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Role of IL-24, IL-29, IL -31 in Rheumatoid arthritis patients

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Abstract

This study was conducted during the period 23/8/2022 to 30/1/2023 in order to identify the role of IL-24, IL-29, IL-31 in patients with rheumatoid arthritis in Al-Diwaniyah city. The results showed: ESR and BMI values were significantly elevated in patients with rheumatoid arthritis compared to healthy persons. The incidence of rheumatoid arthritis was significantly raised in women compared to men. Body mass index had a significant influence on the incidence of rheumatoid arthritis, while age did not significantly affect the incidence of rheumatoid arthritis. The average levels of IL-24, IL-29 and IL-31 were (138.323, 152.997 and 80.731) ng/L respectively in blood serum of patients with rheumatoid arthritis, compared to (91.026, 100.402 and 57.257) ng/L respectively in blood serum of healthy persons. The level of IL-24, IL-29 and IL-31 increased significantly ($P < 0.01$) in rheumatoid arthritis patients compared to healthy persons. The values of correlation coefficients ranged between ESR, IL-24, IL-29, IL-31 (0.634 and 0.735) and were highly significant. Sex did not have a significant effect on the level of interleukins, age did not have a significant effect except for IL-31, and body mass index did not have a significant effect in healthy persons. Sex had no significant influence on the level of interleukins, age also had no significant effect, and body mass index had no significant effect except for IL-24 in patients with rheumatoid arthritis.

Keywords

Rheumatoid arthritis, IL-24, IL-29, IL-31.

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease with variable clinical signs, characterized by slight to intense inflammation of the joints that can lead to pain, dehydration, and joint destruction, as well as joint deformities and disability. It is an idiopathic inflammatory disease characterized by symmetrical peripheral polyarthritis and is the most prevalent. Since it is a systemic disease, it can cause many extra-articular appearances like fatigue, pericarditis, lung involvement, peripheral neuropathy, vasculitis and subcutaneous nodules. In addition to the physical effects and permanent changes in activity and lifestyle, it can affect the mental state of the individual and cause diseases such as depression (Caden et al., 2003 ; AIHW, 2009 ; Sajad and Mohammad , 2020) .

In autoimmune diseases, the body produces an immune response when the immune system unable to distinguish some of the body's (self) tissues from foreign (non-self) substances that attack its own healthy tissues. This reason is not well understood , although some people may have a genetic risk of infection with autoimmune diseases (AIHW, 2009).

The rate of disease prevalence in the world is about 1% of the world's adult population. Women are three times more probable to be infected with the disease than men. The onset of the disease is often in the fourth

and fifth decades of life. The main cause of the disease is linked to heredity, in addition to the participation of environmental factors (Caden et al., 2003; Sajad and Mohammad , 2020 and Kontzias , 2022).

Interleukin 24 belongs to the interleukin-10 family, which acts through its specific heterologous receptors IL-20RA/IL-20RB and IL-20RB/IL-22RA1 that lead to different pathways of action and cellular responses. IL-24 is a multifunctional cytokine that may regulate immune response, tissue homeostasis, host protection and tumor genesis. Its pathological ability by causing inflammation and infiltration of immune cells to damage tissues . Elevated IL-24 is related with chronic inflammation and autoimmune diseases like rheumatoid arthritis, spondyloarthropathy, psoriasis and inflammatory bowel disease. It has a preventive effect in cardiovascular diseases, bacterial infections and anti-tumor effects (Wang et al., 2002 ; Persaud et al., 2016 and Zhong et al., 2022).

Recent researches have explained that IL-29 is a energetic member of the type III interferon IFN family. It is able to regulate the levels of IL-6, IL-8 and IL-10 secreted by monocytes (Jordan et al., 2007 and Xu et al., 2015) . Type III IFNs act by binding to their receptors composed of the IL-28 receptor (IL-28Ra, also identified as IFNLR1) and the IL-10R2 chain (Commins et al., 2008). IL-29 is expressed in dendritic cells, T cells, and intestinal epithelial cells and leukemia cells (Guenterberg et al., 2010) . IL-29 can enhance inflammatory cytokine production and is contributed in joint destruction in rheumatoid arthritis (Chang et al., 2017).

IL-31 belongs to the interleukin-6 superfamily, which acts through its heterologous IL-31RA receptor and Oncostatin M receptor β chain (OSMR β) (Nakashima et al.,2018 and Furue et al.,2018). It is expressed by immune cells like activated macrophage, dendritic cells, eosinophils, basophils and epidermal keratinocytes also peripheral cutaneous nerves (Nakashima et al., 2018 and Furue et al., 2018). The research aims to identify the role of interleukins 24, 29 and 31 in rheumatoid arthritis .

Materials and methods

This study was conducted during the period 23/8/2022 to 30/1/2023 in order to identify the role of IL-24, IL-29, IL-31 in patients with rheumatoid arthritis. Blood samples were collected in Al-Diwaniyah Teaching Hospital, based on the diagnostic criteria established by the American College of Rheumatology (ACR) 1987 and the European League Against Rheumatism (EULAR) 2010 (Gerlag et al ., 2012) . ESR was measured and the RF factor test was performed .The number of patients reached 70 persons, in addition to 30 healthy persons as a control group. The sample included males and females of different ages, in addition to calculating the body mass index. Laboratory analyzes were conducted in Al-Diwaniyah Teaching Hospital and College of Veterinary Medicine - University of Al-Qadisiyah . Kits used in this study are Human IL-24 , IL-29 and IL-31 Elsa Kit from the Chinese company BTLAB.

Results and discussion

Rheumatoid arthritis

ESR was used in this study as an indicator of inflammatory and disease activity in addition to RF in the diagnosis of rheumatoid arthritis. The results showed that the level of ESR was significantly higher in patients with rheumatoid arthritis compared to the healthy group (Table 1). This increase is a response to inflammation, when inflammation occurs the high percentage of fibrinogen in red blood cells causes them

to stick together, which are deposited faster due to their increased density (Harrison, 2015). This result agreed with (Xu et al., 2015 and Hamza, 2021).

The group of rheumatoid arthritis patients differed from the healthy group by significantly increasing both age and weight (Table 1). Also, the group of rheumatoid arthritis patients showed a significantly higher body mass index than the healthy group (Table 1). This result agreed with (Zhang et al., 2014 ; Feng et al., 2019 and Hamza, 2021). While this result differed with (Turesson et al., 2016). This is due to the fact that adipose tissue produces and secretes a wide range of inflammatory factors, including adipokines like leptin, cytokines like IL-1β, IL-6, and TNF-α (Vidal et al., 2015 and George et al., 2017).

Table 1. Some criteria for the study sample

Parameters		N	Mean	± Std. Error	Minimum	Maximum	P value
ESR mm/h	Control	30	9.8667	0.65167	5.00	16.00	(P < 0.01)
	Patient	70	62.7000	2.65905	29.00	110.00	
Age year	Control	30	33.5000	2.66210	17.00	65.00	(P < 0.01)
	Patient	70	45.6286	1.72956	21.00	73.00	
Weight Kg	Control	30	73.3333	2.57277	45.00	117.00	(P < 0.01)
	Patient	70	81.6857	1.76902	55.00	132.00	
BMI Kg/m^2	Control	30	27.8800	0.85434	20.10	42.00	(P < 0.05)
	Patient	70	30.6329	0.76414	21.80	52.50	

Control (Healthy) : RF^- , Patient : RF^+

It is clear from (Table 2) that sex had a significant effect on the incidence of rheumatoid arthritis, as the percentage increased in females compared to males. This is attributable to the fact that sex hormones are contributed in the immune response, as estrogen has a stimulating role for the female immune system, and androgen acts as a natural immunosuppressant in males. An increase in the concentration of estrogens and a decrease in the concentration of androgens were observed in the synovial fluids of patients with rheumatoid arthritis (Tobon et al., 2010 and Islander et al., 2011). This result agreed with (Mourad, 2012; Aga and Al-Tae, 2021 and Hamza, 2021).

Age did not significantly affect the incidence of rheumatoid arthritis (Table 2) . The highest incidence rate was for the age group 40-49 years, followed by the age group 50-59 years, which constituted 45.714% of the total incidence. AIHW (2009) indicated that the highest incidence rate was for ages 35-64. Aga and Al-Tae (2021) explained that the highest incidence rate was for the age group 46-55 years, followed by the age group 36-45 years .

The body mass index had a significant effect on the incidence of rheumatoid arthritis (Table 2), as the highest incidence rate for the category was 30-34.9. Armstrong et al., (2006) and Naranjo et al., (2008) found that more than 60% of patients with rheumatoid arthritis were overweight or obese as measured by body mass index. Zhang et al., (2014) also showed that a higher incidence of rheumatoid arthritis is associated with being overweight or obese. Hotamisligil (2006) also reported that adipose tissue is not just an inactive energy store, but rather an endocrine organ connected to the central nervous system with a set of essential functions, like the production of hormones and proteins contributed in physiological and pathological practices, involving immunity and inflammation.

Table 2 . Distribution of disease incidence among patients in the study sample

Parameters		N	RA%	P value (X^2)
Sex	Male	13	18.571	(P < 0.01)
	Female	57	81.429	
Age Year	< – 29	12	17.143	N.S
	30 – 39	11	15.714	
	40 – 49	19	27.143	
	50 – 59	13	18.571	
	60 – 69	10	14.286	
	70 – >	5	7.143	
BMI Kg/m^2	18.5 – 24.9	16	22.857	(P < 0.01)
	25 – 29.9	13	18.571	
	30 – 34.9	32	45.714	
	35 – 39.9	2	2.857	
	40 – >	7	10	

N.S : non-significant

The level of interleukins 24,29 and 31 in the blood serum

The level of IL-24 was significantly increased in the serum of patients with rheumatoid arthritis compared to healthy people (Table 3). This result agreed with (Kragstrup et al., 2008; Kragstrup et al., 2016 and Chen et al., 2018). Kragstrup et al., (2008) indicated that cytokines contribute to disease pathogenesis through the recruitment of neutrophil granule cells and mononuclear cells into the synovial fluid of the joint. Chung et al. (2021) also reported that cytokines boost the production of inflammatory molecules from different immune and non-immune cells and recruit inflammatory cells like neutrophils and macrophage to the location of inflammation.

The level of IL-29 was significantly increased in the serum of patients with rheumatoid arthritis compared to healthy people (Table 3). This result agreed with (Wang et al., 2012 ; Xu et al., 2015; Chang et al., 2017 and Junior et al., 2020).

Chang et al., (2017) indicated that IL-29 can enhance inflammatory cytokine production and participate in joint destruction in rheumatoid arthritis. Wang et al., (2012) reported that IL-29 is capable to activate synovial fibroblasts in rheumatoid arthritis to produce pro-inflammatory cytokines.

The level of IL-31 was significantly elevated in the serum of patients with rheumatoid arthritis compared to healthy people (Table 3). Hoeck et al., (2012) explained that dendritic cells stimulated with IL-31 release several pro-inflammatory cytokines such as IL-6 and TNF-α . Raap et al., (2017) reported that eosinophils stimulated with IL-31 produced pro-inflammatory cytokines IL-1α, IL-6 and chemokines.

In this regard, Salvo et al., (2018) indicated that there is a correlation between the levels of IL-31 in the serum and tissues of patients with many autoimmune and inflammatory diseases. Herrera et al., (2020) also noted a significant increase in the level of IL-31 in the blood serum of patients with psoriatic arthritis. Liu et al., (2015) found higher levels of IL-31 in serum and mucosa samples of allergic rhinitis patients.

Table 3. The level of interleukins 24,29 and 31 in the blood serum

Parameters		N	Mean	± Std. Error	Minimum	Maximum	P value
IL24 ng/L	Control	30	91.0267	1.45616	64.12	102.61	(P < 0.01)
	Patient	70	138.3237	1.49389	119.05	171.37	
IL29 ng/L	Control	30	100.4020	0.86498	87.62	112.28	(P < 0.01)
	Patient	70	152.9971	2.58982	113.08	215.69	
IL31 ng/L	Control	30	57.2570	0.22757	55.90	61.39	(P < 0.01)
	Patient	70	80.7314	1.06026	70.59	118.12	

Control (Healthy) : RF^- , Patient : RF^+

Correlation coefficient between ESR and IL-24, IL-29,IL-31

The values of correlation coefficients between ESR and IL-24, IL-29,IL-31 ranged (0.634 - 0.735) and were highly significant .The values of correlation coefficients between IL-24, IL-29, and IL-31ranged (0.702 - 0.729) and were highly significant (Table 4). These associations support the possibility of using them as indicators for the diagnosis of disease. Elevated IL-24 is related with chronic inflammation and autoimmune diseases like rheumatoid arthritis (Wang et al., 2002; Persaud et al., 2016; Chen et al., 2018 and Zhong et al., 2022). Kragstrup et al., (2016) found that IL-24 is raised in the blood plasma of patients with rheumatoid arthritis.

IL-29 is highly pathogenic in autoimmune diseases such as rheumatoid arthritis (Xu et al., 2015). The results of Chang et al., (2017) showed an increase in IL-29 levels in the blood serum of patients with rheumatoid arthritis.

Arellano et al., (2021) showed that a factor inhibiting macrophage migration (MIF) plays a role in systemic inflammation and joint destruction in rheumatoid arthritis and may be associated with IL-31 secretion. Cornelissen et al., (2012) reported that IL-31 prompts IL-20 and IL-24 expression in keratinocytes as they are rapidly stimulated by an IL-31 response.

Table 4 . Correlation coefficient between ESR and IL-24, IL-29,IL-31

	IL24	IL29	IL31
ESR	0.715**	0.634**	0.735**
IL24		0.710**	0.729**
IL29			0.702**

** : Correlation is significant at the P< 0.01 .

Influence of sex , age and BMI on the level of IL-24 , IL-29 and IL-31 in a healthy group

It is clear from Table (5 A) that there is no significant effect of sex on the level of IL-24, IL-29 and IL-31 in the blood serum of healthy individuals. This means that the sex hormones did not appear to have a role at the level of the studied interleukins.It is clear from Table (5 B) that there is no significant effect of age on the level of IL-24, IL-29 in the blood serum of healthy persons , except for IL-31, as the age category 60-69 years was superior to rest of the age categories.

It is clear from Table (5 C) that there is no significant effect of BMI on the level of IL-24, IL-29 and IL-31 in the blood serum of healthy persons .

Wang et al., (2022) explained that obesity and high-fat diets cause chronic inflammation through the secretion of pro inflammatory cytokines like TNF, IL-1, IL-2, IL-6, IL-8 and IFN, by fat cells or immune cells infiltrated into adipose tissue.

In this regard, Aga and Al-Tae (2021) did not find any significant effect of sex and age when they studied the level of IL-6 in the blood serum of healthy persons .

Table 5 A . Influence of sex on the level of IL-24 , IL-29 and IL-31 in a healthy group

Parameters	Sex	N	Mean	± Std. Error	P value
IL24 ng/L	Male	5	96.007	5.058	N.S
	Female	25	91.959	3.199	
IL29 ng/L	Male	5	99.238	3.054	N.S
	Female	25	99.693	1.932	
IL31 ng/L	Male	5	57.680	0.643	N.S
	Female	25	57.701	0.407	

N.S : non-significant

Table 5 B. Influence of age on the level of IL-24 , IL-29 and IL-31 in a healthy group

Parameters	Age	N	Mean	± Std. Error	P value
IL24 ng/L	< - 29	13	93.730	3.592	N.S
	30 - 39	7	89.127	3.718	
	40 - 49	2	98.530	6.832	
	50 - 59	6	97.134	4.422	
	60 - 69	2	91.394	9.115	
IL29 ng/L	< - 29	13	101.883	2.169	N.S
	30 - 39	7	99.323	2.245	
	40 - 49	2	99.581	4.125	
	50 - 59	6	98.595	2.670	
	60 - 69	2	97.945	5.504	
IL31 ng/L	< - 29	13	56.721 b	0.457	(P < 0.05)
	30 - 39	7	57.301 b	0.473	
	40 - 49	2	56.259 b	0.869	
	50 - 59	6	56.908 b	0.563	
	60 - 69	2	61.263 a	1.160	

N.S : non-significant , Means with different letters are significantly different

Table 5 C. Influence of BMI on the level of IL-24 , IL-29 and IL-31 in a healthy group

Parameters	BMI	N	Mean	± Std. Error	P value
IL24 ng/L	18.5 - 24.9	8	92.417	3.882	N.S
	25 - 29.9	11	94.893	3.626	
	30 - 34.9	9	89.591	3.719	
	40 - >	2	99.030	9.458	
IL29 ng/L	18.5 - 24.9	8	97.982	2.344	N.S
	25 - 29.9	11	101.243	2.189	
	30 - 34.9	9	97.971	2.245	
	40 - >	2	100.665	5.711	
IL31 ng/L	18.5 - 24.9	8	58.181	0.494	N.S
	25 - 29.9	11	57.807	0.461	
	30 - 34.9	9	57.984	0.473	
	40 - >	2	56.790	1.203	

N.S : non-significant

Influence of sex , age and BMI on the level of IL-24 , IL-29 and IL-31 in a group of patients

Table (6A) shows that there is no significant effect of sex on the level of IL-24, IL-29 and IL-31 in the blood serum of patients with rheumatoid arthritis. This means that the sex hormones did not appear to have an effect on the level of the studied interleukins.

Table (6 B) shows that there is no significant effect of age on the level of IL-24, IL-29, IL-31 in the blood serum of patients with rheumatoid arthritis.

Table (6 C) shows that there is no significant effect of BMI on the level of IL-29, IL-31 in the blood serum of patients with rheumatoid arthritis, except for IL-24, as all categories outperformed category 35-39.9.

In this regard, Aga and Al-Tae (2021) did not find any significant effect of sex and age when they studied the level of IL-6 in the blood serum of patients with rheumatoid arthritis.

Table 6 A. Influence of sex on the level of IL-24 , IL-29 and IL-31 in a group of patients

Parameters	Sex	N	Mean	± Std. Error	P value
IL24 ng/L	Male	13	135.897	4.142	N.S
	Female	57	136.773	2.533	
IL29 ng/L	Male	13	152.883	7.284	N.S
	Female	57	156.434	4.454	
IL31 ng/L	Male	13	82.986	3.019	N.S
	Female	57	81.823	1.846	

N.S : non-significant

Table 6 B. Influence of age on the level of IL-24 , IL-29 and IL-31 in a group of patients

Parameters	Age	N	Mean	± Std. Error	P value
IL24 ng/L	< - 29	12	141.076	4.518	N.S
	30 - 39	11	132.258	4.687	
	40 - 49	19	132.625	3.533	
	50 - 59	13	135.133	3.855	
	60 - 69	10	135.371	4.616	
	70 - >	5	141.549	6.201	
IL29 ng/L	< - 29	12	163.733	7.944	N.S
	30 - 39	11	145.380	8.241	
	40 - 49	19	148.699	6.213	
	50 - 59	13	153.880	6.778	
	60 - 69	10	158.015	8.116	
	70 - >	5	158.244	10.902	
IL31 ng/L	< - 29	12	80.944	3.293	N.S
	30 - 39	11	81.293	3.416	
	40 - 49	19	80.859	2.575	
	50 - 59	13	79.646	2.809	
	60 - 69	10	88.594	3.364	
	70 - >	5	83.093	4.519	

N.S : non-significant

Table 6 C. Effect of BMI on the level of IL-24 , IL-29 and IL-31 in a group of patients

Parameters	BMI	N	Mean	± Std. Error	P value
IL24 ng/L	18.5 - 24.9	16	137.222 a	3.751	(P < 0.05)
	25 - 29.9	13	144.551 a	3.556	
	30 - 34.9	32	138.142 a	2.551	
	35 - 39.9	2	121.309 b	9.437	
	40 - >	7	140.453 a	5.208	
IL29 ng/L	18.5 - 24.9	16	151.056	6.595	N.S
	25 - 29.9	13	165.775	6.252	
	30 - 34.9	32	148.942	4.485	
	35 - 39.9	2	158.813	16.593	
	40 - >	7	148.707	9.157	
IL31 ng/L	18.5 - 24.9	16	81.611	2.734	N.S
	25 - 29.9	13	85.355	2.592	
	30 - 34.9	32	79.435	1.859	
	35 - 39.9	2	82.040	6.878	
	40 - >	7	83.583	3.796	

N.S : non-significant

Means with different letters are significantly different

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