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Gastritis and peptic ulcers are associated with the lower levels of plasma lipids: possible involvement of histamine

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Summary

Background: Histamine receptors are involved to regulate lipid metabolism, so the hypothesis will arise that pathological states with abnormal histamine levels are associated with altered plasma lipids.

Objectives: To study the profile of plasma lipids in patients with gastritis and peptic ulcer (GPU).

Methods: In a case-control study, 70 dyspeptic patients were selected according to clinical criteria and using gastroduodenoscopy and compared with sex and age matched normal subjects.

Results: There were no significant differences in age, sex, and the prevalence of hypertension and diabetes between two groups. But allergy, the familial history of allergy and dyspeptic and *H. pylori* infection were more prevalent in case group compared with controls. The levels of the indices of inflammation and body hydration were the same in two groups. Patients with dyspeptic compared with the controls had the lower concentrations of serum triglyceride (139.2±44.3 vs. 153.4±91.3), p≤0.553), total cholesterol (174.6±32.4 vs. 192.8±52.0, p≤0.073, LDLc (93.4±20.2 vs. 105.4±32.2, p≤0.015) and NonHDLc (130.2±38.1 vs. 159.2±42.2, p≤0.008). The level of HDL had not a significant change (43.4±7.8 vs. 43.5±12.7, p≤0.930). Dyspeptic state had negative significant correlation with total cholesterol, LDLc and NonHDLc but not HDLc. Neither the markers of inflammation nor the indices of body hydration had significant correlation with GPU.

Conclusions: The GPU patients relative to normal group had the lower levels of serum lipids. The hypolipemic effects may be attributed to increased level of histamine in GPU patients.

EDN: AWTQRT

Keywords: Cholesterol; Gastritis; Lipids; Peptic ulcer; Triglycerides

Conflict of interests. The authors declare no conflict of interest.

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Гастрит и язвенная болезнь связаны с более низким уровнем липидов в плазме: возможно участие гистамина

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Резюме

Введение: Гистаминовые рецепторы участвуют в регуляции липидного обмена, поэтому возникает гипотеза о том, что патологические состояния с аномальными уровнями гистамина связаны с измененными липидами плазмы.

Цель: изучить профиль липидов плазмы крови у больных гастритом и язвенной болезнью (ГЯ).

Методы: В исследовании случай-контроль 70 пациентов с диспепсией были отобраны в соответствии с клиническими критериями и с помощью гастродуоденоскопии и сравнены с нормальными субъектами того же пола и возраста.

Результаты. Между двумя группами не было выявлено существенных различий по возрасту, полу и распространенности гипертонии и диабета. Но аллергия, семейный анамнез аллергии и диспепсии, а также инфекция *H. pylori* были более распространены в группе больных по сравнению с контрольной группой. Уровни показателей воспаления и гидратации организма были одинаковыми в двух группах. У пациентов с диспепсией по сравнению с группой контроля наблюдались более низкие концентрации сывороточных триглицеридов (139,2±44,3 против 153,4±91,3), p≤0,553, общего холестерина (174,6±32,4 против 192,8±52,0, p≤0,073, ЛПНП (93,4±20,2) против 105,4±32,2, p≤0,015) и Non-HDLc (130,2±38,1 против 159,2±42,2, p≤0,008). Уровень ЛПВП достоверно не изменился (43,4±7,8 против 43,5±12,7, p≤0,930). Диспептическое состояние имело отрицательную значимую корреляцию с общим холестерином, ЛПНП и не-ЛПВП, но не с ЛПВП. Ни маркеры воспаления, ни показатели гидратации организма не имели значимой корреляции с ГПУ.

Выводы: у пациентов с ГПА по сравнению с нормальной группой наблюдались более низкие уровни сывороточных липидов. Гиполипемические эффекты могут быть связаны с повышенным уровнем гистамина у пациентов с ГПА.

Ключевые слова: холестерин; Гастрит; Липиды; Пептическая язва; Триглицериды

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Introduction

About 85 per cent of the patients with gastritis and peptic ulcers (GPU) have excessive secretion of gastric juice i.e. acid and pepsin. The remainders 15% have reduced mucosal defense barrier and inadequate pancreatic alkaline juice [1]. All three factors have genetic basis, so that development of GPU is strongly hereditary. Stressful conditions, cigarette smoking, ingestion of aspirin and alcohol are also important to cause GPU [2, 3]. The secretion of acid from parietal cells of stomach is under control of histamine, gastrin and acetylcholine [4]. Histamine mainly through H2-receptors either mediate or potentiate the action of other secretagogues. Colonization of *Helicobacter pylori* (*H. pylori*) in antrum is also predisposing to GPU [2].

Karpouza *et al*. have studied the relationship between *H. pylori* infection and the profile of plasma lipids in 137 patients with upper gastrointestinal symptoms [6]. They found that cholesterol and LDLc but not triglyceride and HDLc were lower in patients with duodenal ulcer relative to other dyspeptic patients independent of *H. pylori* infection. Inversely, Kim *et al*. reported in 462 elderly Koreans that *H. pylori* infection is significantly associated with the elevated serum levels of total cholesterol and LDLc but not triglyceride and

HDLc [7]. Sung *et al.* evaluated the prevalence of *H. pylori* infection and its association with cardiovascular risk factors in 58981 healthy Korean adults [8]. Their findings showed that *H. pylori*-seropositive group had higher mean values for cholesterol, triglyceride, LDLc, apo B and lower values for HDLc and apo A1. They concluded that *H, pylori* infection is associated with plasma lipids as cardiovascular risk factors, independent from the presence of peptic ulcer. Chimienti, *et al.* measured IgG- and CagA-antibody and serum lipids in 211 health subjects. Infected subjects showed increased levels of total- and LDL-cholesterol and Lp(a) [9]. Jia *et al.* studied plasma lipids and *H. pylori* infection in 961 patients who underwent coronary angiography [10]. Their finding showed that there is not a significant association between *H. pylori* infection and occurrence and severity of coronary artery disease (CAD), although H-pylori seropositive group had lower levels of HDLc. Opposite results was found by Pieniazek *et al.* that showed significant correlation between *H. pylori* infection and CAD [11].

Therefore, the attentions have been paid mainly on *H. pylori* infection and the role for histamine has been ignored [6–11]. They concluded that *H. pylori* infection has extra gastric metabolic effects such as modifying lipid metabolism which may play a role in promoting atherosclerosis [11, 13]. Nevertheless, the findings are controversial and do not offer any mechanism. Moreover, they do not show a causative relationship between *H. pylori* infection and plasma lipids.

In the previous study, we indicated that histamine inhibits VLDL secretion from rat liver and decreases plasma lipids by using both H1- and H2-receptors [14]. Histamine also participates in glycogen metabolism via H1-receptors to regulate plasma glucose [15]. We deduced that histamine has hypolipemic effects in spite that it is known as atherogenic factor. Thus, it is proposed that the pathological conditions with high histamine level such as GPU can alter the plasma lipids directly. In the current study, the profile of plasma lipids have been measured in GPU patients compared to normal individuals.

Methods and subjects

Experimental design, subjects and clinical assessment

The experiment was a cross sectional case-control study. The protocol is in accordance with the declaration of Helsinki and was approved by the ethics committee of our university. The patients group was 70 dyspeptic subjects, who were recognized as gastritis and peptic ulcer (GPU) according to clinical criteria or gastroduodenoscopy at Emam hospital of university of Mazandaran. Subjects with malignancy, thyroid, liver, renal, acute infection, coronary artery diseases (CAD) or receiving antilipidemic and antihistamine drugs were excluded. The control group consists of 70 ages and sex matched asymptomatic healthy subjects who underwent a routine health check-up at clinical laboratory and were apparently free from any disease including of dyspeptic.

Biochemical and hematological measurements

The measurements were done on fresh blood and serum. All hematological and biochemical parameters were measured by routine laboratory methods [16]. Serum triglyceride and total cholesterol were measured enzymatically by GPO-PAP and CHOD-PAP methods respectively (Pars-Azmon Inc., Tehran). HDL-cholesterol was measured by precipitation method and LDLc was calculated using Friedewald's equation [17]. *H. pylori* infection was evaluated by urease test and histological examination using modified Giemsa stain. Patients were considered to be *H. pylori* positive if both tests were positive [8–11].

Statistical analysis

The results are presented as the means ±SD. The significance of any differences in the means and proportions were tested with student's t-test and Kruskal-Wallis analysis respectively. All p-values are two-tailed and differences were considered significant if p-values were 0.05. Bivariate correlation analysis was performed to address the correlation of GPU with other parameters (SPSS version 21).

Results

Demographic and clinical parameters of the patients

There were no significant differences in age, male gender and the prevalence of hypertension and diabetes between two groups (Table 1). But allergy, the familial history of dyspeptic and *H. pylori* infection were more prevalent in case group compared with the normal group. The levels of the indices of inflammation (leukocytes counts and ESR) and body hydration (i.e. BUN, creatinine, hematological parameters) were the same in two groups. Patients with dyspeptic compared with the controls had the lower concentrations of serum triglyceride, total cholesterol, LDLc and NonHDLc. Whereas, the level of HDLc and atherogenic index i.e. log(triglyceride)/HDLc did not change significantly between two groups. (Figure 1).

Correlation of dyspeptic with clinical parameters

Dyspeptic state did not show any association with diabetes and hypertension but had significant direct correlation with allergy and familial history of dyspeptic status (Table 2). Dyspeptic had negative significant correlation with total cholesterol, LDLc and NonHDLc but not HDLc and atherogenic index. Neither the markers of inflammation nor the indices of body hydration had significant correlation with dyspeptic state [18].

Table 1.
Demographic and clinical characteristics in gastritis and peptic ulcer (GPU) patients and healthy controls

	Control (n≈70)	GPU (n≈70)	P
Clinical characteristics:			
Age, year	50.9±10.5	49.1±15.2	0.515
Gender, male, % (n)	48.6 (34)	57.6 (38)	0.177
Allergy, % (n)	11.4 (8)	51.4 (36)	0.001
Family history of GPU, % (n)	8.7 (6)	48.6 (34)	0.001
Smoking, % (n)	14.3 (10)	11.4 (8)	0.842
Diabètes mellites, % (n)	2.9 (2)	5.6 (4)	0.136
Hypertension, % (n)	14.3 (14)	25.0 (18)	0.100
H. pylori infection, % (n)	8.7 (6)	68.6 (48)	0.001
Drugs:			
H2-Antihistimine, % (n)	0 (0)	14.3 (10)	-
Anticollinergic, % (n)	0 (0)	11.4 (8)	-
Prazole drugs, % (n)	0 (0)	25.7 (18)	-
Biochemicals:			
Glucose, mg/dL	96.1±20.0	96.9±15.1	0.813
BUN, mg/dL	16.5±4.9	15.7±9.4	0.706
Creatinine, mg/dL	0.94±0.18	0.94±0.19	0.701
Hemoglobin, g/dL	13.8±1.5	13.9±2.1	0.464
RBC, cells/nL	4.8±0.5	4.9±0.6	0.549
Hematocrit, %	41.3± 3.6	41.7±5.3	0.669
Leukocyte counts, cells/nL	6.7±1.9	6.4±1.6	0.435
ESR, mm/hr	13.4±11.9	13.1±10.3	0.938
	12 (2–37)	9 (1–49)	0.464
Platelet counts	251.6±62.1	212.9±59.9	0.147
Lipids profile:			
Triglycerides, mg/dL	160.6±96.8	139.6±52.9	0.259*
	135(60–303)	121 (45–440)	
Total cholesterol, mg/dL	203.1±51.1	183.0±39.0	0.070
LDLc, mg/dL	125.1±37.7	103.3±27.1	0.015
HDLc, mg/dL	43.5±12.7	43.4±7.8	0.930
NonHDLc	159.2±42.2	130.2±38.1	0.008
Log(triglyceride)/HDLc	0.052±0.156	0.051±0.010	0.652

Note: The continuous and categorical variables were compared by t- and χ2-tests, respectively. The number in each group has shown in parentheses. The results are presented as the means ±SD and median (range). Mann-Whitney test (*)

Table 2.
The correlation coefficients (r) of GPU with other clinical parameters

Clinical characteristics:	r	P
Age	-0.070	0.559
Sex	0.111	0.352
Allergy	0541	0.001
Family history	0626	0.001
Diabetes mellitus	-0.093	0.442
Hypertension	-0.036	0.781
Glucose	-0.087	0.480
Triglycerides	-0.139	0.259
Total cholesterol	-0.209	0.087
LDLc	-0.311	0.015
NonHDLc	-0.331	0.010
HDLc	-0.007	0.958
BUN	-0.114	0.407
Creatinine	-0.012	0.933
Leukocytes counts	0.032	0.471
ESR	0.014	0.927
Hemoglobin	0.054	0.674
Erythrocytes counts	0.092	0.492
Hematocrit	0.043	0.753

Note: The values of coefficients (r) were determined by using bivariate correlation analysis

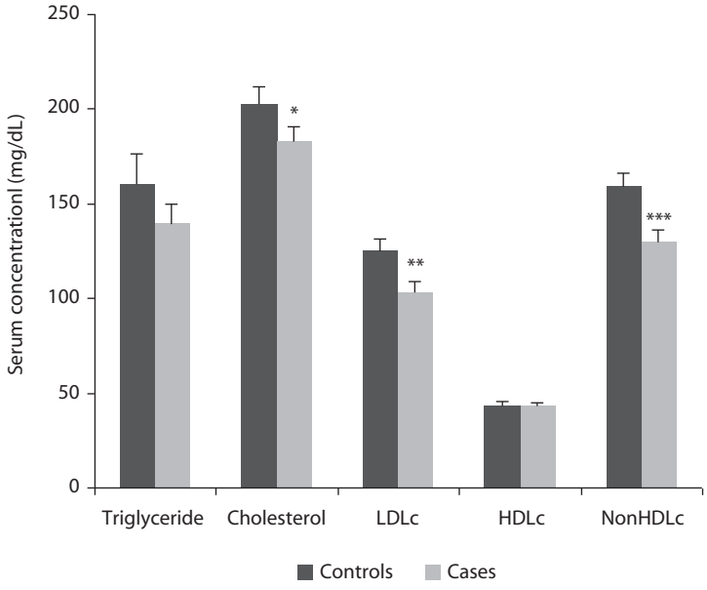

Figure 1. The levels of serum lipids in GPU and control groups.
Note:
The results are presented as the means ± SE.
*, ** And *** indicate that the corresponding values are significantly different from their respective controls at the confidence levels of p≤0.070, p≤0.015 and p≤0.008 respectively.

Discussion

In the current study, the profile of serum lipids was compared in the patients of gastritis and peptic ulcer (GPU) with the control healthy individuals. The findings indicate that, patients with dyspeptic compared with the controls had the lower levels of serum triglyceride, total cholesterol, LDLc and NonHDLc, whereas HDLc and atherogenic index had not a significant change. In addition, GPU did not exhibit any association with the markers of inflammation and the indices of body hydration [18]. The results were in accordance with the findings of Karpouza *et al.* [6] and also with the basic experiments in rats [14]. Anyway, there is a limited report about the relation of GPU and plasma lipids. The most parts of the studies are about the relation of *H. pylori* infection and plasma lipids [7–13]. Colonization of *H. pylori* in the stomach will induce chronic gastritis which is a low-grade inflammation leading to local complications (peptic ulcer and cancer) and extra-gastric metabolic consequences [12]. The extra-gastric manifestations are probably mediated by the cytokines and acute phase proteins produced by the inflamed mucosa [12]. In general, the link between the *H. pylori* infection and metabolic changes is inconstant and controversial. The overall conclusion of these studies is that, *H. pylori* infection is associated with higher levels of plasma total- and LDL-cholesterol and lower concentrations of HDLc [7–11]. This pattern of lipids is atherogenic [16], so it is assumed that *H. pylori* infection is promoting atherosclerosis. In practice, some studies show significant association between *H. pylori* infection and CAD [8, 11], whereas others failed to indicate such link [10]. Pieniazek *et al.* showed that the prevalence of *H. pylori* infection was twice in CAD group relative to normal controls [11]. They also found that hsCRP was higher in CAD patients, whereas we and also one review article showed that hsCRP is not an independent risk factor for CAD [19, 20]. Inversely, it has been shown that eradication of *H. pylori* improves clinical symptoms and quality of life in patients with peptic ulcer, and increases the level of plasma lipids and incidence of hyperlipidemia [21]. Moreover, no study has indicated an independent and causal relationship between *H. pylori* infection and CAD. Uncertainties regarding the metabolic consequences of *H. pylori* infection must be clarified in the future.

Histamine has a major role in the regulation of acid secretion and hence in the pathogenesis of GPU [1]. This hypothesis is confirmed more by the fact that histamine potentiates several times the actions evoked by pentagastrine or cholinergic agonists [1, 4]. It is reported that histamine increases vascular permeability for LDL particles [22], and promotes formation of atherosclerotic lesions [23]. Thus, histamine is assumed to be an atherogenic agent [14]. On other hand, we indicated in an experimental study in rats that, histamine has hypolipemic effect via inhibition of VLDL secretion from the liver [14]. So, it is proposed that the pathological states with high histamine activity such as GPU and allergy can alter directly the plasma lipids [24]. Histamine as a biogenic amine, is synthesized in mast cells and basophils and stored with proteoglycans within intracellular granules [1]. The intracellular bound form of histamine is biologically inactive; immune- and non-immunologic stimuli can trigger the release of histamine. Histamine acts locally by binding with specific plasma membrane receptors. Free histamine is metabolized rapidly to methyl imidazole acetic acid (MIAA) and excreted via urine [3]. Therefore, the level of histamine in plasma or the excretion of MIAA from urine is not reflected the histamine activity correctly [26]. For this reason, we did not measured histamine or MIAA in this research, so that the histamine activity is more shown by clinical signs in GPU and allergic patients. In the other words, clinical signs are better index than plasma histamine or urine MIAA for GPU and allergy. Unfortunately, all studies have been focused on *H. pylori* infection by now and the role of histamine has been disregarded. In the current study, the patients with GPU relative to normal subjects had the lower levels of serum lipids. Although the changes were in normal ranges, they were either statistically significant or showed the tendency to be significant. The minor statistically differences may not

be clinically useful, but they show the physiological mechanism of the changes. The hypolipemic effect may be attributed to the higher levels of histamine in dyspeptic patients. A similar pattern in plasma lipids may be seen in the allergic patients, the subject that remained to be determined. In addition, the use of antihistamine drugs may affect the profile of plasma lipids and progression of atherosclerosis.

Conclusion

The patients with gastritis and peptic ulcer relative to normal subjects had the lower levels of serum triglyceride, total cholesterol, LDLc and NonHDLc but not HDLc and atherogenic index.

Declarations

Competing interests: All authors declare that they have no conflict of interest.

Authors' contributions: Prof F performed gastroduodenoscopy and evaluated the patients. Prof R designed the study, analyzed the data and wrote the manuscript. Dr. L was MD student and collected the anthropometric data.

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