Determination the Relationships between Body Mass Index and Incidence of Rheumatoid Arthritis

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Abstract
Rheumatoid arthritis (RA) a class of systemic auto immune disturbances and manifest its Self with progression inflammation of several Joint in the body. The present results was co conducted to evaluate some hematological parameters and some biomarkers in Patients affected with RA of both Sexes (men and women) . The individuals who had involved in the present Study were 80 subject of Patients and healthy individual and they classified according to gender into two Subclasses, the first one involved 40 males that divided into 20 Males Patients with RA and 20 Males healthy control. The second class had also 40 females of them 20 females affected with RA and 20 healthy females as a control group .All ages of Subject were ranged between 40-79 years old and then according to their age's war classified into four age groups (40-49, 50-59 60-69, 70-79 Years old) . The demographical data that obtained from the Present study indicated that the Percentage ratio of women with RA was 60% higher than Men with RA who had recorded 40% The distribution of Patients according to their age groups the Percentage ratios were the following to 49 first group 30%, Second group 30% Third group 25% fourth group 15% respectively). In addition the Percentage ratios of RA Patients according to body Mass index (BMI) it was found Patients with that had BMI equal to 25 -33 kg/m² comprised 70% higher than those patients who had BMI ranged between 19-23 kg/m² (30%). The changes of hematological Parameters had been exhibited a significant increase ($P<0.001$) in the Level of white blood cells (WBCs), in all RA patients groups when compared with those healthy one. The correlation Coefficients occurring among Studied hematological Parameters recorded the following data, it was found that then is a significant positive correlation ($r=0.43$, $Sig=0.005$) occurring between ESR and WBCs The observations recorded around studied biomarkers including rheumatoid factor (RF), fibrinogen, tumor necrosis factor alpha (TNF), and granulocytes-monocytes Colony stimulating factor (GM-CSF) were showed a significant elevation ($P<0.05$) in all levels, of these biomarker of all patients groups compared to healthy subjects .These studied biomarkers appear closely associated with BMI therefore their levels were significantly high $P<0.05$ in RA Patients with BMI 25-33 kg/m² Comparing to those patient had BMI ranged between 19 - 23 kg/m² .The Correlation coefficients of biomarkers with other Studied Parameters as follow, there is a significant Positive correlation between ESR and TNF-α , ESR and GM-CSF, ESR and RF, GM-CSF and Platelets, Gm-CSf and WBS, Gm-CSF and granulocytes, GM-CSF and fibrinogen, GM-CSF and RF, Gm-CSF and CRP, TNF-α and GM-CSR , TNF-α and platelets , TNF-α and WBC, TNF and granulocytes, TNF-α and RF , TNF-α and CRP ,WBC, and CRP, Rf and platelets, RF and WRCs , of all Patients with RA.
Keyword: rheumatoid factor (RF), fibrinogen, tumor necrosis factor alpha (TNF), and granulocytes-monocytes Colony stimulating factor (GM-CSF)

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune multifactorial complex disease, The key feature of this complex autoimmune disorder is the inflammation of the small joints [1].
The core pathological features of RA are abnormal. the proliferation of the synovial cell, invasion of inflammatory cell, formation of rheumatoid vasospasm, cartilage degradation, and the bone, and then the deterioration of the joint [2, 3].
Symptoms of stiffness and discomfort, along with general malaise and weakness, often occur in many types of arthritis.) [4].
The first is that infection with the pathogen may provoke inflammatory factors leading to arthritis, or perhaps the second possibility is that the immune imbalance in patients gave an opportunity to the pathogen to enhance its presence in the host with the disease [5].
This is why the prevalence of RA can reach up to 1% of the general population in some countries. The lifetime risk of developing RA is 3.6% in women and 1.7% in men [6, 7].
Environmental conditions play an important role in human autoimmune development. These causes or factors include unfettered environmental conditions such as air, drink, and chemical substances, whether natural or manufactured, as well as infection and by-products of radiation and manufacturing [8].
Pro-inflammatory cytokines, including TNF, IL-6, and IL-1, play an important role in perpetuating

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inflammatory and destructive processes in RA. TNF is a key pro-inflammatory cytokine among them as its overexpression is sufficient to induce arthritis in mice (hTNFtg) [9].

TNF stimulates osteoclast genesis both indirectly and directly. Firstly, TNF upregulates RANK and c-fms (M-CSF receptor) expression in osteoclast precursors and RANKL expression in synovial fibroblasts in conjunction with IL-6 [10].

Secondly, TNF directly stimulates the differentiation of osteoclasts from mononuclear precursors in synovial tissues in synergy with RANKL [11].

Low-grade inflammation, reflected in the overproduction of acute phase proteins such as C-reactive protein (CRP), pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TFN-α) has been established as a risk factor for several neuropsychiatric disorders , including depression and schizophrenia. Moreover, low-grade inflammation in children and adolescents has been associated with the development of co- and multi-morbid conditions to mental health pathologies [12].

2. Methods

Collection of blood samples

The present work was performed in many locations including hospitals (Marjan teaching hospital and Imam Al–sadiq hospital) and location including Babylon university/college of science for women and private laboratories. The present study was initiated at a beginning of November 2021 to April 2022.

The total number of individuals was eighty (80) of men and women of these twenty (20) men were complained from Rheumatoid arthritis and twenty (20) men were apparently healthy were selected as a control group.

The remaining individuals (40) women, of them, twenty (20) women were affected with Rheumatoid arthritis and twenty (20) women also they were selected as a control group.

All persons of study, had ages ranged between 40-79 years old. The subjects (patients and healthy control) of the present study were classified according to their ages in to four categories (40-49, 50-59, 60-69, 70, 79 years old). Excluded criteria (diabetes melitus,osteoporosis ,thyrotoxicosis ,malignant diseases and pregnancy).

All patients were admitted to hospital and health care centers to check up their own healthy and received therapeutic options. Concerning control subjects, they were selected from public health centers, workers in hospitals, and person who have normal medical history of both sexes.

Determination of Granulocytes monocytes-colony stimulating factor and tumor necrosis factor alpha.

Measurement of Granulocytes monocytes-colony stimulating factor was carried out according to instruction applied by Thermo Fisher/USA Company whereas determination of tumor necrosis factor alpha was performed according to instructions of Karmania Pars Gene /Iran Company.

Complete Blood Count (CBC) assay

Whole blood sample in EDTA tube was used immediately to get complete blood count using automated 3-part hematology auto analyzer, samples were swirled several times to mix the sample and then processed in the auto analyzer to get result within 60 seconds, result printed out and recorded.

Statistical Analysis

Results of the present study were illustrated as means ± standard

Deviation (SD). The values were statistically analyzed by using SPSS 23

Program and analysis of variance were explained. The lowest significant

Differences (LSD) among studied groups was $p< 0.05$.

3. Results

1. Distribution of patients according to gender.

From present finding it was noticed that women suffer from rheumatoid arthritis more than of men .A average of 60% of women and 40% for men. As explained in Figure 1.

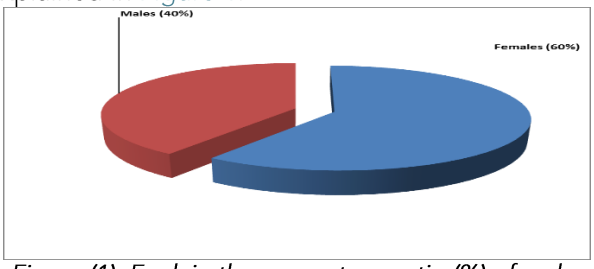

Figure (1): Explain the percentage ratio (%) of males and females affected with rheumatic arthritis.

2. Distribution of patients according to age groups.

The present study, observed the rate of rheumatoid arthritis patients according to age groups as follows:

-Patients age from 40 to 49 years were 30% of patients .

-Patients age from 50 to 59 year were 30% of patients..

-Patients age from 60 to 69 years or more were 25% of patients.

-Patients age from 70 to 79 years or more were 15% of patients.

As explained in Figure 2.

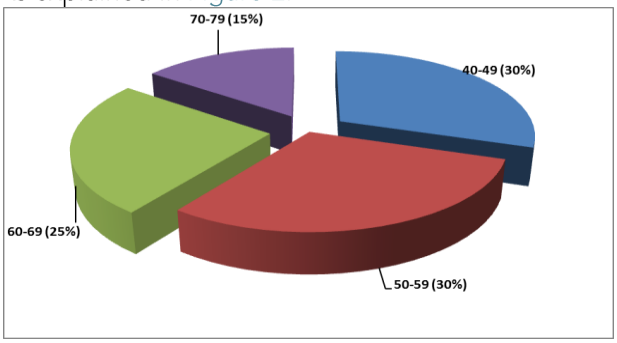

Figure (2): Represents the percentage ratio (%) of age groups of patients with rheumatic arthritis.

3. Distribution of patients according to body mass index:

From this study it had been that people with high body mass are affected more than people who have normal body mass, with an average of 70% for people who have excessive body mass and 30 % for people with normal body mass.
This was showed in Figure 3

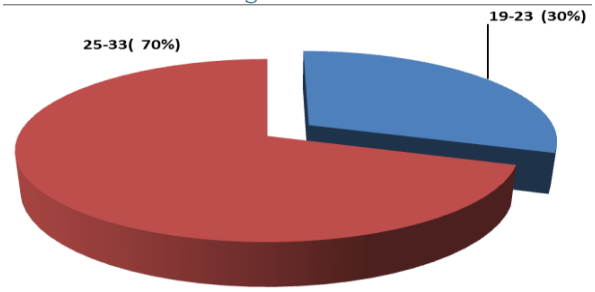

Figure (3): Shows the percentage ratio (%) of body mass index for patients affected with rheumatic arthritis

4. Blood parameters in rheumatoid arthritis patients and healthy people.

This results that were shown in table 1 explained a significant heightening P<0.01 in the levels of, WBCs, Granulocyte and lymphocyte (8.51±0.16 cell/mm3, 80.68±5.55 %, 16.99±1.55 %,) respectively in matching with those healthy control groups (5.98±0.17 cell/mm3, 69.04±4.71 % and 28.82±2.78 %) respectively Table (1): Shows the results of hematological parameters (WBCs, Granulocytes and Lymphocytes) of patients affected with rheumatic arthritis and healthy subjects.

Groups Parameters	Patient (n=40)	Control (n=40)	Pvalue≤0.05
	Mean ±S.E		
WBC (cell/mm3)	8.51±0.16	5.98±0.17	0.0002**
Granulocyte (%)	80.68±5.55	69.04±4.71	0.0001**
Lymphocyte (%)	16.99±1.55	28.82±2.78	0.0003**
-All values are mean ±SE - Results with two strikes are significantly different at P≤0.01 -Results with one a strike are significantly different at P≤0.05			

5. Illustrate the biochemical markers in Rheumatoid Arthritis Patients and Healthy People.

The results that were shown in table 2 explained a significant heightening p<0.01 in the levels of tumor necrosis factor (TNF) and granulocyte monocyte colony stimulating factor (GM-CSF) (20.39±1.58 pg/ml , and 340.93±13.69 pg/ml, respectively in matching with those healthy control groups (5.10±1.48 pg/ml and 114.38±11.05 pg/ml, respectively.

Table (2): Illustrate the biochemical markers (TNF and Gm-CSF) of patients affected with rheumatic arthritis and healthy control.

Groups Parameters	Patient (n=40)	Control (n=40)	Pvalue≤0.05
	Mean ±S.E		
TNF (pg/ml)	20.39±1.58	5.10±1.48	0.0001**
Gm-CSF (pg/ml)	340.93±13.69	114.38±11.05	0.0001**
-All values are mean ±SE -Results with two strikes are significantly different at P≤0.01. -Results with one a strike are significantly different at P≤0.05.			

6. Blood parameters in rheumatoid arthritis patients and healthy people according to gender.

Data that were illustrated in table 3 , showed a significant increase P<0.05 in levels, of total white-blood cells, Granulocytes , (8.50±1.5 cell/mm3 and 79.98±12.1 % respectively) and record a significant drop P<0.05 in levels of Lymphocyte (17.53±2.1 %) in male Patient , while indicated a significant increase P<0.05 in levels of total white- blood cells, Granulocytes (8.53±1.3 cell/mm3 and 81.38±8.4% , respectively) and showed a significant drop P<0.05 in levels of Lymphocyte (16.46±3.3%) in female Patient , when compared with healthy control group in levels of total white- blood cells, Granulocytes, Lymphocyte , (5.88±0.7 cell/mm3, 69.70±7.9% and 28.36±2.4% respectively) in males healthy control group , and the levels of total white- blood cells, Granulocytes and Lymphocyte for females healthy control group(6.08±2.1 cell/mm3 , 68.37±5.4% and 29.28±6.3% respectively).

Table (3): Shows the results of hematological parameters (WBCs, Granulocytes and Lymphocytes) of patients and control affected with rheumatic arthritis according to gender.

Groups Parameters	Males		Females		LSD(0.05) (gender*group)
	Patient	Control	Patient	Control	
	Mean ±S.E				
WBCs (cell/mm3)	8.50±1.5	5.88±0.7	8.53±1.3	6.08±2.1	0.581*
Granulocytes (%)	79.98±12.1	69.70±7.9	81.38±8.4	68.37±5.4	2.227*
Lymphocyte (%)	17.53±2.1	28.36±2.4	16.46±3.3	29.28±6.3	2.276*
-All values are mean ±SE -Results assigned with different letters significantly different at p<0.05 -Results assigned with different letters non-significantly different at p>0.05					

7. The results of biochemical markers (tumor necrosis factor, rheumatoid factor and granulocyte monocyte-colony Stimulating factor) of patients affected with rheumatic arthritis and control group according to gender.

Table (4) illustrated the results recorded a significant increase p<0.05 in the levels of tumor necrosis factor, rheumatoid factor and granulocyte monocyte-colony Stimulating factor (19.06±2.3 pg/ml , 24.30±8.2 IU/l and 339.00±17.8 pg/ml respectively) in males patients when compared with control group in the levels of tumor necrosis factor, rheumatoid factor and granulocyte monocyte-colony Stimulating factor (6.02±0.9 pg/ml, 11.07±0.3 IU/l and 113.45±10.3 pg/ml respectively) in males , while

in females patient the values pointed out a significant elevation P<0.05 in the levels of tumor necrosis factor, rheumatoid factor and granulocyte monocyte-colony Stimulating factor(21.73 ±6.3 pg/ml , , 25.93±3.4 IU/l and 342.85 ±25.3 pg/ml respectively) when compared with control group in the levels of tumor necrosis factor, rheumatoid factor and granulocyte monocyte-colony Stimulating factor(4.17±0.6 pg/ml, 11.38±1.3 IU/l and 115.30±15.4 pg/ml respectively) in females

Table (4): Illustrate the biochemical markers (tumor necrosis factor , rheumatoid factor and granulocyte monocyte-colony Stimulating factor) of patients affected with rheumatic arthritis and control groups according to gender

Groups Parameters	Males		Females		LSD(0.05) (gender*group)
	Patient	Control	Patient	Control	
	Mean ±S.E				
TNF (pg/ml)	19.06±2.3	6.02±0.9	21.73 ±6.3	4.17±0.6	2.708*
Rf (IU/l)	24.30±8.2	11.07±0.3	25.93±3.4	11.38±1.3	1.495*
Gm-CSF (pg/ml)	339.00±17.8	113.45±10.3	342.85 ±25.3	115.30±15.4	9.156*

-All values are mean ±SE
-Results assigned with different letters significantly different at p<0.05

8. Hematological parameters according to gender and age groups of patients affected with rheumatic arthritis and healthy control of both sexes.

Results which were illustrated in the following table (5) they explained the effects of age periods on some hematological parameters (total white blood cells, granulocytes% and lymphocytes of both patients and control, some of the results significantly different at p<0.05 when compared among different age groups according to LSD values. Table (5): Shows the results of hematological parameters (WBCs, Lymphocytes and Granulocytes) of patients affected with rheumatic arthritis and healthy groups according to gender and age.

Groups Parameters	Age (year)	Male		Female		LSD(0.05)
		Patient	Control	Patient	Control	
		Mean ±S.E				
WBC (m/mm3)	40-49	8.52±0.6	5.24±0.6	7.83±1.2	5.12±0.5	1.105
	50-59	8.15±1.2	5.84±1.2	8.49±0.9	5.75±0.5	
	60-69	8.26±1.7	6.00±0.3	8.82±0.8	6.24±1.2	
	70-79	9.08±1.8	6.43±0.1	8.97±1.3	7.22±0.6	
Granulocytes (%)	40-49	77.80±22.1	67.60±12.4	80.32±12.4	65.78±12.3	4.056
	50-59	78.18±13.4	66.88±7.8	79.18±9.2	65.64±6.7	
	60-69	81.12±7.8	71.82±12.4	82.94±11.1	70.98±8.2	
	70-79	82.82±11.11	72.50±8.8	83.06±8.6	71.08±9.1	
Lymphocytes (%)	40-49	19.88±2.3	30.64±2.6	17.70±2.2	32.18±6.3	4.055
	50-59	19.16±2.2	31.12±3.1	18.72±1.7	32.34±9.2	
	60-69	16.48±1.7	26.16±2.2	14.86±1.2	27.10±4.7	
	70-79	14.60±0.9	25.50±1.9	14.56±1.5	25.48±5.5	

-All values are mean ±SD
-Results assigned with different letters significantly different at p<0.05

9. The results of biochemical markers according to gender and age groups of patients affected with rheumatic arthritis and healthy control of both sexes.

All the results had been recorded in the table(6) were a significantly increase (P<0.05) in levels of (tumor necrosis factor and granulocyte monocyte-colony Stimulating factor) as the values are shown in the table, in all age groups (40-49,60-69,70-79) in male and female with rheumatic arthritis when compared with healthy groups.

Table (6): Illustrate the biochemical markers (tumor necrosis factor and granulocyte monocyte-colony Stimulating factor) of patients affected with rheumatic arthritis and healthy groups according to gender and age.

Groups Parameters	Age (year)	Male		Female	LSD(0.05)	
		Patient	Control	Patient	Control	
		Mean ±S.E				
TNF (pg/ml)	40-49	16.30±2.1	2.50±0.3	18.90±2.1	1.78±0.06	2.364*
	50-59	16.38±1.2	4.32±0.5	21.66±1.6	2.82±0.1	
	60-69	20.90±1.1	8.26±0.2	21.88±3.3	4.52±0.03	
	70-79	22.64±0.9	9.00±1.2	24.46±3.7	7.56±0.9	
Gm-CSF (pg/ml)	40-49	313.20±17.8	108.40±17.4	314.00±23.2	111.00±7.8	9.036*
	50-59	333.20±6.9	114.20±11.6	331.60±15.6	115.40±10.1	
	60-69	344.20±18.9	114.40±9.8	349.20±12.6	116.80±9.9	
	70-79	365.40±36.2	116.80±13.9	376.60±9.8	118.00±7.4	

-All values are mean ±SD
-Results assigned with different letters significantly different at p<0.05

10. The results of biochemical markers (tumor necrosis factor and granulocyte monocyte-colony Stimulating factor) of patients affected with rheumatic arthritis according to BMI.

The results that were shown in the table (7) indicated a significant evaluation p<0.01 in the level of tumor necrosis factor and granulocyte monocyte-colony Stimulating factor (22.74±1.6 pg/ml and 358.40±11.9 pg/ml respectively) in patients when compared with control groups in the level tumor necrosis factor and granulocyte monocyte-colony Stimulating factor (7.08±1.4 pg/ml and121.80±1.9pg/ml, respectively)

Table (7): Biochemical marker according to BMI(kg/m2) of patients with rheumatic arthritis and control groups

BMI groups Parameters	BMI (Kg/m2)		P≤0.05
	Patient (25-33)	Control (19-23)	
	Mean±S.E		
TNF(pg/ml)	22.74±1.6	7.08±1.4	≤0.0001**
Gm-CSF (pg/ml)	358.40±11.9	121.80±1.9	≤0.0001**

All values are mean ±SE
-Results with two a strikes are significantly different at P≤0.01
-Results with one a strike are significantly different at P≤0.05

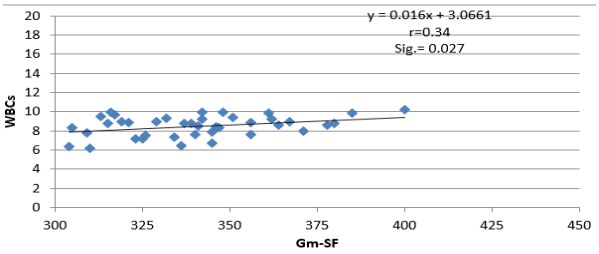

Figure (4): Correlation coefficient between Gm-SF and WBCs.

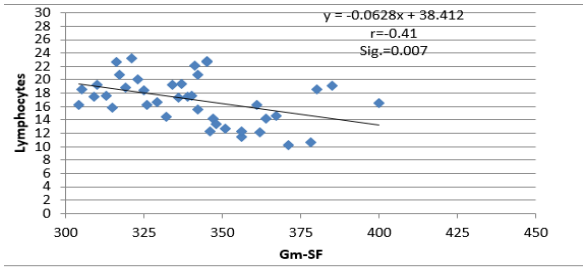

Figure (5): Correlation coefficient between Gm-SF and lymphocytes.

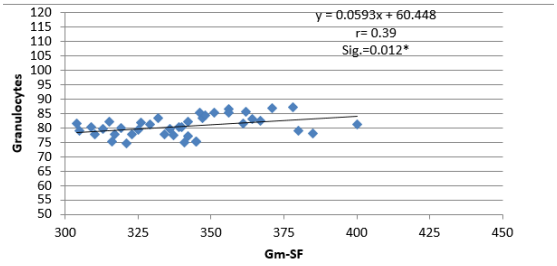

Figure (6): Correlation coefficient between Gm-SF and granulocytes.

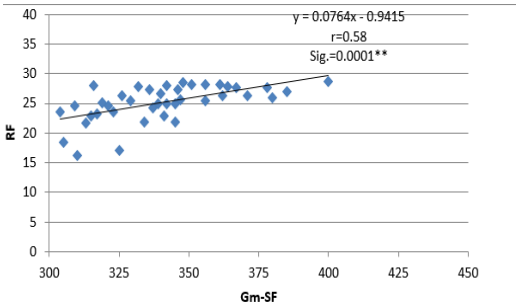

Figure (7): Correlation coefficient between Gm-CSF and RF.

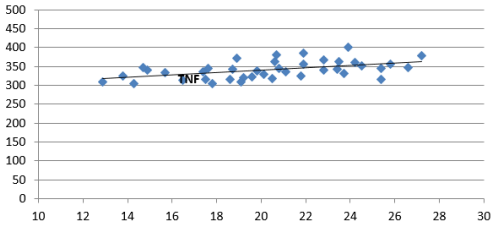

Figure (8): Correlation coefficient between TNF-α and Gm-CSF.

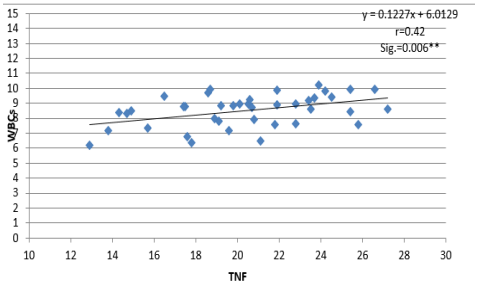

Figure (9): Correlation coefficient between TNF-α and WBCs.

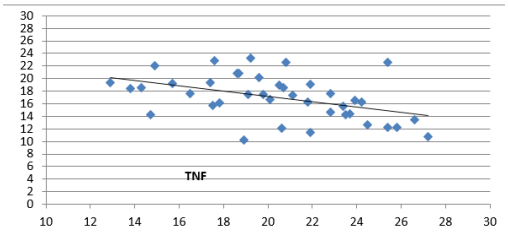

Figure (10): Correlation coefficient between TNF-α and lymphocytes.

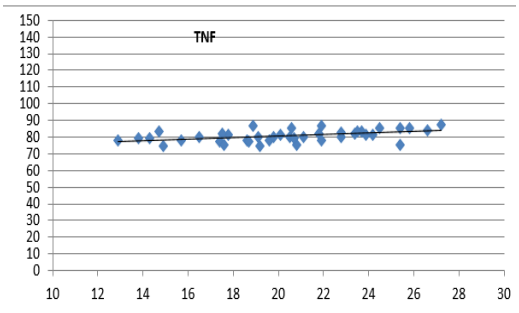

Figure (11): Correlation coefficient between TNF-α and granulocytes.

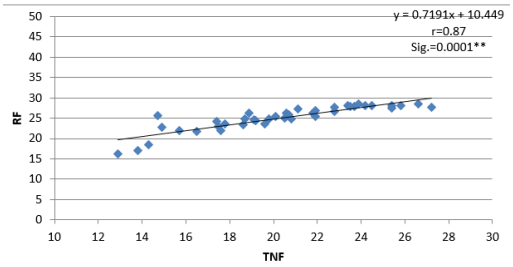

Figure (12): Correlation coefficient between TNF-α and RF.

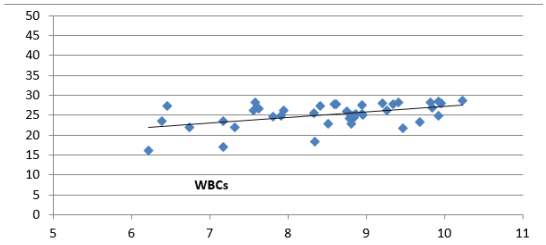

Figure (13): Correlation coefficient between WBCs and Rf.

Table (8): the best cut off, sensitivity and specificity for prediction of the disease activity by parameters.						
Parameter	Sensitivity	Specificity	AUC	Cut off	95% confidence	p-value
TNF-α	0.825	0.975	0.865	10.600	0.770-0.960	≤0.0001
Gm-CSF	0.875	0.700	0.914	118.50	0.846-0.982	≤0.0001
RF	0.825	0.675	0.864	12.700	0.779-0.950	≤0.0001

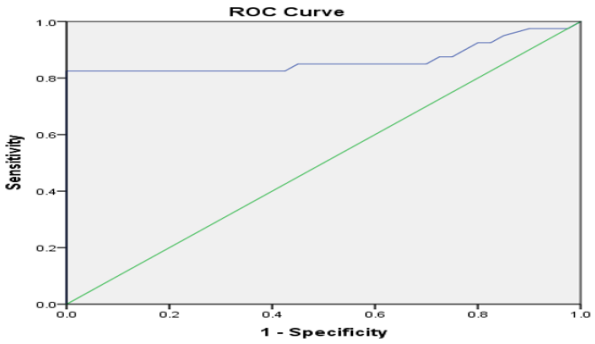

Figure (14): ROC curve for prediction of the disease activity by TNF

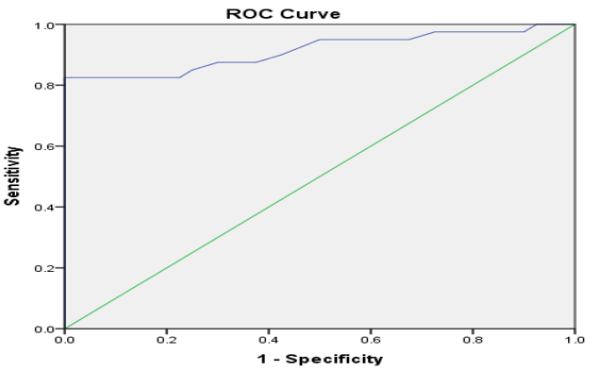

Figure (15): ROC curve for prediction of the disease activity by Gm-CSF

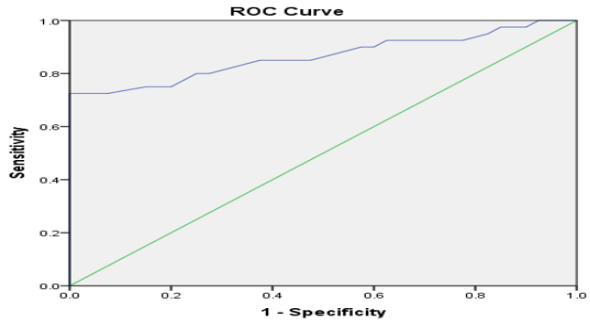

Figure (16): ROC curve for prediction of the disease activity by RF

4. Discussion

Figure (1) that were yield from the present study indicated that women affected with rheumatoid arthritis (RF) constituted 60% whereas comprised 40%

Without doubt, these observations were matched with previous studies that indicated gender differences play important roles in incidence and development of RA and those findings were consistent in their conclusions that confirm the incidence and severity of RA is higher in women than of men as well as the outcomes of this disease is poor in affected females [10] Age of women is also enhance the development of disease (RA) , since, it is found that women under 50 years old have 4 to 5 times but this ratio is decreased above 60 years old [13].

Recent study conducted by Maranini et al. [14], they reported sex affected incidence and progressive of different autoimmune disease in particular rheumatoid arthritis at the same time influence treatment programs.

From pervious observations that conducted to explain how estrogen affects inflammatory mediators, The invite experimental study was involved monocyte and macrophages that are derived from blood human and treated with 17 beta estradiol, The final result reported profuse production of pro-inflammatory mediators at low level doses such as IL-1 , IL-6 , TNF-α that in turn up regulates inflammatory processes, but on other hand , a higher concentration of 17-beta estradiol leads to decrease those inflammatory mediators [15].

Sex hormones were suggested to have implication or interactions in incidence of RA and its pathogenesis, women are affected with RA at nearly menopause (< 40 years old) Figure (2), on the other hand, Testosterone, concentration tend to decrease slowly at 50 years old.

Another previous study had also been recognized that prevalence and incidence of RA is higher among elderly people [10].

It is previously proposed that expanding of life expectancy of individual is related with increased incidence of RA, many suggestion were designed that established the accumulated damage of DNA, oxidative stress, and physiological disturbances are implicated in development of RA [16].

Study of [17],it published that the severity of RA is associated with age and the observations of this study was supported through increase concentration of powerful inflammatory marker (CRP) in patient with RA.

Some of previous studies established that old patients with RA have high joint damage, but other studies showed no differences in damage of that young and old human [6, 18].

Abnormal accumulation of adipose tissue in people who have heavy weights is associated with activation of inflammatory and autoimmune processes.

Excess adipose tissue are source in secretion of pro-inflammatory and inflammatory mediators and chemokines [19, 20] .

The prominent knowledge includes the role of obesity in rheumatoid arthritis is strong among women rather than men, The implication of obesity in incidence of chronic diseases return to excessive systemic inflammatory processes, this concept is consistent with physiological issue that reveals adipose tissue is an active tissue because of its ability to secret several cytokines called adipocytes which contribute in many immunological processes that are negative or positive within the body [21].

Recent study explored that the activity of RA is associated linearly with gender and BMI, The women is more acceptable to disease than of men, Since, The high level of BMI is significant related with increase pro-inflammatory state and this relation appear clearly with increased levels of C-reaction protein in obese human [22] figure(3) .

The results of tables for the gender(3) ,and age groups(5) indicated an increase significant in value of WBCs and the result of correlation -CSF and WBCs ,TNF-α and WBCs, RFand WBCs(r=0.34,sig=0.027) ,(r=0.42, sig=0.006) and (r=0.48,sig=0.001)respectively.

The present data of this study are consistent with recent study which established by Targońska-Stępniak et al. [23], which confirmed that levels of WBCs are significantly higher in patient with RA, as well as, this study found that neutrophil – to – lymphocyte and platelet to lymphocyte ratios were significantly higher in those patient with RA as well as lymphocyte to monocytes ratios have been recorded significant increase, These findings are also associated with elevation of erythrocyte sedimentation rate (ESR) and CRP.

From physiological point view, it is well know that the components of immune system include lymphocytes, monocytes, neutrophils, and platelets, these components have a significant function during chronic inflammation especially RA [24].

Choe et al. [25] they assess the hematological parameters in RA patients, the blood parameters are affected with systemic inflammation and autoimmune inflammation their observations indicate that CRP, ESR, neutrophil to lymphocyte, platelet to lymphocyte, and neutrophil to hemoglobin were markedly increased in those patients with RA.

More ever, an evidence proved the strong relationship between RA and neutrophil to lymphocyte ratio and platelet to lymphocyte ratio [26].

The inflammatory process occurring in RA can to affect erythropoiesis process, it was found that two reasons implicated in incidence of anemia associated with RA, the first one involved that gene encoding erythropoietin may be suppressed by actions of pro- and inflammatory mediator including TNFα, IL-1, IL-6, and CRP (11) the second, the pro inflammatory mediators can counteract the stimulatory effects of erythropoietin on progenitor cells in bone marrow (12).

Moreover, increase levels of pro-inflammatory markers such as IL-1β, TNF-α, and IL-6, They are together act to induce hepatic synthesis of CRP as well as from the extra hepatic tissue including adipose tissues, monocytes, lymphocytes, neurons, and smooth muscle cells of vasculature [27].

The results of tables for the gender(4) , age groups (6) and BMI(7) indicated an increase significant in value of RF and the result of the ROC / AUC =0.865, while the correlations between TNF-α and GM-CSF , TNF-α and WBCs , TNF-α and lymphocytes , TNF-α and granulocytes , TNF-α and RF , (r=0.50, sig =0.001) ,(r=0.42, sig =0.006), (r=0.45 , sig =0.005) , (r=0.48 , sig =0.002) , (r=0.87 , sig=0.0001) respectively.

Another study described the relationship between T-cell and TNF-α especially T-regulator and T-effector cells in those patients with RA, and the substantial efforts were carried out to inhibit and prevent progression of RA by application of several therapies, of those, inhibitors of TNF-α therapies since TNF-α inhibitors can effect T-regulatory cells and then controlling RA [28].

The possible definition of RA is an auto immune disturbances that results from chronic inflammatory processes affecting bones and joint and its causes remain unknown [29].

Generally, it is previously known that TNF-α had been diagnosed as a factor that has ability to cause necrosis of tumor mass, as well as this factor is described to has additional interactions in pathological conditions of that autoimmune diseases, it binds with specific two receptors that can triggers signal transduction cascades within the cell and these signal leads to different cellular functions including differentiation, development, and survival, however, excessive stimulation of TNF-α signaling pathways can be associated with chronic inflammatory diseases that eventually causing autoimmune diseases in particular RA [30].

Another previous study aimed to explained the role of TNF-α in insulin resistance of patients with RA and then this study concluded that TNF-α is positively correlated with insulin resistance in patients complained from RA as well as, it has significant roles in development of atherosclerosis [31].

The results of tables for the gender(4) ,age groups (6), and BMI (7) indicated an increase significant in

value of RF and the result of the ROC / AUC =0.914, while the correlations between GM-CSF and WBCs , GM-CSF and lymphocytes , GM-CSF and granulocytes , GM-CSF and RF (r=0.34 , sig =0.027) , (r=0.41 , sig =0.007) , (r=0.34 , sig=0.012) , (r=0.58 , sig=0.0001) respectively.

The differentiation and development of hematopoietic cells that called myeloid is a mechanism that depends on special cytokines called granulocyte _ monocyte colony stimulating factor that abbreviated GMCSF, this factors also to act as pro-inflammatory mediators and exerts in pathgenetic mechanism of RA, this invitro studies established that GM-CSF has ability to activate macrophages, in particular, in locations of chronic inflammations, this is markedly diagnosed increase of GM-CSF concentration within affected synovial fluids of individuals with RA in matching with those healthy individuals, furthermore, the specify of GM-SCF in perception of intensive pain had also been recognized therefor, administration of antibodies that block GM-CSF should be used (6).

GM-CSF is well documented to has role in development and progression of inflammatory processes which associated with RA and many suggestions indicate that blocked the GM-CSF can improve the RA status, in this context, it clearly recognized that loss of GM-CSF level leads to decrease of synovitis and matrix metalloproteinase that mediates epitope expression [32].

There is a fact established that the expression of GM-CSF on peripheral lymphocytes in patients affected with rheumatoid arthritis and this expression is modulated by using drug affecting rheumatoid arthritis through determination of CRP and also established that expression of GM-CSF in RA did not correlate to duration of illness and administration of anti-TNF alpha caused drop of GM-CSF in both B and T effector cells [33].

It is well found that an evidence confirms GM-CSF receptors are associated and correlated with severity of several inflammatory diseases especially those autoimmune diseases of those rheumatoid arthritis had been recognized [34].

5. Conclusions

In conclusion, the mentioned date that explained above ,the gender and age are consider predisposing factors in incidence of RA because of sexual hormones as well as BMI, that is associated with Systemic inflammation.

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