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ORIGINAL ARTICLE

The role of T helper 17 cells in *Helicobacter pylori* associated chronic gastritis

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ABSTRACT

Background: *T helper 17 (Th-17) cell, a proinflammatory subset of CD4 T cells, have an essential role in immunity against Helicobacter pylori (H. pylori) infection.* ***Objectives:*** *This study aimed to evaluate expression of selected Th-17 cells associated cytokines (IL-17, IL-21, IL-22, IL-23, IL-26 and TNF-α) in H. pylori-infected patients and to recognize their responsibility in H. pylori associated chronic gastritis with different severity.* ***Methodology:*** *This study is a case control study. The case group included 25 H. pylori-positive patients suffering from chronic gastritis. The control group included 25 age and sex-matched healthy individuals without any dyspeptic symptoms and negative for H. pylori. Infection with H. pylori in all participants was determined by detection of H. pylori stool antigen by enzyme-linked immunosorbent assay (ELISA) kit. Certain cytokines expression (IL-17, IL-21, IL-22, IL-23, IL-26 and TNF-α) in serum samples from all participants were tested using ELISA.* ***Results:*** *Comparing the serum cytokines expression in cases and controls, IL-17, IL-21 IL-23 and TNF-α were significantly higher in cases while IL-22 and IL-26 were higher in cases but not statistically significant. Both serum IL-17 and TNF-α expressions were statistically significant higher in cases with moderate or severe forms of chronic gastritis than in cases with mild form of chronic gastritis. However, the levels of IL-21, IL-22, IL-23 and IL-26 showed insignificant variation regarding chronic gastritis severity.* ***Conclusion:*** *Th-17 cells are responsible for the pathogenesis of H. pylori infection and the severity of gastritis. So, down regulation of Th-17 cells associated cytokines offers a promising therapy to diminish H. pylori associated gastritis.*

INTRODUCTION

H. pylori infects more than 50% of the world population. It infects and/or colonizes gastric mucosa, causing gastric illness with variable severity[1]. *H. pylori* infection induces inflammation which is mediated by gastric mucosal T helper type 1 (Th-1) cells throughout interferon gamma IFNγ release. However, only Th-1 response is not enough to clarify the pathogenesis of *H. pylori*-induced gastritis[2]. Th-17 cell, a proinflammatory subset of CD4 T cells, are considered to have an essential role in immunity to *H. pylori* infection[3]. It was proposed that Th-17 cells come first and may control Th-1 response and contribute to *H. pylori* pathology[4]. Th-17 response enhances the gastric inflammation both in mice and in humans[5]. The Th-17 cytokines profile consists of IL-17A, IL-17F, IL-21, and IL-22. Both IL-21 and IL-23 support the Th-17 cells extension and maintain Th-17 cell population[6]. In fact, IL-17 is one of the earliest cytokines found in *H. pylori*–infected gastric mucosa[7]. *H. pylori*-infected mucosa was found to have IL-17 elevation in both RNA and protein intensity compared to non-infected mucosa[8]. IL-17 has a role in activation and recruitment of polymorphonuclear leukocytes, a key determinant of *H. pylori* associated gastritis. IL-17 encourages production of matrix metalloproteinases from fibroblasts causing mucosal damage[9]. Moreover, a study reported that in gastric carcinoma, Th-17 cells infiltrate the tumor and secretes IL-17 leading to tumor progression[10].

This study aimed to evaluate expression of selected Th-17 cells associated cytokines (IL-17, IL-21, IL22, IL-23, IL-26 and TNF-*α*) in *H. pylori*-infected patients and to recognize their role in *H. pylori* associated chronic gastritis with different severity.

METHODOLOGY

Study design

This case control study was performed over a period of three months (from December, 2020 to February, 2021). The study was approved by

Institutional Review Board of the Faculty of Medicine, Mansoura University (code number: R.21.02.1197). The case group included 25 *H. pylori*-positive patients who attended the Gastroenterology Outpatient Clinic in Mansoura University Hospitals, Egypt. All the patients had chronic gastritis according to criteria of the Sydney grading system[11]. The control group included 25 age and sex-matched healthy individuals negative for *H. pylori*, not complaining from any dyspeptic symptoms and did not have any health problems necessitating medical awareness. *H. pylori* infection in all participants was determined by detection of *H. pylori* antigen in stool. Control individuals who demonstrated a positive result for *H. pylori* stool antigen were then excluded. For detection of *H. pylori* antigen in stool, fresh stool samples were collected and stored at ⁻80°C until they were worked on. For detection of selected serum cytokines, the blood specimens were also collected from all participants, centrifuged, and the serum was stored at −80°C until work.

Exclusion criteria

The exclusion criteria for all participants were:

1) Individuals consuming antacids, H2-blockers, proton-pump inhibitors, bismuth compounds, antibiotics, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs throughout the 4weeks preceding samples collection; 2) Individuals suffering from of an autoimmune disorder; 3) Those whose stool samples were positive for parasites.

Detection of H. pylori stool antigen

The stool samples were investigated for fecal *H. pylori* antigen using ELISA kit (Epitope Diagnostic, USA) according to manufacturer instructions. The test is a qualitative, sandwich ELISA that uses polyclonal *H. pylori* antibodies. The cut-off value was obtained at OD450 nm using an ELISA reader. Negative cut-off=0.165 and positive cut-0ff=0.135.

Detection of serum cytokines

The level of cytokines (IL-17, IL-21, IL-22, IL-23, IL-26 and TNF-α) were measured in serum samples according to manufacturer instructions, using ELISA kits from Mabtech, Sweden for all cytokines except IL-26 that was obtained from Bioassay Technology, China. For each cytokine, the test is quantitative, sandwich ELISA using monoclonal antibody.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The association between two variables was evaluated using Chi-square or Fisher Exact tests for categorical variables, while Student *t* tests for continuous parametric variables and Mann Whitney test for continuous non parametric variables, with $P<0.05$ considered significant.

RESULTS

This study was conducted on 25 *H. pylori*-positive dyspeptic cases (17 males and 8 females) with age ranging from 25 to 65 years; and 25 *H. pylori*-negative control individuals (15 males and 10 females) with age ranging from 20 to 70 years. Among cases group, 15 patients exhibited mild chronic gastritis, 8 exhibited moderate gastritis and 2 patients had severe gastritis. By comparing expression of serum cytokines (IL-17, IL-21, IL-22, IL-23, IL-26, and TNF-α) in cases and controls (table 1 and figure 1), it was found that IL-17, IL-21 IL-23 and TNF-α were significantly elevated in cases while IL-22 and IL-26 were elevated in cases but was statistically insignificant. Both serum IL-17 and TNF-α expressions were significantly elevated in patients who exhibited moderate to severe chronic gastritis than in patients with mild chronic gastritis. However, levels of IL-21, IL-22, IL-23 and IL-26 showed insignificant variation regarding severity of chronic gastritis (Table 2 and figure 2). The ROC (receiver operating curve) of studied cytokines was conducted for prediction of *H. pylori* infection. Cut off values, AUC values (area under ROC) and performance characteristics are shown in table 3 and figure 3. Out of studied cytokines, the best for prediction of *H. pylori* infection was TNF-α followed by IL-23, IL-17 and IL-21.

Table 1: Cytokines expression in serum samples of case and control groups

Cytokine	Cases N=25		Controls N=25		*P* value
	Median (pg/mL)	Range (pg/mL)	Median (pg/mL)	Range (pg/mL)	
IL-17	14.3	(9.3-18.6)	8.4	(4.13-10.9)	<0.001*
IL-21	19.3	(4.3-37.6)	8.7	(2.1-14.8)	<0.001*
IL-22	10.2	(2.9-30.2)	12.4	(2-26.3)	0.846
IL-23	22.9	(8.4-38.1)	7.7	(1.1-11.8)	<0.001*
IL-26	15.8	(1.8-32.1)	10.7	(1.1-31.2)	0.168
TNF- α	768.4	(441.6-932.9)	328.9	(254.7-638.8)	<0.001*

** = significant difference*

Table 2: Serum cytokines expression regarding the severity of chronic gastritis

	Cases with mild chronic gastritis N=15		Cases with moderate to severe chronic gastritis N=10		*P* value
	Median (pg/mL)	Range (pg/mL)	Median (pg/mL)	Range (pg/mL)	
IL-17	11.9	(9.3-15.1)	17.2	(15.8-18.6)	<0.001*
IL-21	19.3	(4.3-28.1)	22.4	(10.5-37.6)	0.166
IL-22	10.5	(2.9-19.7)	10	(7.5-30.2)	0.222
IL23	22.9	(8.4-38.1)	23.5	(12.1-33.7)	0.868
IL-26	18.6	(1.8-28.4)	6.5	(3.5-32.1)	0.360
TNF- α	725.2	(441.6-797.2)	876.4	(811.6-932.9)	<0.001*

* = significant difference

Table. 3 Validity of studied cytokines for prediction of *H. pylori* infection

	AUC	95% CI	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IL-17	0.956	(0.906-1)	10.95	84	100	100	86.2
IL-21	0.843	(0.731-0.955)	11.4	76	76	76	76
IL-22	0.516	(0.35-0.682)	11.1	44	40	76	76
IL-23	0.971	(0.932-1)	10.6	92	88	76	76
IL-26	0.614	(0.448-0.78)	15.65	52	84	76	76
TNF-α	0.998	(0.993-1)	646	96	100	76	76

AUC: area under ROC (receiver operating curve), CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

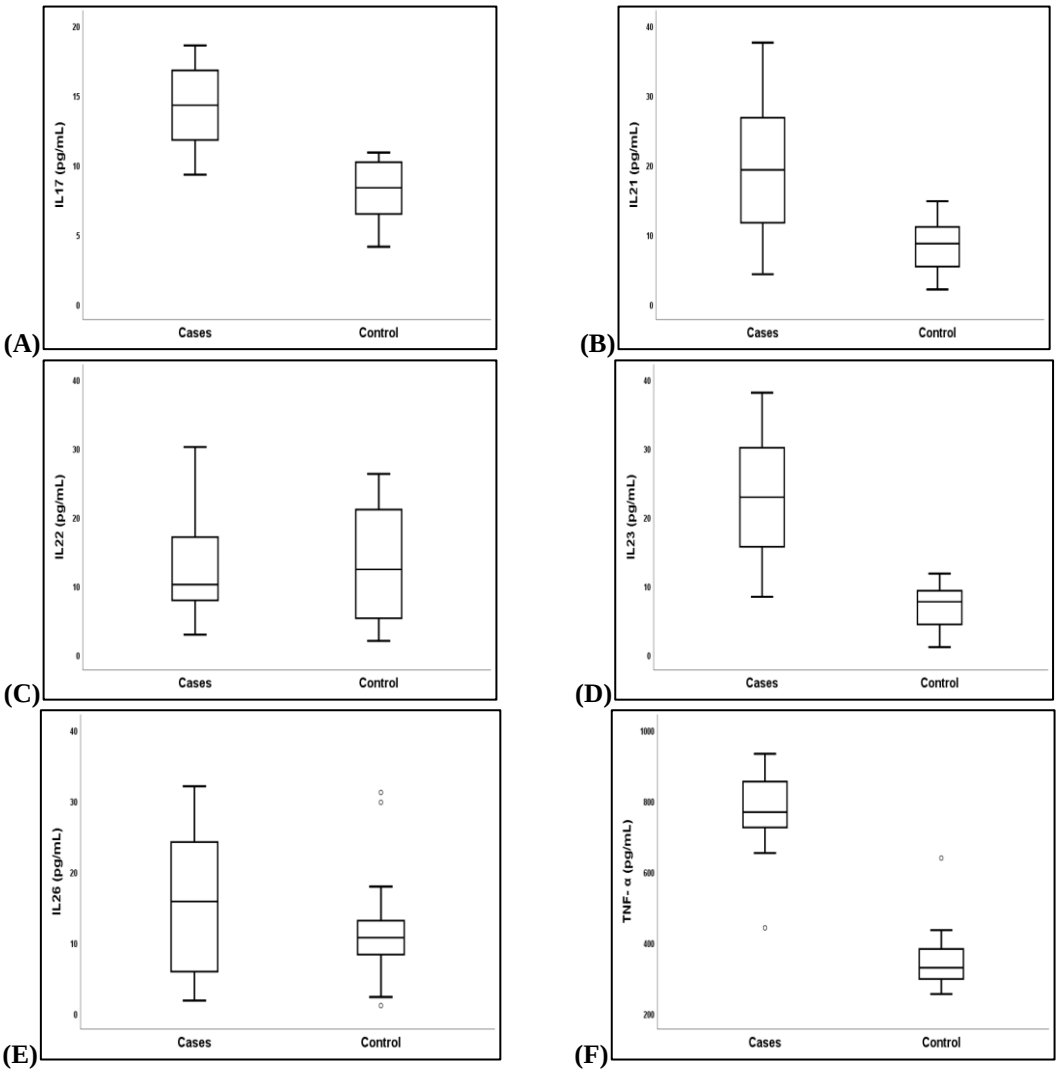

Fig. 1: Cytokines expression in cases and controls, (A) IL-17, (B) IL-21, (C) IL-22, (D) IL-23, (E) IL-26 and (F) TNF-α

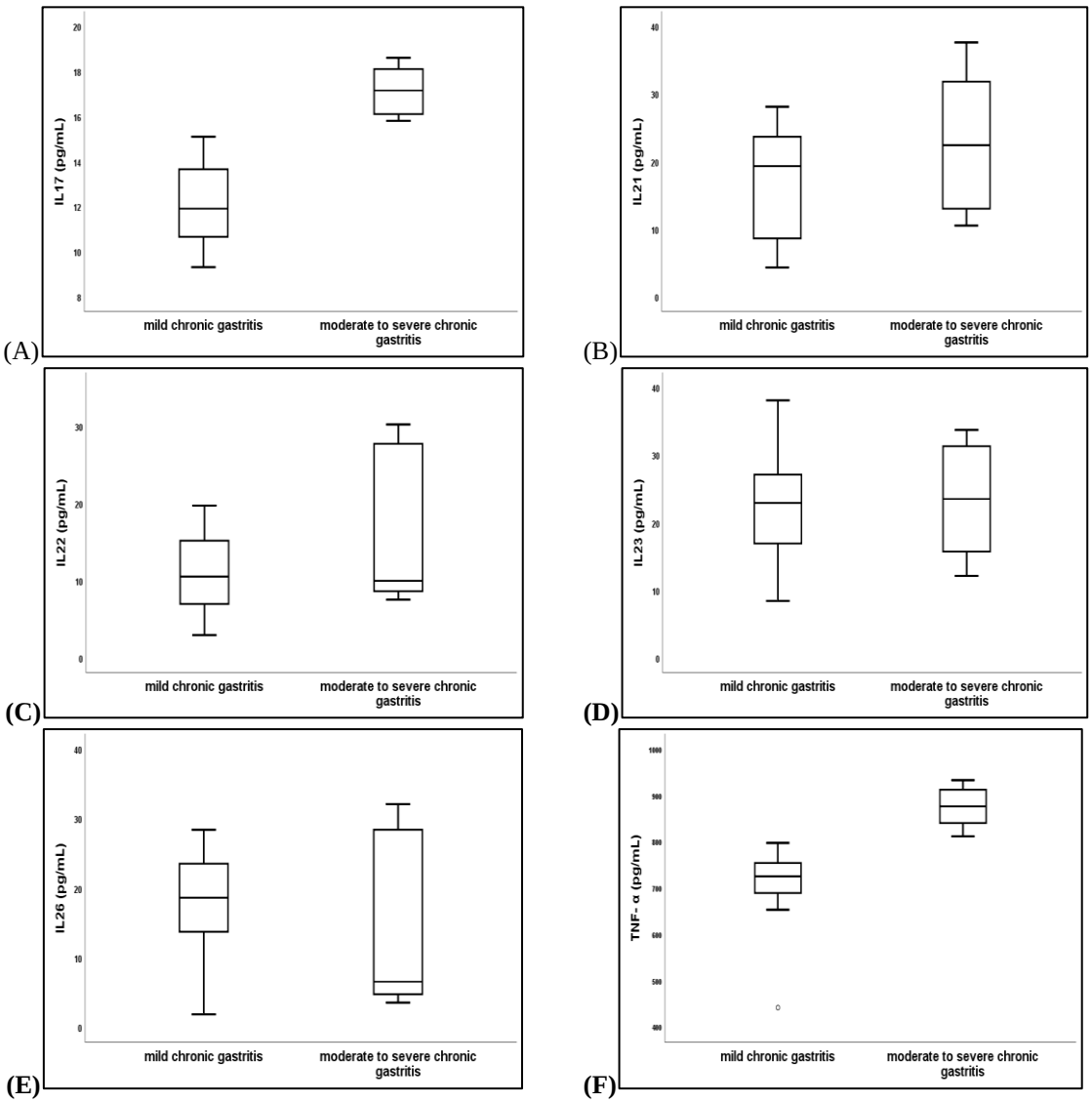

Fig. 2: Serum cytokines expression regarding the severity of chronic gastritis, (A) IL-17, (B) IL-21, (C) IL-22, (D) IL-23, (E) IL-26 and (F) TNF-α

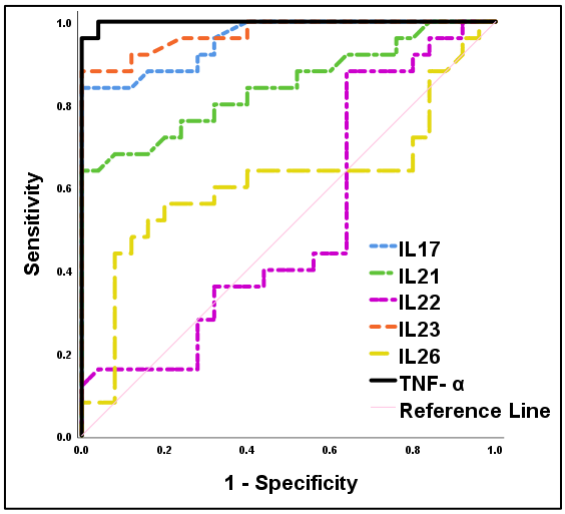

Fig. 3: ROC curve of studied cytokines for prediction of *H. pylori* infection

DISCUSSION

In the greater part of the world population, *H. pylori* is one predominant member of gastric microbiota[12]. Harmful outcomes of colonization by *H. pylori* vary from gastritis to gastric cancers[13]. It was found that the gastric mucosal and circulating Th-17 cells were significantly elevated in cases (whether the infection was an active or a past infection) compared to the healthy controls[14]. Notably, Th-17 cells produce numerous proinflammatory cytokines that trigger innate immunity, antibacterial action, regulate B cell response, and contribute in wound healing[12]. These immunological changes, occurring in the gastric mucosa, influence the immune response and determine the final outcome of these patients[15]. So, this research was done to study involvement of Th-17 cell associated cytokines (IL-17, IL-21, IL-22, IL-23, IL-26 and TNF-α) in regulating immune response to *H. pylori* chronic gastritis.

In this work, IL-17 was significantly elevated in cases in comparison to controls (P<0.001) and was also statistically significantly higher in patients who exhibited moderate to severe chronic gastritis than in patients who had mild chronic gastritis (P<0.001). Similar to our findings, Gil et al detected an increased level of proinflammatory cytokines including IL-17 in *H. pylori*-infected gastric biopsies as compared to non-infected controls[16]. Moreover, Shiomi et al found that IL-17 has a role in activation of inflammation and *H. pylori* proliferation[17]. This inflammation is possibly due to the activation of IL-8 expression in the epithelium, which subsequently recruits neutrophils within the gastric sub-mucosa and lamina propria[18]. Also it was found a down-regulation of IL-8 level in cultures treated by anti-IL-17A antibodies in a dose-dependent way and subsequently reduced inflammation[19]. This offers a promising therapeutic aim to diminish *H. pylori* associated gastritis[20].

The Th-17 cells also produce IL-21, which intensifies Th-17 response in an autocrine manner[21]. IL-21 maintains both Th1 and Th17 and inhibits Treg cell response in the gastric mucosa during chronic *H. pylori* infection. IL-21 also stimulates B lymphocytes proliferation and switching isotypes. So, IL-21 activates *H. pylori*- specific antibody response[22]. In our study, IL-21 was significantly elevated in cases in comparison to controls (P<0.001) and was higher in patients who exhibited moderate to severe chronic gastritis than in patients who had mild chronic gastritis but not statistically significant (P=0.166). Similarly, a study in Sri Lanka detected higher levels of IL-21 in *H. pylori* infected cases and in cases who exhibited moderate to severe chronic gastritis but without significant association[23]. Another study done in Iran reported that IL-21 level was significantly greater in *H. pylori*-infected patients but unlike to our study, a significant correspondence was detected between IL-21 level and the degree of severity of *H. pylori* associated gastritis[24].

Interleukin-22, a member of the IL-10 cytokine family, is another cytokine produced by Th-17 cell in response to IL-23[25]. It is also produced by Th-22 cell and innate lymphoid cells. In our research, IL-22 was elevated in cases in comparison to controls and was higher in cases who exhibited moderate to severe chronic gastritis than in cases who had mild chronic gastritis, but that was not statistically significant in both conditions (P=0.846& P=0.222 respectively). It was found that *H. pylori* infection could stimulate cell IL-22 expression[26]. In addition, Shamsdin also reported that IL-22, similar to IL-17A, was higher in patients who suffered from *H. pylori* associated gastritis and peptic ulcer diseases[13]. The IL-22 could stimulate the expression of the proteins responsible for the acute phase inflammatory response and stimulate the antimicrobial genes such as β-defensin-2 and β-defensin-3 in human body. So, the synergistic outcome of both IL-17 and IL-22 results in increased gastric inflammation and gastric damage[27]. More than one study found that high level of IL-22 increases matrix metallopeptidases, and enhances the neutrophil migration to the inflammation site, and consequently exaggerates the tissue damage[28,29].

Regarding IL-23, it is secreted by numerous immunological cells in the gastric mucosa such as dendritic cells, macrophages, and neutrophils. IL-23 is very important for Th-17 response to *H. pylori*. IL-23 activates IL-17 expression throughout STAT3 (signal transducer and activator of transcription)-dependent pathway[30]. In this work, IL-23 was significantly elevated in cases in comparison to controls (P<0.001) and was higher in patients who exhibited moderate to severe chronic gastritis than in patients who had mild chronic gastritis but that was not statistically significant (P=0.868). Correspondingly, Koussoulas and co-investigators observed an elevation of IL-23 levels in *H. pylori*-associated gastric biopsies[31]. Moreover, Horvath et al found that IL-23 could enhance neutrophils and monocytes infiltration in *H. pylori* infected gastric epithelium and therefore could activate the immune reaction and induce gastritis in response to *H. pylori*[32].

In our work, IL-26 was elevated in cases in comparison to controls and was higher in patients who exhibited moderate to severe chronic gastritis than in patients who had mild chronic gastritis, but not statistically significant in both conditions (P=0.168 & P=0.360 respectively). IL-26 is co-expressed with IL-17 and IL-22 via Th-17 cells[33]. IL-26 is an antimicrobial protein which can kill extracellular bacterial infection[34]. It plays an important role in stimulation of cell growth and prevention of apoptosis of human gastric cancer cells, and it may be a helpful prognostic pointer and

therapeutic target of human gastric cancer [35]. On the contrary, Dixon et al reported that *H. pylori* infection could not enhance IL-26 expression in humans[12].

In this study, TNF-*α* was significantly elevated in cases in comparison to controls (P<0.001) and was also statistically significant higher in patients who exhibited moderate to severe chronic gastritis than in patients who had mild chronic gastritis (P<0.001). Siregar et al reported that increased level of TNF-α was significantly greater in *H. pylori* infection and were highly associated with the degree of chronic gastritis[35]. IL-17 can encourage TNF-α secretion through stimulation of other proinflammatory cytokines IL-1, IL-6, and matrix metalloproteinases[36]. So, the increased level of TNF-α in our study can be explained by the significant elevation of IL-17 in the cases as compared to the controls. Furthermore, TNF-α is a proinflammatory cytokine that can stimulate endothelial cells to express adhesion molecules and attract the neutrophils to the site of inflammation. Additionally, TNF-α activates T cells and stimulates macrophages and monocytes to produce cytokines, and so these findings could explain the significant association of TNF-α and the degree of chronic gastritis[35].

CONCLUSION

Our study highlights the responsibility of Th-17 cells in the pathogenesis of *H. pylori* infection and the degree of severity of associated gastritis. So, down regulation of Th-17 cell associated cytokines offers a promising therapeutic aiming at diminishing *H. pylori* associated gastritis.

Conflicts of Interest

- The authors declare that they have no financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

REFERENCES

1. Correa P, Piazuelo M B. Natural history of *Helicobacter pylori* infection. Dig Liver Dis. 2008; 40 (7): 490-6.
2. Smythies L E, Waites K B, Lindsey R J, Harris P R, Ghiara P, Smith P D. *Helicobacter pylori*-induced mucosal inflammation is Th1 mediated and exacerbated in IL-4, but not IFN-g, gene-deficient mice. J Immunol. 2000; 165: 1022-9.
3. Kao J Y, Zhang M, Miller M J, Mills J C, Wang B, Liu M. *Helicobacter pylori* immune escape is mediated by dendritic cell-induced Treg skewing and Th17 suppression in mice. Gastroenterology. 2010; 138: 1046-54.
4. Niu Q, Zhu J, Yu X, Feng T, Ji H, Li Y, Zhang W , Hu B. Immune response in *H. pylori*-associated gastritis and gastric cancer. Gastroenterol Res Pract. 2020; Article ID 9342563, 9 pages.
5. Serrano C, Wright S W, Bimczok D, Shaffer C L, Cover T L, Venegas A, Salazar M G, Smythies L E, Harris P R, Smith P D. Downregulated Th17 responses are associated with reduced gastritis in *Helicobacter pylori*-infected children. Mucosal Immunol. 2013; 6: 950-9.
6. Liang S C, Tan X Y, Luxenberg D P. Interleukin IL-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. JEM. 2006; 203 (10): 2271-9.
7. Algood H M, Gallo-Romero J, Wilson K T, Peek R M, Cover T L. Host response to *Helicobacter pylori* infection before initiation of the adaptive immune response. FEMS Immunol Med Microbiol. 2007; 51: 577-86.
8. Chen P, Ming S, Lao J, Li C, Wang H, Xiong L, Zhang S. CD103 promotes the pro-inflammatory response of gastric resident $CD4^+$ T cell in *Helicobacter pylori*-positive gastritis. Front Cell Infect Microbiol. 2020; 10: Article 436.
9. Serrano C, Wright S W, Bimczok D, Shaffer C L, Cover T L, Venegas A, Maria G Salazar M G, Downregulated Th17 responses are associated with reduced gastritis in *Helicobacter pylori*-infected children. Mucosal Immunol. 2013; 6 (5): 950-9.
10. Iida T, Iwahashi M, Katsuda M, Ishida K, Nakamori M, Nakamura M, Naka T. Tumor-infiltrating CD4+ Th17 cells produce IL-17 in tumor microenvironment and promote tumor progression in human gastric cancer. Oncol Rep. 2011; 1 25: 1271-7.
11. Dixon M F, Genta R M, Yardley J H, Gorrea P. Classification and grading of gastritis. The updated Sydney system. Am J Surg Pathol. 1996; 20: 1161-81.
12. Dixon B E , Hossain R, Patel R V, Scott Algood H M. Th17 cells in *Helicobacter pylori* infection: a dichotomy of help and harm. Infect Immun. 2019; 87 (11) e00363-19.
13. Shamsdin S A, Alborzi A, Rasouli M, Hosseini M K. Alterations in Th17 and the respective cytokine levels in *Helicobacter pylori*-induced stomach diseases. Helicobacter. 2015; 20 (6): 460-75.
14. Serelli-Lee V, Ling L, Ho C. Persistent *Helicobacter pylori* specific Th17 responses in

patients with past *H. pylori* infection are associated with elevated gastric mucosal IL-1*β*. PLoS One. 2012; 7: 1-11.

15. Freire de Melo F, Rocha A M C, Rocha G A, Pedroso S H SP, de Assis B S, Fonseca de Castro L P. A regulatory instead of an IL-17 T response predominates in *Helicobacter pylori*-associated gastritis in children. Microbes Infect. 2012; 14:341-7.
16. Gil J H, Seo J W, Cho M S, Ahn J H, Sung H Y. Role of Treg and TH17 cells of the gastric mucosa in children with *Helicobacter pylori* gastritis. J Pediatr Gastroenterol Nutr. 2014; 58 (2): 245-51.
17. Shiomi S, Toriie A, Imamura S, Konishi H, Mitsufuji S, Iwakura Y,Yamaoka Y, Ota H, Yamamoto T, Imanishi J, Kita M. IL-17 is involved in *Helicobacter pylori*-induced gastric inflammatory responses in a mouse model. Helicobacter. 2008; 13: 518-24.
18. Mizuno T, Ando T, Nobata K, Tsuzuki T, Maeda O, Watanabe O, Minami M, Ina K, Kusugami K, Peek RM, Goto H. Interleukin-17 levels in *Helicobacter pylori*-infected gastric mucosa and pathologic sequelae of colonization. World J Gastroenterol. 2005; 11:6305-11.
19. Luzza F, Parrello T, Sebkova L, Pensabene L, Imeneo M, Mancuso M, La Vecchia AM, Monteleone G, Strisciuglio P, Pallone F. Expression of proinflammatory and Th1 but not Th2 cytokines is enhanced in gastric mucosa of *Helicobacter pylori* infected children. Dig Liver Dis. 2001; 33: 14-20.
20. Shi Y, Liu XF, Zhuang Y, Zhang JY, Liu T, Yin Z, Wu C, Mao XH, Jia KR, Wang FJ, Guo H, Flavell RA, Zhao Z, Liu KY, Xiao B, Guo Y, Zhang WJ, Zhou WY, Guo G, Zou QM. *Helicobacter pylori*-induced Th17 responses modulate Th1 cell responses, benefit bacterial growth, and contribute to pathology in mice. J Immunol. 2010; 184: 5121-9.
21. Meng X, Yu X, Dong Q, Xu X, Li J, Xu Q, Ma J, Zhou C. Distribution of circulating follicular helper T cells and expression of interleukin-21 and chemokine C-X C ligand 13 in gastric cancer. Oncol Lett. 2018; 16: 3917-22.
22. Yasmin S, Dixon BREA, Olivares-Villagomez D, Algood HMS. Interleukin-21 (IL-21) downregulates dendritic cell cytokine responses to *Helicobacter pylori* and modulates T lymphocyte IL-17A expression in the Peyer's patches during infection. Infect Immun. 2019; 11: e00237-19.
23. Arachchi P S, Fernando N, Weerasekera M M, Senevirathna B, Weerasekera D D, Gunasekara C P. Proinflammatory cytokine IL-17 shows a significant association with *Helicobacter pylori* infection and disease severity. Gastroenterol Res Pract. 2017; Article ID 6265150, 7 pages.
24. Bagheri N, Azadegan-dehkordi F, Shirzad M. Mucosal interleukin-21 mRNA expression level is high in patients with *Helicobacter pylori* and is associated with the severity of gastritis. Cent Eur J Immunol. 2015; 40 (1): 61-7.
25. Lee J S, Cella M, Colonna M. AHR and the transcriptional regulation of type-17/22 ILC. Front Immunol. 2012; 3:10.
26. Zhuang Y, Cheng P, Liu X, Peng L, Li B, Wang T. A pro-inflammatory role for Th22 cells in *Helicobacter pylori*-associated gastritis. Gut. 2014; 64: 1368-78.
27. Sanaii A, Shirzad H, Haghighian M, Rahimian , Soltani A, Shafigh M, Tahmasbi K, Bagheri N. Role of Th22 cells in *Helicobacter pylori*-related gastritis and peptic ulcer diseases. *Mol Biol Rep*. 2019; 46: 5703-12.
28. Andoh A, Zhang Z, Inatomi O, Fujino S. Interleukin-22, a member of the IL-10 subfamily, induces inflammatory responses in colonic subepithelial myofibroblasts. Gastroenterology. 2005; 129: 969-84.
29. Liang S C, Nickerson-Nutter C, Pittman D D, Carrier Y, Debra G, Goodwin D G. IL-22 induces an acute-phase response. J Immunol. 2010; 185: 5531-8.
30. Cheung P F, Wong C K, Lam C W. Molecular mechanisms of cytokine and chemokine release from eosinophils activated by IL-17A, IL-17F, and IL-23: implication for Th17 lymphocytes-mediated allergic inflammation. J Immunol. 2008; 180: 5625-35.
31. Koussoulas V, Vassiliou S, Giamarellos-Bourboulis E J. Implications for a role of interleukin-23 in the pathogenesis of chronic gastritis and of peptic ulcer disease. Clin Exp Immunol. 2008; 156, (1): 97-101.
32. Horvath D J, Washington M, Cope V A, Algood H M S, Blanchard T, Bimczok D. IL-23 contributes to control of chronic *Helicobacter pylori* infection and the development of T helper responses in a mouse model. Front Immunol. 2012; 3: 1-9.
33. You W, Tang Q, Zhang C, Wu J, Gu C, Wu Z, Li X. IL-26 promotes the proliferation and survival of human gastric cancer cells by regulating the balance of STAT1 and STAT3 activation. PLoS One. 2013; 8: e63588.
34. Woetmann A, Alhede M, Dabelsteen S, Bjarnsholt T, Rybtke M, Nastasi C, Krejsgaard T, Andersen M H, Bonefeld C M, Geisler C, Givskov M, Odum N. Interleukin-26 (IL-26) is a novel anti-microbial peptide produced by T cells in response to

staphylococcal enterotoxin. Oncotarget. 2018; 9: 19481-9.

35. Siregar G A, Halim S, Sitepu R R. Serum TNF-*α*, IL-8, VEGF levels in *Helicobacter pylori* infection and their association with degree of gastritis. Acta Med Indones. 2014; 47 (2): 120-6.

36. Jovanovic D V, Di Battista J A, Martel-Pelletier J. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-*β*, and TNF-*α*, by human macrophages, J Immunol, 1998; 160: 3513-21.