NEW STUDIES IN HEALTH SCIENCES

Editor: Asst. Prof. Bişar AMAÇ

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Chapter 1

Differential Diagnosis of Multiple Sclerosis

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Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disorder of the central nervous system that presents with various clinical manifestations(1). It is one of the most common causes of neurological disability in the young adult population(2). There are no specific markers for the diagnosis of MS. Diagnosis depends mainly on medical history and neurological examination. Attacks are defined as new neurological deficits lasting more than 24 hours, which may be due to an anatomical location, in the absence of fever or any infection. Usually neurological deficit develops within 2 to 4 weeks and usually resolves completely or partially within 6 to 8 weeks spontaneously or after corticosteroid treatment(3).

Pathophysiology

Pathophysiological findings highlight the importance of the interaction between genetics and environment(2). Several factors appear to play a significant role in an individual's risk of developing MS, including polygenic susceptibility, Epsteine Barr virus (EBV) seropositivity, low vitamin D concentrations, smoking, obesity, and low ultraviolet B exposure. EBV seropositivity is strongly associated with MS. Infectious mononucleosis doubles the risk of developing MS(4). Although there is no specific diagnostic biomarker of MS, recent evidence suggests that EBV plays an important role in the causal pathway of MS(5).

MS diagnosis

When diagnosing MS, the concept of a lack of a better explanation has remained a fundamental element of MS diagnostic criteria for many years(6). Diagnosis of MS can be quite challenging due to its variable clinical features and lack of specific tests. Since early treatment is very important for the treatment of the disease, a definitive diagnosis is essential(7). The diagnosis of MS is based on neurological symptoms and signs, as well as evidence of the spread of Central nervous system (CNS) lesions across space and time. Diagnostic criteria for MS are based on logical interpretation of clinical evaluations of MRI findings and cerebrospinal fluid (CSF) test results, guided by the 2017 McDonald criteria. It includes the need to adequately exclude other disorders that may mimic MS before a diagnosis of MS can be confirmed(8).

The presence of simultaneous enhancing and non-enhancing lesions in the first attack meets the criteria for spread over time without the need for a second clinical attack(9). In patients with typical clinically isolated syndrome (CIS), if there is clinical or radiological evidence of spread in space, involvement in at

least 2 of 4 regions (cortical/juxtacortical, periventricular, infratentorial, spinal) and CSF-specific oligoclonal band (OCB), a definitive MS is diagnosed without the need for timely spread to be demonstrated on MRI or a second clinical attack(10). Approximately more than 95% of patients with a definitive diagnosis of MS have been found positive for OCB in their CSF. It is not found in their serum. Therefore, it is an important diagnostic indicator. Rarely, OCB is not present early in the disease course. The 2017 McDonald criteria significantly shorten the time to MS diagnosis. More CIS patients are completing an MS diagnosis with a single MRI scan at the time of first clinical symptom(10, 11).

In the inflammatory phase, lesions may show nodular, homogeneous, or ring-like enhancement on contrast-enhanced T1 MRI. The coexistence of enhancing and non-enhancing lesions is a common feature. New lesions retain contrast for up to a month. In MS, tumefactive lesions may present with contrast enhancement in an open-ring pattern. In MS, spinal lesions are located in the periphery of the spinal cord and more frequently in the lateral and posterior white matter column(12).

Which diseases are included in the differential diagnosis with MS?

MS is a white matter disease. It has been shown that there are two factors that most reliably define the differential diagnosis of non-MS patients. The first is the absence of typical symptoms, and the second is the absence of typical findings in MRI and CSF examination(13). Simultaneous contrast enhancement in all lesions, large lesions showing mass effect and contrast enhancement, large and edematous lesions, and presence of meningeal contrast enhancement should be taken into consideration in the differential diagnosis of diseases other than MS(3). Research has shown that the most common disease misdiagnosed as MS is migraine, alone or in combination with other diagnoses, accounting for 22% of misdiagnosed patients. Caution should be taken if the contrast enhancement is not homogeneous and persists for months. On the other hand, CSF findings such as protein concentration exceeding 100 mg/dL, pleocytosis above 50 cells/mm^3, or the presence of neutrophils, eosinophils, or atypical cells are rare in MS and should require consideration of other diagnoses(7).

Small-vessel disease (SVD)

SVD does not affect the temporal lobes. It especially caused by chronic hypoxia, constitutes the most common differential diagnosis for white matter lesions on brain MRI. This can occur as an age-related event and is more common in smokers, those with hypertension, diabetes, migraine and various other

vascular disorders(10). One of the most common radiological MS mimics is nonspecific white matter disease(14).

Susac syndrome (SS)

SS consists of the triad of encephalopathy, retinal artery branch occlusions, and sensorineural hearing loss. SS, also known as retinocochleocerebral vasculopathy, is a rare condition most commonly seen in women between the ages of 18-40. The three situations do not have to occur simultaneously. MRI is the diagnostic tool of choice in SS, which is thought to be caused in part by a series of microinfarctions(3). Susac syndrome, like MS, may also involve the corpus callosum(12).

Optic neuritis, Nmosd (neuromyelitis optica spectrum disorders) and Mogad (Anti-mog associated disease)

Atypical findings for MS include bilateral or severe optic neuritis in addition to fever or persistent vomiting(4). Optic perineuritis with optic nerve sheath enhancement on MRI is atypical for multiple sclerosis and is suggestive of MOGAD, neurosarcoidosis, tuberculosis, or neoplastic infiltration. Involvement of the long anterior optic nerve segment is suggestive of MOGAD, whereas involvement of the posterior optic nerve segment or chiasm and optic nerve is typical of Aquaporin-4-IgG (AQP4-IgG) positive NMOSD and neurosarcoidosis. MS-related myelitis typically presents with short and peripherally located T2 hyperintense lesions on axial images within the dorsal or lateral columns, and lesions in MS are usually shorter than 2 vertebral segments in length. Centrally located lesions covering more than half of the spinal cord cross-sectional area or longitudinally widespread T2-hyperintense lesions (>3 vertebral segments) should first consider diagnoses other than MS(6). MS and NMOSDs are two similar but different diseases. It was difficult to distinguish these diseases from each other until the discovery of AQP-4-IgG. Correct identification of these two diseases is crucial for appropriate drug therapy in clinical practice. AQP-4-IgG plays a crucial role in the diagnosis of NMOSD, and serum titers do not show any significant difference between relapse and remission phases(15).

Acute disseminated encephalomyelitis (ADEM)

ADEM is an acute inflammatory demyelinating disease usually triggered by viral infection or vaccination. ADEM usually affects children and young adults, with a monophasic course and complete recovery within one month. ADEM lesions are indistinguishable from MS alone, but the T2-weighted signal abnormality of ADEM in the deep white matter, cortical gray matter, and deep

gray nuclei tends to be symmetrical and combined, and the relative preservation of the periventricular white matter are distinctive findings of MS. Unlike MS, ADEM rarely affects the corpus callosum and does not result in black holes. Spinal cord lesions in ADEM typically extend longitudinally and are located in the thoracic cord. As in MS, enhancement can be seen in large ADEM lesions, and enhancing and non-enhancing lesions can be seen together. Follow-up imaging (after a minimum delay of 6 months) is a useful tool to distinguish ADEM from MS in which ADEM lesions resolve completely or partially without evidence of new lesions on subsequent imaging(3).

Lyme disease

Lyme disease almost never mimics the classic clinical and MRI presentation of MS, and routine screening in the absence of a specific indication will produce more false positives than true positives(13).

Progressive multifocal leukoencephalopathy (PML)

PML is a rapidly progressive demyelinating central nervous system disease caused by reactivation of the JC virus. Lesions can occur in any region, including the basal ganglia, thalamus, corpus callosum, brainstem, and cerebellar peduncles. Lesions are usually large. They may initially be focal but quickly coalesce and become progressive(12). In PML, radiological contrast enhancement is weak or absent. The presence of hypointense on T1, hyperintense on T2, brightening in diffusion, bilateral large white matter lesions, and clinical findings of rapidly progressing encephalopathy, seizures, and aphasia are suggestive of PML(16). Diagnosis of PML can be made based on CSF polymerase chain reaction analysis for JC viral DNA(3).

Neurosarcoidosis

In neurosarcoidosis, diffuse or nodular enhancement of thickened leptomeninges around the base of the brain is a dominant feature on MRI. Neurosarcoidosis can also affect any cranial nerve. Clinically, the 7th cranial nerve is most commonly affected. Neurosarcoid parenchymal deposits are seen as periventricular hyperintensities and enhancing masses on T2 MRI. A proportion of patients with neurosarcoidosis develop ischemic or hemorrhagic stroke, which is thought to be a complication of the associated vasculitis. Intramedullary spinal cord signal abnormalities are rarer in neurosarcoidosis than in MS(3).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

It is a rare, inherited cerebral small vessel disease that causes ischemic strokes and cognitive impairment in adults. The disease is caused by mutations in NOTCH3, a gene on chromosome 19. Clinical manifestations include cerebrovascular disease, migraine with aura, cognitive impairment, and mood disorders. Brain T2 MRI typically shows diffuse periventricular white matter (WM) hyperintensities involving the anterior temporal lobes and external capsules. There is usually no spinal cord involvement(17). Cerebral microbleeds detected on SWI MRI reflect hemosiderin accumulations in the vessel walls. It is a marker of vasculopathy, most commonly due to amyloid angiopathy or arteriolosclerosis(18).

Central nervous system vasculitis (CNS vasculitis)

CNS vasculitis is a type of vasculitis characterized by fibrinoid necrosis of small arteries and veins less than 200 mm in diameter in the meningeal and parenchymal regions of the central nervous system. Brain MRI in the early stages may be normal. Later, increasing and merging white matter lesions may be seen. Multiple ischemic lesions that are not limited to a single vascular region, large intraparenchymal hematomas and leptomeningeal enhancement area may be seen. Microbleeds can be seen on SWI MRI(19). MR angiography has poor sensitivity in detecting the disease. Digital subtraction angiography is considered the preferred technique in diagnostic examination in cases of multiple segmental narrowing and dilation of arteries(3).

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy

GFAP astrocytopathy is an inflammatory disorder of the central nervous system. GFAP astrocytopathy may mimic the MRI features of MS and should be included in the differential diagnosis of MS. The most sensitive and specific biomarker of GFAP astrocytopathy is anti-GFAP alpha antibody in CSF. One of the radiological signs of GFAP astrocytopathy is linear radial contrast enhancement of cerebral white matter on brain MRI(20).

Radiological isolated syndrome (RIS)

Diagnostic difficulty arises in individuals who have typical MS brain MRI lesions that meet MRI criteria for extension in space, but who do not have clinical findings sufficient for diagnosis, referred to as RIS, or a clinical presentation suggestive of typical CIS. However, the detection of spinal cord lesions and

oligoclonal bands in an individual with RIS does not preclude diagnoses other than multiple sclerosis, and a broad differential diagnosis is required(6).

Laboratory examinations in MS research

Many tests are required to diagnose MS. However, most of the tests cause delays in diagnosis and misdiagnosis. Their specificity is low and false positives may occur. Serological tests are frequently performed in patients presenting with a preliminary diagnosis of MS. However, studies have shown that even if an abnormal test result occurs, it does not change the diagnosis in any patient and often leads to diagnostic delay and additional unnecessary tests and procedures. OCB may sometimes be present in patients with other neuroinflammatory disorders, and their presence should be interpreted with caution. Since low-titer antinuclear antibodies (ANA) are common, especially in patients with MS, nonspecific antibodies that may not be clinically significant are frequently detected(21). Detailed laboratory examinations in the diagnosis of MS do not significantly change the diagnosis. It causes delay in diagnosis and unnecessary tests. When clinical, MRI and CSF-specific OCB tests are evaluated together for the diagnosis of MS, if the diagnosis probability is quite high, additional detailed tests lead to diagnostic confusion and are not recommended. In some cases where the diagnosis of MS is quite strong, false positivity rates of the highly specific MOG-IgG test have been observed. NMO-IgG test should performed with live cell-based assay techniques. The enzyme-linked immunosorbent assay method may false positives. CSF specific OCB test is the most important laboratory method supporting the diagnosis(8).

Results

MRI is the most powerful tool in distinguishing MS from similar diseases and monitoring disease activity(22). However, it can be difficult to distinguish MS from other MS-mimicking diseases. This is because the amount of data available on the frequency of alternative diagnoses in real life is small(23). Clinical findings are important in distinguishing MS-like diseases(24). Screening and detection of systemic, inflammatory, autoimmune, collagen vascular diseases, detection of high autoantibodies in MS patients, including lupus anticoagulant or antiphospholipid antibodies, has no clinical significance. These are also found in a high percentage of MS patients. They serve no purpose other than delaying diagnosis(13).

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Chapter 2

Occupational Diseases From A Physiotherapist Perspective

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Abstract

A robust work environment is essential for both global and national socioeconomic progress. Occupational diseases act as indicators of working conditions and environmental quality, emphasizing the necessity to manage various risks, including chemical, biological, physical, ergonomic, and psychosocial factors. Physiotherapists frequently encounter occupational diseases that deteriorate due to repetitive, strenuous tasks performed in static positions, affecting different organ systems. These conditions can lead to pain and functional limitations. Prevention is of paramount importance, and preventive physiotherapy is being recognized as an effective approach. Physiotherapists play a crucial role in alleviating the burden on the healthcare system by implementing interventions in workplaces, conducting educational programs, and engaging in rehabilitation efforts. The integration of physiotherapists into multidisciplinary teams highlights the importance of comprehensive education on occupational diseases and enhances public health strategies addressing these diseases by including them in healthcare policies. Occupational diseases can lead to various conditions in individuals, such as lateral epicondylitis, carpal tunnel syndrome, patellofemoral pain syndrome, disc herniations, and posture disorders like kyphosis and lordosis. Ergonomic measures related to repetitive movements, excessive force usage, and working in the same position due to the nature of the job should be implemented. Various assessment methods should be used to determine and prevent the postural correctness of employees and the associated pain. This study details what occupational diseases are, assessment methods from a physiotherapy perspective, treatments, and preventive measures that can be taken to avert these diseases.

Keywords: Occupation, Workplace, Occupational Disorders, Risk Factors, Prevention, Worker's Health, Musician's Health

Occupational Disease

In the definition of health made by the World Health Organization (WHO), it is stated that *"people should be in a state of complete physical, mental and social well-being"*. The contemporary definition of health recognizes that *"illness and disability can and often do co-exist with healthy living"* (1). However, these do not include occupational diseases as they are preventable. Turkish National Social Security Institution (SSI) defines occupational diseases as *"temporary or permanent illness, physical or mental disability that the insured person suffers due to a recurring cause arising from the nature of his/her work or the conditions of his/her work"* (2).

In the earliest historical stages of the development of society and life, many important representatives of medicine were also interested in the social aspects of health care. For example, Hippocrates (460-370 BC), Aristotle (384-322 BC) and Ibn Sina (Avicenna) (980-1037 AC) were the first to mention occupational diseases, describing dust in the lungs of stone and metal workers. As the nature of work activity changed, new diseases emerged and it took decades for people to begin to associate them with their work. Along with the disciplines of occupational health and vocational rehabilitation, the literature on occupational diseases is expanding (3).

A healthy working environment is crucial for economic and social development at global and national level. The occurrence of occupational diseases is a very important indicator of working conditions and the quality of the working environment. Important occupational health issues that need to be addressed globally include chemical, biological, physical, ergonomic and psychosocial risks (3).

Risk Groups

The most important disadvantages of occupational diseases are that they are difficult to diagnose at the onset and differential diagnosis cannot be made from other diseases (4).

According to SSI statistics, a total of 955 insured employees contracted occupational diseases in 2022 and 8 of them lost their lives (Table 1) (5). These data were divided into 99 classes according to their economic activities and the highest risk groups are shown in Figure 1 (5).

Table 1. Distribution of Insured Persons with Occupational Diseases and Died as a Result of Occupational Diseases by Gender

		Female	Male	Total
Suffering from occupational disease	**4a insured**	182	771	953
	4b insured	0	2	2
Died as a result of occupational disease	**4a insured**	1	7	8
	4b insured	0	0	0

4a: Persons working under contract in a private business, 4b: Business owners.

According to gender, men are at a significantly greater risk of developing occupational diseases. The ratio of working women to men should not be ignored here. Although the death rate among those diagnosed with an occupational disease is as low as 0.83%, these results are quite distressing considering that almost all occupational diseases are preventable.

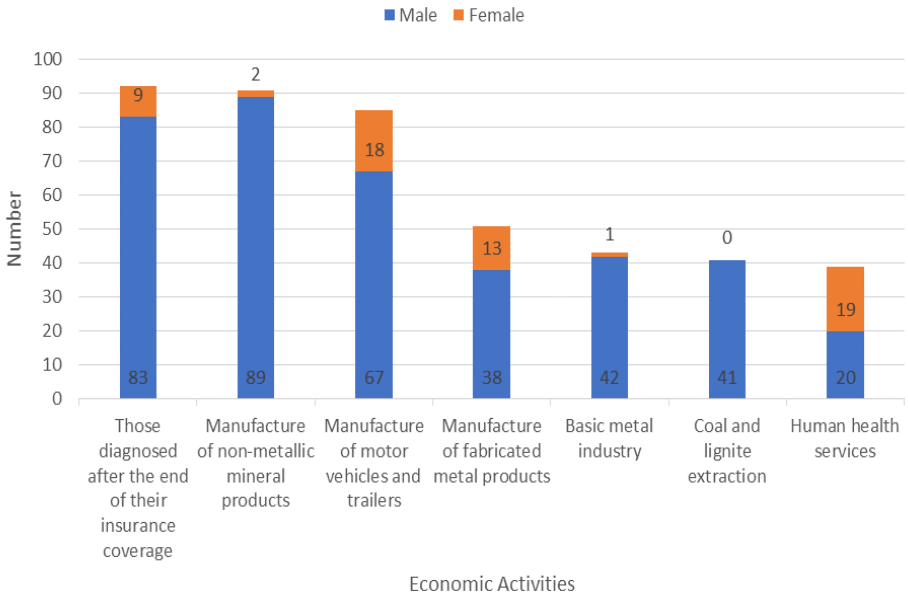

Figure 1. Distribution of Insured Persons Mostly Affected by Occupational Disease by Economic Activity and Gender (adapted from SSI Occupational Accident and Occupational Disease Statistics for 2022).

According to economic activities, the highest risk of occupational disease is observed in the manufacturing industry. In general, the more risky sectors in terms of occupational disease can be characterized as those with high physical activity or those who work with physical labor. The risk of occupational disease is less in sectors that are not very physically active, which are also characterized as office workers. However, it should not be forgotten that this rate may change with the development of technology. Considering the fact that active labor has been replaced by robotic systems in recent years and that the time individuals spend in front of computers is increasing, it can be predicted that physically inactive workplaces will be more risky in terms of occupational diseases in the future.

Classification of Occupational Diseases

The list of occupational diseases established by international and national legal systems plays an important role in both prevention, treatment and compensation for occupational diseases. While the first list of occupational diseases of the International Labour Organization (ILO) consisted of 10 items, the current list of occupational diseases approved in 2010 and consisting of a total of 106 items in four basic categories for the diagnosis of diseases is given below (6):

1. Occupational diseases caused by exposure to agents arising from work activities [41 chemical, 7 physical, 9 biological agents]
2. Occupational diseases by target organ systems [26 agents]
3. Occupational cancers [21 agents]
4. Other occupational diseases [2 agents]

Occupational diseases according to the target organ systems that directly concern physiotherapists consist of a total of 26 items under 4 subtitles: 12 respiratory system diseases, 4 skin diseases, 8 musculoskeletal system disorders and 2 mental and behavioral disorders (6).

Respiratory Diseases:

1. Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis)
2. Silicotuberculosis
3. Pneumoconioses caused by non-fibrogenic mineral dust
4. Siderosis
5. Bronchopulmonary diseases caused by hard-metal dust
6. Bronchopulmonary diseases caused by dust of cotton, flax, hemp, sisal or sugar cane (bagasosis)

7. Asthma due to identified sensitizing agents and irritants inherent in the work process

8. Extrinsic allergic alveolitis caused by the inhalation of organic dusts or microbially contaminated aerosols, arising from work activities

9. Chronic obstructive pulmonary diseases caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities

10. Diseases of the lung caused by aluminium

11. Upper airways disorders caused by recognized sensitizing agents or irritants inherent to the work process

12. Other respiratory diseases not mentioned in the preceding items where a direct link is established scientifi cally, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the disease(s) contracted by the worker (6).

Skin Diseases:

1. Allergic contact dermatoses and contact urticaria caused by other recognized allergy-provoking agents arising from work activities not included in other items

2. Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

3. Vitiligo caused by other recognized agents arising from work activities not included in other items

4. Other skin diseases caused by physical, chemical or biological agents at work not included under other items where a direct link is established scientifi cally, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the skin diseases contracted by the worker (6).

Musculoskeletal Disorders:

1. Radial styloid tenosynovitis due to repetitive movements, forceful exertions and extreme postures of the wrist

2. Chronic tenosynovitis of hand and wrist due to repetitive movements, forceful exertions and extreme postures of the wrist

3. Olecranon bursitis due to prolonged pressure of the elbow region

4. Prepatellar bursitis due to prolonged stay in kneeling position

5. Epicondylitis due to repetitive forceful work

6. Meniscus lesions following extended periods of work in a kneeling or squatting position

7. Carpal tunnel syndrome due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist, or a combination of the three

8. Other musculoskeletal disorders not mentioned in the preceding items where a direct link is established scientifi cally, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the musculoskeletal disorder(s) contracted by the worker (6).

Mental and Behavioural Disorders:

1. Post-traumatic stress disorder

2. Other mental or behavioural disorders not mentioned in the preceding item where a direct link is established scientifi cally, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the mental and behavioural disorder(s) contracted by the worker (6) (Taken from the list of occupational diseases published by the International Labour Organization in 2010).

Occupational Diseases in the Musculoskeletal System

Work-Related Musculoskeletal Diseases

Musculoskeletal disorders; they are injuries or disorders of muscles, nerves, tendons, joints, cartilages and spinal discs. In work-related musculoskeletal disorders, the working environment and job performance are effective in the emergence of this condition, while the situation worsens or becomes chronic due to working conditions. Working conditions that may lead to musculoskeletal disorders include continuous lifting of heavy objects, daily exposure to whole-body vibration, continuous overhead activities, long-term flexion position of the neck, repetitive hard work, prolonged sitting, incorrect posture, stress or non-ergonomic working environments (7,8). There is often a relationship between working conditions and musculoskeletal disorders in the neck, shoulders, elbows, hands, wrists and back. Although the neck, upper extremities and back are the most common areas, it is possible to encounter musculoskeletal disorders all over the body (9). As a result of musculoskeletal disorders, employers face high costs such as absenteeism of employees, loss of productivity, increased health services, disability and workers' compensation costs. Non-fatal injuries such as sprains, strains, or lacerations account for about 30% of all injuries, while musculoskeletal injuries cost about $13 billion annually. Thus, the prevention of occupational diseases and the dissemination of healthy life have an important place in terms of protecting human health, increasing work efficiency and reducing economic burdens. Physiotherapists who can effectively implement training, ergonomic

approaches, workplace safety changes, exercise prescription, monitoring/follow-up and hands-on manual interventions are an important part of the team in managing musculoskeletal diseases in both prevention and treatment aspects (10,11).

Overuse injuries are injuries that develop due to repeated movement. These injuries can occur in professional or everyday activities, such as dancers and/or musicians, as well as athletes. The most common causes of overuse injuries include factors such as improper technique, equipment or ground, overtraining, insufficient rest, incorrect posture, repetitive movements, not stretching or warming up. Overuse injuries usually affect soft tissues such as muscles, tendons, ligaments, or bursae and show symptoms such as inflammation, pain, edema, or limitation of movement (12-14).

Musculoskeletal disorders can be examined under 3 regions as upper and lower extremity and spine problems. Problems scattered in these 3 regions; It can be diversified by affecting joints, muscles, tendons, nerves and vessels such as nerve compression, muscle injuries, tendinopathies, mechanical low back pain, spondylolisthesis, disc herniations, myofascial pain, Raynaud's phenomenon (8,10).

Work-Related Upper Extremity Musculoskeletal Disorders

It can be defined as a multifactorial syndrome affecting the neck and upper extremities, in which inflammatory and degenerative disorders cause pain and functional loss. Below are the occupational diseases that meet this definition (9,10,15):

- Neck pain with referred pain
- Rotator cuff syndrome
- Medial and lateral epicondylitis
- Cubital tunnel syndrome
- Carpal tunnel syndrome
- Radial tunnel syndrome
- Flexor and extensor tendinitis of the hand and fingers
- De Quervain's tenosynovitis
- Ulnar nerve compression in Guyon's tunnel
- Raynaud's phenomenon or peripheral neuropathy associated with hand and arm vibrations
- Osteoarthritis of the elbows, wrists and fingers

Work-Related Lower Extremity Musculoskeletal Disorders

It can be defined as conditions that affect the muscles, joints, nerves, cartilage and tendons of the hip, knee, foot and leg. Below are the occupational diseases of the lower extremities that meet this definition (10,16,17):

- Prepatellar bursitis
- Plantar fasciitis
- Achilles tendinitis
- Piriformis syndrome
- Patellofemoral pain syndrome
- Osteoarthritis
- Meniscus lesions
- Stress fractures

Work-Related Musculoskeletal Disorders in the Spine

These are conditions that affect the muscles, nerves, discs, joints and ligaments in the neck, back and low back areas. Since the spine forms a connection point, it can also affect the upper and lower extremities. Below are the occupational diseases that meet this definition (10,18,19):

- Neck/Back/Low back pain
- Neck/Back/Low back flattening
- Disc herniations
- Scoliosis
- Kyphosis
- Lordosis
- Stenosis
- Spondlylolisthesis

Occupational musculoskeletal diseases (OMD) are important public health problems that negatively affects the physical and psychological health of employees and reduces work efficiency and quality of life. OMD can lead to the ailments categorized above. The effects of these disorders on spine health may occur as posture disorders. Posture can be defined as the way the body stands. In a healthy posture, the head, shoulders, hips and feet are in a certain order, while the spine maintains its natural curves. However, depending on the profession, factors such as staying in the same position for a long time, lifting heavy loads, bending can disrupt the posture and change the curves of the spine. In addition, with the change in living conditions, OMD is also increasing. Especially during the pandemic period, factors such as working from home, distance education, and

social isolation negatively affect spine health. In this case, the load distribution on the spine is disturbed, and the muscles, ligaments and discs that support the spine are overstretched or weakened. This can cause wear, damage and deformities to the spine. These symptoms reduce the quality of life of the person. Mood disorders such as depression, anxiety, and stress can also be seen in people with posture disorders. Therefore, correction and preservation of posture is of great importance for the prevention and treatment of OMD (10,11,18).

Posture

Posture is the position of the human body at any given moment and the alignment of different joints of the body at that moment. The position of each joint in the human spine affects the position of other joints. Correct posture is the optimal alignment that creates minimal stress on all joints, allowing the body to perform activities that require the least amount of energy. Ideal postural alignment when viewed from the lateral is defined as a straight line passing slightly in front of the earlobe, cervical vertebral bodies, shoulder joint, middle of the rib cage, lumbar vertebral bodies, hip joint, knee joint and then the lateral malleolus (20).

Increased stress on joints due to any static position can cause posture disorders, which can be caused by several different reasons. Hypomobile or hypermobile joints and muscular imbalances may result in impaired postural alignment. Optimal flexibility and strength of the muscles can prevent postural disorders by supporting the correct alignment of the joints. The human body can also correct postural malalignment on its own by performing segmental compensation to eliminate a structural disorder in a different part of the body (20,21).

Posture Disorders

Improper posture occurs as a result of the imbalance between muscles, ligaments and spine. Improper posture causes asymmetry in the head, shoulders, spine and pelvis. To maintain this abnormal posture, the muscles are overloaded and tense. Over time, muscle spasm and pain occur. Anterior tilt of the head, kyphosis in the thoracic region and scoliosis in the spine are common postural disorders. Disorders of alignment in the spine cause mechanical pain in the neck, back and low back over time. Postural disorders create negative chain reactions over time. Postural disorders such as scoliosis and kyphosis cause the rib cage to narrow. This narrowing in the ribcage affects the functionality of both the lungs and the diaphragm, causing the respiratory system to not function at an optimum

level. Pathological conditions occurring in the spine also affect the nerves that provide innervation to the lower and upper extremity muscles (22,23).

There are many factors that affect posture including familial factors, structural disorders, daily living activities and occupational status. These factors have a determining effect on the development and alignment of posture (22).

People spend most of their time performing their profession throughout their lives. During this period, occupational diseases related to the musculoskeletal system occur due to factors arising from working conditions and occurring during the performance of the job (24). One of the occupational musculoskeletal system problems is posture disorder. Employees' posture reacts according to the physical and environmental factors created by the work environment. These physical and environmental factors include repetitive movements, high force use, improper body postures, working in the same posture, loud noise and vibration, high or low temperatures, and inadequate airing. (25).

One of the most important reasons why people working in different sectors in business life experience postural problems is inappropriate working postures. Overhead activities, lying back, kneeling, squatting, sitting by increasing the kyphotic posture, bending forward and backward negatively affect the musculoskeletal system and disrupt the postural alignment, causing pain and different pathologies in both the spine and extremities (26). In 2015 Duranoğlu et al., planned a study on the musculoskeletal system problems seen in musical instrument training and its effect on performance, with the participation of 4th year conservatory students and academicians from 6 universities across Turkey. As a result of the study, conservatory students and academicians reported that their existing low back, neck, back, shoulder and arm pain increased after practical lessons (27).

Working in the same position for a long time and making repetitive movements while working are the most important factors that negatively affect posture correctness in business life (25). Yamamato et al. planned a study to examine the posture and repetitive movements of employees working in the same position for a long time, which may cause pain in their spines. The postures of 118 male workers working as cutting, packaging and crane operators in the factory were analyzed. It has been reported that workers in all three departments complain of back, low back and leg pain. (28).

Spine problems should be reduced to a minimum level with ergonomic arrangements to be made in working life, taking into account both physical and environmental factors. In this regard, care should be taken to ensure that the temperature, humidity and air conditioning of work places are at optimum levels. Due to the nature of the job, ergonomic precautions must be taken regarding

working in the same position, excessive use of force, and repetitive movements. Various evaluation methods should be used to determine and prevent the postural correctness and the resulting pain of employees.

Evaluation

Evaluation of occupational groups exposed to physical and psychological risks is important for prevention and treatment (29). Occupational diseases can be evaluated under the titles of pain, musculoskeletal system problems, posture and physical activity from a physiotherapist perspective. These evaluation methods are given below.

Pain Assessment:

McGill - Melzack Pain Questionnaire (MMPQ), Visual Analog Scale (VAS) and Algometer are frequently used in pain assessment.

MMPQ is a questionnaire used to measure the nature, localization, change during the day and intensity of pain. The MMPQ consists of four parts. In the first part, the patient is asked to indicate the localization of the pain on the body diagram. The patient is asked to indicate with the letters "T" if the pain is deep, "F" if it is on the surface of the body, and "T F" if it is deep and on the surface In the second part, the patient is asked to choose the words that most closely describe their pain. This may help to determine the type of pain. In the third section, the relationship of pain with time is questioned. In this section, there are words to determine the frequency and continuity of pain, and the reasons that increase and decrease pain. The fourth section includes five word groups ranging from "mild" pain to "unbearable" pain and six questions to determine the severity of pain (30). If only the intensity of pain is to be measured, the Visual Analog Scale (VAS) can be used. VAS is an assessment method consisting of a 10 cm ruler on which the individual scores the severity of pain between 0 and 10. 0 means "I have no pain" and 10 means "I have extreme pain, I cannot stand it". The algometer, on the other hand, is a device that measures the pain level of the individual by applying pressure on the skin at a 90-degree angle. The value of the pressure is recorded in kg/cm^2 units. While applying pressure, the first pressure value at which the patient feels pain is recorded (31).

Musculoskeletal System Evaluation

Cornell Musculoskeletal Disorders Questionnaire

The Cornell Musculoskeletal Disorders Questionnaire (CMDQ) is a questionnaire used to identify musculoskeletal disorders, pain, severity, frequency and impact on ability to work. The CMDQ is a 60-item scale that asks

about pain, aches and discomfort in 20 body parts over the past week on an anatomical diagram. The CMDQ score is calculated by giving a relative value for frequency, severity and limitation in work-related tasks. In the calculation made for each region, the answers 'never, 1-2 times a week, 3-4 times a week, at least 1 time every day, many times every day' are multiplied by 0, 1.5, 3.5, 5 and 10, respectively, in the evaluation of the frequency of pain experienced by the participants within a week. For the evaluation of pain intensity, the answers 'mildly severe, severe, very severe' and for limitation 'not at all hindered, a little hindered, very much hindered' are multiplied by 1, 2, 3 respectively. With this process, a score ranging from 0-90 is obtained. With this score, the "Discomfort Score" is calculated for each region evaluated. In addition, the Total Cornell Score can also be obtained by summing these scores from all regions. In the questionnaire, in the regions where the right and left sides are questioned separately, the side with the highest score is considered valid (32).

Nordic Musculoskeletal System Questionnaire

Nordic Musculoskeletal System Questionnaire (NMQ) examines individuals' physical activity in nine body areas (neck, shoulder, elbow, wrist/hand, back, low back, hip/thigh, knee and ankle/foot) in the last 12 months, in the last month and in a week. It is a questionnaire that questions musculoskeletal system disorders (33). Dawson et al. have developed the Nordic Musculoskeletal Questionnaire and created a more comprehensive questionnaire called Expanded Nordic Musculoskeletal Questionnaire (ENMQ) and conducted a validity-reliability study. In the ENMQ, there is a figure that anatomically shows nine regions: neck, shoulder, back, elbow, hand/wrist, low back, hip/thigh, knee, foot/ankle. With this questionnaire, it is questioned whether the individual has pain; the age at the onset of pain, hospitalization due to pain and change of duty; whether he/she has experienced pain in the last one week, one month and one year; whether the pain affects his/her daily life, whether he/she has applied to hospital due to pain; use of painkillers and whether he/she has received a medical report due to pain (34).

Posture Assessment

Posture assessment can be performed anteriorly, posteriorly and laterally with the help of a plumb line, and there are also more objective methods such as the New York Posture Analysis or an application such as PostureScreen.

New York Posture Analysis

New York Posture Analysis is scored by examining posture disorders that may occur in 13 different parts of the human body. The total score is between 13 and 65. In the score evaluation, if the total score is ≥45, the posture is classified as

"very good", 40-44 as "good", 30-39 as "moderate", 20-29 as "poor" and ≤19 as "bad". After the total score classification, a score of 5 is given to those in the "very good" group, 4 to those in the "good" group, 3 to those in the "fair" group, 2 to those in the "poor" group and 1 to those in the "poor" group (35).

PostureScreen Mobile

"PostureScreen Mobile" is a mobile application designed for the evaluation of static posture and its validity and reliability have been established (36). In the application, after the photographs of the individuals are taken, certain reference points such as the midpoint of the upper lip, the upper point of the right-left acromioclavicular joint, and the episternal notch are marked and the application offers posture assessment by measuring the deviations from the gravity center of the body as angle and tilt (Figure 2.).

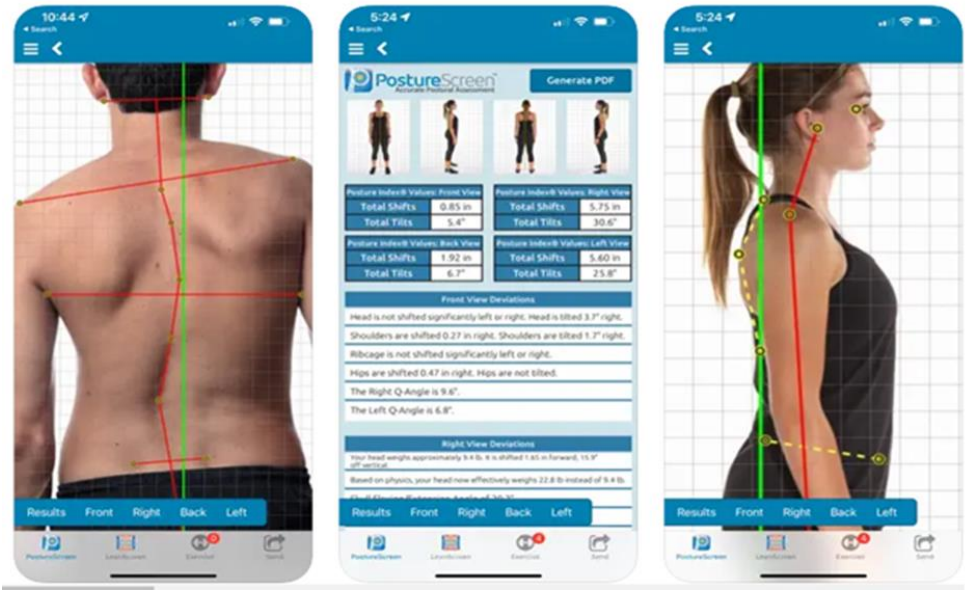

Figure 2. PostureScreen Mobile Application

Physical Activity Assessment

International Physical Activity Survey

The International Physical Activity Questionnaire (IPAQ) is a questionnaire that assesses an individual's level of physical activity over the past seven days used to determine physical activity level. The energy required for activities is

calculated by MET-minute score. Standard MET values have been established for these activities.

These MET values are 3.3 MET for walking, 4.0 MET for moderate physical activity, 8.0 MET for vigorous physical activity, and 1.5 MET for sitting. Using these values, the daily and weekly physical activity level is calculated. The MET value of the activity is calculated by multiplying the number of days per week and the number of minutes per day. For example; the walking MET-min/week score of a person who walked 4 days and 40 minutes in the last week is 3.3 x 4 x 40 = 528 MET-min/week. The total MET value is (walking + moderate + severe + vigorous + sitting) MET-min/week. In addition to this continuous scoring, physical activity levels of individuals are classified as inactive, minimally active and active according to the numerical data obtained.

Those with a total MET value of less than 600 MET-min/week are inactive, those between 600-3000 MET-min/week are minimally active, and those with more than 3000 MET-min/week are active (37).

Treatment Recommendations / Prevention

From the past to the present, musculoskeletal disorders are frequently observed in humans, and in recent years, with the advancement of technology and the development of online job opportunities, there has been a noticeable increase in musculoskeletal disorders among office workers. The literature includes numerous studies on delaying, preventing, and treating these diseases. In a systematic review by Hoe et al. (2018), which included 15 randomized controlled trials (2165 workers), it was found that taking additional breaks while working could reduce neck and upper extremity discomfort among employees (38). Lietz et al. (2020) found that various ergonomic interventions aimed at preventing musculoskeletal disorders among dentists had positive effects on the prevalence of musculoskeletal disorders or working posture in their study (39). According to Pleasas et al. (2020), based on a limited number of studies, ergonomic dentist chairs and the use of dental loupes in dental clinics led to improved working postures. They reported that the use of loupes alleviated shoulder, arm, and hand pain (40). Van Hoof et al. (2018) stated that adding stretching exercise intervention was better than just performing routine activities for nurses with and without back pain. Combining manual handling training with back and spine school was superior to passive physiotherapy, and a multidimensional intervention was not superior to a general exercise program in reducing back pain in nurses (41). In an interventional study by Soler-Font et al. (2019), involving 473 nurses and nursing assistants, where a program was implemented to prevent occupational risk factors and promote a healthy lifestyle, they found a statistically

significant decrease in the risk of neck, shoulder, and upper back pain in the intervention group compared to the control group at the 12th month (42).

The Back and Neck School is a program that aims to reduce the load on the spine during work and rest and teaches proper body usage. Our spine consists of 33 vertebrae, grouped into cervical, thoracic, lumbar, and sacral regions based on their levels. The cervical and lumbar regions are the most mobile, while the thoracic and sacral regions are more rigid (49). Additionally, the muscles around the spine, especially those in the back and neck, play a crucial role. Weakness in the back and neck muscles can lead to disc herniations. To prevent musculoskeletal disorders, weakened back and neck muscles should be strengthened. The Back School program includes education on the anatomy of the back and neck, training on proper posture and postural disorders, along with isometric abdominal exercises, hip flexion, bridge exercises, cat-cow stretches, supine psoas stretches, supine hamstring stretches, and standing quadriceps stretches, among many others (43). These exercises have various effects, such as reducing pain, strengthening weak muscles, reducing mechanical stress on spinal structures, correcting posture, and improving physical fitness.

Photo 1. An example of anatomical information during back school training on the human skeleton

Photo 2. An example of anatomical information on a model during back school training

Compared to passive physical therapies (massage, ultrasound therapy, etc.), the Back School program shows significant improvement in reducing pain and greatly enhances the posture of workers. The adoption of the Back School program for the treatment of employees with chronic back problems should be a recognized treatment option and standard when designing occupational health policies and procedures. In a study conducted by Rodríguez et al. (2022), they observed that the effectiveness of the Back School program increases with its intensity. However, they also noted that the program is effective in reducing back and neck pain and injuries in the first 6 months, leading to a significant improvement in workers' conditions (44). In a study by Jaromi et al. (2012), the use of active physical therapy methods in nurses experiencing chronic low back pain resulted in a significant reduction in pain intensity and improvement in body posture (45).

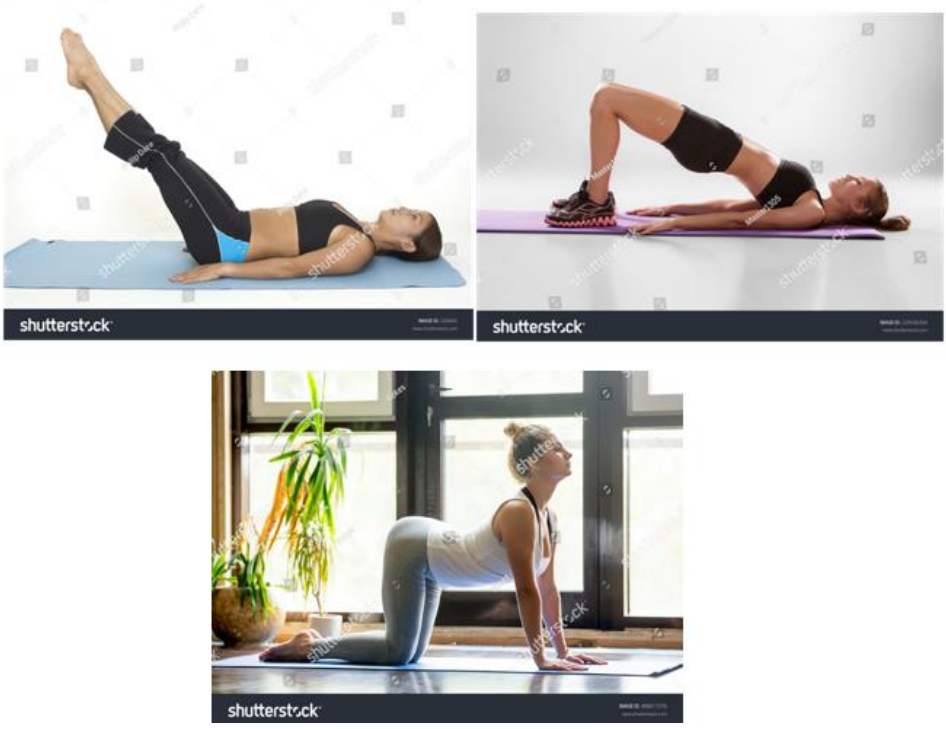

Photo 3. Examples of exercises from the back and neck school

Office workers often spend long hours in a static neck posture, engaging in repetitive hand/wrist movements, and frequently adopting kyphotic (rounded) back postures. These positions contribute to the development of musculoskeletal disorders. In a study conducted by Lee et al. (2021) on office workers, they found that ergonomic workstation interventions were effective in reducing the intensity of pain in the neck, shoulders, upper back, and wrists/hands (46). To prevent the formation of occupational diseases in office workers, conscious computer use is necessary. The desk height should be equal to the height of the elbows. The adjustment of chair height should maintain a ratio close to the popliteal fossa to seat height. The monitor height should be at eye level. The recommended distance between the eyes and the monitor is between 40 to 75 cm. The keyboard and mouse should be placed at a distance that allows the forearm to rest on the table. The mouse should align with the shoulder and be placed near the keyboard (46,47). In a intervention study comparing the effects of thoracic spine manipulation and mobilization exercises on chronic neck pain in 26 office workers, Seo et al. (2020) noted significant changes in both groups after the intervention compared to before the intervention (48). Additionally, beyond office workers, Penkala et al. (2018) mentioned that some medical science

students experienced a high level of musculoskeletal problems during laboratory training even before entering the workforce (54).

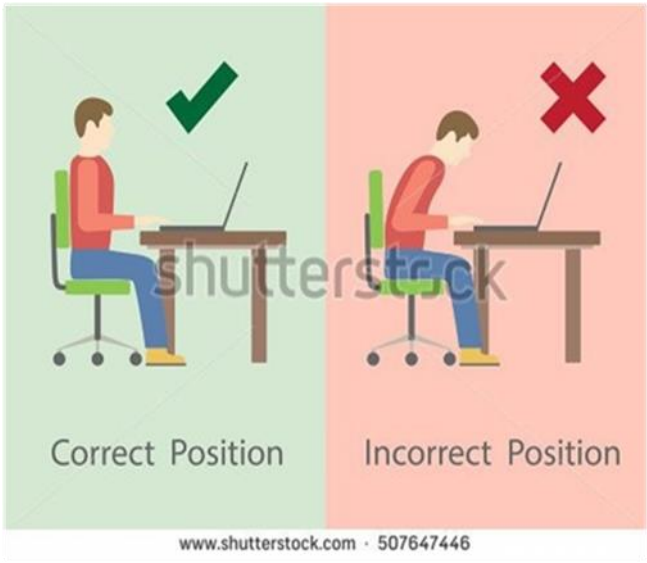

Figure 3. Correct and incorrect posture during computer use

Musicians often experience musculoskeletal disorders. For example, more than 60% of professional violinists suffer from musculoskeletal disorders, particularly involving the cervical spine and upper extremities (50). Violinists are at a higher risk of neck pain compared to other musicians because playing the violin requires static positioning and rapid, finely synchronized finger and repetitive upper extremity movements (51). Similarly, playing an instrument like the piano for long hours with significant force can lead to overuse injuries in the upper extremities (64). Additionally, musicians frequently encounter problems such as focal dystonia, tendonitis, tenosynovitis, arthritis, and epicondylitis (65,66). The Alexander Technique is known as a psychoeducational and practical method. It can be used as a self-help method to prevent unnecessary cervical muscle activation. Taheri et al. (2017) stated that the application of the Alexander Technique is believed to be potentially beneficial in improving postural stability, muscle coordination, and relaxation in musicians with chronic pain (52). Another technique is the Feldenkrais Method. The Feldenkrais Method is a self-discovery process that uses movement. Its goal is to organize an individual to move with minimal effort and maximum efficiency. This technique promotes awareness through movement. In the Feldenkrais Method, the practitioner focuses on the musician's relationship with the instrument. Questions are asked about how the instrument is held, how much time is

spent practicing each day, and how challenging the practice is. Additionally, alternatives to sitting, standing, or holding the instrument when feeling tired are explored. The answers to these questions have been noted to lead to lessons designed to make the act of playing an instrument at least comfortable, injury-preventive, and preferably enjoyable (53)

Photo 4. Correct posture when playing the piano

Photo 5a.- 5b. Incorrect postures when playing the piano (a and b)

Skeletal muscle disorders are commonly observed in athletes. In the literature, sports such as archery have been identified to have the highest risk of injury in the upper extremities, marathons in the lower extremities, and triathlons and weightlifting in the torso. In most examined sports, muscle/tendon strains and ligament tears are the most common diagnoses associated with musculoskeletal injuries, while athletics, karate, and soccer have the highest injury incidence rates (55). For example, soccer, with over 260 million players worldwide, is one of the most popular sports. Soccer is also a sport with a high risk of injury (56). In a

systematic review, Olivares-Jabalera et al. (2021) demonstrated that some exercise-based strategies may potentially be effective in reducing both the incidence of anterior cruciate ligament injuries and the risk factors associated with such injuries in adult soccer players (57). Nambi et al. (2020) found that isokinetic back training applied to soccer players with chronic back pain was more effective in reducing pain intensity and improving sports performance compared to core stabilization training (58).

Photo 6. Injured soccer player

Musculoskeletal disorders, primarily affecting the back, neck, and upper and lower extremities, are among the most common occupational diseases. In a study by Chen et al. (2023) examining work-related musculoskeletal disorder symptoms in Taiwanese and Thai workers, they indicated that carrying heavy materials (>20 kg) more than 20 times a day was the most significant risk factor for musculoskeletal disorders for both groups (59). Hossain et al., in their study on textile workers, found that the back and neck regions were the most affected areas (60). Muñoz-Poblete et al. (2019) stated in their study with 120 healthy workers that muscle resistance training exercises were an effective preventive measure for factory workers exposed to risks and found a protective effect on pain (61). Aje et al., in their study with factory workers, reported a decrease in injury rates with a program including 8-minute stretching exercises (62). In an intervention study among workers in different units of a factory, Hemati et al.

(2020) noted a significant decrease in ergonomic risk factors and a reduction in the rate of musculoskeletal complaints. This study suggests that implemented ergonomic interventions, such as installing an adjustable conveyor belt, purchasing ergonomic chairs, teaching the correct use of equipment, and installing an elevator for workers' movement, are effective in preventing musculoskeletal disorders (63).

Photo 7. Worker carrying a load

CONCLUSION

Repetitive and challenging musculoskeletal functions and their long-term performance in static postures increase the load on soft tissues and joints and lead to occupational diseases characterized by pain and dysfunctions. Occupational diseases are among the disease groups that should be handled carefully in terms of causing labor losses and the economic burden they cause. It is extremely important to take precautions before it occurs, as well as to be treated after it occurs. Especially with the increasing importance of preventive health practices and the understanding of the importance of preventive physiotherapy approaches in the health system, the duties of physiotherapists in this regard are increasing. Increasing the employment of physiotherapists, who will be at the forefront with studies such as workplace physiotherapy practices, taking protective measures with training programs, rehabilitation practices after injuries, will create the potential to reduce the economic burden on the health system. It is important to train physiotherapists, who should take

part in the health team with a multidisciplinary working approach, as well-equipped health professionals in the training processes, in order to positively affect the view of occupational diseases, by staying in parallel with the policies of the country that improve public health in the prevention and treatment of occupational diseases.

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Chapter 3

Effective Roles of Mast Cells Mediating Chronic Inflammation in Directing the Pathogenesis of the Psoriasis

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Abstract

Psoriasis, a chronic inflammatory skin disease, involves complex immunological and cellular processes that contribute to its pathogenesis. Mast cells, well-known mediators of allergic and inflammatory responses, are key players in regulating the complex inflammatory milieu observed in psoriatic lesions. Mast cells contribute to adaptive immune processes directly through antigen presentation or indirectly by augmenting lymph nodes. Moreover, their ability to activate immune cells in psoriatic skin lesions adds depth to our understanding of the immunopathogenesis of the disease. Evidence suggests that mast cell responses in psoriasis are influenced not only by the severity of inflammation encountered, but also by the type of immune cells involved. In particular, the number of activated mast cells is significantly higher in psoriatic lesions compared to non-lesional psoriatic skin and healthy individuals, emphasising their role in disease progression. This chapter aims to elucidate the active role of mast cells in directing the pathogenesis of psoriasis through chronic inflammation. Understanding the diverse features of mast cell biology in the pathogenesis of psoriasis holds promise for the development of novel therapeutic strategies. Targeting mast cell activation pathways may offer alternative ways to reduce chronic inflammation and effectively modulate psoriatic processes. Future research efforts focused on the functional consequences of immune cell and mast cell interactions are crucial to resolve the intricacies of psoriasis pathogenesis and advance targeted therapeutic approaches.

Keywords: Psoriasis, Mast Cells, Chronic Inflammation, Pathogenesis, Adaptive Immune Response

Introduction

Psoriasis is a chronic inflammatory skin condition caused by the rapid multiplication of skin cells at a pace two to three times quicker than normal, and it is not contagious between individuals (Yang et al., 2024). Psoriasis is typically identified by redness, scaling, itching, and thickness of the skin, along with skin flaking and cracking, joint swelling and pain, hair loss, and nail discoloration, is primarily caused by an inflammatory response that can impact any area of the body (Rendon & Schäkel 2019). Psoriasis is linked to several triggering factors, including air pollution, sunburns, specific foods, alcohol, cigarettes, physical skin trauma, certain medications, infections, psychological causes, stress, allergies, hormonal changes, epigenetic variations, and immune system hyperactivity (Singh, 2024). One of the reasons for this inflammation that causes psoriasis is that skin cells are produced and accumulated faster than normal due to hyperactivity of the immune system, or that the settlement of the pathogenic substances such as bacteria on the skin surface (Yu et al., 2022). As a result of psoriasis, inflammatory lesions may develop and manifest throughout the body (Yang et al., 2024). Nonetheless, psoriasis lesions are visible, predominantly on the skin. The inflamed skin areas caused by psoriasis are commonly found on the elbows, knees, scalp, lumbosacral area, joints, genital area, and other body folds (Boehncke, 2018). Psoriasis can also impact other organs and tissues in the body such as eyes, oral tissue, heart, kidneys, liver, pancreas, and veins (Li et al., 2024). Therefore, these inflamed organs and tissues lead to cardiometabolic diseases, gastrointestinal diseases, kidney diseases, malignancy, infection, obesity, diabetes, metabolic syndrome, psoriatic arthritis, and mood disorders (Takeshita et al. 2017) as well as ocular complications, and oral manifestations may involve the oral mucosa or the tongue (Rajguru et al. 2020). In recent years, studies on the pathogenesis of psoriasis have brought about effective treatments for the pathogenesis of chronic inflammatory diseases in a dominant Il-23/Th17 axis (Carmona-Rocha et al. 2024). In addition to genetic factors, the role of epigenetic mechanisms and skin flora is also of great importance in the pathology of psoriasis (Rendon & Schäkel 2019).

Immune Cells in Psoriatic Skin

As the first line of defense against infections and the primary barrier separating an organism from its surroundings, the skin is a secondary peripheral lymphoid organ (Abdallah et al., 2017). The skin, which acts as a barrier against the external environment, consists of three layered layers known as the epidermis, dermis and hypodermis (Yousef et al., 2022). The epidermis is a multilayered layer of skin with a high rate of proliferation and differentiation and contains hair

stem cells, keratinocytes, melanocytes, Langerhans cells, and Merkel cells (Amoh & Hoffman, 2017; Tohgi et al., 2017; Brown & Krishnamurthy, 2022). The dermis is a fibrous structure that produces collagen, elastic tissue and vasculature, nerve endings, hair follicles, structural proteoglycans, contains immune cells such as mast cells and macrophages, fibroblasts and various glands (Brown & Krishnamurthy, 2022). The skin is also rich in antigen-presenting cells, macrophages, mast cells, resident T-lymphocytes, local endothelial cells and tissue granulocytes. This richness makes the skin an important immune organ (Lanna et al., 2019). Various factors such as pathogens, chemicals, antigens, and ultraviolet radiation cause the production of cytokines that stimulate skin cells and the complex interaction between cells. The related cytokines produced by the cells ensure that the interactions between cells and immune cells in the skin are kept in balance (Coimbra et al., 2012). Keeping the interaction between different cells in the organism and external pathogens in a healthy balance depends on maintaining the immune homeostasis of the skin (Li et al. 2024). The emergence of various skin diseases and the organism's incapacity to carry out its intended functions are caused by an imbalance in the immune homeostasis that the skin provides (Abdallah et al., 2017; Li et al. 2024). In other words, inflammatory skin diseases are directly related to the disruption of cellular homeostasis, and psoriasis, in particular, reveals this dysregulation of cellular homeostasis through loss of immune tolerance. Moreover, other skin diseases, such as atopic dermatitis, eczema, etc., show a predominant inflammatory phenotype, which is a manifestation of this cellular imbalance (Lanna et al., 2019; Orsmond et al., 2021).

A variety of microorganisms, such as bacteria, archaea, viruses, and fungi colonise human skin to form the cutaneous microbiota. The relationship between human skin and this cutaneous microbiota is thought to mediate various inflammatory skin diseases through immune system cells (Grice & Segre, 2011; Sanford & Gallo, 2013). Immune cells in human skin protect against skin inflammation by triggering immunological tolerance against these harmful antigens. Any damage to the skin microbiota or disruption of homeostasis causes dysbiosis. While the normal microbiome does not cause skin diseases, genetic factors, infections, some metabolic syndromes, and persistent inflammatory conditions cause abnormal microbiomes leading to inflammatory skin diseases such as psoriasis (Ferček et al., 2021; Chen et al., 2023). The increase in bacterial populations that can alter local immunological settings to the extent of altering the normal microbiome of the skin exacerbates skin inflammation (Ferček et al., 2021). As a result, the homeostasis of the immune system in the tissue is disrupted, which can lead to the development of different dermatological diseases (Lanna et al., 2019; Chen et al., 2023). The altered and dysregulated microbial

balance also contributes to the irregular and high proliferation of keratinocytes in psoriatic skin. This has been reported in previous studies genetic defects of keratinocytes cause specific IL-17-mediated psoriasis-like inflammation in mice, and a dysregulated keratinocyte-immune cell relationship occurs (Mosca et al., 2021; Karbach et al., 2014).

Inflammatory Mediators 'Mast Cells'

Mast cells are found in the epidermis and dermis layers of the skin, bronchial mucosa and airways of the lungs, intestinal mucosa and near nerves. They are also involved in vasodilatation of blood vessels, smooth muscle contraction and enhancement of glandular secretion. However, the skin is rich in mast cells, which account for 8% of the total number of cells in the dermis (Chang et al. 2022). Mast cells are the main initiators and regulators of innate and adaptive immunity. Their complex communication with other cells ensures the maintenance of barrier function and immune homeostasis (Lefrançais et al., 2014). Mediators released by the regulation of mast cells, particularly histamine, have a significant effect on allergen-induced inflammation in the skin. In addition, mast cells also influence other immune cells by releasing cytokines and chemokines. Mediators released from mast cells are heparin, histamine, chymase, protease, carboxypeptidase A. In addition, mast cells produce many vasoactive, pro-inflammatory, chemoattractant cytokines, namely transforming growth factor-β (TGF-β), tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin -1 (IL-1), IL-18, IL-33, stem cell factor (SCF), granulocyte-macrophage colony stimulating factor (GM-CSF), chemokine (C-C motif) ligand 2 (CCL2), CCL3, CCL4, CCL5 and CCL20 secretes (Woźniak et al. 2021). Mast cells are found near both vascular and lymphatic vessels. Therefore, when inflammation occurs anywhere in the body, mast cells can travel via blood and lymphatic vessels to inflammatory sites and generate a wide range of localised and systemic inflammatory responses. Due to the similarity between endothelial cells of blood and lymph vessels, the same and rapid response to mast cell mediators can occur in endothelial cells of both blood and lymph vessels (Kunder et al. 2011).

Heparin is a polysaccharide that plays an important role in many body functions and is secreted by mast cells, which are part of the immune system and are involved in inflammation, tissue repair, and allergic responses. Therefore, heparin may influence the expression of inflammatory and immunological responses by regulating mediators in mast cells, which are effector cells for inflammation and immunity (Jerzyńska et al., 2000). Heparin is also known as an anticoagulant that prevents blood clotting. Mast cells are located near blood vessels and can affect the clotting process. By regulating this process, heparin can

prevent excessive clotting and help maintain healthy blood circulation (Humphries et al., 1999). Mast cells release biological compounds, such as histamine, when exposed to allergens. These compounds can lead to inflammation and dilation of blood vessels that cause allergic symptoms (Dileepan et al., 2023). Heparin can regulate mast cells to release chemicals that react to histamine and other allergens. In this way, the severity and duration of allergic reactions can be controlled. In addition, mast cells play an important role during inflammation by fighting against foreign substances that damage tissues and attack the body. Heparin can modulate the response of mast cells to regulate the inflammatory process (Kashiwakura et al. 2020). This can help control inflammation and reduce tissue damage. As a result, heparin helps to control allergic reactions, inflammation, and blood clotting by regulating the function of mast cells. Heparin is required for granule formation in connective tissue mast cells. Therefore, the importance of heparin for mast cells is of great importance for the body's immune system and circulatory system. Oral heparin is known to be an immunosuppressor, but the mechanism by which it suppresses the immune system is unclear (Kashiwakura et al. 2020).

Histamine is found in all body tissues; however, it is mostly found in the lungs, basophils, and mast cells. Histamine is stored in high concentrations in mast cells and causes an increase in vascular permeability (Dileepan et al., 2023). Histamine increases vascular permeability by causing vasodilatation. As vascular permeability increases, immune cell penetration increases because of plasma migration from blood vessels to the interstitial space. This leads to a further increase in inflammation. Since histamine is also secreted to ensure communication between different immune cells of the immune system, it can cause allergic symptoms, an inflammatory response, and anaphylactic symptoms (Kamiya et al., 2019). It has other important functions such as regulating the sleep-wake cycle, food intake, thermal regulation, movement, and cognitive functions such as emotions/aggressive behaviour, memory, and learning. In addition, it has known effects on blood vessels, sensory nerves, glands, and the activation of neutrophils and eosinophils (Xie & He, 2005). Histamine also mediates autoimmune events, gastric acid secretion, and haematopoiesis. In humans, immunoregulation of histamine is mediated by G protein-coupled histamine receptors. These mechanisms may vary depending on cellular differentiation, microenvironmental effects, host genetic factors, and comorbidities (Patel & Mohiuddin, 2023).

Dynamic Interactions between Immune Cells and Mast Cells

Many immune cells such as dendritic cells, T lymphocytes, neutrophils, macrophages, natural killer cells, mast cells and other immune cells affect psoriasis caused by hyperactivity of the immune system. Immune cells attack their own healthy cells and at the same time interact with skin cells to induce abnormal differentiation and proliferation of keratinocytes, thus promoting the progression of psoriasis (Yu et al. 2022). This interaction between keratinocytes and immune cells, which is critical in the pathogenesis of psoriasis, creates an inflammatory cycle (Kamata & Tada, 2023). This chronic disease can often last a lifetime with periodic exacerbations and remissions, but specific treatment methods can alleviate its symptoms. Researchers who have realised the importance of knowing the pathogenesis of psoriasis in the success of the methods applied in the treatment of psoriasis have conducted many studies on this subject and have found that many immune system cells contribute to the formation of psoriasis (Kamiya et al., 2019). The main factor in the development of psoriatic inflammation is the imbalance between regulatory T cells (Tregs) and effector T cells. Tregs are involved in the development and maintenance of immune homeostasis by stimulating effector T cells through various interleukins. In particular, the Th1/Th17 axis plays an important role in the initiation and maintenance of the psoriatic inflammatory cycle (Carvalho & Hedrich, 2021).

Mast cells form the first line of defence for the innate immune system. Mast cells are granulocytes derived from cells of myeloid origin. While immature ones can circulate in the peripheral blood, their maturation takes place in connective tissue (Metcalfe et al., 1997). When an antigen is encountered in the organism, the proinflammatory effects produced by mast cells cause circulating immune cells to aggregate to the inflammatory site, making them one of the primary cells causing psoriasis (Kamiya et al., 2019). The granules in mature mast cells contain various chemical substances, cytokines, proteoglycans, and proteases. The substances in these granules are released out of the cell as mediators because of degranulation caused by calcium mobilisation (Turner & Kinet, 1999; Tkaczyk et al., 2003). In addition, mast cells are activated simultaneously with degranulation. Degranulation is mediated by various cell surface receptors such as FcϵRI, toll-like receptors (TLR), Mas-related G-protein-coupled receptor X2 (MRGPRX2) and cytokine receptors. Degranulation by the FcϵRI receptor on mast cells is accompanied by binding of antigen-specific immunoglobulin E (IgE) to the receptor (Mukai et al. 2018). Excessive amounts of mediators released because of hyperactivity of mast cells lead to conditions such as oedema, vasodilatation, mucus secretion, and bronchoconstriction (Numata et al., 2022). Clinical manifestations of these conditions include various inflammatory and

autoimmune diseases such as allergic rhinitis, asthma, urticaria, anaphylactic shock, angioedema, psoriasis and psoriatic arthritis (Mohajeri et al., 2019; Ahmed & Jan, 2023). Inflammatory mediators increase the permeability of blood vessels so that immune cells can move through the bloodstream towards the affected tissue. Mast cells re-synthesise mediators after degranulation and repopulate granules, allowing them to circulate (Burwen, 1982).

Mast Cells in the Psoriatic Inflammatory Response

Microvascular abnormalities are a prominent and characteristic histopathological feature of psoriasis. Therefore, twisted, dilated, and elongated capillaries play an important role in the pathogenesis of psoriasis and constitute one of the pathological criteria for diagnosis (Hern et al., 1999). In psoriatic plaques, intercellular blood flow increases due to increased vasodilatation. In addition, another consequence of vasodilatation is vascular permeability. Molecular regulators of vascular permeability include growth factors and inflammatory cytokines (Claesson-Welsh. 2015). In addition, vascularisation is also affected by mast cells and their mediators. In inflamed skin, vasodilatation leads to an increase in vascular density, allowing more blood and therefore more immune cells to migrate to the area (Thangam et al., 2018). This means that there is a chronic, structural dilation of the arterioles present in psoriatic skin, because psoriatic skin has more vascular networks than non-psoriatic skin (Hern et al., 1999). Another important pathological parameter in psoriatic skin is erythema. Erythema is the reddening of damaged skin or mucous membranes because of congestion (blood collection) in dilated capillaries as a result of invasion of immune cells during environmental factors, injury, infection, allergy, etc (Kamiya et al., 2019). In areas of erythema, blood vessels dilate, blood flow slows down, and vascular permeability increases (Hern et al., 2005). This allows more plasma to escape from the blood vessels and thus increases the amount of fluid in the interstitial space. Indirectly, the number of immune cells in the interstitial space also increases, causing oedema in that area (Fong & Crane, 2023). As a result, mast cell-derived inflammatory mediators interact with the lymphatic vessels and become directly responsive to inflammatory signals (Armstrong & Read, 2020).

After stimulation, mast cells shape the inflammatory milieu and control the activation state of many cells crucial for adaptive immunity (Zhou et al., 2022). At the site of the psoriatic lesion, mast cell-derived TNF promotes the influx of monocyte-derived DCs by inducing up-regulation of E-selectin expression by the local vascular endothelium, which then increases in draining lymph nodes (McLachlan et al.,2003). CCL20 production by mast cells probably contributes to the uptake of DC precursors from the blood into tissues (Shelburne et al., 2009).

Mast cells have been shown to promote the activation of skin-resident Langerhans cells in response to bacterial products such as peptidoglycan or Gram-negative bacteria, leading to increased numbers of Langerhans cells in draining lymph nodes (Jawdat et al. 2006). This may exacerbate psoriatic inflammation. Furthermore, mast cell products can directly modulate DC activation and antigen presentation (Amaral et al., 2007). For example, histamine has been suggested to promote antigen uptake, cross-presentation, and up-regulation of co-stimulatory molecules required for T cell activation (Stelekati et al. 2009). Mast cell products can promote DCs to acquire a TH2 cell-inducing phenotype and recruit effector T cells to sites of infection (Hrubisko et al. 2021). Moreover, mast cells can present antigens to T cells. Initial evidence that mast cells function as antigen-presenting cells (APCs) was provided by the findings that activated mast cells increase the expression of MHC class II and co-stimulatory molecules and were imaged in physical interaction with T cells *in vivo* (Galli et al., 2005; Bischoff, 2009). The hyperactivity of heparin and various growth factors involved in wound repair leads to epidermal hyperplasia, which contributes to the pathogenesis of psoriasis (Yoshida et al., 2008). In psoriasis, the quantity of mast cells in pruritic lesions exceeds that in non-pruritic lesions (Nakamura et al., 2003). Furthermore, the number of activated mast cells is higher in psoriatic lesions compared to non-lesional psoriatic skin and healthy individuals, whereas the presence of resting mast cells is almost negligible in psoriatic skin lesions (Zhang et al., 2021). During etanercept (Tumor Necrosis Factor (TNF) inhibitor) treatment, the presence of resting mast cells in psoriatic skin lesions was observed to decrease (Zhang et al., 2021). These findings suggest that the role of mast cells in the pathogenesis of psoriasis warrants further investigation (Numata et al., 2022). Among the available histamine receptors, antagonists targeting the H1 receptor or H2 receptors generally prove ineffective in reducing chronic symptoms in psoriasis (Schaper-Gerhardt et al., 2020). Subsequent studies have demonstrated the presence of histamine in psoriatic skin. One study indicated that antihistamines targeting H1 receptors moderately alleviate itching in psoriasis patients (Domagała et al., 2017). TNF, another histamine mediator, enhances permeability by restructuring the cytoskeleton (Kunder et al., 2011). Consequently, vessels with increased permeability facilitate the migration of mast cells to the inflamed psoriatic area.

Conclusion

Recent research underscores the critical role of mast cells in psoriasis, mediating between innate and adaptive immunity through antigen presentation and lymph node augmentation, which enriches our understanding of their

coordinated activation of immune cells in psoriatic inflammation. The scarcity of studies on mast cells' role as immunological memory effectors in chronic psoriasis highlights a gap in our pathogenetic knowledge, pointing to the need for future preclinical research on immune-mast cell interactions and their implications. Investigating mast cell biology, including their activation in various inflammatory states, could pave the way for novel prophylactic or therapeutic approaches in psoriasis, potentially through the development of mast cell inhibitors to modulate immune responses.

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