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A chemical-pathological study to evaluate the role of vitamin D, ESR, and RF and the prevalence of rheumatoid arthritis and its correlation with disease activity in the centers of Dhi Qar Governorate

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Abstract
This study assesses the correlation between vitamin D levels, Erythrocyte Sedimentation Rate (ESR), Rheumatoid Factor (RF), and the prevalence of Rheumatoid Arthritis (RA) in Dhi Qar Governorate, exploring their association with disease activity. Sixty individuals with RA and a control group of twenty healthy individuals were analyzed for vitamin D3, ESR, and RF levels. Results indicated significant differences between the groups, with RA patients showing higher ESR and RF levels and lower vitamin D3 levels. The study underscores the potential influence of these biomarkers on RA disease activity and suggests the necessity for further research into their roles in RA management.

Keywords: Rheumatoid Arthritis, Vitamin D, ESR, RF, Disease Activity, Dhi Qar Governorate

Introduction
Rheumatoid arthritis (RA) and other autoimmune diseases have been associated with vitamin D deficiency. It is thought to have immunomodulatory and anti-inflammatory properties. The correlation between blood levels of Vitamin D and the severity of RA is a topic of great interest with potential treatment implications.

Materials and Methods
Study design
The study was carried out in collaboration with Dr. Adeeb Al-Azbaji's laboratories for advanced medical exams in the Shatra District of the Nasiriyah Governorate. Additionally, samples were collected from healthy persons between the dates of 2/2/2024 and 24/3/2024. The Imam Hussein Teaching Hospital's Laboratory Division has given it its approval. Sixty individuals with rheumatoid arthritis of both sexes were enrolled in the study; there were twenty-two females and eighteen men, aged 31 to 70. A control group of twenty (20) healthy individuals, ten (10) of whom were male and ten (10) of whom were female, was also contrasted with them. For both sexes, the age range was (31-70) years. As seen in Chart (1.2.1).

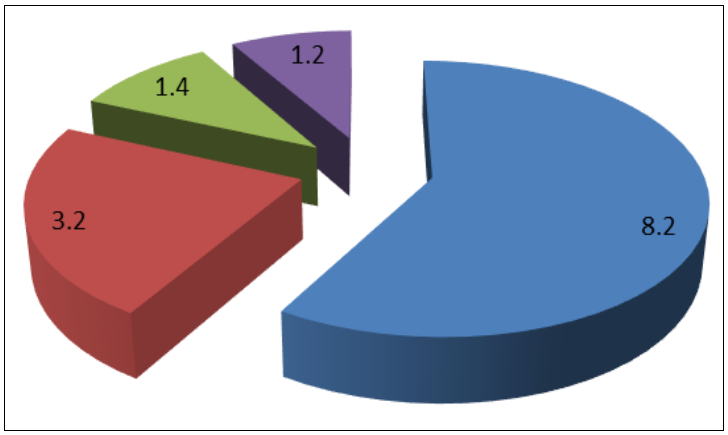

Chart 1: Outlines the criteria that were measured as well as the research sample's design.

Analytical statistics

At the beginning of the study, the Kolmogorov-Smirnov and Shapiro-Wilk tests were employed in evaluating the standard distribution of RF, ESR, and vitamin D3 measures. We used ANOVA and student t test to analyze the variables and discovered that there was no statistically significant variation in the parameters. The data outcomes were expressed as mean ± standard deviation (SD). The remaining parameters were given as a percentage of frequencies which were expressed for them. The Pearson bivariate correlation was the metric used to study the relationship between specified elements. An ROC curve for the each parameter was generated to determine the parameters' sensitivity and specificity, and AUC. The statistical software SPSS v. 25.0, Graph Pad Prism v. 6, and MedCalc were used in the last experiments.

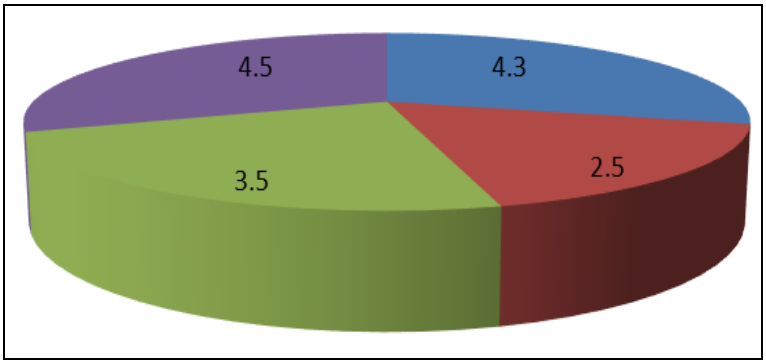

Chart 2: The Kolmogorov-Smirnov and Shapiro-Wilk tests

Results and Discussion

ESR, RF, and vitamin D3 in relation to study groups

The current study's results indicate that there are substantial differences (p<0.05) between the study groups and ESR, RF, and vitamin D3. Patients had higher mean ESR and RF levels (84.05±33.79 and 17.35±5.08) compared to healthy individuals (38.62±15.53 and 10.55±3.22), respectively. Conversely, the average vitamin D3 levels were lower in patients (21.00±9.68) compared to healthy individuals (32.40±13.45) (table 1 and chart 2) respectively.

Table 1; Evaluation of vitamin D3, RF, and ESR with study groups

Groups		N	Mean	SD	P value
ESR	Patients	40	84.05	33.79	p<0.001***
	Healthy	20	38.62	15.53	
RF	Patients	40	17.35	5.08	p<0.001***
	Healthy	20	10.55	3.22	
Vitamin D3	Patients	40	21.00	9.68	p<0.001***
	Healthy	20	32.40	13.45	

Chart 3: Evaluation of vitamin D3, RF, and ESR with study groups

According to the current study, RA patients had higher ESR levels than healthy individuals, and these findings were consistent with those of [1]. Additionally, the current result is consistent with other earlier studies that found that although ESR has significantly poorer specificity than CRP and RF [2], It is able to be raised in rheumatoid arthritis (RA) and used as a diagnostic test to identify the extent of the disease. Numerous investigations have discovered a link between elevated levels of CRP and ESR and improved radiographic and functional outcomes in individuals with rheumatoid arthritis (RA). Although CRP may have advantages in advanced stages of the disease by being less affected by factors such as immunoglobulin levels and anemia, increased ESR is more likely to be a more accurate indicator of these outcomes in early RA [4]. However, more than 40% of people with rheumatoid arthritis exhibit normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [5]. Furthermore, people who initially had elevated baseline levels may still have consistent readings even after their clinical state improves due to medication. It is worth noting that ESR measurements may also differ. In a sizable observational research using a practice-based registry that included more than 9,000 patients, it was shown that 26 percent of patients had inconsistent ESR and CRP values, while having active RA as determined by joint counts and global assessments. Mainly by modifying the expression of many genes in the kidneys, parathyroid glands, small intestine, and bone, vitamin D affects the metabolism of minerals and bone [6]. The activation of VDR by 1,25 (OH) 2D helps in maintaining an adequate calcium-phosphate product in the collagen matrix of the bone by promoting the absorption of calcium and phosphate in the intestines and the reabsorption of calcium in the renal tubules. 1,25 (OH) 2D directly impacts bone [7] by promoting the production of osteocalcin, the main non-collagenous protein in the skeleton, and activating the receptor activator of nuclear factor kappa-B-dependent bone resorption. Furthermore, 1,25 (OH) 2D directly inhibits the production of PTH, leading to a decrease in bone resorption. It also encourages osteocytes to create FGF-23, which in turn increases the excretion of phosphate in the urine [8].

Low levels of vitamin D3 were found in RA compared to health in the current investigation, and these findings were consistent with those of [9]. Consistent with our findings, a cross-sectional research conducted by Atwa *et al*. found that vitamin D deficiency was much more prevalent among individuals with RA [10]. Haque *et al*. conducted another retrospective research. Shown that vitamin D deficiency affected 61% of RA patients [11]. A prospective cohort research was carried out on 29,368 normal women in order to investigate the relationship between RA activity and vitamin D. They added vitamin D supplements to their meals. Over the course of the 11-year follow-up, the cohort only reported 152 occurrences of RA in these women, indicating a substantial decrease in the incidence of RA with higher use of vitamin D supplements [12]. Patients with RA are more likely to have vitamin D insufficiency, which may be one of the factors for RA to develop or worsen. Serum vitamin D levels in RA patients often decline as the illness progresses. To make sure that all RA patients are getting the necessary quantity of vitamin D, a thorough assessment of their vitamin D status is required. More investigation is necessary to fully use vitamin D's antiproliferative, immunomodulatory, and anti-inflammatory qualities in the treatment of a range of autoimmune rheumatic illnesses [13]. Acute phase response is most commonly measured with ESR markers because of its affordability, repeatability, and dependability. The RA is clinically active disease and strong relation between these two indicators and the clinical disease activity are observed. An earlier research 16 reported strong relationships between ferritin levels in serum with CRP, ESR and platelet count among RA patients, which are all indicators of disease activity. Furthermore, another investigation had released that the level of the soluble inflammatory molecule C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) is higher in the patients who had rheumatoid arthritis (RA) and that this level of the inflammatory markers is associated with the severity of the disease. Thus, indexes may be a part of the inflammatory processes that causes disease, and they can be used as signs of disease activity during the diagnosis and treatment of RA (Rheumatoid Arthritis). In the words of Sargin *et al*. (2018) [18], the data which were analyzed using the statistics method called linear mixed model have shown the increasing slopes of erythrocyte sedimentation rate (ESR) among RA patients. RA patients had higher ESR counts before starting of anti-TNF drug therapies, but they showed a big drop 3 and 6-months after the treatment. Erythrocyte sedimentation rate (ESR) test is a measurement of the sedimentation of red blood cells in a vertical tube containing plasma. The rate mainly corresponds to the level of fibrinogen. The latter is one of many indicators of true inflammation. The variables, e.g. the size, shape, and quantitites of erythrocytes, other components of plasma like immunoglobulins, altogether give rise to erythrocyte sedimentation rate (ESR). Different pathological conditions can raise the ESR level, among others renal failure, nephrotic syndrome, infection, malignancy, and tissue damage, and local or systemic inflammation. The fact that the ESR values are slightly higher in women than in men and that they tend to rise with age indicates that the condition may be more common among older women. Moreover, among the causes, there are a lot of them, like abnormal red blood cell shape, hyperleukocytosis, heart failure, and severe weight loss, that can result in low ESR. The ESR (Erythrocyte Sedimentation Rate) serves as a non-specific marker, and it is only natural that it does not always indicate inflammation. Nevertheless, ESR measurements remain a valuable diagnostic tool alongside clinical manifestations and newer serologic tests in the management of RA. The ACR/EULAR Classification Criteria for RA in 2010 are based on a number present that include ESR values of 18 or above. ACR has validated and placed two out of the six tools for disease activity in RA in its armamentarium. For the assessment of these parameters, the physician may use the Simplified Disease Activity Index (SDAI) and the Score for Disease Activity 28-ESR or CRP (DAS28-ESR or DAS28-CRP) 19, that include the examination of ESR and CRP levels. The ACR Guideline for Treatment of RA in 2015 (often used in the clinical setting), which endorses the use of indicators of activity, does not, however, specify preference for those based on laboratory measures over those that are not so based. Moreover, the guidelines don't provide specific directions for checking exactly these parameters in a full range of RA patients. Now, the guidelines are being updated, and the next release is scheduled in autumn of 2021. There is a common finding between CRP and ESR levels and positive outcomes in Radiographic and functional patient outcomes in Rheumatoid arthritis (RA). Although CRP Because of its decreased susceptibility to other variables like immunoglobulin levels and anemia, it may be more beneficial in advanced stages of the disease; nonetheless, increasing ESR is probably a more reliable prediction of these outcomes in early RA 22. However, more than 40% of individuals with rheumatoid arthritis exhibit normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [23]. Furthermore, people who initially had elevated baseline levels may still have consistent readings even after their clinical state improves due to medication. It is worth mentioning that ESR measurements may also differ. In a sizable observational research using a practice-based registry that included more than 9,000 patients, it was shown that 26 percent of patients had contradicting erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, despite showing active rheumatoid arthritis (RA) based on joint counts and overall assessments. Rheumatoid factors (RF) are linked to rheumatoid arthritis (RA) as well as other autoimmune and non-autoimmune illnesses. A prevalence rate of 4% has been seen in young individuals, healthy adults, and the elderly for the condition known as 25. Rheumatoid factors (RF) are autoantibodies that specifically target the Fc region of IgG. The rheumatoid factor is a dependable diagnostic and prognostic test for rheumatoid arthritis. Until recently, the primary serologic criterion used to diagnose RA was the presence of high levels of IgM RF, which is quite specific for diagnosing RA in cases of long-term polyarthritis 26. The higher prevalence of RF-positive individuals compared to RF-negative patients is attributed to the presence of pentameric IgM antibodies that specifically bind to the Fc region of human immunoglobulin G. This binding leads to an elevation of RF levels in autoimmune disorders or inflammation. Given that rheumatoid arthritis is characterized by inflammation, Rheumatoid arthritis is characterized by inflammation, hence the level of this protein will be elevated in individuals without any health issues. Choices, according to the studies that were looked at. Anti-CCP antibody titers are greater in the blood of individuals with erosive RA, and several

studies have revealed a direct correlation between anti-CCP antibodies in the serum and joint damage. A prior study found that whereas 52.9% of RA patients tested positive for RF, all RA patients tested positive for ACCP antibodies [28]. The pathophysiology of autoimmune illnesses, such as RA, has been repeatedly linked to vitamin D, according to literature. The authors, Tracy *et al*. (2017) [30], consider RA to be caused by the interactions between some environmental factors and an individual's genetic predisposition. Consequently, defects in key immune system pathways can result which leads to impairment of both innate and adaptive responses and thus put balanced autoimmunity and endurance at risk. Vitamin D may be a protective factor for RA, but smoking which is one of the major environmental risk factors still remains as a significant factor. On the downside, people who suffer RA may have to decrease the amount of time they devote to Outside activities as mobility is impaired. And thus, with their lesser exposure to sunlight as the primary source of vitamin D, they may also experience deficiencies of other necessary vitamins, which will worsen their condition. The main targets of the treatment of RA are to decrease disease activity and improve joint functionality continuously. Regular monitoring of blood levels of 25-OHD3 is also essential for the treatment. As a result, immediate treatment and diagnosis can help the patients to experience a drop in disease activity by 30%, which can then enable them to have a better quality of life. A research has been published that, for a period of five years, the people who took vitamin D supplements with or without omega-3 fatty acid had shown a 22% decrease in the chances of autoimmune disorders. On the flip side however, the intake of omega-3 fatty acid supplements along with or alone with vitamin D, however, saw a 15% reduction in the occurrence of autoimmune disease, though the reduction wasn't statistically significant.

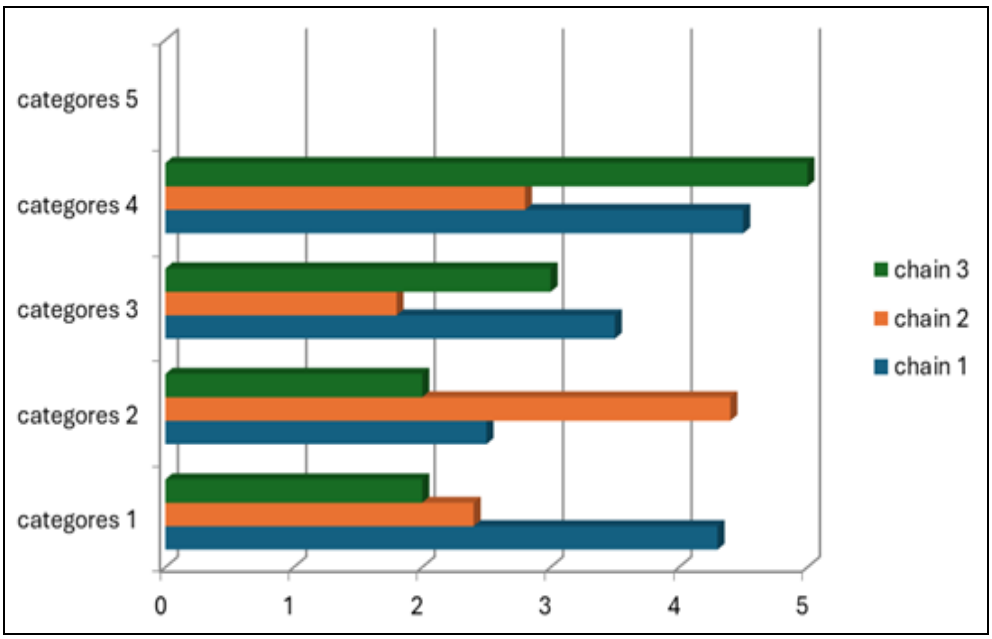

Chart 4: Distribution of categories according to the decrease and increase of autoimmune diseases.

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