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Original Research

The Relationship between Obesity and Rheumatoid Arthritis

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Abstract

Objectives: In recent years, both the prevalence of obesity and the incidence of RA have been rising. Our aim was to assess the association between overweight or obesity and rheumatoid arthritis (RA). Obesity is arguably the most worrying current public health crisis because it is both extremely common and leads to numerous adverse health outcomes. It is not, therefore, surprising that obesity has important implications for rheumatoid arthritis (RA) and its management. Obesity is an inflammatory state, with excess visceral adiposity being associated with elevation in systemic cytokines, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) . This observation has led to the hypothesis that obesity may drive and contribute to the development and perpetuation of systemic inflammatory conditions including inflammatory arthritis. In support of this concept, there appears to be a strong relationship between metabolic obesity, psoriasis, and psoriatic arthritis, with a significant reduction in the risk of psoriasis among those losing weight after bariatric surgery. A similar study, however, found no reduction in the risk of RA in patients undergoing bariatric surgery. The measurement of inflammatory biomarkers such as ESR and CRP is another objective way to assess disease activity, but these biomarkers may also be subject to bias. We showed that patients with RA who were obese were more likely to have elevated inflammatory markers, similar to what is seen in the general population. The influence of obesity on inflammatory markers has important implications for the interpretability of these measures as a disease activity measure, particularly among obese women

Keywords: ESR and CRP, Obesity, Arthritis, Plausible

Introduction

Obesity is a controversial risk factor for rheumatoid arthritis (RA). A link between obesity and RA is plausible, since biologic mechanisms of inflammation are present in adipose tissue, and these may be linked to chronic systemic inflammation (Eriksson, et al.,2019). In fact, important advances in understanding of adipokines have elucidated their crucial role as mediators of inflammation and immune response, which are implicated in the pathophysiology of rheumatic diseases, such as RA (Cutolo, et al.,2014). While several studies have examined the potential influence of obesity on the development of RA, the results have been inconsistent. Two large United States studies found no association between obesity and the risk of RA, while 2 European studies found significant, sizable risks for RA associated with obesity (i.e., odds ratios of 1.6 and 3.7) (Naranjo, et al.,2015). Reasons for the inconsistencies include the low prevalence of obesity in studies performed >15 years ago, and lack of power to detect a modest risk for RA associated with obesity. If obesity confers even a modest risk for development of RA, it could have a large impact on the incidence of this disease, given the epidemic increases in the prevalence of obesity in recent years (Armstrong et al.,2020).

Following a 4 decade period of decline, the incidence of RA has been on the rise since 1995 (Stavropoulos-Kalinoglou,2011). The cause of this recent rise in incidence is unknown. It is most likely that changes in environmental risk factors account for the rising incidence, because genetic factors do not change so quickly in populations.

Aim of the study:

In recent years, both the prevalence of obesity and the incidence of RA have been rising. Our aim was to assess the association between overweight or obesity and rheumatoid arthritis (RA).

The evaluate the relationship between vitamin D and RA, as well as the relationship between vitamin D and RA disease activity.

2.1 - Autoimmune diseases

are a family of more than 80 chronic, and often disabling. illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. While many of these dis- eases are rare, collectively they affect 14.7 to 23.5 million people in this country, and - for reasons unknown - their prevalence is rising. Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment.

Autoimmune disease, then, refers to the harmful effects of autoantibodies. Many such antibodies have been described, antithyroid antibodies, anti-platelet antibodies and antibodies to glomerular basement membrane (GBM) being a few examples.[Vidal et al.,2015]

Unfortunately, in clinical practice, autoimmunity has assumed a wider meaning and has been extended to include certain immune complex diseases, such as polyarteritis nodosa (PAN) and systemic lupus erythematosis (SLE). In these, injury is thought to occur at sites where complexes of antigen and anti- body are deposited in the walls of blood vessels.

Even more confusing is inclusion of diseases such as scleroderma and polymyositis under the umbrella of autoimmunity, as their pathogenesis is uncertain; some have suggested they are caused by cell-mediated autoimmunity, but this is controversial.[García-Poma A,2019]

2.2-Rheumatoid Arthritis

elaborated as Rheumatoid Arthritis is a systemic chronic inflammatory condition that might affect numerous organs and tissues in a human body, but mainly it attacks the synovial joints. These methods result in the inflammatory synovitis (synovium) response. Factors that lead to an increase in the risk of rheumatoid arthritis are age, sex, family history, smoking, obesity, and exposure to pollutants. RA holds the ability to put a person at a higher risk of developing other medical conditions if it is not controlled timely. A syndrome named carpal tunnel is another common condition found in people suffering from rheumatoid arthritis.[Stavropoulos-Kalinoglou,2018] Trauma, infection, smoking cigarettes are some of the examples of external triggers which can trigger the reaction of the auto-immune system, which results in chronic joint

inflammation and synovial hypertrophy in addition to a potential of other manifestations, which will be theorized for going on in people prone genetically.[Baker JF,2019] The pathological process of the disease usually results in destructing the articular cartilage as well as the joints ankylosis

2.3-Symptoms of Rheumatoid Arthritis

Common symptoms of rheumatoid arthritis include:

RA affects people differently. In some people, RA starts with mild or moderate inflammation affecting just a few joints.[Aletaha D,2020]

Rheumatoid arthritis can cause other medical problems, such as:[van Riel PL,2019]

- Joint pain at rest and when moving, along with tenderness, swelling, and warmth of the joint.
- Joint stiffness that lasts longer than 30 minutes, typically after waking in the morning or after resting for a long period of time.
- Joint swelling that may interfere with daily activities, such as difficulty making a fist, combing hair, buttoning clothes, or bending knees.
- Fatigue – feeling unusually tired or having low energy-
- Occasional low-grade fever
- Loss of appetite

2.4-Diagnosis

Getting an accurate diagnosis as soon as possible is the first step to treating RA effectively. A doctor with specialized training in treating arthritis (called a rheumatologist) is the best person to make a correct diagnosis, using medical history, a physical examination and lab tests.[Bruce B,2018]

Medical history. The doctor will ask about joint symptoms (pain, tenderness, stiffness, difficulty moving), when they started, if they come and go, how severe they are, what actions make them better or worse and whether family members have RA or another autoimmune disease.

Physical examination. The doctor will look for joint tenderness, swelling, warmth and painful or limited movement, bumps under the skin or a low-grade fever.

Blood tests. The blood tests look for inflammation and blood proteins (antibodies) that are linked to RA:

- Erythrocyte sedimentation rate (ESR, or "sed rate") and C-reactive protein (CRP) levels are markers for inflammation. A high ESR or CRP combined with other clues to RA helps make the diagnosis.
- Rheumatoid factor (RF) is an antibody found (eventually) in about 80 percent of people with RA. Antibodies to cyclic citrullinated peptide (CCP) are found in 60 to 70 percent of people with RA. However, they are also found in people without RA.

Imaging tests. RA can cause the ends of the bones within a joint to wear down (erosions). An X-ray, ultrasound, or MRI (magnetic resonance imaging) scan can look for erosions. [Van der Heijde,2019]

2.5-Treatments

Although there is no cure, there are many treatments available to help reduce symptoms of RA. A doctor may prescribe the following medications to provide relief of symptoms and improve joint function in the spine:[Younis KR,2017]

Non-steroidal antiinflammatory medications (NSAIDs). This class of medication reduces inflammation. NSAIDs include ibuprofen (Advil, Motrin) and celecoxib (Celebrex).

Disease-modifying antirheumatic drugs (DMARDs). This class of medication decreases inflammation and slows the progression of RA. DMARDs include methotrexate (Rheumatrex, Trexall, Otrexup, Rasuvo), leflunomide (Arava), hydroxychloroquine (Plaquenil), and sulfasalazine (Azulfidine).

Biologic agents (sometimes referred to as biologic DMARDs). This class of medication suppresses certain substances in the body that cause inflammation and joint damage involved in RA. Biologic agents include abatacept (Orencia), adalimumab (Humira), anakinra (Kineret),

certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi).

In rare cases, surgery may be required when RA has greatly affected the joints in the spine. If the deterioration of the joints in the spine has led to compression of the spinal cord or instability of the spine, the goal of surgical intervention is to decompress the spinal cord and stabilize the spine.

2.6-The relationship between vitamin D and RA

Vitamin D is a secosteroid hormone involved in bone and calcium metabolism. It is involved in the regulation of calcium homeostasis, as it regulates calcium absorption from the gastrointestinal system . The hormone is synthesized in the skin by the action of ultraviolet irradiation . Vitamin D has extraskeletal effects as well. The nonclassical actions of vitamin D are currently under discussion. Vitamin D has been found to have immunomodulatory actions. Vitamin D deficiency has been shown to be correlated with the appearance of autoimmune diseases, such as diabetes mellitus type 1 and multiple sclerosis [Giles et al.,2020].

Rheumatoid arthritis (RA) is an autoimmune disease of unknown aetiology . Both T and B lymphocytes are involved in the pathogenesis of the disease. The role of T lymphocytes as well as that of B lymphocytes in the pathogenesis of RA has been further proved by the therapeutic efficacy of methods affecting both T and B lymphocytes, namely the biological agents.[Levitsky,2017]

Vitamin D deficiency may increase the risk for the development of RA . Recently, the role of vitamin D deficiency in the pathogenesis of RA, as well as the relationship between vitamin D deficiency and the activity of RA is discussed.

2.7-The relationship between ESR and RA

Erythrocyte sedimentation rate (ESR) can be used for inflammatory monitoring in the RA patients routinely, although ESR is not an etiologic diagnosis. It is caused by ESR procedure is simple, practical, convenient, economical, point-of-care inspection, and has important clinical significancell-13.

The ESR depends on many factors (Zacharski, 1976), some of them independent of the inflammatory response, but despite this it is a good practical guide in several diseases[Pedersen,2016].

2.8- Obesity as a Risk Factor for Rheumatoid Arthritis

individuals who are obese are at an increased risk of developing RA.the accumulation of white adipose tissue that results from obesity contributes to this finding, given that this tissue secretes adipokines, such as leptin, adiponectin, resistin, and visfatin, all of which may be involved in immunity and inflammation. demonstrating an increased risk of RA in individuals with a higher body mass index (BMI)[Wesley, et al.,2019]

A more recent study published in Arthritis Care and Research by researchers from Denmark showed an increased risk of developing RA from higher body fat percentage, higher waist circumference, and obesity.this finding was noted in women, but not men[Lu B,2014] “

3-Materials and methods

3.1- Equipments and Materials

Processing company and origin	Device or tool name
Sigma (Germany)	Centrifuge
Fisher scientific (Germany)	Incubator
Biotic (USA)	Printer
Hedaeces Christ (Germany)	Autoclave
Shaker (Italy)	Horizontal shaker
Nantong (China)	ESR tubes
Nantong (China)	EDTA tubes
Nantong (China)	ESR rike
BDH (England)	Ethanol alcohol
Biokit (Fenland)	Micropipette & Tipes
Unolok (England)	Syringes 5ml
Nantong (China)	Latex
Nantong (China)	Westergren tube
Unolok (England)	Pipettes
Nantong (China)	Sodium Citrate
Nantong (China)	Control Positive
Nantong (China)	Control Negative
Unolok (England)	Slide

3.2-Sample collection methods

How to perform an ESR analysis

To perform an ESR test, a healthcare professional will take a blood sample from a vein in a person's arm using a small needle.

After the needle is inserted, a small amount of blood will be collected in a test tube, and this can cause a slight tingling feeling when the needle is inserted or removed, and this procedure usually takes less than five minutes.

How to perform an Vitamin D testing

Vitamin D testing requires a rapid blood test that takes no more than 5 minutes. During the test, a laboratory technician takes a blood sample from a vein in the arm using a small needle. After the needle is inserted into the vein, a small amount of blood is collected in a test tube for later analysis in the laboratory using special equipment.

How to perform an rheumatoid factor analysis

In this analysis, the specialist takes a sample of the patient's blood, and puts it on a special slide with the addition of some substances that interact with the blood components looking for the antibody of the rheumatoid factor. The analysis does not require fasting or performing some conditions for other analyzes. It is performed by the patient at any time without adhering to certain conditions.

3.3-working methods

The method of work[ESR TEST]

The common way to do the ESR test is called the Westergren method, and it uses a special pipette with a length of 300 mm and a scale from zero to 200 mm.

1. The blood sample is placed in a special tube that contains an anticoagulant (sodium citrate), so the sample must be mixed well with the anticoagulant.

2. A Westergen pipette is inserted into the opening of the tube containing the blood sample, and the pipette is pressed until the blood level reaches zero. The pipette is placed vertically by means of a special stand.

3. Record the sedimentation rate one hour after placing the pipette in the tube.

The method of work[Vitamin D testing]

Step1 Reconstituting

Draw 2.5 mL Detection Buffer C into the VD Lyophilized Marker Bottle and shake it thoroughly.

Step2 Reacting

Draw 75 µL Serum or Plasma, 75 µL Releasing Buffer A and 150 µL Reconstituted Marker sequentially into a blank centrifuge tube, mix it well then incubate at room temperature for 10 minutes.

Step3 Loading

Draw 75 µl Sample Mixture and load it into the sample well of Test Cartridge.

Step4 Testing

Insert the Test Cartridge, click "Start Test" to start testing. The test result will be displayed on the screen after 15 minutes.

The method of work[Rf Analysis]

1. Labeled "latex" on a Rfreagent slide. Put 20 µm of . Latex with dark circles, then apply 20 microns of serum on it

2.Flipping is done by moving the slide in a circular manner for 2.2 minutes. minutes

And it is diluted - (if no small granules appeared, the result is negative. The analysis is repeated by the method of dilution to make sure of the result and to avoid the prozone.

If small granules appear, they are positive.

4.Results and Discussion

1. Base line characters of participants

Based on age groups, the current study showed the age group 50-41 years recorded highest percentage for patients (35%) and age group >70 years recorded highest percentage for healthy (30%). The age group 61-70 year recorded least percentage of patients and healthy (10% and 15%) respectively.

Based on gender, the current findings showed the percentage of males and females in patients (30% and 70%) than healthy (45% and 55%) respectively (table 1).

Table 1; baseline characters of participants

			Groups		Total
			patients	Healthy	
Age groups (years)	31-40	N	11	3	14
		%	27.5%	15.0%	23.3%
	41-50	N	14	3	17
		%	35.0%	15.0%	28.3%
	51-60	N	5	5	10
		%	12.5%	25.0%	16.7%
	61-70	N	4	3	7
		%	10.0%	15.0%	11.7%
	>70	N	6	6	12
		%	15.0%	30.0%	20.0%
Gender	Males	N	12	9	21
		%	30.0%	45.0%	35.0%
	Females	N	28	11	39
		%	70.0%	55.0%	65.0%

The present study show a higher incidence of RA in female in comprise to the male are attributed to the different factor such as hormonal factor which include estrogen hormone; In current study the female/male ratio more than 3:1 in favor of female. This result is consistence with most of studies(Alpízar-Rodríguez *et al*. (2017) and Alanzy, *et al*. (2018) and Klein and Morgan (2020).

The hormonal hypothesis for female-biased autoimmunity remains the most convincing, although estrogens tend to promote autoimmunity and androgens appear to protect against it, there is enough evidence to indicate that genetic factors play a role with epigenetic mechanisms are linked to sex variations. Male patients have more muscle mass and stamina, which allows them to avoid functional losses (Altohmoschi *et al.*, 2021).

2.Relation of ESR, RF, and vitamin D3 with study groups

Results of present study showed there is significant differences ($p<0.05$) between ESR, RF, vitamin D3 and study groups. The mean levels of ESR and RF were highest in patients (84.05±33.79 and 17.35±5.08) than healthy (38.62±15.53 and 10.55±3.22) respectively. In contrast, the mean levels of vitamin D3 was lowest in patients (21.00±9.68) than healthy (32.40±13.45) (table 2 and figure 1).

Table 2; comparative of ESR, RF, and vitamin D3 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	

The present study showed high levels of ESR in patients with RA than healthy, and these results matched with results Khorshidi-Sedehi et al., (2021). Also, the current result is in agreement with the various previous study that concluded that ESR level can be elevated in RA and can be used as a screening test to assess disease severity but has much lower specificity than CRP and RF Assasi *et al* ., (2015).

ESR is the most widely used markers for measuring acute phase response due to their reliability, reproducibility, and cost-effectiveness. Both of these markers correlate closely with the clinical disease activity of RA (Mercan *et al*., 2016). Previous study show RA patients, there was a significant correlation between serum ferritin levels and CRP, ESR, and platelet count, which reflect disease activation (Seyhan *et al.*, 2014). Another studies suggested RA patients have high levels of inflammatory markers (CRP & ESR), and these levels are correlated with the disease activity. These findings suggested a possible role of these markers in the pathogenesis and can be used as markers of disease activity in the diagnosis and treatment of RA (Shrivastava *et al*., 2015). Sargin *et al.*, (2018) who showed that linear mixed model analysis confirmed that ESR increased significantly with RA and ESR was higher before anti-TNF treatment in RA patients, and they decreased significantly after 3 and 6 months of treatment.

Vitamin D deficiency is more common in RA patients and may be one of the causes leading to development or worsening of RA. In RA, as the disease activity increases, the serum Vitamin D levels tend to decrease. There is a need for proper evaluation of Vitamin D status in all RA patients to ensure the intake of the recommended amount of Vitamin D. Further research is required so that the antiproliferative, immunomodulatory, and anti-inflammatory properties of Vitamin D could be exploited to treat a variety of autoimmune rheumatic diseases (Meena et al., 2018).

Treatment for RA is pointed towards decreasing disease activity, maximizing joint function, and, along these lines, keeping a check on serum 25-OHD3 levels. The inception of treatment early in the disease could cover the effects of vitamin D deficiency, causing a decline in the proportion of disease activity (Sukharani et al., 2021).

Recent study showed the vitamin D supplementation for five years, with or without omega 3 fatty acids, reduced autoimmune disease by 22%, while omega 3 fatty acid supplementation with or without vitamin D reduced the autoimmune disease rate by 15% (not statistically significant) (Hahn et al., 2022).

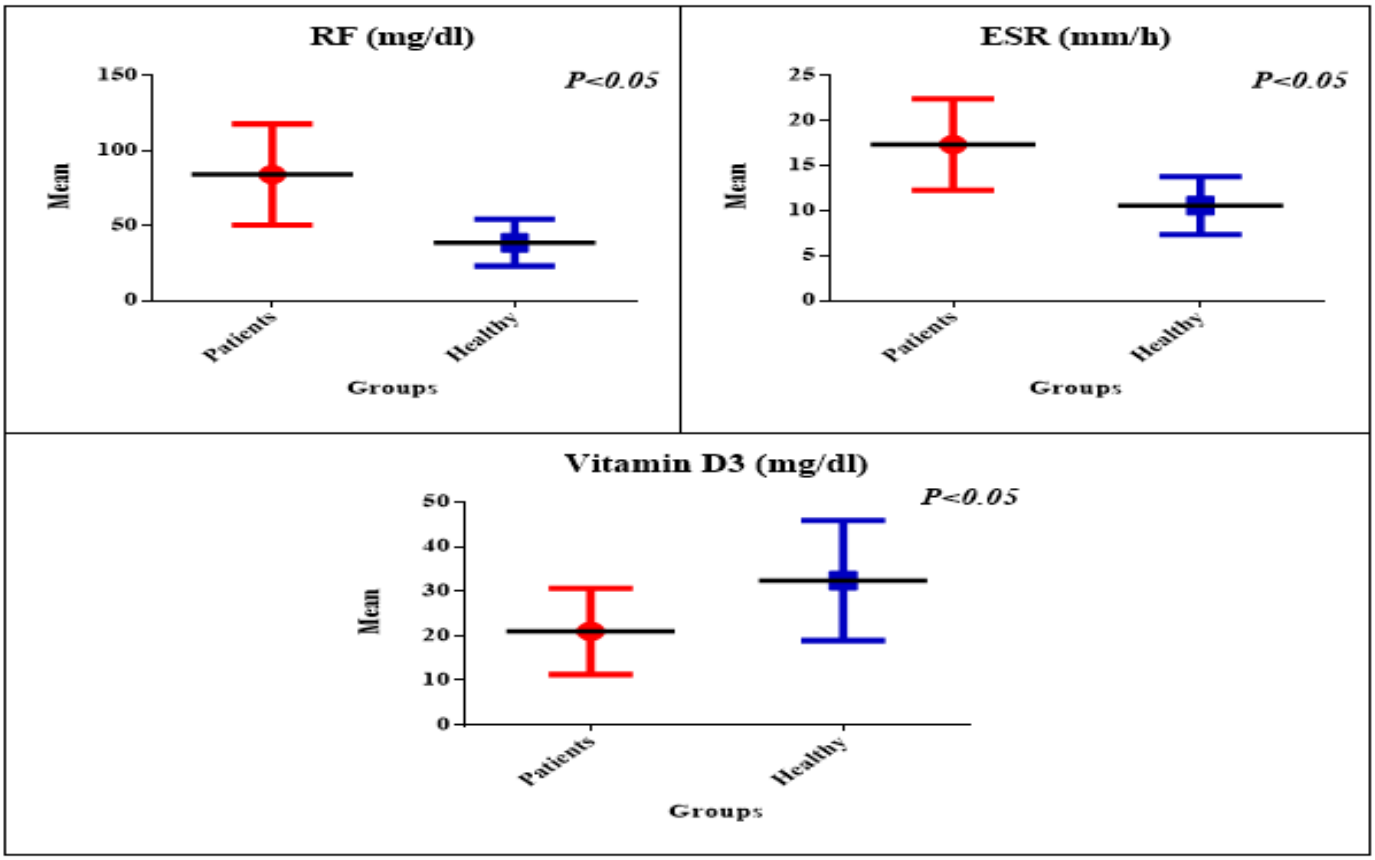

Figure 1; comparative of ESR, RF, and vitamin D3 with study groups

3. correlation relationship among ESR, RF, and vitamin D3 parameters

The present study showed there is significant correlations among ESR, RF, and vitamin D3. The vitamin D3 is significant negative correlate with ESR (r=-0.418**) and RF (r=-0.336*). The RF is significant positive correlate with ESR (r=0.791**) (table 3).

Table 3; correlation relationship among ESR, RF, and vitamin D3 parameters

		ESR	RF	D3
ESR	Pearson coefficient	1	.791**	-.418**
	Probability		.000	.007
RF	Pearson coefficient	.791**	1	-.336*
	Probability	.000		.034
D3	Pearson coefficient	-.418**	-.336*	1
	Probability	.007	.034	

The relationship between the elevated level of the ESR and RA is attributed to the elevation of the level of the fibrinogen which causing the red blood cell to sticky and increasing the sedimentation of the erythrocyte Lapić *et al* ., (2020).

4. Relation of ESR, RF, and vitamin D3 with age groups of patients

The conducted study showed there is no significant difference (p>0.05) between ESR and RF among age groups of patients, but we found there is significant different between vitamin D3 among groups, where >70 and 41-50 years scored highest mean (31.37±9.80 and 23.96±8.82), while 31-40 and 61-70 years scored lowest mean (14.25±6.22 and 13.20±5.39) respectively (table 4).

Table 4; comparative of ESR, RF, and vitamin D3 with age groups of patients

Age groups		N	Mean	SD	P value
ESR	31-40	11	68.18	23.16	p>0.05
	41-50	14	92.50	34.85	
	51-60	5	87.40	13.65	
	61-70	4	87.50	49.07	
	>70	6	88.33	47.82	
RF	31-40	11	20.08	2.25	p>0.05
	41-50	14	16.35	5.85	
	51-60	5	14.02	4.22	
	61-70	4	18.43	5.50	
	>70	6	16.71	6.15	
D3	31-40	11	14.25	6.22	p<0.05*
	41-50	14	23.96	8.82	
	51-60	5	21.32	9.52	
	61-70	4	13.20	5.39	
	>70	6	31.37	9.80	

Previous study showed age and sex were independently associated with the levels of both acute phase reactants in early RA, although the effects appeared to be strongest on the ESR. These results emphasize the need to take these external factors into account when interpreting disease activity in patients with early RA. Because the acute phase reactants tend to increase with age, independent of other core measures of disease activity, the disease activity of older-aged patients might be overestimated (Yun et al., 2010). Like sex differences, the increasing ESR levels with age might be explained by certain immunological or hematological changes and, for instance, hormonal changes in women who reach the menopause (Siemons et al., 2014).

5. Relation of ESR, RF, and vitamin D3 with gender of patients

The conducted study showed there is significant difference ($p<0.05$) between ESR and RF with gender of patients, but we found there is no significant different ($p>0.05$) between vitamin D3 and gender. The mean levels of ESR was high in males (106.67±36.64) than females, while RF was high in females (18.40±4.71) than males (table 5).

Table 5; comparative of ESR, RF, and vitamin D3 with gender of patients

Gender		N	Mean	SD	P value
ESR	Males	12	106.67	36.64	P<0.05*
	Females	28	74.36	27.89	
RF	Males	12	14.90	5.24	P<0.05*
	Females	28	18.40	4.71	
D3	Males	12	24.12	11.24	p>0.05
	Females	28	19.66	8.81	

Siemons et al., (2014) showed the ESR values are more likely to be elevated in women than in men, and these results matched with present study. It is well-established that pathological elevation of the ESR may be due to elevation of the fibrinogen level and high levels of disorders in women than men.

Mun et al., (2021) showed the patients with RA, RF and ACCP were higher in males than in females, but the difference was not statistically significant, and these results contrast to present studyt showed high levels of RF in females than males with significant difference . However, another study performed by Alwan and Ghali, (2021) showed a significant association between Anti-CCP level and the female gender. RF and ACCP considered discriminative biomarker to RA diagnosis.

Statistical analysis

The RF, ESR, and vitamin D3 parameters were first tested for normality (Kolmogorov-Smirnov and Shapiro-Wilk test). All parameters that fit both tests (no significant difference) were given as mean ± standard deviation (SD) and compared by using student t test and ANOVA test. The other parameters were given as percentage frequencies. The pearson bivariate correlation was employed to understand the correlation between certain parameters. Receiver operating characteristic (ROC) curve was constructed for each parameter, and the area under the curve (AUC), sensitivity and specificity were consequently estimated. The statistical package SPSS v. 25.0, Graph pad prism v. 6 and MedCalc were employed to carry out these analyses.

Conclusions

Prevalence of obesity in RA varies according to BMI cut-off points. Overweight and obesity were associated with higher inflammatory activity characterised by a higher count of tender and swollen joints. A positive correlation was found

between swollen joint amount and the majority of the body fat mass indicators assessed. Body composition assessment/improvement should be an important part of the routine care of RA patients.

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