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Disease and treatment-related comorbidities in rheumatoid arthritis

Romatoid artritte hastalık ve tedavi ilişkili komorbiditeler

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Abstract

Rheumatoid arthritis (RA) is a chronic, progressive disease affecting systemic connective tissues, including synovial membranes in joints and extra-articular systems. The global prevalence is estimated between 0.5% and 2%, with a higher incidence observed in women, individuals with a family history, and smokers. The disease's etiology is primarily attributed to immune processes in the synovial membrane and fluid of joints. Importantly, RA is a systemic condition affecting joints, organs, and systems, including the cardiovascular, renal, pulmonary, and neuropsychiatric systems. In one study, 40% of RA patients experienced complications, with a significant incidence of 8.3% among those with cardiovascular disease, interstitial lung disease, osteoporosis, and metabolic syndrome. Sustained inflammation and immune dysregulation, hallmark features of RA, significantly contribute to the onset and progression of associated comorbidities. Comorbidities frequently coexisting with RA encompass cardiovascular diseases, pulmonary disorders, osteoporosis, malignancies, and infections. Such comorbidities exert a direct impact on patient quality of life, functional capacity, and mortality rates. The emergence of these comorbid conditions is not solely attributable to the disease itself but may also be influenced, either positively or negatively, by the therapeutic agents employed.

Keywords: Rheumatoid arthritis, comorbidity, treatment

Öz

Romatoid artrit (RA), eklemlerdeki sinoviyal membranlar ve eklem dışı sistemler de dahil olmak üzere sistemik bağ dokularını etkileyen kronik, ilerleyici bir hastalıktır. Küresel prevalansın %0,5 ile %2 arasında olduğu tahmin edilmektedir; kadınlarda, aile öyküsü olanlarda ve sigara içenlerde daha yüksek bir insidans gözlenmektedir. Hastalığın etiyolojisi öncelikle sinovyal membrandaki ve eklem sıvısındaki bağışıklık süreçlerine atfedilir. RA, kardiyovasküler, renal, pulmoner ve nöropsikiyatrik sistemler de dahil olmak üzere eklemleri, organları ve sistemleri etkileyen sistemik bir hastalıktır. Yapılmış bir çalışmada RA tanılı hastaların %40'ında komplikasyon görülmüş olup bunların arasında kardiyovasküler hastalık, interstisyel akciğer hastalığı, osteoporoz ve metabolik sendromu görülme insidansı %8,3 saptanmıştır. RA'nın ayırt edici özellikleri olan sürekli enflamasyon ve immün düzensizlik, ilişkili komorbiditelerin başlangıcına ve ilerlemesine önemli ölçüde katkıda bulunur. RA'ya sıklıkla eşlik eden komorbiditeler kardiyovasküler hastalıklar, akciğer hastalıkları, osteoporoz, maligniteler ve enfeksiyonlardır. Bu tür komorbiditeler hastanın yaşam kalitesi, fonksiyonel kapasitesi ve mortalite oranları üzerinde doğrudan etkili bulunmuştur. Bu komorbid durumların ortaya çıkması yalnızca hastalığın kendisine atfedilemez; kullanılan terapötik ajanlar tarafından da olumlu veya olumsuz etkilenmektedir.

Anahtar Kelimeler: Romatoid artrit, komorbidite, tedavi

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive disease affecting systemic connective tissues, including synovial membranes in joints and extra-articular systems. The global prevalence is estimated between 0.5% and 2%, with a higher incidence observed in women, individuals with a family history, and smokers.[1] The disease's etiology is primarily attributed to immune processes in the synovial membrane and fluid of joints. Cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6 released from synovial macrophages induce inflammation,

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leading to bone erosion.[2] Importantly, RA is a systemic condition affecting joints, organs, and systems, including the cardiovascular, renal, pulmonary, and neuropsychiatric systems. In one study, 40% of RA patients experienced complications, with a significant incidence of 8.3% among those with cardiovascular disease (CVD), interstitial lung disease, osteoporosis, and metabolic syndrome.[3]

Sustained inflammation and immune disregulation, hallmark features of RA, significantly contribute to the onset and progression of associated comorbidities.[4,5] Comorbidities frequently coexisting with RA encompass CVDs, pulmonary disorders, osteoporosis, malignancies, and infections. Such comorbidities exert a direct impact on patient quality of life, functional capacity, and mortality rates. The emergence of these comorbid conditions is not solely attributable to the disease itself but may also be influenced either positively or negatively by the therapeutic agents employed. Following the advent of traditional conventional disease-modifying antirheumatic drugs (csDMARDs), TNF-α inhibitors have been developed to target the inflammatory pathways and cytokines integral to the disease's etiopathogenesis.

Furthermore, the recent introduction of biologic disease-modifying antirheumatic drugs (DMARDs) [biologic disease-modifying antirheumatic drugs (bDMARDs)] and targeted synthetic DMARDs [targeted synthetic disease modifying antirheumatic drugs (tsDMARDs)] into treatment regimens have facilitated the suppression of inherent inflammation, therefore enhancing disease control and mitigating the risk of comorbidity development due to unchecked inflammation. However, the prohibitive cost of these novel agents has resulted in varying degrees of access limitations within national healthcare economies.[6,7] Concurrently, the complexities of managing disease-associated comorbidities likewise impose a significant financial burden on national healthcare systems. This review aims to summarize RA-associated comorbidities considering existing scientific literature.

Cardiovascular Disease

CVD is the leading cause of mortality among patients with RA. Compared to age- and sex-matched individuals from the general population, patients with RA have a 1.5- to 2.5-fold increased risk of developing CVD.[8] CVD encompasses coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, and associated risk factors like hypertension and dyslipidemia. A meta-analysis by a Canadian research group found the CVD mortality rate was 50% higher in RA patients compared to the general population, exceeding mortality from other comorbidities.[9,10] RA-associated chronic inflammation, along with traditional CVD risk factors and the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CS), all contribute to the heightened CVD risk.[11] The prevalence of CVD risk factors, including smoking, hypertension, insulin resistance, dyslipidemia, and obesity, is substantially increased in the RA population compared to the public.[12] Meta-analyses have demonstrated regular use of CS and NSAIDs increases cardiovascular events among RA patients.[13]

The underlying mechanism of increased CVD risk in RA involves inflammation-mediated endothelial dysfunction and loss of vascular elasticity. Changes in structural proteins of the vasculature accelerate atherosclerosis, which can be detected by measuring carotid intima-media thickness.[14] Elevated serum C-reactive protein (CRP) levels and higher disease activity also increase CVD risk. The presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) correlates with more frequent cardiovascular events.[15] Compared to the general population, RA patients have a 2- to 3-fold increased risk of myocardial infarction, a 2-fold increased risk of heart failure and sudden cardiac death, and a 1.7-fold increased risk of stroke.[16] In evaluating individual CVD risk independent of RA, variables such as age, gender, smoking status, blood pressure, lipid profile, and diabetes mellitus are considered. These parameters are incorporated into the Framingham and Systematic Coronary Risk Evaluation (SCORE) algorithms to assess a 10-year CVD risk.[17,18] The European Society of Cardiology (ESC) advocates for a quinquennial CVD screening for patients.[19] According to SCORE, risk stratification is categorized as low risk for scores below 5%, moderate risk for scores between 5-10%, high risk also between 5-10%, and very high risk for scores exceeding 10%.

For patients with a 10-year cardiovascular risk of 10% according to Framingham risk scoring and 5% per SCORE, both lifestyle modifications and lipid-lowering agents are advised.[17,18] Importantly, lifestyle interventions are universally endorsed for all patients irrespective of risk level. In addition, the ESC specifically advocates for risk stratification in hypertensive patients, recommending the incorporation of antihypertensive medications for those with grade 2 hypertension or grade 1 coupled with high CVD risk.[19] While the 2009 European League Against Rheumatism guidelines recommended a 1.5-fold multiplication factor for calculating total CVD risk in RA patients with a disease duration exceeding ten years, RF or anti-CCP positivity, and extra-articular manifestations,[20] the 2016 update expanded these criteria. It now advises applying this factor even in newly diagnosed RA patients with elevated CVD risk irrespective of the disease stage or extra-

articular involvement.[21] Carotid ultrasonography serves as a screening tool for asymptomatic atherosclerotic plaques, the presence of which may foretell future acute coronary events.[14] Effective disease control and suppression of inflammation significantly mitigate CVD risk. csDMARDs, particularly methotrexate, and bDMARDs, especially TNF inhibitors, have proven efficacious in this regard.[15] Conversely, a study on tofacitinib among tsDMARDs revealed a higher rate of major adverse cardiovascular events in individuals over 50 with one or more cardiovascular risk factors compared to those on TNF inhibitors.[22,23]

Moreover, NSAIDs frequently used in RA treatment regimens carry their own cardiovascular risks. While naproxen exhibits a safer risk profile, diclofenac is contraindicated in various cardiac conditions. Recent evidence extends similar caution to the use of ibuprofen.[21] Beyond CVD, RA patients may also experience various forms of cardiac involvement such as pericardial effusion, valve nodules, and structural and functional left ventricular changes, collectively termed "silent rheumatoid heart disease".[24,25]

Lung Involvement

Another substantial comorbidity in RA is extra-articular pulmonary involvement. Remarkably, between 60-80% of RA patients develop complications related to the lungs.[26] These complications can affect various lung structures, including airways, parenchyma, vascular formations, and pleura. Within the airways, one can find conditions such as bronchiolitis, bronchiectasis, cricoarytenoid arthritis, and rheumatoid nodules. Furthermore, the lung parenchyma may be affected by various forms of interstitial lung disease (ILD), including usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organizing pneumonia.[25] Vascular complications, including pulmonary hypertension and vasculitis, are also not uncommon. Additionally, pleural diseases like pleuritis, pleural effusion, pneumothorax, and empyema are observed. Beyond these more direct complications, patients also face secondary risks such as drug toxicity, infections, and amyloidosis. Of these, parenchymal involvement is particularly concerning as it manifests the highest morbidity and mortality rates. Specifically, ILD carries a significant mortality rate of 10-20%.[2] A high-resolution lung tomography (HRCT) study identified four major lung disease patterns in RA. UIP was found in 37% of cases, NSIP in 30%, obliterative bronchiolitis in 17%, and organized pneumonia in 8%.[27,28] Intriguingly, although RA predominantly affects women, a 4-fold male predominance has been observed in cases of RA-associated ILD.[26]

Factors such as heightened disease activity, advanced age, non-pulmonary extra-articular manifestations, and smoking history significantly contribute to the risk of pulmonary complications in RA. In particular, those with a smoking history exceeding 25 packs per year exhibit an elevated risk.[29] Moreover, lower baseline measurements of predicted forced vital capacity (FVC) or diffusion capacity of the lung for carbon monoxide (DLCO) -defined as more than a 10% decrease in FVC or over a 15% decrease in DLCO- are associated with an increased risk and higher mortality rates.[23,26] In the context of bronchiectasis in RA lung involvement, the disease and the immunosuppressive agents used in treatment serve as independent risk factors for developing lower respiratory tract infections.[30] These agents also carry the risk of inducing pulmonary toxicity, thereby exacerbating morbidity and mortality. For example, methotrexate, a cornerstone in RA treatment, can sporadically lead to interstitial pneumonitis. While estimates are variable, the incidence rate ranges between 0.43-1%, and mortality increases to 17% during a 3-year follow-up of treated patients.[31-33] Methotrexate-associated pneumonitis is categorized as a hypersensitivity reaction, and the condition often improves with drug discontinuation and the addition of CS. Sulphasalazine, another treatment agent, is also known to cause pneumonitis. In these cases, pulmonary infiltrates and eosinophilia have been observed in half of the affected patients, and there have been documented instances of respiratory failure and death despite drug discontinuation.[26]

Furthermore, biologic agents account for approximately a 1% rate of ILD development.[34] ILD's morbidity and mortality rate due to TNF-α inhibitors also stands at 1%, most commonly occurring in patients treated with infliximab.[34-36] Finally, rituximab has been implicated as another potential source of pulmonary toxicity.

To assess lung-related manifestations in RA, clinicians commonly rely on HRCT, pulmonary function tests, and various markers of disease activity. When it comes to treatment, the core principles revolve around several strategies: Firstly, the suppression of disease activity is achieved using immunosuppressive agents; secondly, any concurrent infections are rigorously managed; thirdly, patients are strongly advised to cease smoking; and finally, in instances where medication leads to complications, the offending drug is discontinued.

Osteoporosis

Osteoporosis (OP) is a bone tissue disorder marked by diminished bone mass and compromised microarchitecture. In the general population, its prevalence ranges from 9-38% in women to 1-8% in men.[37] For RA patients, the incidence is notably higher, approximately doubling that of the general population and reaching up to 30%- or even

50% in postmenopausal women.[38] Interestingly, fractures can manifest in RA patients even in the absence of low bone mineral density.[39] Both OP and RA share key risk factors, namely female gender and smoking. Additional variables contributing to the development of OP in RA encompass genetics, family history, advanced age, postmenopausal status due to estrogen deficiency, CS usage, low body weight, insufficient levels of calcium and vitamin D, immobility, and chronic inflammation. Furthermore, delays in initiating treatment can also exacerbate the condition.[40] Factors that further elevate the risk of OP and consequent fractures in RA patients include severe disease activity, periarticular bone erosions, a disease duration exceeding ten years, elevated Health Assessment Questionnaire scores, and the presence of autoantibody positivity such as RF and ACPA.[38]

ACPA positivity is an independent factor for the loss of trabecular bone mass.[41] One study revealed that RA patients with anti-CCP positivity had a heightened 10-year fracture risk according to the FRAX score.[42] Both systemic and intra-articular CS commonly used in RA treatment contribute to secondary OP and osteoporotic fractures. Notably, the associated risk intensifies with the duration and dose of CS usage.[40,43] The likelihood of developing secondary OP is exceptionally high for patients who consume more than 5 mg of CS daily and continue this regimen for over three months.[44] Additionally, CSs exacerbate the risk of falls and fractures by inducing muscle weakness.[45] Osteoclasts play a pivotal role in bone loss in RA. The receptor activator of nuclear factor-κB (RANK) is predominantly expressed in these cells. The ligand for RANK, known as receptor activator of nuclear factor-κB ligand (RANKL), is found in mesenchymal cells like synovial fibroblasts. Its expression is amplified by proinflammatory cytokines such as TNF-α and IL-6. However, the osteoclastogenic activity of RANKL is inhibited by osteoprotegerin, a member of the TNF superfamily involved in bone remodeling.[46-48] Any imbalance in the RANK/RANKL/osteoprotegerin axis shifted in favor of RANK/RANKL due to cytokines and inflammation, increasing osteoclastic activity. This then leads to a reduction in bone mineral mass and the onset of osteopenia or OP in RA. Numerous studies indicate that the employment of anti-inflammatory therapies, including DMARDs, mitigates bone loss in RA.[49,50] The basic underlying mechanism is to control inflammation and prevent bone loss caused by inflammation by suppressing cytokines that increase bone loss as mentioned above.

Regarding the World Health Organization classification, bone mineral density is categorized via T-scores determined through bone mineral densitometry. In this framework, T-scores ranging between -1 and -2.5 are indicative of osteopenia, whereas scores below -2.5 are classified as OP.[51] Given these parameters, it is strongly recommended that patients at risk, particularly those utilizing CSs, should incorporate calcium and vitamin D supplements into their regimen. For those diagnosed with OP, the addition of antiresorptive agents-such as bisphosphonates, teriparatide, or denosumab-is advised. To monitor the efficacy of these therapeutic interventions, patients should undergo annual assessments of their bone mineral density.

Malignancy

In a comprehensive meta-analysis encompassing 21 studies, RA was identified as an independent risk factor for lymphoma, doubling the risk of developing this malignancy.[52] This elevated risk is notably correlated with extended disease duration and high levels of disease activity. It is postulated that this phenomenon could be a lymphoproliferative disorder stemming from the chronic activation of B-cells.[53] Furthermore, the presence of RF also adds to the risk profile.[5] A retrospective study involving 84.475 RA patients revealed a significant increase in the risk of lung, liver, and esophageal cancers. In contrast, a reduced risk was observed for prostate, breast, and ovarian cancers.[54] The elevated risk of lung cancer is often attributed to the smoking habits prevalent among these patients. Interestingly, a decreased risk of colon cancer was noted, which is hypothesized to be linked to the use of NSAIDs.[52] Among the various lymphoma subtypes, diffuse large B-cell lymphoma is most frequently associated with RA.[55]

As for the risk factors in terms of treatment agents, a meta-analysis examining 49 studies on TNF inhibitors-a class of treatment agents-found no generalized increase in the risk of malignancies, lymphomas, or non-melanoma skin cancers. However, the analysis did highlight a potential elevated risk of melanoma.[56] As for Janus kinase inhibitors (JAKi), which have recently been one of the controversial issues in terms of malignancy, a meta-analysis focusing on JAKi, a newer class of treatment agents, revealed no significant difference between JAKi and either placebo or methotrexate regarding increased risk of malignancy. Nevertheless, JAKi was linked to a higher incidence of malignancies when compared to TNF inhibitors.[57] As scientific data accumulates, we will have more ideas about this subject.

Infection

Severe infections in RA contribute to heightened levels of morbidity and mortality, ranking as one of the top three leading causes of death.[58,59] Various factors amplify the risk of such infections, including male gender, advanced age, a prolonged history of RA, low educational attainment, suboptimal nutritional status, and obesity.

[60-67] Several comorbidities further elevate this risk, such as renal dysfunction, pulmonary conditions, pre-existing lung diseases, and diabetes mellitus.[61,65-70] Elevated disease activity is also intricately linked with a greater likelihood of infection. Patients commonly experience respiratory and urinary tract infections.

Glucocorticoid treatment has been singled out as a factor that heightens infection risk. Existing research indicates that this risk is dose-dependent; specifically, an elevated risk has been identified in patients receiving up to a daily dose of 10 mg of prednisolone.[71] Contrastingly, available data suggests that the use of csDMARDs, such as methotrexate, does not result in an increased risk of serious infections or associated mortality.[72] A meta-analysis evaluated the risk of severe infection when methotrexate was added to bDMARDs compared to monotherapy. The findings suggested that adding methotrexate did not elevate the risk of serious infections.[73] Contrarily, a Japanese cohort study indicated that although methotrexate usage was inversely correlated with the incidence of all infections, it was associated with a heightened risk of pneumocystis pneumonia.[61] Comparisons between bDMARDs and csDMARDs revealed an augmented risk of infection in the bDMARD group.[69,74] Further corroborating this, another expansive meta-analysis found that patients treated with standard or high doses of bDMARDs faced an increased risk of infection compared to those administered low doses of bDMARDs.[74]

The use of TNF inhibitors is associated with an elevated risk of reactivating latent infections. Specifically, a meta-analysis demonstrated a three-fold increase in the risk of tuberculosis reactivation in patients using TNF inhibitors compared to those on a placebo or receiving no treatment.[75] This risk appears to be mitigated in patients treated with etanercept when compared to those administered adalimumab and infliximab.[62,76,77] Likewise, rituximab treatment presents a high risk of tuberculosis reactivation.[62] Additionally, there exists a risk of hepatitis B reactivation under both TNF inhibitor and rituximab treatments.[78,79] To assess the risk of these severe infections, a scoring system was developed based on the German Rheumatoid Arthritis Observation of Biologic Therapy registry. This scoring model incorporates multiple variables such as age, disability metrics, existing comorbidities like chronic lung disease and renal failure, history of prior infections, failure of previous treatments, and the current treatment regimen.[80]

Neuropsychiatric Involvement

RA significantly impacts both the central and peripheral nervous systems (PNS). Central nervous system complications predominantly manifest as cervical myelopathy, affecting an estimated 43-86% of RA patients.[81-83] Such involvement is generally attributed to pannus bone erosion in the first and second vertebrae, subsequently causing transverse ligament laxation and vertebral instability.[84] The extent of cervical vertebrae involvement correlates directly with the severity and duration of RA and may present with various symptoms, including occipital headaches, vertigo, paresthesia, and deficits in vision and hearing. Notably, if conditions such as vertebrobasilar insufficiency or brainstem compression are present, failure to intervene promptly may result in a one-year mortality rate as high as 50%.[82,84] While advanced cases may be discernible through conventional radiography, magnetic resonance imaging remains the gold standard for diagnosis.[85] Exceptionally severe manifestations, such as meningitis and transverse myelitis, have been reported, the former being more prevalent among patients with a prolonged history of seropositivity even in disease remission.[25,86] Additionally, chronic inflammation is implicated in microvascular and microglial activation, potentially predisposing patients to dementia, including Alzheimer's disease.[81]

PNS involvement in RA occurs in up to 20% of patients. It may manifest in various forms, such as entrapment neuropathies (e.g., carpal tunnel syndrome), mononeuritis multiplex, distal sensory neuropathy, and sensorimotor neuropathy. The underlying pathophysiological mechanism is primarily attributed to vasa nervorum vasculitis, leading to vascular ischemia, axonal degeneration, and neuronal demyelination.[25] Furthermore, pharmacological interventions for RA are not without neurological side effects; NSAIDs may induce psychosis, cognitive dysfunction, and aseptic meningitis. Methotrexate is associated with headaches and concentration difficulties, while TNF inhibitors may paradoxically induce autoimmune conditions like Guillain-Barré syndrome and demyelinating polyneuropathy.[87] Epidemiological data further indicate that RA is concomitant with mood disorders, notably depression and anxiety, which occur in 13-20% and 21-70% of RA patients, respectively.[88,89] Factors such as persistent pain, fatigue, and functional disability contribute to diminished quality of life and correlate with these mood disorders onset. Other variables, such as disease duration, CRP levels, active disease status, and vitamin D deficiency, have also been linked with the presence of mood disorders.[88]

Renal Involvement

Renal complications in RA may arise not only intrinsically from the disease but also from the nephrotoxic effects of pharmacological treatments. Although infrequent, mesangioproliferative and membranoproliferative

glomerulonephritis (GN) may manifest due to intrarenal immune responses and inflammation instigated by RA. A recent retrospective and observational study examining 67 renal biopsies from RA patients revealed the most prevalent histopathological findings: renal amyloidosis accounted for 31%, followed by mesangial GN at 18%, membranous nephropathy at 17%, extracapillary proliferative GN at 15%, focal segmental glomerular sclerosis at 9%, minimal change nephropathy at 5%, and tubulointerstitial nephritis also at 5%.[90] It is noteworthy that renal complications frequently arise from chronic inflammation due to long-standing disease, as well as from the nephrotoxic side effects of therapeutic agents.

Conclusion

RA is not merely a disease characterized by joint inflammation and physical dysfunction; rather, it encompasses a broad spectrum of multisystemic involvement that adversely impacts the quality of life. The inflammatory pathology intrinsic to RA and the pharmacological interventions contribute to substantial morbidity and mortality. Effective management extends beyond merely controlling inflammation and necessitates cautious monitoring and treatment of associated comorbidities. Early diagnosis, appropriate therapeutic interventions, individualized treatment plans, and timely mitigation of exacerbating factors are critical for reducing morbidity and enhancing the quality of life for affected individuals.

Authorship Contributions

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