JOURNAL OF TECHNIQUES

Journal homepage: http://journal.mtu.edu.iq

RESEARCH ARTICLE - MEDICAL TECHNIQUES

Rheumatoid Arthritis Effects on Kidney and Liver and their Correlations with CDAI

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Article Info.

Article history:

Received
12 July 2022

Accepted
28 August 2022

Publishing
15 November 2022

Abstract

Rheumatoid arthritis (RA) is a disease characterized by chronic autoimmune inflammation of body joints, causing movement disability, loss of functions, joint damage, and many complications. Persistent usage of anti-rheumatic drugs has several side effects, which may cause heart, kidney, or liver diseases.

This study aims to assess the influence of RA duration on kidney and liver enzymes and study the correlation between these enzyme levels and RA disease activity (CDAI). This study collected a total of 150 blood samples. 100 samples for RA patients (61 were seropositive, 39 were seronegative), and 50 for healthy Control. throughout the period from November 2021 to February 2022. The blood samples were collected from Baghdad Teaching Hospital / Rheumatology Consulting Clinic. General information had been collected from each subject according to a questionnaire that had been applied for this purpose.

The age groups of patients and control were between 22-72 years, and 26-62 years old, respectively. The female participants were more than the male counterparts. The blood samples were taken from patients and control groups to screen liver and kidney functions by an automated biochemical system using the SELECTRA PRO X2 device, in addition to the ESR test. The study showed that the levels of urea, creatinine, GPT, and GOT were either normal or slightly elevated and they are non-significantly associated with RA disease activity, the little effect of RA on kidney and liver may be related to the low doses of methotrexate and corticosteroid therapy which used mostly for these patients and didn't reach to toxicity.

Publisher : Middle Technical University

Keywords: RA; B. urea; S. creatinine; GOT; GPT; CDAI.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune symmetrical chronic inflammatory disease that begins with small joints (hand and foot) then affects the large joints and may cause damage to bone and cartilage. It strikes about 1% of the population around the world. Its common symptoms are morning stiffness that lasts more than 1 hour, joint pain, swelling, immobility, erosion, and deformity [1]. bone erosion due to RA may start within the first 2 months of the disease with a rate reaching 10%, and this percent of erosion is increasing to 60% of RA patients ratio within the first 3 years from the beginning of the disease, resulting in joint damage [2]. RA like most autoimmune diseases affects females more than males with a ratio reach to 3:1 of patients number, it's caused by unclear perfectly but mostly it's thought to be due to environmental agents like tobacco, contaminated air, some viral infections, gastric microbes, diet, body activity (job), stress, socioeconomic state, or by other causes like genetic, epigenetic (mutations), immune status (thyroid, diabetes mellitus), hormonal (early menopause, breastfeeding which minimizes the chance of RA) [3]. Environmental conditions also have a critical role in disease invading people, about 11% of the population suffer from periodontitis, bacterial inflammation of the tissue that surrounds teeth. Periodontitis has a similar etiology to RA, this inflammation leads to produce citrulline [4]. The joints are lined by synovium that yields the synovial fluid which acts to grease the joint to reduce their friction, besides alimentation of bone and cartilage that help in motility and activity. During RA the antibodies produce and secrete the chemicals that trigger the synovium inflammation, so reduce the amount of synovial fluid leading to chronic RA which if persists can progress to rheumatoid vasculitis, which in an immune-compromised patient may attack blood vesicles and joints. RA damages the connective tissue and the tendon which bind the muscle and bone so there will be a defect in the joint site and composition, causing erosion and deformities, and finally bone damage [5]. Immune responses in RA are includes both innate and adaptive immunity. T cells, B cells, and macrophages are the essential cells that contribute to RA immune response, by the production of cytokines, chemokines, pro-inflammatory proteins, and fibroblast, which accumulate in the tissues and produce inflammatory cells causing tissue damage [6]. Rheumatoid arthritis immune pathogenesis is starting with the generation of autoantibodies against post-translationally modified proteins, then, tissue tolerance falls and inflamed joint happened, and years followed asymptomatic autoimmunity and gradual immune system rearranged when effector T cells appear after the tissue invasion and macrophages cannot protect joints. Synovitis is transforming from acute to chronic damage when synovial stromal cells become auto-aggressive effector cells [7].

Nomenclature			
ACR	American College of Rheumatology	CR.	Creatinine
ESR	erythrocyte sedimentation rate	GPT	Glutamate pyruvate transaminase
EULAR	European League Against Rheumatism	GOT	Glutamate oxaloacetate transaminase
CDAI	clinical disease activity index	N.S	non-significant
B.	Blood	H.S	highly significant
S.	Serum		

Renal dysregulation may be associated with RA as a result of the effect of some medications, and it may be effective by age, hypertension, and duration of disease, besides other complications like cardiovascular disease (CVD) which is the most common RA complication that may influence kidney function. RA therapy may affect on kidney causing secondary amyloidosis, and membranous nephropathy, while some kidney diseases may occur due to RA, not drugs such as mesangial glomerulonephritis. nowadays these complications are reduced prominently as a result of the use of new treatments that reduce nephrotoxic [8]. It is found that a continuous increase in the acute inflammatory rate represented by CRP can lead to chronic kidney disease [9]. The current study showed that B. urea, S. creatinine, GOT, and GPT was non-significant at a P-value > 0.05. Liver enzymes may be elevated with a long period of using chemical RA drugs, although its uses in association with other treatments may reduce this influence markedly [10]. The liver may be affected by the biochemical treatment of RA, and those patients may develop hepatocellular carcinoma after cirrhosis, due to the toxicity of the drug which may cause hepatocyte damage in rare cases [11]. Assessing the disease activity for RA patients is important to guide the physician and give an appropriate reflection about the health state of the patient and help in managing the treatment in a good manner, it indicates prognosis, it is used to estimate the inflammation perfectly, expected joint destruction [12]. There are several manners to assess the disease activity, in the current study we depend on the clinical disease activity index (CDAI) to quantify the measurement of RA, which depend on the patients' and physician global assessment (0-10), and the tender joint count, and swollen joint count it is a simplest and fastest manner to measure the disease activity because it can be calculated directly, it doesn't depend on the analytical measurement it can obtain by summation of counts CDAI=TJC +SJC+EGA+PGA (tender joint count+ swollen joint count + evaluator global assessment+ patient global assessment) and the score assessed as follow: 0-2.8 remissions, 2.9-10 low, 10.1-22 Moderate, 22.1-76 high [13]. Erythrocyte sedimentation rate (ESR) is a secondary marker of inflammation, it is a simple and non-expensive test but it is not limited to a certain disease, it demonstrates the protein (fibrinogen) level in blood which accelerates the sedimentation of red blood cells, its negatives are due to their slow response to treatment, so cannot be useful alone inpatient situation detection [14]. Its coefficient is beside other investigations in the prognosis of some diagnosed diseases like rheumatoid disease, and Hodgkin's disease. Its highly elevated level may indicate a serious infection such as autoimmune disease, metastatic malignancy, and vascular disease. if its level was highly increased without significant symptoms the test should be repeated after a while [15]. ESR is different by sex, as usual, it is higher in females than in males, and its level is raised respectively with age, people more than 65 years old have a duplicate ratio than young age person, fat person, tobacco uses, alcohol donors, and people who doing exercise continuously, also have raised level than those without [16]. its elevated level can be attributed to pregnancy or anemia which causes logical elevation. it is an aid in diagnosing chronic infections due to its long half-life, while the CRP has a short half-life so it is used mainly to detect acute infections [17].

2. Materials and Methods

2.1. Study design

In this study 150 blood samples were collected, 100 for RA patients and 50 for healthy control, the patients were taken from Baghdad Teaching Hospital / Rheumatology consulting clinic in the period from November 2021 to February 2022, and RA patients were diagnosed depending on the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR), 5 ml of blood was taken from each person, 3 ml of blood in gel tube to obtain serum for biochemical tests and the rest 2 ml of blood was collected in EDTA tube for ESR test. The age range was 22-72 years for patients, while it was 26-62 years for control. The biochemical tests were determined for; B. Urea, S.Creatinine, S.GPT, and S.GOT, these tests were done by an automated biochemical analyzer SELECTRA PRO-XL which is used as a fully automated chemical analyzer in biochemical tests, in which 250 µl of the working reagents was added to 30 µl of serum samples automatically, after 7 minutes, then read at 340-800 nm after 11.5 min to get the result, ESR test was done by auto ESR analyzer, 1.28 ml of EDTA blood was added to the 0.4 ml of 3.8% sodium citrate, after mixed it stood in Westergreen pipette, the result then appears after about 30 minute on the monitor, then the result transformed to the measuring time of 60 min by using the correlation curve.

2.2. Inclusion criteria

A rheumatoid arthritis patient was taken for this study was

- From both sexes.
- At any adult's age.
- At any duration of diagnosis even the newly diagnosed cases.
- With any type of RA treatment.

2.3. Exclusion criteria

All the RA patients and controls were taken except the cases with the followed criteria:

- Less than 18 years old.
- Pregnancy.
- Malignancy.
- Other autoimmune diseases.

3. Results

Table 1 shows that the mean ± SE for patients and controls in age, duration, and gender, had a highly significant difference observed in age (years) at p-value = 0.00, while the p-value can not be computed for the duration of the disease due to its absence in the control group. The gender shows a significant difference between the male and female with a p-value = 0.05

Table 1 Demographic picture of the study group

Parameters		Study group	No.	Mean	Std. Error	Chi-square	t-test	*P-value
age (Years)		Patient	100	48.82	1.23	39.2	6.5	0.00
		Control	50	37.98	1.12			(H.S)
Duration of		Patient	100	10.38	0.82	-	-	-
disease(Years)		Control	0[a]	.	-			
Gender	Male	patient	15	-	-	3.69	-	0.05 (S)
		control	14					
	female	patient	85					
		control	36					

H.S: highly significant, S: Significant

Table (2) observed that the greatest number of RA patients' number are 33 (33.0%) had a duration of disease of (1-5) years, while the lowest RA patients' number 2 (2.0%) had a duration of disease (>30) years.

Table 2 Distribution of the patients with rheumatoid arthritis according to the duration of disease

Categorical duration of disease/Years		Study Group Patients
(< 1) years	NO.	3
	%	3.0%
(1-5) years	NO.	33
	%	33.0%
(6-10) years	NO.	28
	%	28.0%
(11-15)years	NO.	14
	%	14.0%
(16-20) years	NO.	12
	%	12%
(21-25) years	NO.	3
	%	3.0%
(26-30) years	NO.	5
	%	5.0%
>30 years	NO.	2
	%	2.0%
Total	NO.	100
	%	100.0%

Table 3 show the mean ± SE for patients and controls at different parameters, it shows that there was no significant statistical difference in B. urea, S. creatinine, GOT, and GPT, at a p-value more than 0.05 on the other hand, duration and CDAI cannot be computed because at least one of the groups is empty, while the ESR show highly significant difference at p-value = 0.00.

Table 3 Comparison of some parameters in the studied groups

Parameters	Study group	No.	Mean	Std. Error	t-test	*P-value
B. urea (mg/dl)	Patient	100	30.48	1.30	1.67	0.09 (N.S)
	Control	50	27.92	0.80		
S. creatinine (mg/dl)	Patient	100	0.63	0.012	0.49	0.6 (N.S)
	Control	50	0.65	0.01		
GOT (mg/dl)	Patient	100	21.83	1.55	1.3	0.8 (N.S)
	Control	50	24.60	1.39		
GPT (mg/dl)	Patient	100	23.79	1.28	1.20	0.3 (N.S)
	Control	50	26.20	1.53		
CDAI	Patient	100	17.6.	0.92	.	-
	Control	0[a]	.	-	.	
ESR (mm/1h)	Patient	100	35.94	2.48	9.8	0.00 (H.S)
	Control	50	8.90	1.192		

H.S: high significant, N.S.: non-significant, GOT: glutamate oxaloacetate transaminase, GPT: glutamate pyruvate transaminase. CDAI: clinical disease activity index, ESR: erythrocyte sedimentation rate.

Table 4 found the association between CDAI and some parameters. The results showed a non-significant association between CDAI and B. Urea, S. creatinine, Got, GPT, and ESR at the p-value >0.05.

Table 4 Association between CDAI and some parameters according to the normal value

Parameter		CDAI Low ≤10		Moderate ≤ 22		High > 22		Total	Chi-square	p-value
		NO	%	NO.	%	NO.	%			
B.Urea mg/dl	15-45	18	19.6%	46	50.0%	28	30.4%	92	0.46	0.7 (N.S)
	>45	2	25.0%	3	37.5%	3	37.5%	8		
S. creatinine mg/dl	0.7-1.2	20	20.2	48	48.5%	31	31.3	99	1.05	0.5 (N.S)
	>1.2	0	0.0%	1	100%	0	0.0%	1		
GOT mg/dl	0-40	19	20.2%	46	48.9%	29	30.9	94	0.04	0.9 (N.S)
	>40	1	16.7%	3	50%	2	33.3	6		
GPT mg/dl	0-45	19	19.8%	46	47.9%	31	32.3	96	1.91	0.3 (N.S)
	>45	1	25.0%	3	75%	0	0	4		
ESR mm/1h	0-20	8	26.7%	15	50%	7	23.3%	30	1.77	0.4 (N.S)
	>20	12	17.1%	34	48.6%	24	34.3%	70		

N.S: non- significant.

Table 5 documented that the CDAI was positively correlated with the levels of s. creatinine, and ESR with (r = 007,0.08), respectively, but this correlation was non-significant at (p-value = 0.4, 0.4), In addition the result of the current study revealed that the CDAI was negatively correlated with the levels of B. urea, GOT, and GPT with (r = -0.013, -0.09, -0.07) respectively, and this correlation was non-significant at p-value = (0.8, 0.3, 0.5), respectively.

Table 5 Correlation between the CDAI according to its score among patients and levels of some parameters according to the cutoff point

Parameter	Pearson Correlation – r	P-value
Age (Years)	0.11	0.2 (N.S)
B.urea (mg/dl)	-0.013	0.8 (N.S)
S.creatinine (mg/dl)	0.07	0.4 (N.S)
GOT (mg/dl)	-0.09	0.3 (N.S)
GPT (mg/dl)	-0.07	0.5 (N.S)
ESR (mm/1hr.)	0.08	0.4 (N.S)

**. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2-tailed), N.S: non-significant, mg: milligram, dl: deciliter, mm: millimeters, hr: per hour, GOT: glutamate oxaloacetate transaminase, GPT: glutamate pyruvate transaminase, ESR: erythrocyte sedimentation rate.

4. Discussion

The age factor in rheumatoid arthritis patients is important as a risk factor [18], in the current study showed a highly significant distribution of age in the studied groups, the result match with Lukas Mangnus et al . (2015), who mentioned the effect of age on the general state of the RA patients [19], also it resembles with [20 -22]. which showed a similar mean age in their RA studies. This result may be related to the most common ages of Iraqi patients that visited the hospital, the sample size, and treatment. On the other hand, the mean disease duration in this study was high, this result match with [23,24], this proportion was gained as a result of the durations of attended patients who need hospitalized treatment after many years of the disease, mostly need a biological treatment after 10 years of the disease onset.

The study also noticed a significant difference between males and females, and show that RA in females was more than in males with a ratio reaching 4:1, this result resembles [25, 26]. This result may be related to the hormonal causes mostly estrogen, which can act to increase the autoimmune disease, In addition to the genetic causes like the X chromosome. The X chromosome suffers more mutations may occur, and the X chromosome has more immune regulatory and immune-mediated genes which aid in an immune response leading to an increase in the rate of autoimmune disease [27].

Furthermore, the study showed that the patients who had a disease duration below 10 years had a higher ratio among the studied group, that's similar to what was mentioned by Hussein (2017), who found a higher disease duration ratio found in the first decade of the disease [28], and compatible with the study of Sakini (2005), that showed the largest duration patients number found in the first 4 years of the disease [29], this result may be related to the higher disease activity in the first years of diagnosis and bad situations of the patients before choosing the appropriate treatment, which triggers the patients to go to the hospital so we found the largest patients ratio in the first years of the disease. on the other

hand, the lowest percentage of disease duration corresponded to the longest duration and that's similar to the study conducted by Pincus (1984), which mentioned that the reason for that low ratio was related to the complications associated with the progression of the disease that may lead to earlier patients' death causing a decrease in their number [30], the reason in this study may be related to the random sampling collection, and concerned with the patient's age range in Iraq, beside the difficulties that accompanied their arrival to the hospitals, all these reasons contributed to decreasing their numbers.

On the other hand, this study also showed non-significant differences in kidney and liver enzymes between RA patients and controls in B. urea, S. creatinine, S. GPT, and S.GOT and this is the same as mentioned by [31, 32]. This may relate to the combined treatment that reduced the toxic influence of the treatment and the regulate using of low doses of therapy.

According to CDAI the p-value cannot be counted due to its absence of control so cannot be compared, its score is increased with many factors. The mean of CDAI was resemble that mentioned by [33]. The prevalence of moderate CDAI scores may be related to other factors (overweight, other diseases, and the job) that influence the response to treatment, and the general patient's state.

The ESR test correlated with RA at a highly significant level with a p-value of 0.00, that's similar to the Vasanthi (2009) study, [34]. ESR is elevated in RA due to the production of proteins mainly immunoglobulin and CRP which attach to the red blood cells and make them aggregate forming rouleaux formation that increased the falling rate of RBC in the other word the ESR level [35], and the ESR is a chronic inflammatory biomarker so it increases markedly in RA and other autoimmune diseases due to antibody accumulation that found in patients' blood leading to faster falling of erythrocyte, and may be due to the anemia that usually associated with RA and accelerate the sedimentation level.

The results in this study also showed non-significant associations of B. urea and S. creatinine with CDAI at a p-value of more than 0.05, which resembles another study done by Couderc et al (2016), that showed a non-significant association of kidney enzymes with CDAI [36]. That may be due to the development of the early diagnostic manners that aid largely to avoid invading other organs and choosing appropriate treatment which leads to good RA management. On the other hand, liver function tests also showed a non-significant association with CDAI, the p-value for GOT, and GPT were more than 0.05, which differed from another study done by Tawfeeq that showed a significant association of liver enzymes with the disease process ($p < 0.05$) [37]. This difference may relate to good RA management and prognosis, early disease diagnosis, using proper therapy dose, and development of patients' awareness, which may have contributed somewhat to their care of treatment and the increase in their psychological acceptance of their situation, that aided to improve their health status, and the development of technology may have a positive role in that.

Furthermore, the current study showed a non-significant association between CDAI and ESR, this differs from Kay et al. (2014) study that showed a significant association between disease activity with ESR [38], this difference between studies may relate to the difference in sampling number, besides that the ESR is not specific for RA, and it is a general chronic inflammatory parameter so it may need a long time to raise and at the same time to return to normal, for that reasons, it was not significantly associated with the disease activity.

This study showed a non-significant positive correlation between age and CDAI that's the same as mentioned by Martin et al.(2014) [39], maybe the onset age of infection affects the severity of the disease and the general state of health for these investigated samples, and the influence of the treatment may have the same response on the activity in young and older patients.

The results also document that the CDAI in RA patients was negatively correlated with the levels of B. urea, GOT, and GPT and this correlation was non-significant at a p-value of more than 0.05, that's the same as what was mentioned by Michael West (1963) that showed a non-significant correlation between GOT, GPT and the RA disease activity, [40]. That's due to reducing the side effects of therapy, and progression of the disease management.

The study also showed that the CDAI is correlated positively with s. creatinine but this correlation was non-significant, and that resembles the study which showed the renal dysfunctions were not related to the disease activity of RA [41].

Furthermore, ESR in this study showed a positive correlation but non significantly correlated with the RA disease activity which differs from a study by Farr; that found a significant correlation between ESR and the disease activity [42], this difference may be related to the reason of sample collections, duration of the disease, and difference in treatment strategies in addition to the samples number.

5. Conclusion

The level of kidney and liver enzymes correlated non- significantly with the severity of the disease activity of rheumatoid arthritis. And the age, duration, and ESR bind significantly with rheumatoid arthritis but not with the severity of the disease.

6. Recommendations

An additional sampling number is required to study the accurate effects of rheumatoid arthritis on the kidney and liver functions during infections in addition to the molecular genetic studies to assess these effects.

Acknowledgement

I would like to express my great gratitude to who helped me widely in the supervision of sampling collections in addition to the administration of Baghdad Teaching Hospital for their role in collecting patient samples and express thanks to the voluntary patients and controls. My great thanks also go to the college of health and medical techniques/ Baghdad for their cooperation.

References

[1] M. R. Martínez, P. Morán-Álvarez, J. Arroyo-Palomo, M. V. Expósito, And M. V. Díaz, "Rheumatoid Arthritis," Med., Vol. 13, No. 30, 2021, Doi: 10.1016/J.Med.2021.03.027.

[2] K. P. Machold Et Al., "Very Recent Onset Rheumatoid Arthritis: Clinical And Serological Patient Characteristics Associated With Radiographic Progression Over The First Years Of Disease," Rheumatology (Oxford)., Vol. 46, No. 2, Pp. 342–349, Feb. 2007, Doi: 10.1093/Rheumatology/Kel237.

[3] V. C. Romão And J. E. Fonseca, "Etiology And Risk Factors For Rheumatoid Arthritis: A State-Of-The-Art Review," Front. Med., Vol.

8, Nov. 2021, Doi: 10.3389/Fmed.2021.689698.
[4] J. Potempa, P. Mydel, And J. Koziel, "The Case For Periodontitis In The Pathogenesis Of Rheumatoid Arthritis," Nat. Rev. Rheumatol. 2017 1310, Vol. 13, No. 10, Pp. 606–620, Aug. 2017, Doi: 10.1038/Nrrheum.2017.132.
[5] D. Di Giuseppe, A. Discacciati, N. Orsini, And A. Wolk, "Ra Causes: What Are The Top Causes Of Rheumatoid Arthritis? - Rheumatoidarthritis.Org," Vol. 16, No. 2, Mar. 2014, Doi: 10.1186/Ar4498.
[6] H. Y. Yap, S. Z. Y. Tee, M. M. T. Wong, S. K. Chow, S. C. Peh, And S. Y. Teow, "Pathogenic Role Of Immune Cells In Rheumatoid Arthritis: Implications In Clinical Treatment And Biomarker Development," Cells 2018, Vol. 7, Page 161, Vol. 7, No. 10, P. 161, Oct. 2018, Doi: 10.3390/Cells7100161.
[7] C. M. Weyand And J. J. Goronzy, "The Immunology Of Rheumatoid Arthritis," Nat. Immunol. 2020 221, Vol. 22, No. 1, Pp. 10–18, Nov. 2020, Doi: 10.1038/S41590-020-00816-X.
[8] S. Mori, T. Yoshitama, N. Hirakata, And Y. Ueki, "Prevalence Of And Factors Associated With Renal Dysfunction In Rheumatoid Arthritis Patients: A Cross-Sectional Study In Community Hospitals," Clin. Rheumatol., Vol. 36, No. 12, Pp. 2673–2682, Dec. 2017, Doi: 10.1007/S10067-017-3804-5/Tables/5.
[9] M. Kochi, K. Kohagura, Y. Shiohira, K. Iseki, And Y. Ohya, "Inflammation As A Risk Of Developing Chronic Kidney Disease In Rheumatoid Arthritis," Plos One, Vol. 11, No. 8, P. E0160225, Aug. 2016, Doi: 10.1371/Journal.Pone.0160225.
[10] S. Akhlaghi Et Al., "Additional Effect Of Etanercept Or Infliximab On The Liver Function Tests Of Patients With Rheumatoid Arthritis: A Cohort Study," Ther. Clin. Risk Manag., Vol. 14, P. 1943, 2018, Doi: 10.2147/Tcrm.S172836.
[11] B. Radovanović-Dinić, S. Tešić-Rajković, V. Zivkovic, And S. Grgov, "Clinical Connection Between Rheumatoid Arthritis And Liver Damage," Rheumatol. Int. 2018 385, Vol. 38, No. 5, Pp. 715–724, Apr. 2018, Doi: 10.1007/S00296-018-4021-5.
[12] E. H. S. O G Segurado, "Vectra Da For The Objective Measurement Of Disease Activity In Patients With Rheumatoid Arthritis - Pubmed," Oct. 30, 2014. Https://Pubmed.Ncbi.Nlm.Nih.Gov/25365086/ (Accessed Mar. 10, 2022).
[13] A. K. Spencer Et Al., "Validation Of A Machine Learning Approach To Estimate Clinical Disease Activity Index Scores For Rheumatoid Arthritis," Open, Vol. 7, P. 1781, 2021, Doi: 10.1136/Rmdopen-2021-001781.
[14] L. Siemons, P. M. Ten Klooster, H. E. Vonkeman, P. L. C. M. Van Riel, C. A. W. Glas, And M. A. F. J. Van De Laar, "How Age And Sex Affect The Erythrocyte Sedimentation Rate And C-Reactive Protein In Early Rheumatoid Arthritis," Bmc Musculoskelet. Disord., Vol. 15, No. 1, Pp. 1–7, Nov. 2014, Doi: 10.1186/1471-2474-15-368/Tables/5.
[15] M. L. Brigden, "Clinical Utility Of The Erythrocyte Sedimentation Rate," Am. Fam. Physician, Vol. 60, No. 5, Pp. 1443–1450, Oct. 1999.
[16] V. Alende-Castro Et Al., "Factors Influencing Erythrocyte Sedimentation Rate In Adults: New Evidence For An Old Test," Med. (United States), Vol. 98, No. 34, P. E16816, 2019, Doi: 10.1097/Md.0000000000016816.
[17] M. K. S. Litao And D. Kamat, "Erythrocyte Sedimentation Rate And C-Reactive Protein: How Best To Use Them In Clinical Practice," Pediatr. Ann., Vol. 43, No. 10, Pp. 417–420, Oct. 2014, Doi: 10.3928/00904481-20140924-10.
[18] P. H. Dessein Et Al., "Traditional And Nontraditional Cardiovascular Risk Factors Are Associated With Atherosclerosis In Rheumatoid Arthritis.," J. Rheumatol., Vol. 32, No. 3, 2005.
[19] L. Mangnus Et Al., "Studies On Ageing And The Severity Of Radiographic Joint Damage In Rheumatoid Arthritis," Arthritis Res. Ther., Vol. 17, No. 1, Pp. 1–10, Aug. 2015, Doi: 10.1186/S13075-015-0740-0/Tables/3.
[20] H. A. Getta, N. Khoshnaw, A. F. Alwan, F. A. Sundus, And R. R. Mirza, "Original Article Types Of Anaemia And Its Correlation With Disease Activity In Patients," Iraqi J. Hematol., Vol. 5, No. 1, Pp. 114–128, 2016.
[21] H. A. Al-Daoseri, M. A. Mohammed Saeed, And R. A. Ahmed, "Prevalence Of Cervical Spine Instability Among Rheumatoid Arthritis Patients In South Iraq," J. Clin. Orthop. Trauma, Vol. 11, No. 5, Pp. 876–882, Sep. 2020, Doi: 10.1016/J.Jcot.2019.06.013.
[22] N. Al-Ani Et Al., "Clinical Outcomes In Iraqi Patients With Rheumatoid Arthritis Following Earlier Or Later Treatment With Etanercept," Open Access Rheumatol. Res. Rev., Vol. 13, P. 57, 2021, Doi: 10.2147/Oarrr.S300838.
[23] A. Zink, J. Listing, C. Klindworth, And H. Zeidler, "The National Database Of The German Collaborative Arthritis Centres: I. Structure, Aims, And Patients," Ann Rheum Dis, Vol. 60, Pp. 199–206, 2001, Doi: 10.1136/Ard.60.3.199.
[24] K. D. Wysham Et Al., "Low Cumulative Disease Activity Is Associated With Higher Bone Mineral Density In A Majority Latinx And Asian Us Rheumatoid Arthritis Cohort," Semin. Arthritis Rheum., Vol. 53, P. 151972, Apr. 2022, Doi: 10.1016/J.Semarthrit.2022.151972.
[25] R. H. Hussein, I. A. Mezheral-Rayahi, And K. Taha, "Rheumatoid Factor Isotypes In A Sample Of Iraqi Rheumatoid Arthritis Patients," J. Glob. Pharma Technol., Vol. 10, No. 8, Pp. 141–145, 2018.
[26] Kadhim D J & Gorial F I, "View Of The Belief About Medicines Among A Sample Of Iraqi Patients With Rheumatoid Arthritis," 2019. Https://Bijps.Uobaghdad.Edu.Iq/Index.Php/Bijps/Article/View/932/806 (Accessed Apr. 16, 2022).
[27] F. Angum, T. Khan, J. Kaler, L. Siddiqui, And A. Hussain, "The Prevalence Of Autoimmune Disorders In Women: A Narrative Review," Cureus, Vol. 12, No. 5, May 2020, Doi: 10.7759/Cureus.8094.
[28] W. A. Hussein, "The Quality Of Life In Patients With Rheumatoid Arthritis In Baghdad,2017: A Cross-Sectional Study," Int. J. Med. Res. Heal. Sci., Vol. 6, No. 11, Pp. 20–34, 2017.
[29] R. A. Sakini, I. K. Abdul-Zehra, And M. S. M. Al-Nimer, "Neuropathic Manifestations In Rheumatoid Arthritis: A Clinical And Electrophysiological Assessment In A Small Sample Of Iraqi Patients," Ann. Saudi Med., Vol. 25, No. 3, Pp. 247–249, 2005, Doi: 10.5144/0256-4947.2005.247.
[30] T. Pincus, L. F. Callahan, W. G. Sale, A. L. Brooks, L. E. Payne, And W. K. Vaughn, "Severe Functional Declines, Work Disability, And Increased Mortality In Seventy-Five Rheumatoid Arthritis Patients Studied Over Nine Years," Arthritis Rheum., Vol. 27, No. 8, Pp. 864–872, 1984, Doi: 10.1002/Art.1780270805.
[31] R. Ahmad And A. Zgair, "Immunological And Biological Manifestation Of Rheumatoid Arthritis Patient In Iraq," 2021.
[32] D. A. Guadagnin, L. V. Mazzali, T. L. Skare, And B. S. Kahlow, "Treating Rheumatoid Arthritis With Leflunomide Monotherapy Versus Combination Therapy With Methotrexate," Eur. J. Rheumatol., Vol. 8, No. 1, P. 12, Jan. 2021, Doi: 10.5152/Eurjrheum.2020.20113.
[33] C. A. Isnardi Et Al., "Pos0312 How Does The Presence Of Depression Impact On Disease Activity Scores In Patients With Rheumatoid Arthritis?," Ann. Rheum. Dis., Vol. 80, No. Suppl 1, Pp. 382–382, Jun. 2021, Doi: 10.1136/Annrheumdis-2021-Eular.1374.
[34] P. Vasanthi, G. Nalini, And G. Rajasekhar, "Status Of Oxidative Stress In Rheumatoid Arthritis," Int. J. Rheum. Dis., Vol. 12, No. 1, Pp. 29–33, Apr. 2009, Doi: 10.1111/J.1756-185x.2009.01375.X.
[35] J. M. Jou, "Erythrocyte Sedimentation Rate (Esr)," Lab. Hematol. Pract., Pp. 638–646, Aug. 2012, Doi: 10.1002/9781444398595.Ch49.

[36] M. Couderc Et Al., "Prevalence Of Renal Impairment In Patients With Rheumatoid Arthritis: Results From A Cross-Sectional Multicenter Study," Arthritis Care Res. (Hoboken)., Vol. 68, No. 5, Pp. 638–644, 2016, Doi: 10.1002/Acr.22713.

[37] H. R. Tawfeeq And J. M. J. Ali, "Assessment Of Liver Enzymes Activity In Patients With Rheumatoid Arthritis In Nineveh Province," Vol. 8, No. 2, Pp. 278–284, 2012.

[38] J. Kay Et Al., "Clinical Disease Activity And Acute Phase Reactant Levels Are Discordant Among Patients With Active Rheumatoid Arthritis: Acute Phase Reactant Levels Contribute Separately To Predicting Outcome At One Year," Arthritis Res. Ther., Vol. 16, No. 1, Pp. 1–10, Feb. 2014, Doi: 10.1186/Ar4469/Tables/6.

[39] W. J. Martin Et Al., "Older Age Of Rheumatoid Arthritis Onset And Comorbidities Correlates With Less Haq-Di And Cdai Response To Etanercept In The Radius 2 Registry," J. Clin. Rheumatol., Vol. 20, No. 6, P. 301, 2014, Doi: 10.1097/Rhu.0000000000000152.

[40] M. West, R. M. Poske, A. B. Black, C. G. Pilz, And H. J. Zimmerman, "Enzyme Activity In Synovial Fluid," J. Lab. Clin. Med., Vol. 62, No. 2, Pp. 175–183, Aug. 1963, Doi: 10.5555/Uri:Pii:0022214363900556.

[41] D. Daoussis Et Al., "Cardiovascular Risk Factors And Not Disease Activity, Severity Or Therapy Associate With Renal Dysfunction In Patients With Rheumatoid Arthritis," Ann. Rheum. Dis., Vol. 69, No. 3, Pp. 517–521, Mar. 2010, Doi: 10.1136/Ard.2008.105049.

[42] M. Farr, D. L. Scott, T. J. Constable,', R. J. Hawker,', C. F. Hawkins,' And, And J. Stuart3, "Thrombocytosis Of Active Rheumatoid Disease," Ann. Rheum. Dis., Vol. 42, Pp. 545–549, 1983, Doi: 10.1136/Ard.42.5.545.