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Markers of Systemic Inflammation in the Pathogenesis of Functional Dyspepsia

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Abstract

The article presents the results of research into the role of systemic inflammation in the pathogenesis and clinical presentation of functional dyspepsia. Elevated serum concentrations of pro-inflammatory cytokines, including TNF-α, IL-1ß, IL-6, IL-8, and low IL-10 levels have been reported in patients with functional dyspepsia. Serum cytokine profiles have been shown to correlate positively with the most pronounced clinical sign of functional dyspepsia, epigastric pain. The serum levels of pro-inflammatory cytokines, TNF-α, IL-1ß and IL-6, were significantly higher in patients with functional dyspepsia and Helicobacter pylori infection. Elevated levels of TNF-α, IL-1ß and IL-8 have been shown to correlate with functional dyspepsia and postprandial distress syndrome, and high concentrations of IL-1β were indicative of functional dyspepsia and epigastric pain syndrome. The expression of pro-inflammatory cytokines in the functional dyspepsia group was much less pronounced than in patients with peptic ulcer, however, it was significantly higher than in healthy controls. The frequency of occurrence of hypercytokinemia in patients with functional dyspepsia has been reported to range from 26 to 41%, from 61 to 80% in the peptic ulcer group and from 2 to 7% in healthy controls. We conclude that cytokine imbalance plays a critical role in the pathogenesis of functional dyspepsia.

Key words: functional dyspepsia, systemic inflammation, cytokines

INTRODUCTION.

Although there has been a great deal of research into functional gastrointestinal disorders (FGIDs), their etiology and pathogenesis remain controversial. According to the currently used concept in functional gastrointestinal disorders, FGIDs are defined as biopsychosocial diseases which are caused by both individual characteristics or attributes and also risk factors (1, 6). The complex interaction between three domains, such as sensorimotor dysfunction, psychosocial impact and neuroregulatory, humoral and immune mechanisms, which have been extensively studied, underlies the currently used concept in FGIDs (3, 8). It has been established that functional dyspepsia is a syndrome with a multifactorial etiology whose main features are motor and sensory dysfunction, the brain-gut axis dysregulation and low grade of immune activation and inflammation (2, 6). Recent studies have proven that the gastrointestinal mucosa is constantly exposed to what is known as "controlled" inflammation which is regulated by the balance of pro- and anti-inflammatory cytokines, neurohormones and neurotransmitters (1, 3, 5). Although no specific signs of inflammation are available for functional dyspepsia, there is evidence that duodenal mucosa is infiltrated by mast cells and eosinophils (duodenal eosinophilia), and functional dyspepsia has been reported to be associated with over-expression of inflammatory markers and neurotransmitters (4, 5, 9). Chronic inflammation leads to secretory and motor gastric dysfunction and increased visceral sensitivity. Numerous investigations into the neuro-endocrine regulatory abnormalities and inflammatory response in functional gut disorders have been carried out by the researchers of the Internal Diseases Departments at the IM Sechenov's First Moscow State Medical University and the Volgograd State Medical University (1, 7). The purpose of this study was to evaluate the role of cytokine imbalance in the pathogenesis and clinical presentation of functional dyspepsia and to analyze the relationship between cytokine levels and the symptoms of functional dyspepsia.

MATERIALS AND METHODS.

A total of 53 patients with functional dyspepsia (31 females and 22 males) aged 18-45 were recruited. The comparative group included 20 patients with confirmed diagnosis of peptic ulcer. Of the 20 patients, 12 were females and 8 males aged 21-47. The control group consisted of age-adjusted 45 apparently healthy subjects (30 females and 15 males). Based on the prevailing clinical manifestations of functional dyspepsia, epigastric pain syndrome or postprandial distress syndrome, the patients were subdivided into two sub-groups. The epigastric pain syndrome group comprised 21 (39.62%) patients, while the postprandial distress group comprised 32 (60.38%) patients. Based on the presence of H. pylori infection, the functional dyspepsia group was subdivided into H. pylori positive (30 patients – 56.60%) and H. pylori negative (23 patients – 43.40%) patients. The severity of functional dyspepsia symptoms was measured using visual analog scale (VAS) scores. Parametric statistical methods were used because of our data had been drawn from a normally-distributed sample population according to the Shapiro-Wilk test and the Gaussian curve. Using correlation analysis we have evaluated relationship between clinical and laboratory data.

RESULTS AND DISCUSSION.

We compared serum levels of pro- and anti-inflammatory cytokines in patients with functional dyspepsia, and these patients were reported to have cytokine imbalance as manifested by significantly increased concentrations of inflammatory mediators, such as IL-1β, IL-6, IL-8, TNF-α, and low pro-inflammatory IL-10 production as compared to healthy controls (Table1). However, circulating levels of pro-inflammatory cytokines in patients with functional dyspepsia were significantly lower than in patients with peptic ulcer, which is consistent with the symptoms of inflammation in peptic ulcer. IL-6 levels were significantly different between the two groups of patients, with the peptic ulcer group having 15-fold higher concentrations than the functional dyspepsia group. It should be noted that decreased IL-10 cytokine levels were more pronounced in the functional dyspepsia group than in the peptic ulcer group, suggesting cytokine imbalance specificity in functional dyspepsia and peptic ulcer.

We analyzed cytokine profiles in patients representing different clinical manifestations of functional dyspepsia and revealed changes in the concentrations of certain cytokines in patients with functional dyspepsia/epigastric pain syndrome and patients with functional dyspepsia/postprandial distress (Table 2). We revealed a dominant cytokine imbalance pattern, with serum levels of IL-1β (in the functional dyspepsia/epigastric pain syndrome group

and the functional dyspepsia/postprandial distress syndrome group), TNF-α and IL-8 (in the functional dyspepsia/postprandial distress syndrome group) being significantly higher than in healthy controls. However, serum IL-10 cytokine levels in the study groups were not significantly higher than in healthy controls. The comparison of serum levels of TNF-α, IL-1β, IL-6, IL-8 and IL-10 between patients with functional dyspepsia/epigastric pain syndrome and functional dyspepsia/postprandial distress syndrome failed to reveal any statistically significant differences.

Along with mean serum concentrations of TNF-α, IL-1β, IL-6, IL-8 and IL-10, we evaluated the frequency of changes in cytokine concentrations in the study groups (Table 4).

Table 1 Mean serum concentrations of TNF- *α*, IL-1β, IL-6, IL-8 and IL-10 in patients with functional dyspepsia, peptic ulcer and in healthy controls, M±m, pg/ml

Group of patients		Concentration of cytokines M±m, pg/ml				
		TNF-α	IL-1β	IL-6	IL-8	IL-10
Patients with functional dyspepsia, n=53		55.03±8.14	59.48±7.64	14.32±3.92	67.82±12.90	4.95±1.20
	t1	3.39	3.12	2.11	3.73	1.97
	p1	<0.05	<0.05	<0.05	<0.05	>0.05
	t2	3.18	13.72	18.35	6.76	11.12
	p2	<0.05	<0.05	<0.05	<0.05	<0.05
Patients with peptic ulcer, n=20		97.22±10.47	246.42±11.27	216.38±10.29	168.55±7.44	57.80±4.60
	t1	6.52	17.29	20.02	19.45	10.25
	p1	<0.05	<0.05	<0.05	<0.05	<0.05
Healthy controls, n=45		24.57±3.81	30.16±5.42	7.24±1.83	18.62±2.07	8.47±1.36

Note: p1 – significance of differences between the studied groups and healthy controls; p2 – significance of between-group differences

Table 2 Serum levels of TNF-*α*, IL-1β, IL-6, IL-8 and IL-10 in patients with functional dyspepsia/epigastric pain syndrome, functional dyspepsia/postprandial distress syndrome and in healthy controls, M±m, pg/ml

Group of patients		TNF-α	IL-1β	IL-6	IL-8	IL-10
Patients with functional dyspepsia/ epigastric pain syndrome, n=21		52.91±14.94	62.52±11.23	12.55±6.05	51.63±17.86	6.04±4.09
	t_1	1.83	2.60	0.84	1.84	0.56
	p_1	>0.05	<0.05	>0.05	>0.05	>0.05
	t_2	2.43	11.56	17.08	6.04	8.40
	p_2	<0.05	<0.05	<0.05	<0.05	<0.05
Patients with functional dyspepsia/postprandial distress syndrome, n=32		61.59±11.62	65.41±13.21	15.51±6.42	89.57±28.74	4.22±1.73
	t_1	3.02	2.47	1.24	2.46	1.93
	p_1	<0.05	<0.05	>0.05	<0.05	>0.05
	t_2	2.28	10.42	16.56	2.66	10.87
	p_2	<0.05	<0.05	<0.05	<0.05	<0.05
	t_3	0.46	0.17	0.34	1.12	0.41
	p_3	>0.05	>0.05	>0.05	>0.05	>0.05
Patients with peptic ulcer, n=20		97.22±10.47	246.42±11.27	216.38±10.29	168.55±7.44	57.8±4.6
	t_1	6.52	17.29	20.02	19.45	10.25
	p_1	<0.05	<0.05	<0.05	<0.05	<0.05
Healthy controls, n=45		24.57±3.81	30.16±5.42	7.24±1.83	18.62±2.07	8.47±1.36

Note: p1 – significance of differences between the study groups and healthy controls; p2 – significance of differences between the study groups and the peptic ulcer group; p3 – significance of differences between the study groups and the functional dyspepsia/epigastric pain syndrome group

Furthermore, serum concentrations of TNF- α, IL-1β and IL-6 in H.pylori positive patients were significantly higher than those in H.pylori negative patients (Table 3). However, there were no significant differences in serum concentrations of IL-8 and IL-10 between the groups of patients with functional dyspepsia.

Table 3 Mean serum concentrations of TNF-*α*, IL-1β, IL-6, IL-8 and IL-10 in patients with functional dyspepsia and H. pylori infection, M±m, pg/ml

Cytokine pg/ml	Patients with functional dyspepsia, n=53			
	H. pylori positive patients, n=30	H. pylori negative patients, n=23	t	p
TNF-α	76.83±10.27	31.24±8.95	3.35	<0.05
IL-1β	87.62±9.34	30.19±5.72	5.24	<0.05
IL-6	20.37±4.86	8.03±2.15	2.32	<0.05
IL-8	73.91±10.04	60.49±7.13	1.09	>0.05
IL-10	3.87±1.05	5.94±1.04	0.78	>0.05

Note: p – significance of differences between H. pylori positive and H. pylori negative patients with functional dyspepsia

Table 4 Frequency of changes in serum concentrations of TNF-α, IL-1β, IL-6, IL-8 and IL-10 in patients with functional dyspepsia, peptic ulcer and healthy controls, n, %

Changes in concentration		Patients with functional dyspepsia, n=53	Patients with peptic ulcer, n=20	Healthy controls, n=45
TNF-α	Increased concentration	22	13	1
		41.51%	65.00%	2.22%
IL-1β	Increased concentration	20	15	2
		37.74%	75.00%	4.44%
IL-6	Increased concentration	14	16	1
		26.42%	80.00%	2.22%
IL-8	Increased concentration	17	15	2
		32.08%	75.00%	4.44%
IL-10	Decreased concentration	16	4	3
		30.19%	20.00%	6.67%

Table 5 Relationship between the leading symptoms and elevated serum levels of TNF-α, IL-1β, IL-6, IL-8 in patients with functional dyspepsia

Clinical presentation (VAS score)	Pearson's correlation coefficient (r)			
	TNF-α, pg/ml	IL-1β, pg/ml	IL-6, pg/ml	IL-8, pg/ml
Intensity of epigastralgia	0,36	0,42	0,51	0,31
Intensity of heartburn	0,15	0,13	0,19	0,15
Intensity of postprandial fullness/distention	0,07	0,18	0,14	0,23
Intensity of early satiation	0,05	0,12	0,17	0,29

Table 6 Relationship between the leading symptoms and elevated serum levels of TNF-α, IL-1β, IL-6, IL-8 in patients with peptic ulcer

Clinical presentation (VAS score)	Pearson's correlation coefficient (r)			
	TNF-α, pg/ml	IL-1β, pg/ml	IL-6, pg/ml	IL -8, pg/ml
Intensity of epigastralgia	0,82	0,56	0,46	0,46
Intensity of heartburn	0,24	0,63	0,51	0,54
Intensity of postprandial fullness/distention	0,12	0,34	0,18	0,25
Intensity of early satiation	0,07	0,14	0,11	0,29

Table 7 Relationship between the leading symptoms (VAS score) and serum level of IL-10 (pg/ml) in patients with functional dyspepsia and peptic ulcer

Clinical presentation (VAS score)	Pearson's correlation coefficient (r)
Functional dyspepsia	
Intensity of epigastralgia	-0,13
Intensity of heartburn	-0,25
Intensity of postprandial fullness/distention	-0,06
Intensity of early satiation	-0,08
Peptic ulcer	
Intensity of epigastralgia	0,2
Intensity of heartburn	0,14
Intensity of postprandial fullness/distention	0,06
Intensity of early satiation	0,27

The correlation analysis of IL-10 concentrations and functional dyspepsia symptoms showed an inverse correlation between the typical clinical features of functional dyspepsia and IL-10 concentrations. It should be noted that in the peptic ulcer group the correlation between the clinical criteria for peptic ulcer and IL-10 concentrations was apparently positive (Table 7).

The data presented in Table 4 show that elevated serum concentrations of TNF-α, IL-1β, IL-8 were significantly more common in patients with functional dyspepsia than in healthy controls. However, the frequency of occurrence of hypercytokinemia in the functional dyspepsia group was lower than that in the peptic ulcer group. It is notable that decreased IL-10 levels were more common in patients with functional dyspepsia than in those with peptic ulcer.

To better understand the relationships between serum cytokine levels and intensity of clinical presentation (evaluated with visual analog scale -VAS) in patients with functional and organic gastrointestinal diseases, we carried out a correlation analysis. The analysis showed that there is a direct correlation with varying degrees of certainty between the intensity of epigastric pain, on the one hand, and serum concentrations of TNF-α, IL-1β , IL-6, IL-8 , on the other hand, suggesting that these cytokines play a role in the genesis of epigastric pain in patients with functional dyspepsia **(**Table 5).

In the peptic ulcer group there was a direct correlation between clinical manifestations of peptic ulcer and serum concentrations of TNF-α, IL-1β, IL-6 and IL-8, suggesting a pathogenic link between the symptoms of the disease and concentrations of pro-inflammatory cytokines (Table 6).

CONCLUSION.

Our findings suggest that functional dyspepsia is characterized by changes in the cytokine expression profile, as manifested by elevated serum concentrations of pro-inflammatory mediators,

such as TNF-α, IL-1β, IL-6 and IL-8, and decreased serum concentrations of IL-10. Serum concentrations of TNF-α, IL-1β and IL-6 in H.pylori positive patients are significantly higher than in H.pylori negative patients. Based on the prevailing clinical manifestations of functional dyspepsia, we have revealed disease-specific patterns and imbalance in cytokine production, manifested as elevated IL-1β concentrations (in the functional dyspepsia/epigastric pain syndrome group and in the functional dyspepsia/postprandial distress syndrome group) and elevated TNF-α and IL-8 concentrations (in the functional dyspepsia/postprandial distress syndrome group). Elevated serum concentrations of TNF-α, IL-1β, IL-8 are significantly more common in the functional dyspepsia group than in healthy controls. There is a direct moderate correlation between the intensity of epigastric pain and serum concentrations of TNF-α, IL-1β, IL-6 and IL-8. However, there is an inverse correlation between the intensity of functional dyspepsia symptoms and serum concentrations of IL-10. Our findings show that regulatory cytokines play a role in the pathogenesis of functional disorders. Moreover, they underlie systemic immune inflammation which plays a role in the pathogenesis and clinical presentation of functional dyspepsia.

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