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Determine the predictive role of immunoglobulins (IgG and IgM) markers and complements proteins (C1 and C5) in pathogenesis rheumatoid arthritis in Iraqi patients

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Abstract

id arthritis (RA) can be defined as debilitating, chronic disease characterized by systemic symptoms such as fatigue, anemia, and osteoporosis in addition to joint deterioration as well as articular inflammation. Women make up approximately 70% of RA patients. RA might strike 1–3% of women at some point in their lives. Between the ages of 30 and 80 years. It can start at any age. Specify the predictive significance regarding complement proteins (C1 and C5) and immunoglobulins (IgG and IgM) markers in the pathogenesis of RA in Iraqi patients. Methods and materials: The current investigation was conducted from February 6, 2024, until November 8, 2024, at Hussein Medical City in Karbala. Thirty blood samples have been collected from healthy individuals and used as a control group for RA. A total of sixty blood samples have been collected from patients who visited Imam Hussein Medical City. Healthy participants and patients were between the ages of 20 and 73. Using a single radial immune assay, immunoglobulins IgG and IgM as well as complement proteins C1 and C5 were identified.

Results: RA patients' age groups and gender percentages differed significantly ($P \leq 0.05$). Patients who were female had a higher percentage (65%) in comparison with males (35%). Those over forty had the highest percentage (83.33%) compared to those under forty who had the lowest percentage (16.67%). The mean (IgG) levels in the patients were (511.32±181.22) and the (IgM) levels were (83.34±30.21), which is significantly higher compared with the control (335.11±113.15) and (37.32±13.32), respectively, with significant differences (less than 0.05). The patients had on average higher levels of (C1) (83.62± 36.21) and (C5) (9.34 ± 24.32) compared to the control (37.12 ± 12.63) and (24.32 ± 9.34), respectively, with a statistically significant difference below the level of ($P \leq 0.05$).

Conclusions: an increase in the incidence of rheumatoid arthritis in females more than males, as well as with increasing age, and an increase in the levels of Complement system proteins (C1 and C5) and immunoglobulins (IgG and IgM) in Iraqi patients with rheumatoid arthritis.

Keywords: C1 and C5 complement, Immunoglobulins IgG and IgM, Rheumatoid arthritis

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تحديد الدور التنبؤي للجلوبيولينات المناعية (IgG) و (IgMوبروتينات المتمم (C1) و (C5في امراضية التهاب المفاصل الروماتويدي في المرضى العراقيين.

حسين سعيد المفرجي [1]

المستخلص

يمكن تعريف التهاب المفاصل الروماتويدي بأنه مرض مزمن موهن يتميز بأعراض جهازية مثل التعب وفقر الدم وهشاشة العظام بالإضافة إلى تدهور المفاصل وكذلك التهاب المفاصل. في الواقع تشكل النساء حوالي 70 ٪ من مرضى التهاب المفاصل الروماتويدي، قد يصيب التهاب المفاصل الروماتويدي 1-3 ٪ من النساء في مرحلة ما من حياتهن. بين سن 30 و80 سنة. ويمكن أن يبدأ في أي عمر. أجريت الدراسة لتحديد الأهمية التنبؤية لبعض الغلوبولينات المناعية (IgG) و (IgMوبعض بروتينات نظام المتمم (C1) و (C5في عينة من المرضى العراقيين المصابين بالتهاب المفاصل الروماتويدي المواد وطرائق العمل: تم إجراء التحقيق الحالي من 6 فبراير 2024 حتى 8 نوفمبر 2024 في مدينة الحسين الطبية في كربلاء. تم جمع ثلاثين عينة دم من أفراد أصحاء واستخدمت

انتساب الباحث

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معلومات البحث

تأريخ النشر: تشرين الاول 2025

كمجموعة سيطرة. تم جمع ستون عينة دم من المرضى الذين زاروا مدينة الإمام الحسين الطبية. كان المشاركون والمرضى الأصحاء تتراوح أعمارهم بين 20 و73 عاما. تم تحديد مستويات C1) و (C5و IgG) و (IgM باستخدام فحص مناعي شعاعي المنفرد. النتائج: اختلفت الفئات العمرية لمرضى التهاب المفاصل الروماتويدي والنسب المئوية بين الجنسين بشكل كبير (أقل من 0.05) وفقا لبيانات هذا البحث. كانت نسبة المرضى من الإناث أعلى (65٪) مقارنة بالذكور (35٪). أولئك الذين تزيد أعمارهم عن 40 عاما لديهم أعلى نسبة (83.33٪) مقارنة بأولئك الذين تقل أعمارهم عن 40 عاما والذين لديهم أدنى نسبة (16.67٪). اما فيما يتعلق بمتوسط مستويات الغلوبولين المناعي (IgG) في المرضى كانت (181.22±511.32) اما الغلوبولين المناعي(IgM) كانت (30.21±83.34) وهي أعلى بكثير مقارنة مع السيطرة 113.15±335.11)) و (13.32±37.32) على التوالي، مع وجود فروق ذات دلالة إحصائية (أقل من 0.05). كانت لدى المرضى متوسط مستويات أعلى من البروتين المتمم (83.62± 36.21) (C1) والبروتين المتمم (9.34 ± 24.32) C5)) مقارنة بالسيطرة (12.63 ± 37.12) و (9.34 ± 24.32) على التوالي، مع اختلاف كبير ذو دلالة إحصائية تحت مستوى (أقل من 0.05). الاستنتاجات: ارتفاع نسبة الإصابة بالتهاب المفاصل الروماتويدي عند الاناث أكثر من الذكور وكذلك مع تقدم العمر، وزيادة في مستويات بروتينات نظام المتمم C1) و (C5والغلوبولينات المناعية IgG) و (IgMفي المرضى العراقيين المصابين بالتهاب المفاصل الروماتويدي.

الكلمات المفتاحية: بروتينات المتمم (C1 و(C5، الغلوبولينات المناعية (IgG و((IgM، التهاب المفاصل الروماتويدي

1. Introduction and literature review

1.1. Rheumatoid Arthritis

About 1% of people have RA, which is the most prevalent chronic form of inflammatory arthritis. It is caused by complex interactions between the environment and genes, which culminate in a symmetrical pattern regarding synovial inflammation as well as a breakdown of immune tolerance [1]. There are various pathways that both regulate and promote inflammation and matrix destruction, which include cartilage and bone degeneration. Immunoglobulin IgA, IgG, and IgM concentrations are higher in RA patients compared to it in the suitable controls (1–3). Increased immunoglobulin concentrations clearly represent the underlying immunological process regarding RA in one way or another, as values tend to decrease after therapy with disease-modifying anti-rheumatic medications [2]. Complement system dysregulation, which is essential for numerous immune innate and adaptive functions, is a major contributor to the pathogenesis regarding various autoimmune diseases. RA can be defined as a synovitis- and extra-articular manifestation-causing chronic inflammatory disease. As a systemic disease, RA could cause extra-articular symptoms such as skin, ocular, pulmonary, cardiac, and neurological problems along with articular involvement. Joint invasion through the immune system results from the actual process. These immune system responses impact cartilage as well as joint capsule, causing inflammation and spreading regarding the joint capsule. Even though the exact RA etiology is still unknown, it is believed to have been caused by a mix of genetic and immune variables, and numerous other autoimmune-initiating factors [2].

1.2 Epidemiology

With a significant burden of functional disability, RA is a significant public health issue. The incidence was between 0.2 to 0.5% in the Middle East, which is comparable to that of the adjacent Arab nations, including Egypt, Saudi Arabia, and Oman, in Iran and Türkiye. Higher prevalences of 1% and 0.7%, respectively, have been found in an Iraqi study and a more recent Kuwaiti investigation. In Babylon, Iraq, the prevalence of RA rose from 1.60% in 2001 to 3.02% in Babylon

–Iraq 2011 [3]. There is a changeable feminine predominance in the RA gender distribution. According to the Oslo RA record, females are three to four times more likely than males to have it [4].

1.3 Etiology

The etiology regarding RA is still unknown, however it is caused by a combination of environmental and genetic factors. RA is linked to genetic factors in twin studies; concordance rates for monozygotic twins range from 15 to 30%, while those for dizygotic twins are 5%. The major histocompatibility complex (MHC-II), as well as CD4T cells of RA patients exhibit intracellular signaling, repertoire, and aging problems. Thus, it is possible that inflammation has a role in chronic RA development [5]. The idea that RA might be caused by primary inflammation as well as RA-related autoantibody production (which is also known as anti-citrulline protein/peptide antibodies) in lungs was made possible by the theory that pollution and smoking raise the risk of developing RA.

1.4 Pathophysiology

Active RA can be characterized by swelling, synovitis, and joint destruction, which are caused by complex inflammatory as well as autoimmune processes involving elements of adaptive and innate immune systems. The genes and environment work together to cause a vulnerable person to become intolerant to self-proteins containing citrulline residue. Antibodies against citrullinated proteins are produced by RA patients. Peptidyl arginine deaminase post-translationally modifies arginyl residues for producing citrulline, an amino acid. Those antibodies are known as anti-citrullinated protein antibodies (ACPA) [6].

1.5 Risk Factors Related to RA

A. **Age:** RA incidence and prevalence rise with age. The peak incidence of RA in patients occurs in most parts of the world between ages 65 and 75 for men and between ages 55 and 64 for women. As people age, the risk rises [7].
B. **Gender:** Hormones are thought to play a part in the 2-3 times higher risk of RA in women than in men. This is supported, in part, by studies that indicate the disease frequently strikes women following significant changes in their hormone levels. Early menopause is one of the factors linked to elevated risks for RA [8].
C. Smoking
D. Family History
E. Obesity
F. Infection
G. Consumption of Alcohol

1.6 Relation of RA with immunological proteins

1.6.1 Immunoglobulin

Glycoproteins called immunoglobulins (Ig), or antibodies are made by plasma cells. Certain immunogens, like the bacterial proteins, instruct B cells to develop plasma cells. Protein-producing cells that are referred to as plasma cells play a role in humoral immune responses towards cellular antigens, synthetic substances, chemicals, viruses, fungi, parasites, and bacteria. Approximately 20% of protein in plasma is made up of immunoglobulins [9].

Autoantibodies that are specific enough to be used as diagnostic as well as prognostic markers

regarding RA are linked to the disease. The two closely related antibodies, antikeratin antibody (AKA) and antiperinuclear factors, as well as rheumatoid factor (RF), were demonstrated to occur before the development of clinical RA. The time interval between collecting specimens and the onset of illness determines the prevalence regarding positive reactions for such antibodies in specimens obtained prior to the onset of illness; if the interval is short, the prevalence is the same as in the disease that has already been diagnosed. Numerous other autoantibody systems, either known or unknown, may also signal the development of RA [10].

1.6.2 Complement proteins.

In defense against foreign pathogens like viruses and bacteria, complement cascade, which is a component of the innate immune system, is significant. The complement cascade involves more than forty proteins, and complement makes up over 10% of circulating protein [11]. Complement disease activation has a role in the pathogenesis of several inflammatory and autoimmune diseases, like RA. Numerous triggers seen in the inflammatory joint, including exposed cartilage proteins like dying cells, fibromodulin, and autoantibodies that have been deposited, could start the classical pathway. Through the activation of complement B cells that produce autoantibodies, which subsequently form immune complexes, contribute to the pathogenesis of RA. Anaphylatoxin C5a seems to be the primary complement activation product that causes tissue damage in RA. However, opsonization with C3b fragments and membrane attack complex deposition are significant. New therapeutic methods to the treatment of human RA are encouraged by the success of complement inhibition in experimental models that have been described thus far [12].

2. Materials and methods

2.1 Samples collection

The current investigation was conducted from February 6, 2024, until November 8, 2024, at Imam Hussein Medical City in Karbala. A total of sixty blood samples have been collected from sixty patients with RA who visited Hussein Medical City, and the consultant physician at the advisory unit at Hussein Medical City Hospital performed an examination and diagnosis on them. To create a control group, a total of thirty blood samples have been collected from people who were otherwise healthy. Healthy participants and patients were between the ages of 20 and 73.

2.2 Method: Five milliliters of human blood were spun for five minutes at 3000 rpm to separate the serum. Using a single radial immune assay, immunoglobulins IgM and IgG as well as complement proteins C1 and C5 were identified.

2.2.1 Principle: Immunoglobulins (IgM, IgG) and complement proteins C5 and C1 levels were measured using this test. It uses the diameters regarding the sedimented circles surrounding the antigen samples to measure the amount of antigen as well as differentiate it from the antibody suspended in the middle of the agarose gel containing particular antibodies.

2.2.2 Procedure:

A. After being extracted, the samples have been allowed to sit at room temperature for fifteen minutes.

B. To allow the evaporation of condensed water droplets in the pits, the plate's cover was taken off, set on a fixed stand, and left at room temperature

for a short while.

C. Five microliters of samples were introduced to each pit in equal amounts, and the pits were not stirred until the samples were absorbed.

D. After covering the plate and moving it to the moist chamber, it was left for 96 hours for IgM and 72 hours for IgG.

E. The sedimentation diameters have been measured using a magnifying lens, and the results were put in comparison with the company's standard tables, which can extract the quantities of immunoglobulins (IgM and IgG).

2.3. Statistical analysis:

The student t test has been utilized in order to assess the significance regarding the differences (comparison of two groups), and the parameters that passed the normality tests (non-significant difference) have been displayed as Mean ±SD. Pearson-Chi-square test revealed significant differences in frequency for the other characteristics (age and gender groups), which had appeared as percentage numbers. There was a significant measurement of P ≤0.05. SPSS v. 23.0 was used to examine our data.

3. Results and discussion:

3.1 Demographic features of patients

RA patients' age groups and gender percentages differed significantly (p less than 0.05), according to the study's data. Patients who were female had a higher percentage age (65%) compared to males (35%). Those over forty had the highest percentage (83.3%), while those under forty had the lowest (16.7%) as shown in Table (1) and Figure (1).

Table (1): Percentage and frequency of age and gender groups of patients

Parameter		patients n. 60	percentage%	*P value*
Gender	**Male**	**21**	**35 %**	***P <0.001******
	Female	**39**	**65%**	
Age groups (years)	**≤ 40**	**10**	**16.7%**	***P <0.01*****
	> 40	**50**	**83.3%**	

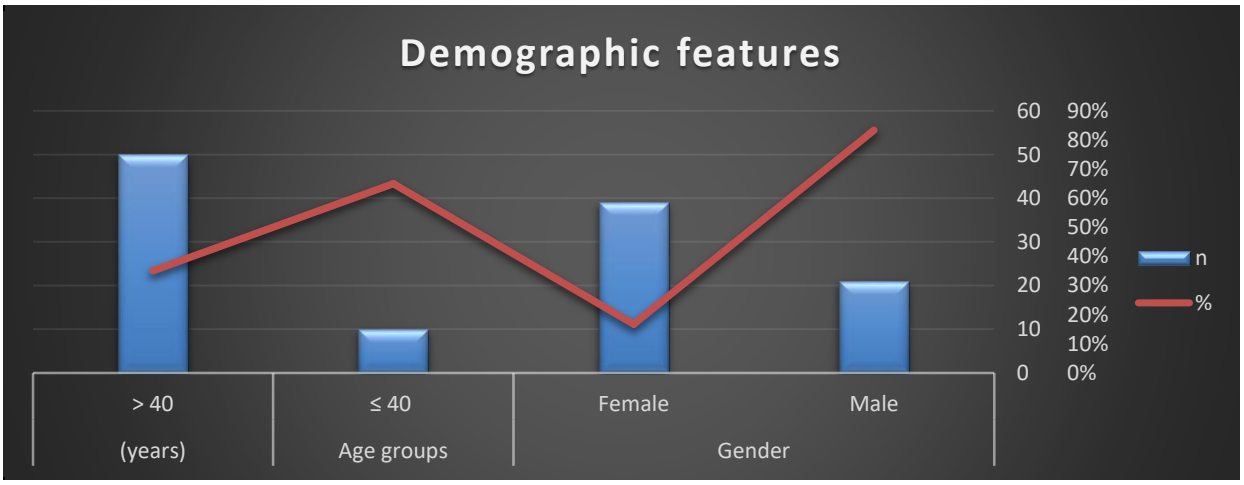

Figure (1): Percentage of age and gender groups of patients with RA

The findings show that RA is more common in females compared to males, and this is because of a variety of factors, such as female sex hormones like progesterone and estrogen, which are anti-inflammatory and play a role in inflammation. These findings are consistent with [13], who found that RA is more common in females compared to males. The existence of genetic variables (related to X chromosome) and sex hormones might also contribute to the considerable number of instances of RA in females, according to [14]. There is a fluctuating feminine predominance in RA gender distribution. According to the Oslo RA record, females are three to four times more likely than males to have it. Women were five times more likely than males to have RA overall, according to a meta-analysis of the disease's prevalence in patients in low- to middle-income nations [4]. According to the current research, the prevalence of RA rises after the age of forty because of immune system impairment and chronic diseases. The symptoms of polymyalgia rheumatica, which include stiffness and discomfort in the shoulder as well as hip joints in the morning, are like those of RA in older adults. It can be difficult to tell the difference between the two diseases, which both affect the elderly [15].

3.2 Mean levels of IgM and IgG within study groups

The current study's findings demonstrated a significant difference ($p<0.001$) between the study groups' mean levels of immunoglobulins IgM and IgG. Compared to controls (335.11±113.15 and 173.32±37.32), patients had the highest mean levels of these immunoglobulins, IgG, and IgM (511.32±181.22) and 83.34±30.21), respectively as shown in Table (2) and Figure (2).

Table (2): comparative of mean levels of IgM and IgG between study groups

Parameters		Patients(n=60)	Controls(n=30)	*P* value
IgG (mg/dl)	Mean	**511.32**	**335.11**	***P <0.001*****
	SD	**181.22**	**113.15**	
IgM (mg/dl)	Mean	**83.34**	**37.32**	***P <0.001*****
	SD	**30.21**	**17.32**	

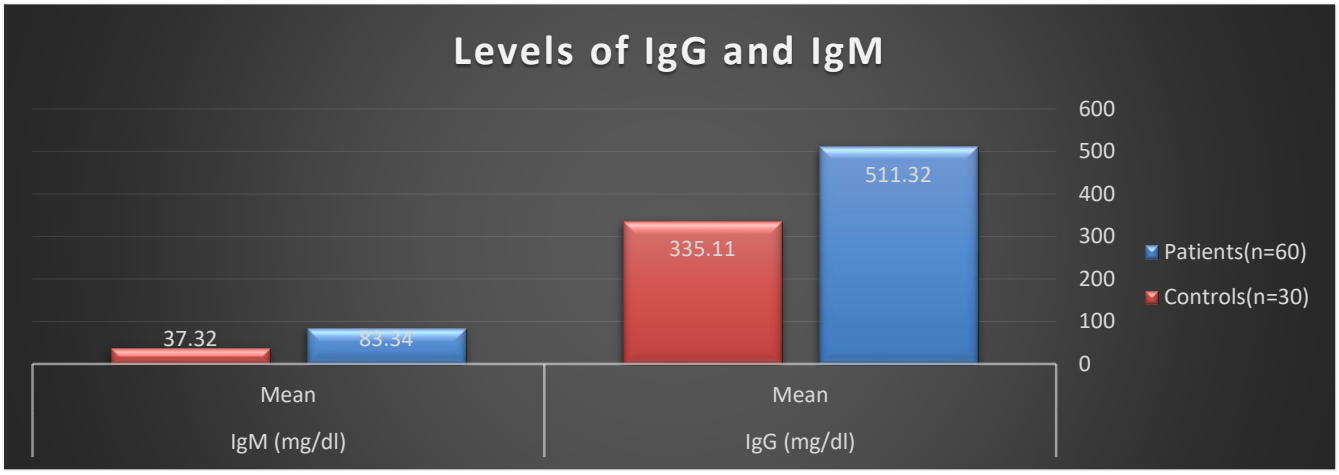

Figure (2): mean levels of immunoglobulins IgG and IgM with study groups

Because of autoantibodies that target several self-proteins, RA is an autoimmune disease that causes joint inflammation. Increased IgM antibody levels that specifically bind to IgG are seen in many patients with poor prognoses. RF is the term used to describe such autoreactive antibodies [16]. As a class of IgG that could bind the Fc region of IgG, RF was one of the first and most extensively researched autoantibodies. IgM-RF is the most clinically utilized RF isotype to predict disease prognosis in RA, a chronic autoimmune disease characterized by persistent synovitis as well as T and B cell infiltration in the joint's synovial membrane. According to [17], the biological role of RF in disease pathogenesis is still unknown. RA is associated with RF antibodies. However, research on the occurrence and generation of RFs has demonstrated that healthy people could have circulating RFs. Remarkably, RF antibodies that were investigated in RA patients exhibit high antigen-binding affinity as well as specificity for IgG obtained throughout affinity maturation and are distinguished by significant somatic mutation [17]. Conversely, RFs in healthy people closely resemble natural autoantibodies, which are a kind of autoantibodies expressed by germline variable gene segments and have limited epitope specificity. Because of this, most naturally occurring autoantibodies are polyreactive and have a poor affinity for attaching antigens to self-molecules. Likewise, RFs in healthy people do not exhibit isotype switching or affinity maturation, indicating a low antigen-binding affinity for IgG [18].

Understanding the pathophysiology regarding RA development is impacted by variations in patterns of autoantibody isotype elevations. These include knowing what causes early autoantibody elevations as opposed to what causes later increases in autoantibody levels and a shift to clinically apparent RA, as well as the way that pre-RA endotypes might affect phenotypes following a RA diagnosis [19].

According to prior research, variations in RA-autoantibody levels indicate the degree of immunosuppression rather than DAS or long-term therapy response. This implies that whereas existing medicines can alter autoantibody levels, doing so has little therapeutic significance [20].

According to earlier findings, autoreactive IgM antibodies that recognize IgG are essential for maintaining IgG homeostasis, and an imbalance between IgM-mediated IgG stabilization as well as degradation may affect the development and course of autoimmune diseases. Therefore, a treatment strategy for autoimmune diseases involving autoreactive IgG may be to restore this balance utilizing low-affinity anti-IgG IgM [18].

3.3 Mean levels of C5 and C1 complements within study groups.

The current study's findings indicated that the mean levels of C5 and C1 complement with study groups differed significantly (p less than 0.05). In comparison to controls (37.12±12.33 and 9.34±2.44), patients had the greatest mean levels of such C1 and C5 complement (83.62± 36.21 and 24.32±9.34, respectively) as shown in (Table 3 and Figure 3).

Table (3): comparative of mean levels of C5 and C1 complement between study groups

Parameters	Patients(n=60)	Controls(n=30)	p value

C1 complement (mg/dl)	Mean	83.62	37.12	***P* <0.001****
	SD	36.21	12.33	
C5 complement (mg/dl)	Mean	24.32	9.34	***P* <0.001****
	SD	**9.34**	**2.44**	

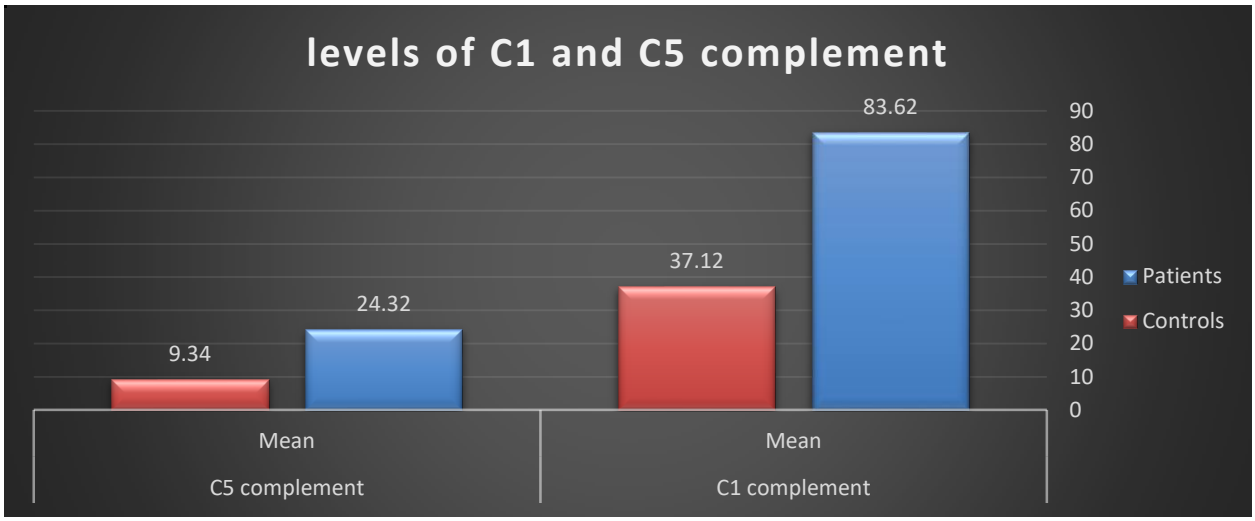

Figure 3 comparative of mean levels of C1 and C5 complement between study groups

According to the current research, RA patients had higher C5 and C1 levels when compared to controls, which is consistent with findings by [12]. Prominent C4 and C3 complement levels in RA patients might indicate pro-inflammatory status and be a risk factor for anti-TNF treatment [21]. According to the authors, the complement system is systemically active in RA patients and might play a significant role in the pathogenesis of RA in the progression from an at-risk condition to a disease with clinical symptoms. It is noteworthy that the complement system is a component of disease processes that are being studied more. At various disease stages (in subjects at risk and subjects with established disease), in the case where initial changes in the synovial membrane occur, there are opportunities to modify complement activation as well as effector pathways with inhibitors. For instance, the synovial membrane experiences the first joint alterations in RA, which results in synovitis. The primary site of inflammatory processes is synovium, which can cause the destruction of nearby cartilage and bone if left untreated. It was hypothesized that an acute inflammatory change takes place at an exceedingly early stage, yet that if the process continues, chronic inflammation that is localized in the synovium will replace it [12]. Prior research has confirmed the role of the immune system in the pathogenesis of RA, indicating that higher C3 levels contribute to the disease's severity and that TNFα levels might be one of the useful biomarkers [23].

Another research provided insight into a potential novel therapy approach that targets proptosis-mediated persistent inflammatory cytokine release and demonstrated a significant role for IL-6 in promoting pentraxin 3 (PTX3) plus C1q-mediated pyroptosis in RA (Wu et al., 2020). In RA as well as spondylar arthritis, [20]. Show that complement C3 is linked to the concurrently elevated prevalence of cardiometabolic risk factors. Therefore, in these rheumatic conditions,

complement C3 ought to be regarded as a helpful indicator of disease activity and insulin resistance.

4. Conclusions:

1. High prevalence of RA in females than males.
2. Increase occurrence of RA after 40 years.
3. Increased immunoglobulins IgG and IgM levels in patients with RA.
4. Increased levels of C1 and C5 complements in patients with RA.

5. Recommendations

1. Detection levels of rheumatoid factor (RF) and Anti-CCP antibody in patients who have RA.

2. Comparative levels of immunoglobulins IgG and IgM as well as to C2 and C3 complements in RA patients before and after treatments.

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