



## Original Article

# Serum Levels of Interleukin-27 in Type 1 Diabetes Children Infected with *Helicobacter Pylori* and Its Association with CagA Positivity

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## ABSTRACT

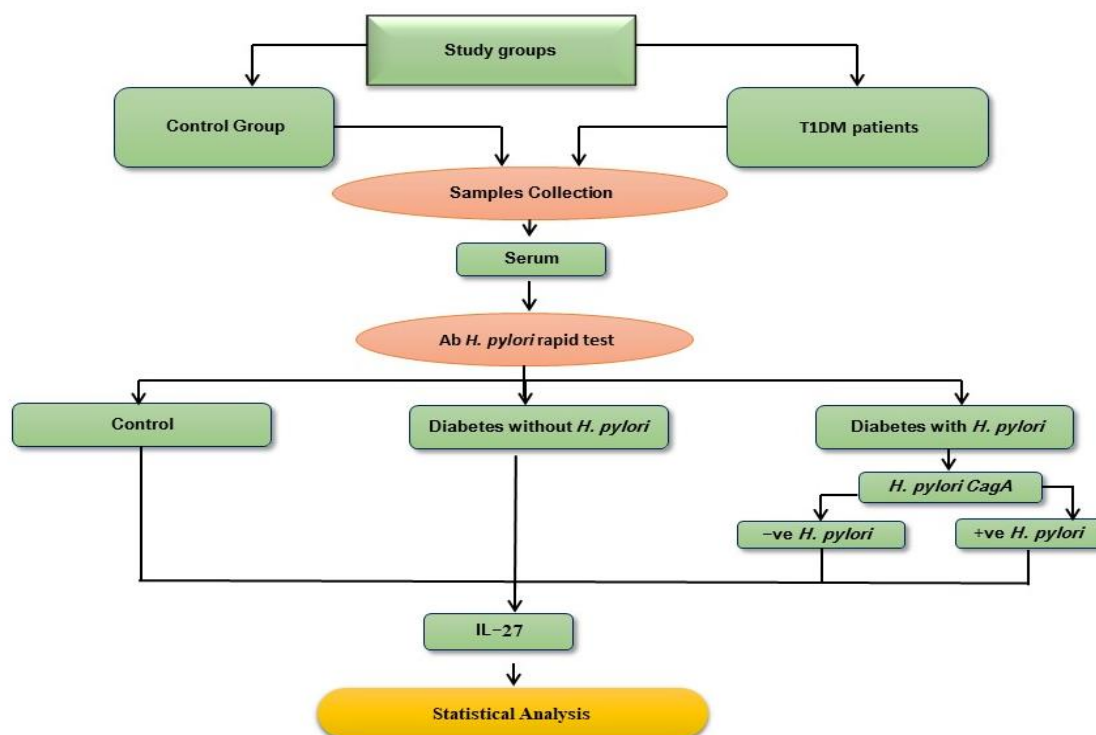
Interleukin-27 (IL-27) is a cytokine that has dual roles in the immune response and contributes to autoimmunity. Type 1 diabetes mellitus is among the foremost important autoimmunity-based diseases. *Helicobacter pylori* were recently observed that their prevalence in diabetic patients increased with capabilities to stimulate the production of various cytokines. The aim of this study was to measure the IL-27 levels in sera of type 1 diabetic children, and therefore the differences regarding presence of *Helicobacter pylori*, and its association with CagA positivity. (204) samples were collected, including (91) males and (113) females from the age group (1-15) years old, from two hospitals in Baghdad. Moral approval and case history were obtained from the parents. Rapid chromatographic immunoassay was used to detect *H. pylori* infection. IL-27 and *H. pylori* CagA tests were performed by using ELISA. The current study showed significant differences among the serum IL-27 concentrations of T1DM patients group with *H. pylori*, without *H. pylori*, and apparently healthy group ( $p= 0.050$ ). We found that serum IL-27 concentrations were significantly different in *Helicobacter pylori*+ and *Helicobacter pylori*- groups ( $p= 0.030$ ). In addition, there was significant differences between CagA positive and CagA negative groups ( $p\leq 0.009$ ). Finally, there was a low positive significant correlation between IL-27 concentrations with CagA positivity (Spearman Correlation= $.341$ ,  $p\leq 0.009$ ) and the correlation direction from the CagA positive toward CagA negative groups. The infection with *H. pylori* leads to decrease IL-27 levels in T1DM children. Moreover, infection with CagA positive strain leads to decline IL-27 production.

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## GRAPHICAL ABSTRACT



## Introduction

The cytokine, interleukin-27, is a member heterodimer of IL-6 and IL-12 superfamily [1], essentially composed of two subunits, EBV-induced gene 3 (*EBI3*) incorporated with p28, and activated antigen-presenting cells are the main producers [1,2]. The cytokine IL-27 is overexpressed in several autoimmune diseases, including uveitis, multiple sclerosis, psoriatic arthritis, systemic sclerosis, rheumatoid arthritis, tuberculosis, Crohn's disease [3], and inflammatory bowel disease [4].

The type 1 diabetes mellitus (T1DM) is a disease of autoimmunity [5,6] results from a destructive mechanism damaging the insulin-producing pancreatic  $\beta$ -cells, elicited by lymphocytes, and inflammatory cytokines [7,8]. Association studies genome-wide have specified more than fifty sites greatly related to T1DM in human beings [9,10] of which a region situated on chromosome 16, which comprises coding genes of 24 proteins, including IL-27 (p28 subunit) that has been identified as a potent candidate [11,12].

*Helicobacter Pylori* is one of the foremost prevalent long-term bacterial infections [13,14], colonizes the gastrointestinal tracts of more than half of the people, and has been linked to the development of acute complications [15].

Furthermore, according to the cytotoxin-associated gene-A (*CagA*), the *H. pylori* is classified into *CagA*-positive and *CagA*-negative strains, and was solidly established that the *CagA*+ strain causes more inflammatory reactions and a higher risk of poor clinical prognosis globally [16,17].

According to the recent studies, an infection with the *H. pylori* bacteria has been related to diabetes, especially type 1 diabetes mellitus [18]. Two studies also reported that there was a relationship between IL-27 and *H.pylori* infection in patients with gastric and/or duodenal ulcers [19,20].

Based on our knowledge, the current study is the first to evaluate IL-27 in T1DM patients infected with *H. pylori*. Therefore, this present study aimed to detect the IL-27 levels in the sera of T1DM children. Moreover, the differences were recognized according to the infection with of *H. pylori*, and its association with *CagA* positivity.

## Material and Methods

Depending upon the case-control design, the present study was conducted at Ibn Al-Baladi Hospital for Children and Maternity and the Specialist Center for Endocrinology and Diabetes, in the Rusafa District, Baghdad. Samples were

collected from 31<sup>st</sup> December 2018 to 15<sup>th</sup> February 2019. The study included 204 cases as 91 males (44.6%) and 113 females (55.4%), diagnosed children T1DM patients under supervision of specialist physician, and control group included 15 apparently healthy children in the age range of 1–15 years old for both genders. Any patient on antibiotics and/or *H. pylori* therapy were excluded. Ethical consent and information were obtained from parents according to the pre-designed questionnaire which include (name, age, gender, clinical information, weight, height, BMI, and number of months since the DMT1diagnosis). Before undergoing weight measurement, patients were instructed to remove any heavy clothing, blankets, and height were measured. Thereafter, the BMI was calculated based on the Centers for Disease Control in the United States [21].

Blood and serum samples were taken from each child to preform *H. pylori* rapid test (serum). For *H. pylori* rapid test SPECTRUM (REF: 1180001, Bioscience) was used. The positive results categorized into weak, moderate, and strong reactions according to the required time for band development (10-15, 3-10, and <3 minutes, respectively). This procedure carried out according to the manufacture instructions. Finally, 87 cases were selected for the next-step experimentation.

The serum concentrations of *H. pylori CagA* was tested by using ELISA technique (HumaReader HS, Germany) through a kit (CagA IgG Enzyme

ImmunoAssay (ELISA) to (quantitatively/qualitatively) determine IgG antibodies to *H. pylori* CagA antigen in human serum and plasma) by a quantitative design to detect the CagA +presence in diabetic patients with *H. pylori*. Samples with a concentration less than arbU/mL (5) were considered negative for CagA antibodies, while samples with higher concentrations were considered positive for CagA antibodies, based on the manufacturer's instructions (DIA.PRO, Italy, INS CAGG.CE/eng). Serum IL-27 concentrations were further measured by the ELISA technique (BioTek, USA) and a kit for IL-27, Homo sapiens (Human) Instruction manual. The manufacturer (Cloud-Clone Crop, USA, IL-27: SEA385Hu) provided cytokine standard known concentration samples expressed in pg/mL, which were used to quantify cytokine levels in serum [8,22].

The obtained data was analyzed by computer via the Statistical Package for Social Sciences (SPSS) for windows software version 26, and a (p-value) of less than 0.05 demonstrates that there are significant differences.

### Results

The detection of serum IL-27 levels was performed by using ELISA, and Table 1 shows descriptive statistic data for the IL-27 level.

**Table 1:** Descriptive statistics for total no. of samples tested for IL-27 level

Marker	No.	Range	Minimum	Maximum	Mean		Std.
					Statistic	Std. Error	
IL-27	87	194.327	1.081	195.408	5.576	2.228	20.790

Statistical analysis by using the independent-samples T-test to find out the relationship of IL-27 levels with gender and family history did not show significant differences between them where it was (p= 0.280 and 0.349, respectively), as represented in Table 2.

After categorizing the *H. pylori* positive samples into weak, moderate, and strong reactions groups, the IL-27 levels indicated a high significant difference (p≤0.002).

**Table 2:** ANOVA test for IL-27 levels according to H. pylori infection

H. pylori infection	No.	Mean	Std.	Std. Error	95% CI for Mean		Min.	Max.	P-value	
					Lower	Upper				
IL-27	Weak	16	3.437	1.161	0.290	2.818	4.056	1.340	5.294	0.002
	Moderate	13	1.980	0.822	0.228	1.482	2.477	1.081	4.355	
	Strong	28	2.890	1.092	0.206	2.467	3.314	1.608	5.815	
	Total	57	2.836	1.165	0.154	2.527	3.145	1.081	5.815	

Independent-samples t-test results showed that there was significant differences in IL-27 concentration levels between Hp+ and Hp- groups (p= 0.030). The results also indicated a high decrease in serum IL-27 levels in group (Hp+), as shown in the following table. In

addition, there were significant differences (p ≤ 0.009) between CagA+ and CagA- groups. Furthermore, cytokine production levels were higher in the group of CagA- cases than those in the group of CagA+ cases, as listed in the following table.

**Table 3:** Differences in IL-27 levels according to gender, family history, H. pylori infection, and CagA positivity

Groups		No.	Mean	Std.	Std. Error Mean	P-value
IL-27	Gender	Male	38	2.832	1.018	0.280
		Female	49	7.704	27.623	
	Family History	No	51	7.340	27.008	0.349
		Yes	36	3.077	3.003	
	H. pylori	Hp+	57	2.836	1.1650	0.030
		Hp-	30	17.024	49.533	
CagA	CagA+	51	2.701	1.0367	0.009	
	CagA-	6	3.985	1.638		0.668

By using ANOVA, the measured serum IL-27 levels revealed significant differences (p=0.050) among the groups of T1DM patients with H. pylori (Hp+), without H. pylori (Hp-), and apparently

healthy group. Likewise, the results indicated a high decrease in serum IL-27 levels in a group (Hp+), as reported in Table 4.

**Table 4:** ANOVA test of differences at IL-27 levels within study groups

Cases	No.	Mean	Std.	Std. Error	95% CI for Mean		Min.	Max.	P-value	
					Lower	Upper				
IL-27	Hp+	57	2.836	1.165	0.154	2.527	3.145	1.081	5.815	0.050
	Hp-	15	17.024	49.533	12.789	-10.406	44.455	1.608	195.408	
	Non Diabetic	15	4.538	4.907	1.266	1.821	7.256	1.886	19.665	
	Total	87	5.576	20.790	2.229	1.145	10.007	1.081	195.408	

Finally, our results showed a low positive significant correlation between IL-27 with CagA positivity (Spearman Correlation=.341, p≤0.009), and the correlation direction is from the CagA positive toward CagA negative groups.

**Discussion**

The findings of this study were in agreement with Santos *et al.* [23], Ahmed *et al.* [24], and Yan *et al.*

[25] in the absence of gender effect and no significant differences based on the family history of diabetes.

Serum IL-27 levels significant differences between Hp+ and Hp- groups came in accordance with those of Rocha *et al.* [20] study in IL-27 in gastric cancer, and H. pylori associated gastroduodenal diseases. Furthermore, the results of the present study were consistent

regarding the absence of gastric mucosa or serum IL-27 of gastric cancer patients. On other hand, Rocha *et al.* [20] study contrasted with our findings where they reported a high level of IL-27 in gastroduodenal diseases, while our results showed a high decrease in serum IL-27 levels in group (Hp+).

The CagA positivity impact on serum IL-27 Levels in our finding came in accordance with that of Jafarzadeh *et al.* [19] study in the presence of significant differences between CagA+ and CagA- groups, but it was contrast in the high mean of IL-27 in people with CagA+ strain. Similarly, our finding of the significant differences in serum IL-27 concentration levels among T1DM patients with *H. pylori* (Hp+), without *H. pylori* (Hp-), and apparently healthy groups, agreed with Jafarzadeh *et al.* [19] study, and disagreed in which group had a higher mean of IL-27 levels. Several studies have described that *H. pylori* CagA+ strains cause a more severe inflammatory reaction in the stomach than CagA- strains [26-28]. However, other studies have found no link between *H. pylori* CagA+ strains and severe gastric mucosal inflammation [29]. Some researchers have demonstrated that *H. pylori* virulence factors, such as CagA had no effect on cytokine expression like IL-6, IL-8, IL-10, and TNF- $\alpha$  [30,31]. While our results revealed that CagA positivity of *H. pylori* had an effect on serum IL-27 levels. The explanation behind the scene might be the special immunological status of diabetic patients [32] and the immunomodulation capabilities of *H. pylori* [33]. The information on how IL-27 is involved in T1DM and its immunopathogenic process in humans is very limited. A study conducted on a Brazilian population indicated that there was no relationship between IL-27 genetic variants and T1DM susceptibility [23]. The induction of diabetes by using streptozotocin, in knock-out mice (EBI3<sup>-/-</sup>) subunit of IL-27 or (WSX-1<sup>-/-</sup>) subunit of IL-27 receptor led to hyperglycemia and increased islet proinsulin level. Furthermore, there was a high infiltrative rate of the immune cells into islets. On other hand, the IL-27 administration to (EBI3<sup>-/-</sup>) and wild type mice groups yielded a markable reduction in the

previously mentioned diabetes-associated parameters, which in turn demonstrated the immunoregulatory role of IL-27 in this mice model of diabetes. In vivo, the IL-27 signaling deficiency intensify streptozotocin induced hyperglycemia and pancreatic islet inflammatory process, while the treatment with recombinant IL-27 had a noticeable inhibitory effect and promoted  $\beta$ -cell protection in T1DM [34-36].

### Conclusion

The most important new data in the present study is the infection *H. pylori* leads to decrease IL-27 levels in T1DM children. Moreover, the infection with CagA positive strain leads to lesser production of IL-27. Lack of secretion of IL-27 contributes to the T1DM development process. Thus, *H. pylori* may contribute to the T1DM etiology by decreasing IL-27 levels.

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### Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

### Conflict of Interest

The author declared that they have no conflict of interest.

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