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Role of COX-2 and mPGES-1 enzymes 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 COX-2 and mPGES-1 enzymes in patients with rheumatoid arthritis, in addition to total body lipids.

The results showed : The average level of COX-2 and mPGES1 enzymes was (59.117 U/L and 264.832 ng/L) respectively in blood serum of patients with rheumatoid arthritis, compared to (20.518 U/L and 103.681 ng/L) respectively in blood serum of healthy persons. The level of COX-2 and mPGES-1 enzymes increased significantly ($P < 0.01$) in patients with rheumatoid arthritis compared to healthy persons. The values of correlation coefficients ranged between ESR and COX-2, mPGES-1 enzymes (0.755 - 0.777) and were highly significant. Sex did not have a significant effect on the level of enzymes, age did not have a significant effect, body mass index have a significant effect of mPGES-1 in healthy persons. Sex had no significant effect on the level of enzymes, age had significant effect of mPGES-1, body mass index had no significant effect in patients with rheumatoid arthritis. The levels of TG,CHOL,HDL,LDL and VLDL were significantly increased in rheumatoid arthritis patients compared to healthy persons.

Key words: Rheumatoid arthritis , COX-2 and mPGES1 enzymes, Total body lipids.

Introduction

Rheumatoid arthritis is a common and chronic autoimmune disease, as it mainly affects the synovial membranes of many joints of the body, which leads to swelling , pain and stiffness that may develop into loss of function and movement (occurrence of disability) (Miehle et al., 2000; Dobkin et al., 2008 and Aletaha et al. 2010).

This disease is considered one of the autoimmune diseases that begins with the loss of immune tolerance, that is, the ability to distinguish between what is self or non-self in an immunologically sensitive host, meaning that the immune system attacks healthy tissues in the body (Harris, 1990 and Sajad and Mohammed, 2020) .

Rheumatoid arthritis is prevalent all over the world (Alamanos et al., 2006 and Bax et al., 2011) . Rheumatoid arthritis influence about 0.5-1% of the world's population and 75% of those affected are women. The peak incidence of this disease is between the ages of 30-50 years (Scott et al., 2010 and Silman and Parson, 2002) .

COX-2 enzyme has been identified as an inducible or pathogenic enzyme that can be stimulated by different chemical, physical or biological agents. It also contributes in the inflammatory response by facilitating prostaglandin biosynthesis (Shimomura et al., 2014). The expression of COX-2 is upregulated in monocytes, macrophages, fibroblasts, synovial cells and endothelial cells. In addition, induction of COX-2 in response to stimulus by pro-inflammatory cytokines like IL-1β and (TNF-α) was observed in synovial fibroblasts of patients with rheumatoid arthritis (Kapoor et al., 2006 and Wu et al., 2013). Yang et al., (2017) indicated that COX-2 has very low expression in normal cells and tissues and is not produced extensively by cells except when induced.

mPGES-1 enzyme belongs to a family of membrane-related proteins involved in the metabolism of prostaglandin and glutathione. It has a major role in the synthesis of PGE2 in vivo (Sampey et al., 2005). Prostaglandin are the central substance contributed in the development of persistent inflammation appear in

diseases like rheumatoid arthritis. Topical inflammation of the synovial tissue is characterized by elevated levels of prostaglandins, mostly PGE2 (Sampey et al., 2005; Kojima et al., 2011 and Fattahi and Mirshafiey, 2012). mPGES-1 doings downstream of COX-2 and catalyzes the final step of PGE2 biosynthesis (Kojima et al., 2011). mPGES-1 binds preferentially to COX-2 and is stimulated in response to different stimuli (Gudis and Sakamoto, 2005).

The research aims to identify the role of COX-2 and mPGES-1 enzymes 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 COX-2 and mPGES-1 enzymes in patients with rheumatoid arthritis, in addition to total body lipids .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 COX-2 and mPGES-1 enzymes Elsa Kit from the Chinese company BTLAB and India company AGAPPE for total lipids.

Results and discussion

The level of COX-2 and mPGES-1 enzymes in the blood serum

The level of COX-2 enzyme was significantly increased in the serum of patients with rheumatoid arthritis compared to healthy people (Table 1). This result agreed with Wang et al., (2020).

Expression of COX-2 has been associated with disease activity in synovial tissues of patients with rheumatoid arthritis (Kapoor et al., 2006). Kapoor et al., (2006) and Wu et al., (2013) observed induction of COX-2 in response to stimulus by pro-inflammatory cytokines like IL-1β and TNF-α in synovial fibroblasts of rheumatoid arthritis patients. COX-2 has been identified as an inducible or pathogenic enzyme that can be stimulated by different chemical, physical or biological agents. It also contributes in the inflammatory response by facilitating the biosynthesis of prostaglandins (Shimomura et al., 2014).

The mPGES-1 enzyme level was significantly increased in the serum of patients with rheumatoid arthritis compared to healthy people (Table 1). In this regard, it was observed that the expression of mPGES-1 increased in the synovial tissue of patients with rheumatoid arthritis (Murakami et al., 2003 and Westman et al., 2004). Sano (2011) showed that mPGES-1 is up-regulated in the synovial fluid in rheumatoid arthritis. Korotkova and Jakobsson (2011) reported that mPGES-1 is overexpressed in rheumatoid arthritis.

The up-regulation of mPGES-1 expression is watched in synovial fibroblasts of rheumatoid arthritis as well as in many other cell types. mPGES-1 is extremely regulated by inflammatory stimuli and contributes in the generation of raised PGE2 in inflammation in response to IL-1β and/or TNF- α (Murakami et al., 2000; Stichtenoth et al., 2001 and Saequsa et al., 2003).

Table 1. The level of COX-2 and mPGES-1 enzymes in the blood serum

Parameters		N	Mean	± Std. Error	Minimum	Maximum	P value
mPGES-1 ng/L	Control	30	103.6817	1.52339	92.04	130.21	(P < 0.01)
	Patient	70	264.8320	4.21449	180.75	363.58	

COX-2 U/L	Control	30	20.5180	0.19911	16.38	22.08	(P < 0.01)
	Patient	70	59.1171	0.66954	48.07	77.54	

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

Correlation coefficient between ESR and enzymes

The values of correlation coefficients between ESR and COX-2,mPGES-1 enzymes ranged (0.755 - 0.777) and were highly significant (Table 2). The values of correlation coefficients between. The correlation coefficient between COX-2 and mPGES-1 enzymes was (0.896) and was highly significant (Table 2). These associations support the possibility of using them as indicators for the diagnosis of disease.

Expression of COX-2 has been related with disease activity in synovial tissues of patients with rheumatoid arthritis (Kapoor et al., 2006). The results of Wang et al., (2020) indicated that the expression levels of COX-2 were significantly increased in the blood serum of patients with rheumatoid arthritis.

Elevated mPGES-1 expression has been observed in the synovial tissue of patients with rheumatoid arthritis (Murakami et al., 2003; Westman et al., 2004 and Korotkova and Jakobsson, 2011).

Wang et al., (2020) found that there is a positive and significant correlation of 0.618 between COX-2 expression levels and ESR, and thus this can be used as an indicator for disease diagnosis.

Table 2. Correlation coefficient between ESR and enzymes

	mPGES1	COX2
ESR	0.755**	0.777**
mPGES1		0.896**

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

Influence of sex , age and BMI on the level of COX-2 and mPGES-1 enzymes in a healthy group

It is clear from Table (3A) that there is no significant influence of sex on the level of COX-2 and mPGES-1 enzymes 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 and enzymes.

It is clear from Table (3 B) that there is no significant influence of age on the level of COX-2 and mPGES-1 enzymes in the blood serum of healthy persons . Wu and Meydani (2004) reported that COX-2 and its product especially prostaglandins (PGE2), play a critical role in dysregulating age-related immune and inflammatory responses, as increased production of PGE2 contributes to the suppression of T-cell function with age.

It is clear from Table (3 C) that there is no significant influence of BMI on the level of COX-2 enzyme in the blood serum of healthy persons , except for mPGES-1, where the 40-> category was superior to rest of the categories.

Table 3 A . Influence of sex on the level of COX-2 and mPGES-1 enzymes in a healthy group

Parameters	Sex	N	Mean	± Std. Error	P value
mPGES1 ng/L	Male	5	109.813	4.139	N.S
	Female	25	110.735	2.618	
COX2	Male	5	20.652	0.680	N.S

U/L	Female	25	21.074	0.430	

N.S : non-significant

Table 3 B. Influence of age on the level of COX-2 and mPGES-1 enzymes in a healthy group

Parameters	Age	N	Mean	± Std. Error	P value
mPGES1 ng/L	< - 29	13	109.986	2.939	N.S
	30 - 39	7	108.381	3.042	
	40 - 49	2	112.570	5.591	
	50 - 59	6	108.451	3.618	
	60 - 69	2	111.982	7.459	
COX2 U/L	< - 29	13	20.819	0.483	N.S
	30 - 39	7	20.013	0.500	
	40 - 49	2	20.790	0.919	
	50 - 59	6	20.897	0.595	
	60 - 69	2	21.796	1.226	

N.S : non-significant

Table 3 C. Influence of BMI on COX-2 and mPGES-1 enzymes in a healthy group

Parameters	BMI	N	Mean	± Std. Error	P value
mPGES1 ng/L	18.5 - 24.9	8	106.398 b	3.176	(P < 0.01)
	25 - 29.9	11	104.271 b	2.967	
	30 - 34.9	9	98.785 b	3.043	
	40 - >	2	131.642 a	7.739	
COX2 U/L	18.5 - 24.9	8	21.108	0.522	N.S
	25 - 29.9	11	20.336	0.488	
	30 - 34.9	9	20.249	0.500	
	40 - >	2	21.759	1.272	

N.S : non-significant

Means with different letters are significantly different

Influence of sex , age and BMI on the level of COX-2 and mPGES-1 enzymes in a group of patients

Table (4 A) shows that there is no significant influence of sex on the level of COX-2 and mPGES-1 enzymes 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 and enzymes.

Table (4 B) shows that there is no significant influence of age on the level of COX-2 enzyme in the blood serum of patients with rheumatoid arthritis, except for mPGES-1, as the age category exceeded 70-> years in the category of 30-39 years.

Wu and Meydani (2004) reported that COX-2 and its product especially prostaglandins (PGE2), play a critical role in dysregulating age-related immune and inflammatory responses, as increased production of PGE2 contributes to the suppression of T-cell function with age.

Table (4 C) shows that there is no significant influence of BMI on the level of COX-2 and mPGES-1 enzymes in the blood serum of patients with rheumatoid arthritis.

Table 4 A. Influence of sex on the level of COX-2 and mPGES-1 enzymes in a group of patients

Parameters	Sex	N	Mean	± Std. Error	P value
mPGES1 ng/L	Male	13	267.788	12.097	N.S
	Female	57	269.526	7.397	
COX2 U/L	Male	13	58.854	1.923	N.S
	Female	57	58.640	1.176	

N.S : non-significant

Table 4 B. Influence of age on the level of COX-2 and mPGES-1 enzymes in a group of patients

Parameters	Age	N	Mean	± Std. Error	P value
mPGES1 ng/L	< - 29	12	271.881 ab	13.193	(P <0.05)
	30 - 39	11	248.990 b	13.687	
	40 - 49	19	273.896 ab	10.319	
	50 - 59	13	257.148 ab	11.257	
	60 - 69	10	266.786 ab	13.480	
	70 - >	5	293.238 a	18.108	
COX2 U/L	< - 29	12	59.727	2.097	N.S
	30 - 39	11	57.897	2.175	
	40 - 49	19	57.932	1.640	
	50 - 59	13	56.885	1.789	
	60 - 69	10	58.602	2.142	
	70 - >	5	61.439	2.878	

N.S : non-significant

Means with different letters are significantly different

Table 4 C. Influence of BMI on the level of COX-2 and mPGES-1 enzymes in a group of patients

Parameters	BMI	N	Mean	± Std. Error	P value
mPGES1 ng/L	18.5 - 24.9	16	272.560	10.954	N.S
	25 - 29.9	13	263.429	10.384	
	30 - 34.9	32	265.825	7.448	
	35 - 39.9	2	291.749	27.560	
	40 - >	7	249.721	15.209	
COX2 U/L	18.5 - 24.9	16	61.367	1.741	N.S
	25 - 29.9	13	59.252	1.650	

	30 - 34.9	32	59.606	1.184	
	35 - 39.9	2	57.184	4.380	
	40 - >	7	56.326	2.417	

N.S : non-significant

The relationship between total lipids and rheumatoid arthritis

Table (5) shows that total body lipids levels (TG, CHOL, HDL, LDL, and VLDL) are higher in the blood serum of patients with rheumatoid arthritis compared to healthy persons.

Gan et al., (2018) showed that TG and VLDL concentrations are increased in the early stages of inflammatory diseases. TNF inhibitor treatment was associated with an increase in TC and LDL concentrations by up to 30% (Navarro et al., 2013 and Kirkham et al., 2013). Liao et al., (2015) noted that there was a significant increase in LDL concentration and an improvement in HDL concentration in patients with rheumatoid arthritis after receiving treatment. Van et al., (2011) explained that anti-inflammatory therapies increase TC, HDL and LDL concentrations to varying degrees in patients with rheumatoid arthritis. Shah et al., (2017) indicated that the increase in TC concentration may be part of a metabolic syndrome that is more prevalent in patients with rheumatoid arthritis. Treatment with anti-inflammatory agents leads to a paradoxical rise in lipids, but this rise may not be related with an increased risk of cardiovascular disease.

Table 5 .The relationship between total lipids and rheumatoid arthritis

Parameters		N	Mean	± Std. Error	Minimum	Maximum	P value
TG mg/dL	Control	30	142.0333	6.24288	93.00	210.00	(P < 0.01)
	Patient	70	183.1429	6.25422	96.00	416.00	
CHOL mg/dL	Control	30	172.8000	4.46864	130.00	206.00	(P < 0.05)
	Patient	70	193.8571	5.79795	112.00	307.00	
HDL mg/dL	Control	30	37.4800	2.21986	28.00	56.00	(P < 0.01)
	Patient	70	50.9800	2.29927	29.00	87.00	
LDL mg/dL	Control	30	76.4333	2.58229	53.00	101.00	(P < 0.01)
	Patient	70	92.4429	3.62631	37.00	164.00	
VLDL mg/dL	Control	30	28.4300	1.25511	18.60	42.00	(P < 0.01)
	Patient	70	36.5157	1.23809	19.20	83.20	

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

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