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Pathophysiology and Molecular Mechanisms: Exploring the Underlying Mechanisms that Lead to the Development and Progression of Rheumatologic Diseases at the Cellular and Molecular Levels

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Abstract: In this study, 80 patients were collected from several different hospitals in Iraq and aimed to exploring the underlying mechanisms that lead to the development and progression of rheumatologic diseases at the cellular and molecular levels. The most prevalent chronic illness in humans and a leading source of lifelong impairment, rheumatic illnesses, are complex conditions that are better understood using molecular genetic techniques in rheumatology. They pinpoint possible infectious causes, with genetic traits impacting disease determinants on an individual basis. Understanding illness causation, severity analysis, therapy selection, and patient data categorization are all improved by researching gene heterogeneity. The clinical and pathological characteristics of rheumatic diseases include heterogeneity tendency to progression. The heterogeneity of the nature of rheumatic diseases is determined by the multifactorial nature of the diseases when certain combinations of environmental factors and polygenic backgrounds influence not only the susceptibility to the disease but also its severity and outcome. Understanding of the molecular genetic complexity and complexity of these disorders is incomplete, and there are currently no criteria for forming patient subgroups for differential treatment. We conclude from this study that the use of genetic analysis methods with microbiological, immunological, and other laboratory diagnostic methods has made it possible to show that the microbial factor and the genetic characteristics of the individual play an important role in the development of rheumatic diseases.

Keywords: Pathophysiology, Genetic, Multifactorial, Molecular, Heterogeneity, Patients.

INTRODUCTION

The illness is closely linked to specific human leukocyte antigen (HLA) alleles, such as HLA-DRB1. Environmental variables that increase a person's risk of sickness include smoking and several forms of infection [DeMik, D. E. *et al*., 2017]. Rheumatoid arthritis is characterized by inflammation of the synovial tissue lining the joints, which initiates a series of reactions. Tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are among the pro-inflammatory cytokines released by activated immune cells, particularly T cells, as they first penetrate the synovium. These cytokines aid in the attraction and stimulation of B cells and macrophages, among other immune cells [Curtis, J. R. *et al*., 2017; Rifbjerg-Madsen, S. *et al*., 2017; Davis, M. A. *et al*., 1992].

Rheumatic diseases are essentially chronic immune diseases that affect the joints and other organs of the body, and there are no clear reasons why a particular person should suffer from rheumatism more than another, but all that matters is that a patient has a susceptibility to the disease, and there are several reasons that increase the possibility of infection. [Creamer, P. *et al*., 2020; Bedson, J. *et al*., 2008; Neogi, T. *et al*., 2009] Diseases include smoking and bacterial or viral infections, which may stimulate the immune system and lead to the appearance of various symptoms of the disease [Wang, K. *et al*., 2018]

Regarding the higher incidence of rheumatic diseases in women compared to men, there is a theory or hypothesis that says that hormones play a major role in stimulating the immune system, and this can be understood by increasing the prevalence of lupus erythematosus among women, as it is 7 to 9 times higher of men.

Rheumatoid arthritis is largely caused by macrophages, which also degenerate joint tissue and cause inflammation. They cause pannus development and synovial hyperplasia by stimulating synovial cells. Autoantibodies are produced by B cells, which worsen joint injury and inflammation. Autoimmune reactions are caused by a dysregulated immune response, which is

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defined by an imbalance between regulatory and effector T cells. [Son, K. M. *et al*., 2016; Dye, S. F. *et al*., 1998; Zhang, Y. *et al*., 2011; Pitcher, T. *et al*., 2016]

Musculoskeletal diseases like osteoarthritis and rheumatoid arthritis are major causes of years lived with disability worldwide, with OA causing a 31.5% increase from 2006 to 2016 and pain, particularly knee pain, being a key symptom. [Jacobs, B. Y. *et al*., 2019; Herold, S. *et al*., 2016]

The current opioid and narcotic abuse epidemic are partly due to the lack of effective pain management therapeutics. Nearly 10% of opioids prescribed in Australia are for OA, and 12% of incident opioid dispensations are attributable to OA and related comorbidities. Despite advances in RA treatment, pain affects almost one-third of early patients with a good clinical response. Understanding the mechanisms underlying pain in these diseases is crucial for optimizing care [Gholami, M. *et al*., 2015; O'Callaghan, J. P. *et al*., 1975; Shiotsuki, H. *et al*., 2010].

It is possible to investigate the processes underlying the pathophysiology of joint degeneration and immune/inflammatory modulation using a number of well-established animal models of OA and RA. [Lynch, J. J. *et al*., 2011; Quinn, L. P. *et al*., 2003] Animal models of arthritis have been used to study pain using a variety of behavioral and neurophysiological techniques. However, care must be used when attempting to generalize findings from animal models to human patients because to the inherent technological hurdles in the quantitative evaluation of pain in animal models. This review covers the methods employed as well as the biological and molecular mechanisms underpinning the pathophysiology of arthritic pain as seen in animal models of OA and RA. Finally, technological innovations have significantly influenced rheumatology research and clinical practice. MRI, flow cytometry, and molecular cloning have improved the diagnosis and characterization of tissue samples. The past decade has seen new technological advancements, enabling more sophisticated interrogation and management of rheumatic diseases [Miller, R. E. *et al*., 2012].

PATIENT AND METHOD

Eighty patients were collected in this study. They were distributed according to gender: 48 male patients and 32 female patients. The patients were collected from several different hospitals in Iraq over a one-year study period from March 2023 to February 2024. The ages of the patients according to the real value and the arithmetic mean of this were 45±. 7.2 years.

Initial information was collected for the patients, which included (height, age, weight, body mass index, marital status of the patients, and leading causes)

Outcomes were assessed according to complication.

To the patients the effects of the disease on the patients' quality of life were measured by relying on the (WHOQOL-BREF) scale.

It has a quality-of-life statement on 30 existing member items and does not, and I would like to delete it for about 30 items. Scores on the Quality-of-Life Questionnaire are all-inclusive items with a range of 0-30, with a lower score indicating a better life.

The relationship between rheumatic patients and sleep duration was measured, as rheumatic diseases are characterized by changes in the structures of the musculoskeletal system, which result from various diseases that collectively lead to pain, which is the most common and frequent symptom. Most studies of pain and sleep in rheumatic diseases have found a high prevalence of insomnia, and many diurnal symptoms such as morning stiffness, pain, and fatigue may be related to a non-restorative sleep pattern or of very poor quality.

There is a relationship between chronic pain and sleep disorders that result from various mechanisms. On the other hand, sleep disturbance in healthy people leads to general body pain and fatigue. Finally, there is a correlation between pain and sleep disturbance, as severe pain during the day leads to sleep disturbance, and this leads to more severe pain the next day, and psychological factors also interact with both pain and insomnia.

Statistical Analysis

The data was analyzed statistically according to the IBM SOFT SPSS 22 program, and Microsoft Excel 2013 was relied upon. The data was analyzed according to the mean value and the slandered division and were calculated Frequency value percentages for the variable of this study.

The data was analyzed logistically, extracting the statistical relationship and determining its strength in this study when the B value < 0.05.

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RESULTS

Table 1: Assessment outcomes according to factors

Variable	Value
Age	
Mean and SD	45±7.2
Sex	
Male f (p %)	48 (60)
Female f (p %)	32 (40)
Causes	
immune cells	20 (25)
cytokines and chemokines	17 (21.25)
Genetic factors	9 (11.25)
environmental stimuli	
Infections	9 (11.25)
smoking	9 (11.25)
hormonal changes	11 (13.7)
Chemicals	5 (6.3)
Education	
Low	20 (25)
Secondary	30 (37.5)
College	20 (25)
High	10 (12.5)
BMI	
Mean ±Sd	29±4.4

Table 2: Assessment outcomes according to complication

	Male	Female	P-value
joint damage	5 (10.4)	4 (12.5)	0.093
deformity	3 (6.25)	3 (9.3)	0.88
chronic pain	3 (6.25)	0	0.09
limited mobility	2 (4.1)	1 (3.1)	0.22
fatigue	2 (4.1)	3 (9.3)	0.892
muscle weakness	0	2 (6.2)	0.001
Disability in severe cases.	0	1 (3.1)	0.09
Total	15 patients	14 patients	

Table 3: Analysis of the impact of rheumatology on patients' quality of life (WHOQOL-BREF)

Variable	Mean ±SD
Sleep duration	10.22±2.2
Psychological fatigue	9.7±3.1
Physical fatigue	13.7±3.22
overweight	14.12±4.98
Perception of health	12.55±2.8
Social relationships domain	6.6±2.4

Table 4: The correlation between our outcomes and sleep

Factor	R correlation	SE	95%CI	β	*P*
Bad sleep	-3.2	1.11	2.23-5.5	−0.16	0.030
Normal sleep	3.8	0.982	1.1-3.83	0.17	0.020
Adequate sleep	11.1	3.02	4.3-11.98	0.19	0.001
Psychological counseling	12.65	4.13	7.7-13.93	0.12	<0.050

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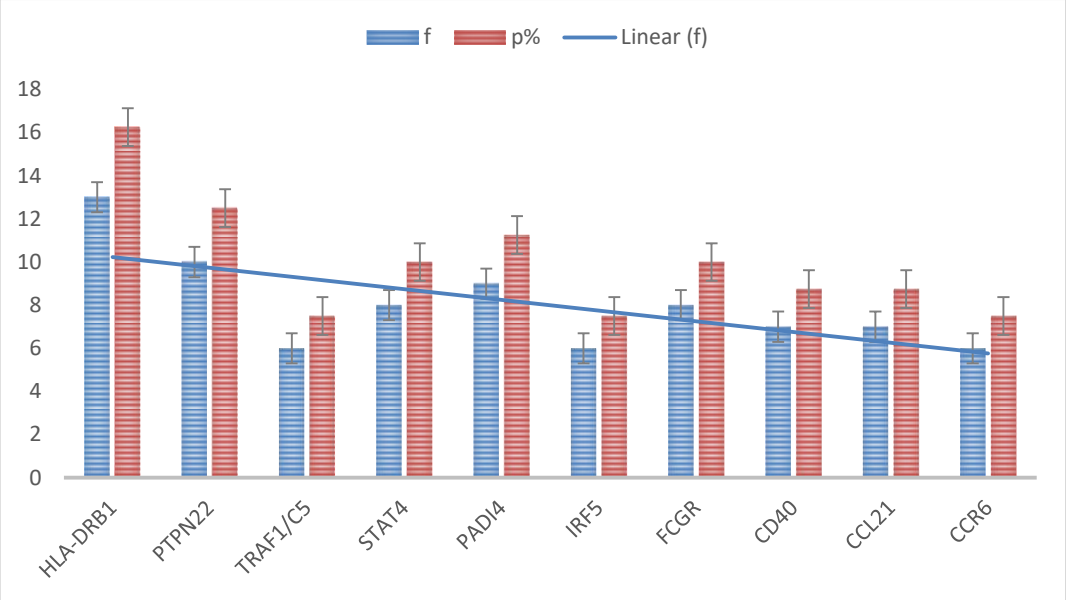

Fig 1: Distribution of genotypes among patients responsible for diseases

Table 5: Correlation between Causative factors with rheumatic diseases

	R correlation	**P-value**
Genetic factors	0.945**	>0.001
immune cells	0.848	0.034
cytokines and chemokines	0.06	0.33
hormonal changes	-0.45	0.55

Rheumatic diseases are complex and can involve multiple genes. Some of the most commonly associated genes in rheumatic diseases include

DISCUSSION

Rheumatoid arthritis (RA) is an inflammatory rheumatic disease of unknown etiology, characterized by symmetrical chronic erosive arthritis (synovitis) of peripheral joints and systemic immune damage to internal organs. The clinical picture is very diverse and largely depends on the predominant localization of inflammatory changes in the connective tissue of various organs. According to WHO data, the incidence of rheumatoid arthritis in the population ranges from 0.6 to 1.3%, while in relatives, it reaches 3-5%, which indicates the genetic determination of pathology. Women get sick 2.5 to 3 times more often than men, especially at the age of 35-50 years, and in later age periods, there is an increase in the incidence of the disease [Nwosu, L. N. *et al*., 2016; Harvey, V. L. *et al*., 2009].

According to several studies, the risk of developing rheumatoid arthritis is associated with the carriage of major histocompatibility antigen class II HLA-DR4 and HLA-DR1, which includes more than 20 alleles. The roles of other genetic factors not directly linked to HLA-DR are also actively discussed. These include gene polymorphisms for peptidyl arginine deaminase, protein tyrosine phosphatase N22 (PTPN22 C1858T), cytotoxic T lymphocyte-associated antigen (CTLA-4 A49G), chemokine receptor five gene CCR5-Δ32, and NO synthetase ENOS 4 a /b gene. Matrix metalloproteinase (MMP) gene MMP9-1562 C/T These genes are the least studied in terms of susceptibility to rheumatic diseases [Ogando, J. *et al*., 2016].

According to various studies, 70%-80% of people with rheumatoid arthritis suffer from sleep disorders. While the prevalence of the disease is higher in women than in men, sleep disorders occur equally in both sexes [Cheng, P. *et al*., 2020].

In the case of fibromyalgia, sleep disorders have been studied the most. Sleep disturbances, in addition to being another symptom, may be implicated as an etiological factor for the disease, which remains complex and multifactorial. The biological temporal distribution of symptoms was modified and was associated with natural diurnal variation in cortisol. [Cuppen, B. V. *et al*., 2016]

Sleep disorders are associated in more than 75% of cases and are accompanied by fatigue and stiffness

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during the morning hours. Poor restorative sleep is associated with the presence of spontaneous pain in muscle masses, tendons, and their insertions. Sleep in patients with fibromyalgia is superficial, easily altered by auditory stimuli, and is little or no restorative. From a polysomnographic point of view, an increase in the number of awakenings and the duration of the first stage was observed, as well as a decrease in slow-wave sleep, REM sleep, and sleep efficiency. Alpha delta activity at the EEG level is a very common finding 14,15. Sleep apnea and periodic limb movements during sleep have been observed in patients with fibromyalgia. Serotonin reuptake inhibitor antidepressants, benzodiazepines, and non-benzodiazepine hypnotics may be of some benefit, although it is very difficult to achieve improvement in sleep in these patients, especially in advanced stages of the disease.

Proinflammatory cytokines such as TNF-alpha and IL 6, which peak at night in response to cortisol levels (a steroid hormone produced by the adrenal gland in response to stress), are constantly elevated, resulting in a vicious cycle of pain. - Inflammation-insomnia-pain. Many current treatments attempt to stop this cytokine cascade. Many studies have shown that in patients with rheumatoid arthritis, disease activity, sleep disturbances, inflammatory mediators, pain, and psychological factors are related to each other, so appropriate treatment to control disease activity and pain may improve sleep disturbances and may relieve daytime symptoms, such as fatigue and stiffness. We must not forget that to the pain caused by the disease; we must add the uncertainty, anxiety, and anxiety caused by the recent diagnosis of the disease.

Study of the activity of MMP-1, -3, and tissue MMP-1 inhibitors in combination with levels of C-reactive protein (CRP) and cytokines in patients with erosive and non-erosive rheumatic diseases revealed a significant increase in proteinase activity in the blood serum of patients with erosive arthritis. Meanwhile, a direct relationship between CRP level and MMP-3 activity has been established, which better correlates with the clinical manifestations of RA. Therefore, it can be said that determining MMP-3 activity and CRP level in the blood serum of patients with rheumatoid arthritis is of diagnostic importance. Study results suggest that MMP-3 activity, more than cytokines, reflects the degree of inflammation in rheumatoid arthritis. This functional potential allows us to consider MMP-3 as one of the main proteins involved in the processes of connective tissue destruction in rheumatoid arthritis.

CONCLUSION

Improving patient outcomes requires research on the cellular and molecular factors underlying rheumatologic disorders. Identification of therapeutic targets and the development of individualized therapies can be aided by knowledge of immune responses, environmental triggers, genetic variables, and cytokine signaling. Millions of people afflicted may benefit from novel treatments and cures brought about by ongoing research, technological developments, and cooperative efforts.

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