensitivity to glucocorticoids, and regular physical activity improves plasticity in the neural network and regulates sympathetic nervous system (SNS) activity.[22] This effect not only reduces SNS activity but also increases vagal nerve activity. Additionally, it increases testosterone, dehydroepiandrosterone, growth hormone, and IGF-1 (insulin-like growth factor 1) levels and reduces renin-angiotensin-aldosterone system activation. These effects are summarized in Table 1.

TYPES OF EXERCISES

Aerobic exercise

Aerobic exercise is a type of exercise that produces aerobic energy, such as jogging, walking, and cycling. It is performed at 50 to 80% of maximum heart rate and aims to increase peak oxygen consumption. Studies have shown that regular aerobic exercise habits can reduce the risk of RA. In patients with RA, it reduces joint damage and the risk of cardiovascular disease, improves fatigue symptoms, increases muscle strength, and improves quality of life.[23-28]

In the meta-analysis conducted by Ye et al.,[23] it was also shown that the pain level was significantly lower in those who performed aerobic exercise. This result created a significant difference in C-reactive

TABLE 1
Neuroendocrine imbalances in RA which physical activity has a modulating role[22]

• Insufficient cortisol production relative to inflammation levels.
• Resistance to the effects of glucocorticoids.
• Elevated sympathetic nervous system (SNS) activity paired with a loss of sympathetic nerve fibers in inflamed tissues.
• Reduced vagus nerve function.
• Lower production of androgens.
• Decreased levels of insulin-like growth factor 1 (IGF-1).
• Impaired insulin sensitivity
• Overactivity of the renin-angiotensin-aldosterone system (RAAS).

RA: Rheumatoid arthritis.

TABLE 2
Strength training guidelines for individualized patient needs[3]

Key recommendations

- Age considerations:
  Older adults should train on alternate days and begin with low intensities (40-50% of one-repetition max). Single sets may be sufficient initially.
- Disease activity:
  In active disease, control inflammation before initiating training. Adapt intensity based on joint damage and physical limitations. Begin with range-of-motion exercises for severely damaged joints.
- Experience and fitness levels:
  Beginners or inactive individuals benefit from supervised sessions with gradual progression, starting with bodyweight exercises Alternating days provide necessary recovery. Simple routines suffice for deconditioned patients.

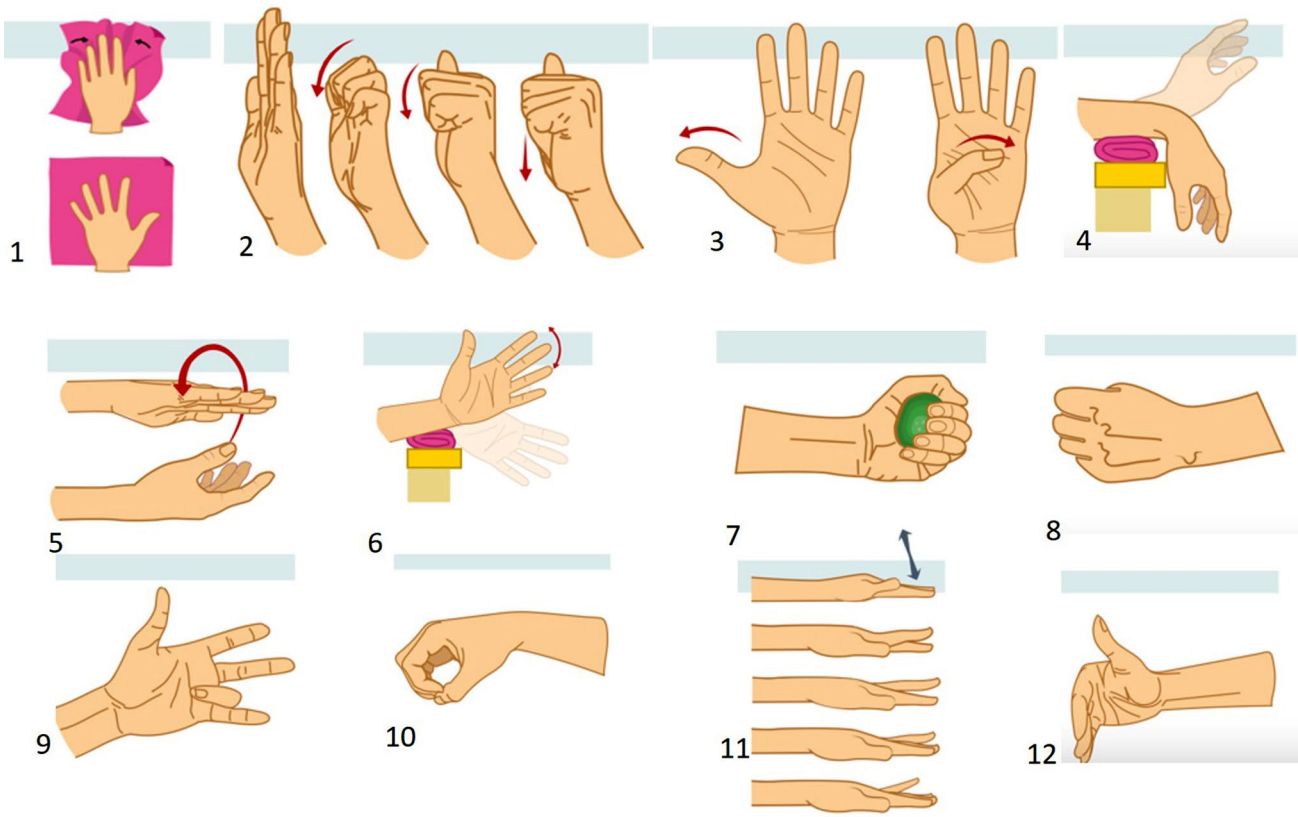

Figure 1. Wrist, hand, and finger exercises.

1. Finger strengthening, 2. Finger tendon stretching, 3. Thumb stretch, 4. Wrist movement, 5. Wrist turning, 6. Hand deviation, 7. Grasping, 8. Make a light fist, 9. Finger curl, 10. "O" shape, 11. Finger lift, 12. "L" shape.

protein values in the long term.[23] In their review, Akram et al.[1] also reported that aerobic exercise has positive effects on cognitive function in patients with RA, with a decrease in inflammatory cytokines and an increase in serotonin and noradrenaline levels.

In a pilot study conducted by McKenna et al.,[29] the effect of walking, the most common aerobic exercise, on sleep quality was examined, and its positive effects were reported.

Strength training exercise

Strength training (ST) is a reliable treatment approach for many sequelae of RA and refers to defined and repetitive movements performed to strengthen muscles and increase muscle mass. It can be done

with one's own body weight, machines, weights, or resistance bands. It has been shown that pain and inflammatory markers are reduced, body composition and functional well-being are improved, and the risks of cardiovascular and other comorbidities are reduced in patients with RA with ST.[3]

The effects of hand strengthening and stretching exercises were shown in the study of Lamb et al.[30] published in 2015, and the subgroup analysis of the same study by Boniface et al.[31] showed that more intense and challenging exercises were more successful in hand functions.

With the accumulation of data, the EULAR (European Alliance of Associations Against Rheumatism) emphasized in 2018 that ST exercises should be part of standard treatment in patients with RA. However, studies have shown that this exercise program, which should be done at least two days a week, is only performed by 1 to 14% of RA patients.[3,32,33] In a meta-analysis conducted in Türkiye, it was reported that coaching programs implemented in the form of face-to-face meetings or phone calls with patients at certain intervals increased compliance with physical activity.[34]

In the review conducted by Küçükdeveci et al.,[35] it was reported that hand exercises had positive effects on fine and gross grip compared to no exercise in the medium (three to 11 months) and long term (≥12 months).

In a study published by Kamo et al.[36] in 2024, it was reported that upper and lower extremity exercises performed with body weight two days a week for six weeks in female patients with RA had significant positive effects on muscle strength, grip strength, range of motion, Health Assessment Questionnaire scores, and the timed up-and-go test at the end of the study. Recommendations for ST are provided in Table 2.[3]

Resistance training could be safely performed to improve muscle strength in patients with RA, even at moderate or high intensities. In recent years, many studies have employed moderate- to high-intensity training and demonstrated its muscle-strengthening effects, suggesting that resistance

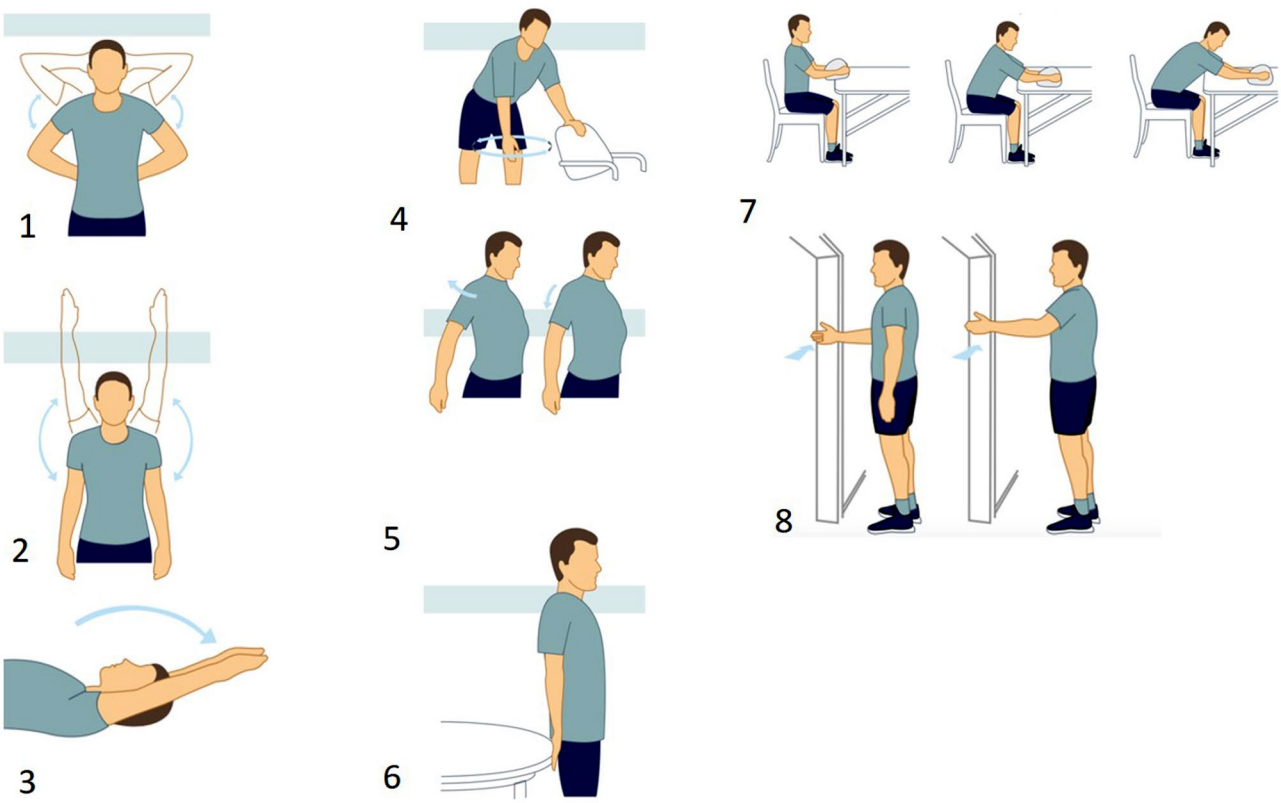

Figure 2. Shoulder exercises.

1. Arms up (while standing), 2. Arm stretching (while standing), 3. Arm stretching (lying down), 4. Draw a circle with your shoulder, 5. Shoulder stretching, 6. Press backward onto the table, 7. Lean forward on the table, 8. a-b Apply pressure to the door.

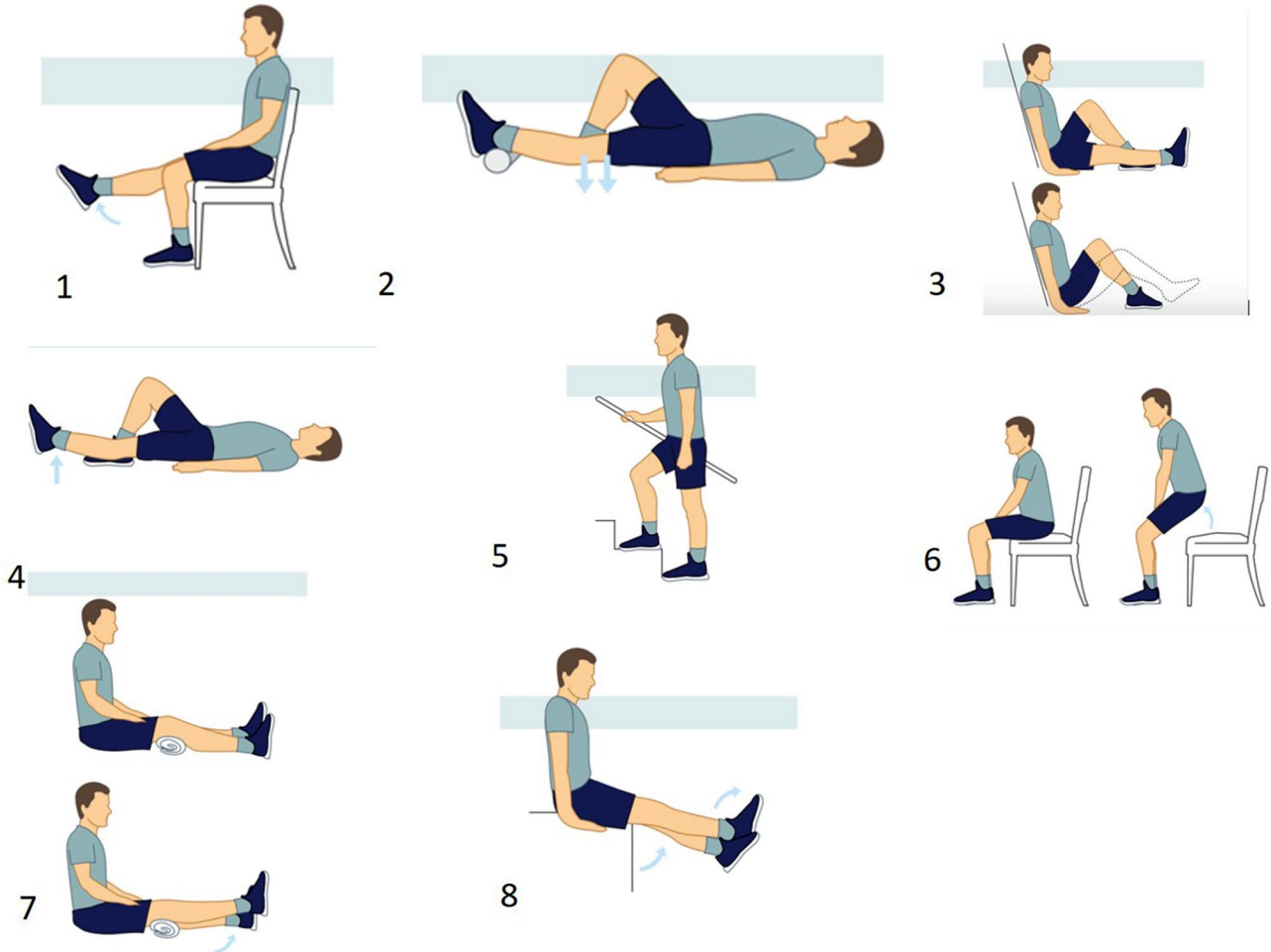

Figure 3. Knee exercises.

1. Leg up (while sitting), 2. Muscle stretching, 3. Leg stretching 4. Leg up (lying down), 5. Climbing stairs, 6. Sitting/standing, 7. Leg exercise with a rolled towel, 8. Crossed legs.

training or a combination of resistance training and aerobic exercise effectively improves muscle strength in patients with RA.[37-39] The exercises we recommend for RA patients are shown in Figures 1 through 4. Additionally, explanations of these exercises are provided as a supplement to be given to patients.

Since there are no clear limits defined regarding the duration, frequency and number of repetitions of exercise in rheumatological diseases, the position statement is to provide specific guidance for rheumatic and musculoskeletal disease researchers as summarized by the IMPACT-RMD Consortium.[40]

In conclusion, information and exercise recommendations in Türkiye are frequently made in addition to drug treatment for inflammatory diseases. The recommended exercises for the joints most affected by RA were summarized in this study. Standardizing these exercises is important for ensuring consistency in future studies and supporting the robustness of data.

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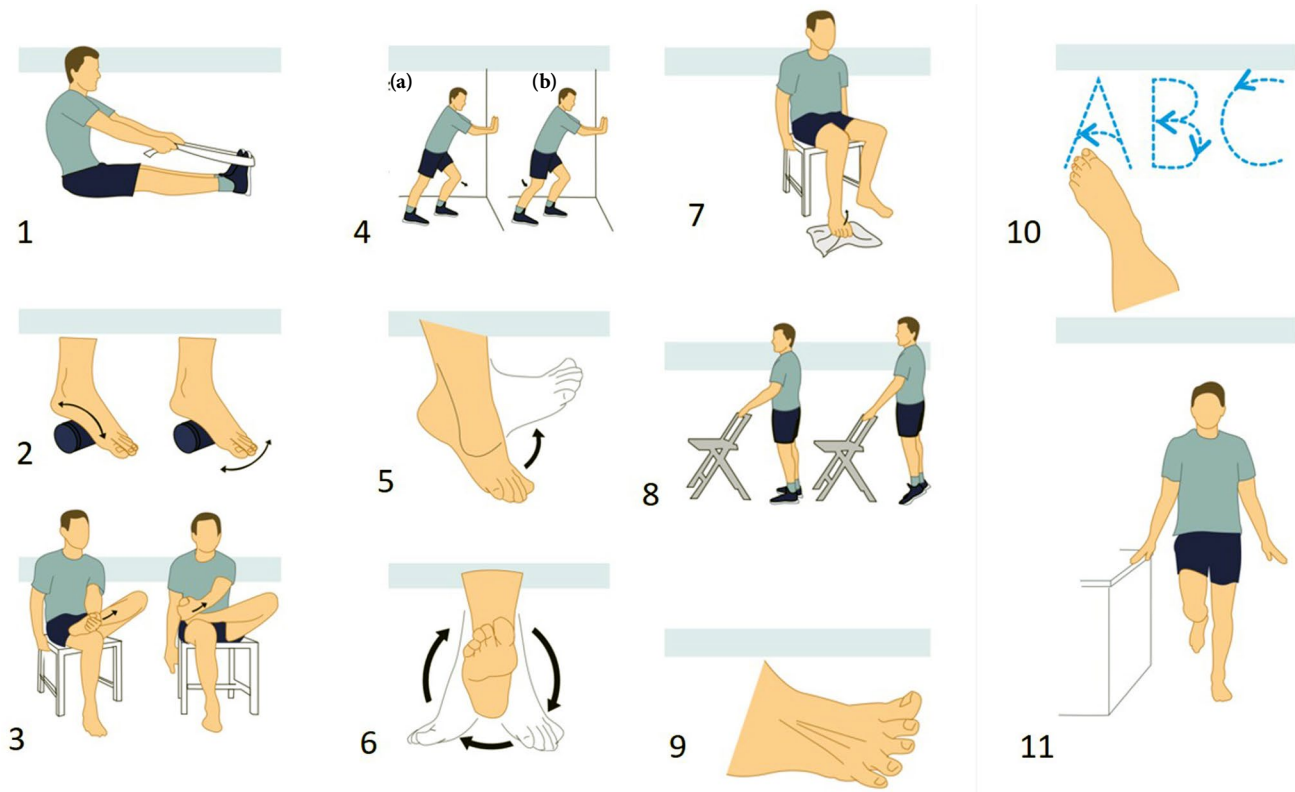

Figure 4. Ankle, foot, and toe exercises.

1. Achilles and plantar fascia streching, 2. Plantar fascia streching, 3. Plantar fascia streching (in sitting), 4. a-b Pushing the Wall, 5. Ankle range of motion, 6. Ankle rotation, 7. Taking towel with feet, 8. Stand on tiptoe, 9. Spread your toes, 10. Writing the alphabet, 11. Balance exercise.

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WRIST, HAND, AND FINGER EXERCISES

1. **Finger Strengthening**
   Begin by spreading your fingers apart with the palm of your hand on a tissue or towel on a table. Press your hand against the table to bring your fingers together, gathering the tissue between your fingers. Repeat. You can also do this exercise without a tissue or towel by pressing your fingers together on the table and then spreading them apart.
2. **Finger Tendon Stretching**
   Start with your fingers straight. Make a hook fist, straighten your hand again. Make a full fist, straighten your hand again. Make a fist with your fingers straight, then straighten your hand again.
3. **Thumb Stretch**
   Hold your hand out in front of you as if making a stop sign. Start with your thumb positioned outward. Move your thumb toward the palm of your hand and then return to the starting position.
4. **Wrist Movement**
   Place your forearm on a flat surface, such as a table, with your hand hanging over the edge and your palm facing down. A towel under your wrist may provide comfort. Keeping your fingers relaxed, move your hand upward until you feel a slight stretch, then return to the starting position.
5. **Wrist Turning**
   Bend your elbow 90 degrees with your palm facing down. Rotate your forearm so that your palm faces up and then down. You can stand or sit to do this exercise.
6. **Hand deviation**
   Support your forearm on a rolled towel on a table or on your knee, with your thumb facing up. Move your wrist up and down through its full range of motion as if you were waving.
7. **Grasping**
   Squeeze a hand exercise ball as hard as you can and hold for 5 seconds, then release. Note: Avoid squeezing movements like this if you have a severe or active flare-up in your hands.
8. **Make a Light Fist**
   Hold your hand with your fingers straight, palm facing down. Slowly close your hand into a loose fist (do not clench) with your thumb outside. Open your hand again, fingers straight out. Repeat 10 times; switch to the other hand.
9. **Finger Curl**
   Hold your hand out to the side with your fingers straight and your thumb facing up. Bend your thumb toward your palm. Hold for two seconds, then straighten. Repeat 5 times with each finger; switch to the other hand.
10. **O Shape**
    Hold your hand with your fingers straight, palm down. Curve your fingers inward until your thumb and fingers touch, forming an "O" shape. Hold for 5 seconds. Repeat 5 times; switch to the other hand.
11. **Finger Lift**
    Place your hand flat on the table, palm down and fingers straight. Slowly lift your thumb off the table, hold for 2 seconds, then lower it. Repeat 5 times with each finger; switch to the other hand.
12. **L Shape**
    Place your hand on the table with the pinky finger down. With your thumb facing up, bend the other four fingers inward until they form an inverted "L" shape. Hold for 2 seconds, then return your fingers to the starting position. Repeat 10 times; switch to the other hand.

SHOULDER EXERCISES

1. **Arms Up (in standing)**
   Place your hands behind your head, so that your elbows are facing out to the sides and press back as far as possible. Hold for five seconds. Then place your hands behind you, again with your elbows pointing out and press back as far as possible. Hold for five seconds. Repeat each movement five times.
2. **Arm Stretching (in standing)**
   Stand comfortably with your arms at your sides. Raise your arms as far as you can comfortably and hold for 5-10 seconds. When your arms are raised, your palms should face each other. Lower them and repeat five times. You can do this exercise by raising your arms in front of you or to the sides.
3. **Arm Stretching (lying down)**
   Lie on your back with your arms at your sides. Raise your arms as high as you can comfortably, palms facing each other. Hold for 5-10 seconds. Return your arms to your sides and repeat five times.
4. **Draw a Circle with Your Shoulder**
   Lean on a chair with one hand. Let your other arm hang down and try to swing it gently back and forth in a circle. Repeat this movement about five times and try to do it about two or three times a day.
5. **Shoulder Stretching**
   Stretch your shoulders back and hold for five seconds. Lower your shoulders down and hold for five seconds. Relax and repeat 10 times.
6. **Press Backward Onto the Table**
   Stand upright with your back to the table and your palms resting on the edge of the table. Gently push your shoulder blades back and your hands toward the table. You are not trying to move the table, just to meet its resistance. This exercise should help strengthen the muscles around your shoulders.
7. **Leaning Forward on the Table**
   Sit upright with your knees bent and feet hip-width apart. Bend your elbows and place your palms on a flat piece of cloth on the table in front of you. Gently slide the cloth forward across the table, bending at the waist and keeping your back straight. Slide your hands as far as comfortable, aiming to straighten your arms. Allow your head to slowly drop forward and hold for five seconds. Slowly slide back down and repeat. If placing your palms flat on the table is uncomfortable, place your palms facing each other for this exercise.
8. **Applying Pressure to the Door**
   a. Stand in a doorway with your elbow bent at a right angle and close to your body. The back of your wrist should be pressed against the door frame. Try to push your arm outward toward the door frame. Hold for five seconds. Do this 10 times on one side, then 10 times with your other arm on the opposite side of the door frame. If you can, try to do two more sets, so that you can do 30 sets with each arm.
   b. This time, start with your other arm and, with your elbow at a right angle, push your palm toward the side of the door frame that you used in part (a). Hold for five seconds. Do this 10 times on one side, then 10 times with your other arm on the opposite side of the door frame. If you can, try to do two more sets, so that you can do 30 sets with each arm.

KNEE EXERCISES

1. **Leg Up (in sitting)**
   Sit in a chair with your back straight. Keep one leg straight and lift it. Slowly count to 10, then slowly lower your leg. Repeat 10 times for each leg.
2. **Muscle Stretching**
   Lie on your back with a rolled towel under your ankle. Bend your other leg at the knee. Use the muscles in your straight leg to push the back of your knee firmly toward the bed or floor. Count slowly to five. Repeat at least five times for each leg. This exercise helps prevent your knee from becoming permanently bent. Try to do this at least once a day while lying down.
3. **Leg Stretching**
   Sit on the floor with your legs straight out in front of you. Slowly bend one knee toward your chest, sliding your foot along the floor until you feel a stretch. Hold for five seconds. Straighten your leg as much as you can and hold this position for five seconds. Repeat 10 times for each leg.
4. **Leg Up (lying down)**
   You can do this exercise lying on the floor or on a bed. Bend one leg at the knee. Keep the other leg straight and lift your foot off the floor or bed. Slowly count to five, then lower it. Repeat five times with each leg every morning and evening.
5. **Climbing Stairs**
   Step up to the bottom step of the stairs with your right foot. Pick up your left foot, then step down with your right foot, then your left foot. Hold on to the railing if necessary. Repeat with each leg until you can't do anymore. Rest for a minute, then repeat twice more. As you get better, use a higher step or skip two steps at a time.
6. **Sitting/Standing**
   Sit in a chair. Stand up without using your hands for support, and then sit down again. Make sure each movement is slow and controlled. Repeat until you can't do anymore. Rest for a minute, then repeat two more times. If the chair is too low, start by lifting from a cushion on the seat, and then try removing the cushion when you no longer need it.
7. **Leg Exercise with Rolled Towel**
   Sit on the floor, couch, or bed with your legs extended in front of you. Place a rolled towel under one knee. Press down on the towel as if you were straightening your knee. Pull your toes and foot toward you so that you feel the stretch in your calf muscles and your heel lift off the floor. Hold for 5 seconds, then relax for 5 seconds. Do this 10 times, then repeat with the other leg.
8. **Crossed Legs**
   Sit on the edge of a table, chair, or bed and cross your ankles. Push your front leg back and your back leg forward until your thigh muscles are tight. Hold this for as long as you can, then relax. Rest for a minute, then repeat two more times. Switch legs and repeat.

ANKLE, FOOT, AND TOE EXERCISES

1. **Achilles and plantar fascia streching:** Wrap a towel around your foot and, keeping your knee straight, draw your toes toward your body. Hold for 30 seconds. Repeat three times for each foot.
2. **Plantar fascia streching:** Sit down and place the arch of your foot on a cylindrical object, such as a tin can. Roll your foot back and forth over the can for a few minutes. Repeat this exercise twice a day.
3. **Plantar fascia streching (in sitting):** Sit down and place one foot on your knee. Grasp the base of your toes and pull them toward your body until you feel a comfortable stretch. Hold for 15-20 seconds. Repeat three times.
4. **Pushing the Wall: (a)** Face the wall, place both hands on the wall at shoulder height and place one foot in front of the other. The front foot should be about 12 inches (30 cm) from the wall. With the front knee bent and the back knee straight, bend the front knee toward the wall until you feel a stretch in the calf of your back leg. Relax and repeat 10 times. **(b)** Repeat **(a)**, but bring the back foot slightly forward so that the back knee is slightly bent. Repeat 10 times.
5. **Ankle range of motion:** Bend your ankle as far as you can toward your body, then point your toes away from your body. Repeat 10 times.
6. **Ankle rotation**: Slowly move your wrist in a circle. Do this 10 times in one direction, then repeat in the opposite direction.
7. **Taking towel with feet:** Sit with a towel on the floor in front of you. Keeping your heel on the floor, squash the towel between your toes. Repeat 10 to 20 times.
8. **Stand on tiptoe:** Using a bench or chair for support, rise up onto your toes with your knees straight. Slowly lower your feet back down. Repeat 10 times.
9. **Spread your toes:** With your feet on the floor, spread your toes as far apart as possible. Hold for five seconds. Repeat this exercise 10 times.
10. **Writing the alphabet**: While sitting, write the alphabet in the air with your thumb, moving only your ankle. Try to write the entire alphabet twice a day
11. **Balance exercise:** Balance on one leg, using a stable object such as a kitchen counter for support. Aim for one minute and see how long you can do this. Try to do this three times and repeat the set twice a day. Take every opportunity to practice standing on one leg - incorporating it into your daily activities will help you improve. Once you feel confident with this basic balance exercise, you can make it harder by standing on a cushion or pillow. Gradually increase the amount of the exercise. Once you can balance easily on a cushion and feel confident, return to standing on the floor and repeat the basic balance exercise with your eyes closer.