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Evaluation of Novel Immunological Mediator in Patients With *Helicobacter pylori* in Baghdad City, Iraq

Thamer Mutlag Jasim*

Department of Laboratory Clinical Sciences, College of Pharmacy,
All Mustansiriya University, Baghdad, Iraq

**Corresponding author*

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A B S T R A C T

Helicobacter pylori (*H.pylori*) infection is endemic in Iraq and important cause of gatrointestinal disorders, as well as an increase in blood levels of certain inflammatory markers. Sixty patients infected with H.*pylori* was inserted in the current study with age (31.4±3.96) randomly selected from Al Yarmok of Teaching Hospital in Baghdad during April 2015. Patients were diagnosed by using stool antigen and CagAIgG. The medical history was taken, body weight and height were measured and body mass index (BMI) was calculated. Serum Monocyte chemoattractant protein 1 (MCP1) was determined, as well as Interleukin 6 (IL-6) and Fetuin A levels. For comparison, thirty apparently healthy subjects which were matched with patients group for age, weight and BMI (n=30, age=30.5±3.77 years; BMI= 27.13± 2.13 kg/m2; mean±SD). The prevalence of anti H.*pylori* Cag A-IgG antibodies in patient group (78.3±9.8 U/ml) significantly higher(<0.0001) than healthy subjects group (4.2±2.8 U/ml). H.*pylori* was capable with a significant rise in the in the inflammatory mediators (fetuin A, MCP1 and IL-6). Fetuin A levels were very highly significant lower($p<0.0001$) in patient, group when compared to healthy subjects(29.53±5.25 vs 53. 45±8.37 respectively). The MCP1 levels which significantly increased($p<0.0001$)in patient group(48.79±6.03) when compared to control group (37.2±6.85). The mean of IL-6 also shown highly significant difference in patient group when compared to healthy control. The current study also shown there was a positive correlation between MCP1 and IL-6.

Introduction

Helicobacter pylori (*H.pylori*) is a highly adapted gastric pathogen that chronically infects more half of the world population (AminTalibi, 2014). *H.pylori* are gram negative, microaerophilic that colonize the stomach gastritis adenocarcinoma and peptic ulcer (Davand *et al*., 2013,Fischer et al., 2009).The Cag A gene, which is the marker for the presence of pathogenicity is land has been shown to be involved induction of proinflammatory cytokine release (Nader Baghert *et al*., 2015).

The secretion of chemokines is an important

part of the host defence against invading pathogen, however, they may also contribute to pathogenesis of disease by promoting mucosal damage and epithelial dysfunction for example, intestinal metaplasia may be induced by cytokines for promoting persistant epithelial cell activation and intracellular signaling(Crabter 1998). Monocyte Chemoattractant Protein-1 (MCP-1) may induce release of oxygen-free radical and proteases from inflammatory cell causing organ damage and fauilure (Klier *et al*.,2001). Biological factors that affect clinical outcome in *H.pylori* infection virulence determinant in *H.pylori* strains, immunological factors in the host are likely to play crucial role, clinical expression mucosa is related to increased production of proinflammatory cytokines, including IL-6 which are believed to contribute to maintaining the gastric inflammation and causing epithelial cell damage(Zandi *et al*., 2013). IL-6 is acytokine with awide variety of biological functions. This is a potent inducer of the acute face response. IL-6 plays an essential role in find differentiation of B cell into log-secreting cells involved in lymphocyte and monocyte differentiation. *H.pylori* infection secreted various cytokines, including MCP1 and thus induced T cell cox-2 expression and activity. Fetuin A inhibit insulin receptor tyrosine activity by blooking autophosphorelation of tyrosinnase and IRS-1 induce lower grade inflammation (A.M.Hennige et al.,2008). Many studies have shown that *H.pylori* infection elevated production of proinflammatory cytokines,regulators of immune and some peptide chemokines such as interleukin 6 (Arabi 2010).The aim of the present study to investigate the relationship of mediator CagA-IgG, MCP-1,IL-6 and Fetuin A among *H.pylori* infection.

Material and Methods

Sixty patients infected with *H.pylori* was inserted in the current study with age *(*31.4±3.96) randomly selected from those attending Al-Yarmook Teaching Hospital in Baghdad during April in 2015. Patients were diagnosed by using stool Ag test (Coris-Bio, BELGIUM). Another test also done -Cag-A IgG (Biocompare,USA) to support the diagnosis. The medical history was taken, body weight and height were measured and body mass index (BMI) was calculated. Serum MCP-1 was determine by using ELISA technique (Elabscience Biotechnology Co. Japan). As well as, human Fetuin -A and IL-6 determine by ELISA kit (RayBiotech, USA).

For comparison, thirty apparently healthy subjects who were matched for age, weight, and BMI [n=30; age=30.5± 3.77 (years); BMI = 27.13± 2.13 (kg/m2);mean ± SD] the control subjects do not suffer from any disease and not taking any medication.

Statistical Analysis

Statistical analysis was performed using SPSS-21 (Statistical Packages for Social Sciences- version 21). Unpaired t-test was used to assess significant difference between means. $P < 0.05$ was considered statistically significant. Receiver operation characteristic method (ROC curve) was performed by MedCalc -12 program(IBM corp 2012).

Results and Discussion

The prevalence of anti-*H.pylori* CagA IgG antibodies in patients group (78.3±9.8 U/ml) significantly higher (<0.0001) than healthy subjects group(4.2±2.8 U/ml), while there were no significant differences between patients and healthy groups in the anthropometric measurements [weight (83.3±6, 82.2±6.4 respectively) and height (172.3±4.6, 174.1±5.27 respectively)], table (1).

H.pylori was capable with a significant

differences in the inflammatory mediators (fetiun-A, MCP-1 and IL-6), as shown in table 2.

Fetuin A levels were very highly significant lower (P<0.0001) in patients group when compared to healthy subjects group (29.53± 5.25 vs. 53.45±8.37)

This was contrary to the MCP-1 levels which significantly increased (P<0.0001) in patients group (48.79± 6.03 compared to control group (37.02±6.85), figure (2).

The mean of IL-6 also shown highly significant difference (P<0.0001) in patients group when compared to healthy control

To find the sensitivity and specificity for each mediator, the receiver operation characteristic was done but it cannot be applied only in the MCP-1 because of the lack in overlap for the results except for the results of MCP-1.

In the current study, there was a positive correlation between MCP-1 and IL-6, as shown in table(3).

The effect of body weight also studied in the present study by divided the patients group to subgroups according to the values of BMIP (as Patient/optimal ≤1 and Patient/overweight>1) as shown in table (4)

BMI Prime, a simple modification of the BMI system, is the ratio of actual BMI to upper limit BMI (currently defined at BMI 25). As defined, BMI Prime is also the ratio of body weight to upper body-weight limit, calculated at BMI 25. Since it is the ratio of two separate BMI values, BMI Prime is a dimensionless number without associated units. Individuals with BMI Prime less than 0.74 are underweight; those with between 0.74 and 1.00 have optimal weight; and those at 1.00 or greater are overweight. BMI Prime is useful clinically because individuals can tell, at a glance, by what percentage they deviate from their upper weight limits. For instance, a person with BMI 34 has a BMI Prime of 34/25 = 1.36, and is 36% over his or her upper mass limit.

Table above shows the multiple comparisons among three groups.1 vs 2, 1 vs 3 and 2 vs 3. In this analysis we found that the two groups (Patient/optimal weight and overweight) did not differ in all parameters. In other words, it means that the BbodiesMIP has no effect on these parameters.

The prevalence of anti-*H.pylori* CagA Ig Gantibodies in patient group significantly higher(<0.0001) than healthy subjects groups, a proportion similar to that reported also in Africa(Sanz-Pelaez *et al*., 2008,Smithsi *et al*2002). There is no significantly significant association with CagAIg positivity and age agreement with (Alsharipours *et al*., 2014).The current study found increase significantly IL-6 levels (Table2) agreed with (Hiroke Nakagawa *et al*.,2015) who found that serum IL-6 level was significantly among *H.pylori* infected in adult Japanese. Other study shown that *H.pylori* infection is associated with increased IL-6 and TNF-α production within the gastric mucosa (Jamshid Vafaeimanesh *et al*., 2014).

Fetuin A is anti inflammatory mediator that participate in macrophage deactivation specially fetuin A, enhance the cellular uptake of cationic inhibitors of proinflammatory cytokines synthesis by macrophage, thus preventing the morbid sequeleae of infection that result from over production of pro-inflammatory cytokines (Ombrellion M *et al*., 2001).

Table.1 The Clinical Characteristics of *H.pylori* Infected Patients Compared to Control Group

		N	Mean	Std. Deviation	Std. Error Mean	P
Age	Control	30	30.53	3.77	0.68	0.36
	Patient	60	31.44	3.96	0.73	
Weight	Control	30	82.20	6.46	1.17	0.49
	Patient	60	83.31	6.03	1.11	
Height	Control	30	174.13	5.27	0.96	0.17
	Patient	60	172.34	4.63	0.86	
CagAIgG	Control	30	4.28	2.80	0.51	<0.0001
	Patient	60	78.36	9.82	1.82	

Table.2 The Immunological Markers in Patients vs. Control Group

		N	Mean	Std. Deviation	Std. Error Mean	P
Fetuin	Control	30	53.45	8.37	1.52	<0.0001
	Patient	60	29.53	5.25	0.97	
MCP1	Control	30	37.02	6.85	1.25	<0.0001
	Patient	60	48.79	6.03	1.12	
IL6	Control	30	4.35	1.16	0.21	<0.0001
	Patient	60	9.25	1.96	0.36	

Table.3 The Correlations Between Studied Parameters in Patients Group

		Wt	Heigh	Cag-A-IgG	Fetuin-A	MCP-1	IL-6
Age	Pearson Correlation	.703**	.438*	-.252-	.010	-.079-	-.015-
	Sig. (2-tailed)	.000	.017	.187	.960	.684	.938
	N	60	60	60	60	60	60
Wt	Pearson Correlation	1	.756**	.134	.145	-.071-	-.017-
	Sig. (2-tailed)		.000	.489	.453	.714	.931
	N		60	60	60	60	60
Heigh	Pearson Correlation		1	.212	.029	.131	-.052-
	Sig. (2-tailed)			.271	.881	.498	.790
	N			60	60	60	60
Cag-A-IgG	Pearson Correlation			1	.098	.084	.075
	Sig. (2-tailed)				.614	.666	.697
	N				60	60	60
Fetuin-A	Pearson Correlation				1	-.152-	.067
	Sig. (2-tailed)					.431	.731
	N					60	60
MCP-1	Pearson Correlation					1	.758**
	Sig. (2-tailed)						.000
	N						60
IL-6	Pearson Correlation						1
	Sig. (2-tailed)						
	N						

Table.4 Studied Parameters in the Subgroups

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.
						Lower Bound	Upper Bound		
Age	Control	30	30.5333	3.77591	.68938	29.1234	31.9433	25.00	41.00
	Patient/optimal	14	28.1429	2.60951	.98630	25.7295	30.5562	25.00	32.00
	Patient/overweight	46	32.5000	3.76386	.80246	30.8312	34.1688	25.00	41.00
	Total	90	30.9831	3.86180	.50276	29.9767	31.9894	25.00	41.00
CagA IgG	Control	30	4.2867	2.80304	.51176	3.2400	5.3333	1.50	12.10
	Patient/optimal	14	76.6000	6.23538	2.35675	70.8332	82.3668	67.00	86.00
	Patient/overweight	46	78.9227	10.78685	2.29976	74.1401	83.7053	43.00	94.00
	Total	90	40.6966	38.02125	4.94995	30.7882	50.6050	1.50	94.00
Fetuin	Control	30	53.4500	8.37190	1.52849	50.3239	56.5761	39.20	76.80
	Patient/optimal	14	28.4286	6.14457	2.32243	22.7458	34.1113	19.60	37.40
	Patient/overweight	46	29.8909	5.04654	1.07593	27.6534	32.1284	21.00	39.00
	Total	90	41.6966	13.91893	1.81209	38.0693	45.3239	19.60	76.80
MCP 1	Control	30	37.0200	6.85527	1.25160	34.4602	39.5798	22.50	48.20
	Patient/optimal	7	50.0429	5.86056	2.21508	44.6227	55.4630	39.60	55.40
	Patient/overweight	22	48.4000	6.17337	1.31617	45.6629	51.1371	41.20	66.30
	Total	59	42.8085	8.73817	1.13761	40.5313	45.0857	22.50	66.30
IL6	Control	30	4.3533	1.16285	.21231	3.9191	4.7876	.70	6.20
	Patient/optimal	7	8.7143	2.20940	.83507	6.6709	10.7576	6.30	11.40
	Patient/overweight	22	9.4227	1.90586	.40633	8.5777	10.2677	7.20	13.30
	Total	59	6.7610	2.93980	.38273	5.9949	7.5271	.70	13.30
BMI	Control	30	27.1347	2.13247	.38933	26.3384	27.9309	22.98	31.16
	Patient/optimal	7	26.3571	.82202	.31070	25.5969	27.1174	24.91	26.96
	Patient/overweight	22	28.5600	1.00762	.21483	28.1132	29.0068	27.36	31.10

Table.5 The Multiple Comparisons among Three Groups

Multiple Comparisons

Dependent Variable	(I) trt	(J) trt	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Age	1	2	2.39048	1.53800	.126	-.6905-	5.4715
		3	-1.96667-	1.02847	.061	-4.0269-	.0936
	2	1	-2.39048-	1.53800	.126	-5.4715-	.6905
		3	-4.35714-*	1.59002	.008	-7.5423-	-1.1719-
	3	1	1.96667	1.02847	.061	-.0936-	4.0269
		2	4.35714*	1.59002	.008	1.1719	7.5423
CagAIgG	1	2	-72.31333-*	3.02302	.000	-78.3692-	-66.2575-
		3	-74.63606-*	2.02153	.000	-78.6857-	-70.5865-
	2	1	72.31333*	3.02302	.000	66.2575	78.3692
		3	-2.32273-	3.12528	.460	-8.5834-	3.9380
	3	1	74.63606*	2.02153	.000	70.5865	78.6857
		2	2.32273	3.12528	.460	-3.9380-	8.5834
Fetuin	1	2	25.02143*	2.96486	.000	19.0821	30.9608
		3	23.55909*	1.98264	.000	19.5874	27.5308
	2	1	-25.02143-*	2.96486	.000	-30.9608-	-19.0821-
		3	-1.46234-	3.06515	.635	-7.6026-	4.6779
	3	1	-23.55909-*	1.98264	.000	-27.5308-	-19.5874-
		2	1.46234	3.06515	.635	-4.6779-	7.6026
MCP1	1	2	-13.02286-*	2.73025	.000	-18.4922-	-7.5535-
		3	-11.38000-*	1.82575	.000	-15.0374-	-7.7226-
	2	1	13.02286*	2.73025	.000	7.5535	18.4922
		3	1.64286	2.82260	.563	-4.0115-	7.2972
	3	1	11.38000*	1.82575	.000	7.7226	15.0374
		2	-1.64286-	2.82260	.563	-7.2972-	4.0115
IL6	1	2	-4.36095-*	.67492	.000	-5.7130-	-3.0089-
		3	-5.06939-*	.45133	.000	-5.9735-	-4.1653-
	2	1	4.36095*	.67492	.000	3.0089	5.7130
		3	-.70844-	.69775	.314	-2.1062-	.6893
	3	1	5.06939*	.45133	.000	4.1653	5.9735
		2	.70844	.69775	.314	-.6893-	2.1062
BMI	1	2	.77752	.70339	.274	-.6315-	2.1866
		3	-1.42533-*	.47036	.004	-2.3676-	-.4831-
	2	1	-.77752-	.70339	.274	-2.1866-	.6315
		3	-2.20286-*	.72718	.004	-3.6596-	-.7461-
	3	1	1.42533*	.47036	.004	.4831	2.3676
		2	2.20286*	.72718	.004	.7461	3.6596

*. The mean difference is significant at the 0.05 level

Figure.1 Mean of Fetuin A in Patient and Control Groups

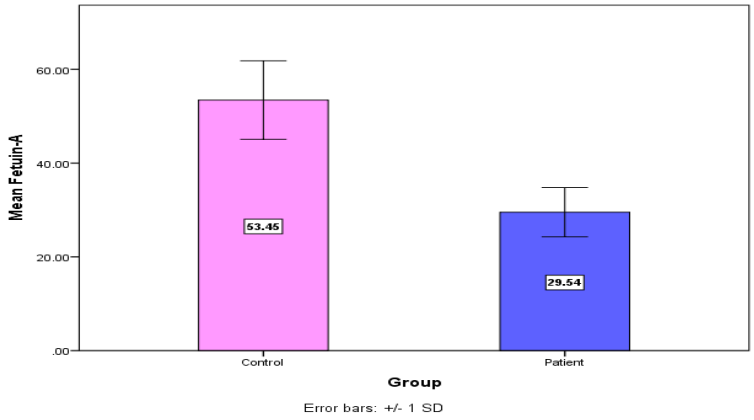


Figure.2 Mean of MCP-1 in Patients and Controls Groups

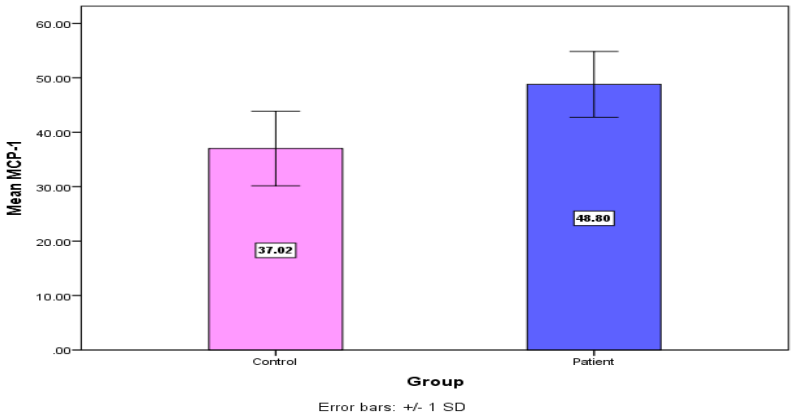


Figure.3 Mean of MCP-1 in Patients and Controls Groups

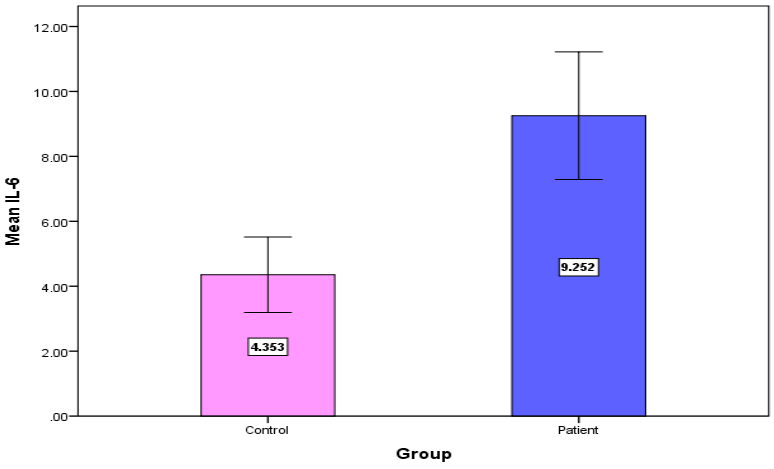
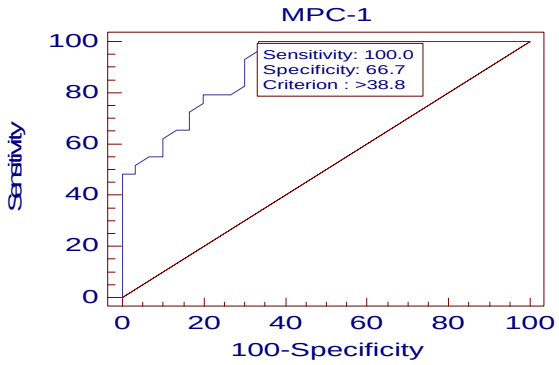


Figure.4 Receiver Operator Curve Analysis for the Investigated Parameters *H.pylori* Patients and Controls



Area under the ROC curve (AUC)	0.898
Standard Error[a]	0.0383
95% Confidence interval[b]	0.792 to 0.962
z statistic	10.406
Significance level P (Area=0.5)	<0.0001

Fetuin A increase significantly in the current study (Fig1,2) and this finding in agreed with (Kebapiclar 2010) Who reported significant increase in anti-inflammatory markers such as Fetuin A. MCP1 to be higher in *H.pylori* positive versa agreed with (Nomura *et al*., 2004). In the current study, there was appositive correlation between MCP1 and,as shown in (Table 3). To our knowledge, there have been no reports for the correlation between MCP1, fetuin A and IL6 in Iraq. To evaluate infurther studies the molecular epidemiology of *H.pylori* infection in the general population.

In conclusion, MCP1was found to be significantly elevated in patients group versus the control group, also there was a significant difference in IL-6 level in *H.pylori* +ve versus healthy group. Fetuin A was found to be high in pateints group when compared to healthy subjects and there positive correlation between IL-6 and MCP-1.

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