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The Pecularities of Serum Leptin Level in Patients with Prolonged Use of Nonsteroidal Anti-Inflammatory Drugs

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ABSTRACT

The aim of our study was to determine a correlation between leptin levels with sex, Helicobacter pylori status, body mass index (BMI) and histological features of gastric mucosa (GM) in patients with prolonged use of non-selective NSAIDs. We examined 94 patients who regularly during the last month used non-selective NSAIDs. The patients were aged 64,1±7,7 years on the average. NSAIDs-gastropathy was detected in 63 patients, in 31 patients visible changes of GM were absent. All patients were divided in 2 groups: with erosive gastropathy and without visible changes of GM. The serum leptin levels were determined in all patients using sandwich leptin solid phase ELISA (DRG-instrument GmbH-Germany). NSAIDs-gastropathy was detected in 63 patients, in 31 patients visible changes of GM were absent. Leptin correlated significantly with BMI (r^2=0,43) and it was higher in women (15,59±6,69) vs men (11,05±6,6), p=0,023. Serum leptin level was increased on 25 % in patients with erosive changes of GM (p=0,04). The described phenomenon is connected with the functioning of local stress-limited system. Changes of the components of the local stress-limited system is proposed to consider as prognostic marker of functional integrity of GM.

Keywords: leptin, NSAID-gastropathy, gastroprotection, H. pylori

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INTRODUCTION

Leptin, the 16-kDa product of ob gene, is a cytokine-like molecule synthesized mainly by the adipose tissue. Since its discovery, leptin has been implicated in many functions: insulin secretion, lipidic homeostasis, reproductive functions, thermogenesis, angiogenesis, immune reactions [1, 2]. Leptin exerts its effects mainly via leptin receptors which have recently been demonstrated to possess immune and inflammatory function [3, 4]. Serum leptin level rises with eating and the influence of gastric leptin signals satiety to hypothalamic center [5]. Leptin production is not restricted only to adipocyte, as it is also detected in human placenta, muscles and gastric chief cells. Leptin expression has been detected in gastric epithelium but the physiologic role of gastric leptin remains unknown. In animal models was shown that mRNA and protein expression of leptin in GM increased after acute damage induced by ethanol or aspirin [6, 7, 8].

On the other hand, data between serum leptin levels and peculiarities of GM in males with chronic use of NSAIDs, the influence of H. pylori on the leptin level and the presence of correlation between the severity of gastritis and the leptin level have been subjects of several investigations with controversial results [9, 10]. Several studies indicate H. pylori infection to be associated with serum leptin levels [11, 12]. Eradication of H. pylori infection has been shown to alter serum and gastric leptin levels. For example, studies by Pacifico et al. [13, 14] demonstrated decreased gastric leptin level in patients with injuries of GM caused by H. pylori infection, while other reports indicate a high [9, 15] serum leptin levels in patients with H. pylori infection. In the study which was done by K.B. Lankarani and colleagues the number of patients was limited and all of them had endoscopically-proven duodenal ulcers. In the study which was described by S. Khudur et al. BMI was not taken into account, only age, sex and H. pylori were considered. At the same time NSAIDs-gastropathy is not always associated with H. pylori, that is why the aim of our work was to study the Hp-negative group of patients with erosions of GM as such data in literature are absent.

MATERIALS AND METHODS

We examined 94 patients who regularly during the last month used non-selective NSAIDs. Excluded from this study were those who had used proton pump inhibitors (PPI), H2-blockers, within past 2 weeks had received bismuth compounds, antibiotics, eradication therapy for H. pylori, patients with prior history of gastroduodenal surgery and pregnant or lacting women. The mean-age of these patients was 63,2±6,0. For all of these individuals gastroscopy with further morphological examination, laboratory examinations were performed. The gastroscopy was performed with the help of fibrogastroscope FUJINON FG-1Z. Light microscopy was performed using a light microscope Olympus BX-41 (Olympus Europe GmbH, Japan). Color micrographs were obtained using a digital camera Olympus C-5050 Zoom. All patients were divided in two groups based on the endoscopic findings: with erosive gastropathy and without visible changes of GM. From each patient 5 ml of venous blood was collected for the detection of leptin levels. The serum leptin levels were determined in all patients using sandwich leptin solid phase ELISA (DRG-instrument GmbH-Germany). Endoscopically obtained biopsies were stained with hematoxylline and eosine. Severity of inflammation was graded according to modified Sydney classification. The diagnosis NSAID-gastropathy was confirmed using such morphological criteria as: pit elongation and foveolar tortuosity, vascular congestion, mucosal villiform transformation and muscular stranding up into the mucosa (Fig. 1). Multiple antral biobsies (3-5) specimens were collected: the one tested by rapid urease test/CLO test and the other was used for histological examination and sent for standard histopathologic examination for detection of H. pylori.

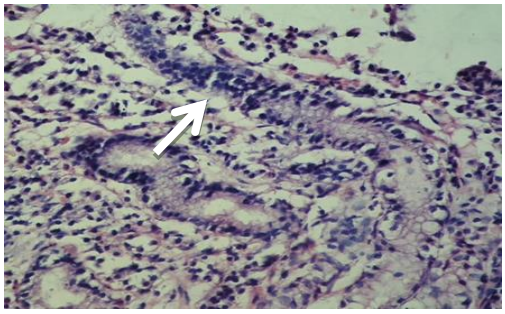

Figure 1: Gastric mucosa layer histopathology from chronic superficial gastritis. Foveolar hyperplasia (indicator). (HE x 400)

Statistical analysis was performed using STATA version 12. Normal distribution of studied parameters for each sampling was checked using Shapiro-Wilka's criteria. Average value (M) error and standard deviation (SD) were calculated to discover significant changes of investigated indices. In order to test the differences between parametric and non-parametric variables in the groups we used independent sample t-test. Sampling comparison was performed using the paired t-test and ANOVA. Differences among values were considered statistically significant if p<0,05. Spearman's correlation coefficient and χ^2 test were performed for quantitative and categorical variables, respectively. P values below 0,05 were considered statistically significant.

The study was approved by Institutional Review Ethical Board of Bogomolets National Medical University and written informed consents were obtained from all patients.

RESULTS

A total of 94 patients with prolonged use of NSAIDs, consisting of 32 males and 62 females, were recruited in this study. The patients were aged 64,1±7,7 years on the average. NSAIDs-gastropathy was detected in 63 patients, in 31 patients visible changes of GM were absent.

Other baseline characteristics (age, gender, body mass index, presence of H. pylori) are shown in Table 1. As demonstrated in Table 1, there was no significant differences in gender, BMI between the two groups. As expected, leptin correlated significantly with BMI (χ^2=16,94; p=0,0001) and it was higher in women (15,59±6,69) vs men (11,05±6,6), p=0,023 (Fig. 2). Serum leptin level was increased on 25 % in patients with erosive changes of GM (p=0,04). Of the 63 subjects 17 were Hp+ and 46 were Hp-. Of 31 subjects 18 were Hp+ and 13 were Hp-. Serum leptin levels were significantly lower in Hp+ (9,78±4,83) vs Hp- (16,57±6,19) patients with NSAID gastropathy (p=0,004). The changes between Hp+ vs Hp- patients without visible changes of GM were not statistically valid (p=0,891). Correlation between the level of leptin and the severity of gastritis was not observed in our study (χ^2=2,74; p=0,86). In our study we didn't observe corellarion between serum leptin level and age (r=-0,064; p=0,54) (Fig. 3).

Table 1: Characteristics of participants

Variables	Patients with NSAIDs-gastropathy	Patients without visible changes of GM	p-value
Count	63	31	
Age (Years) (mean±SD)	64,1±7,7	64,1±7,4	P=0,18
Gender (M:F)	20:43	12:19	P=0,5
BMI (Kg/m^2)	27,4±3,2	27,5±4,03	P=0,91
H. pylori positive	17	18	P=0,003

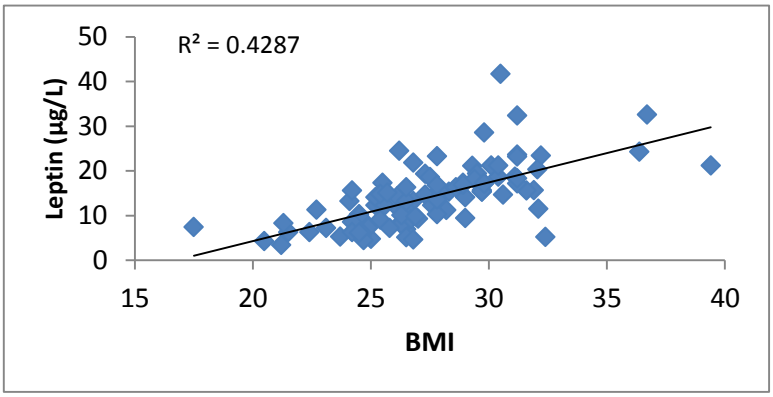

Figure 2: Correlation between leptin levels and BMI

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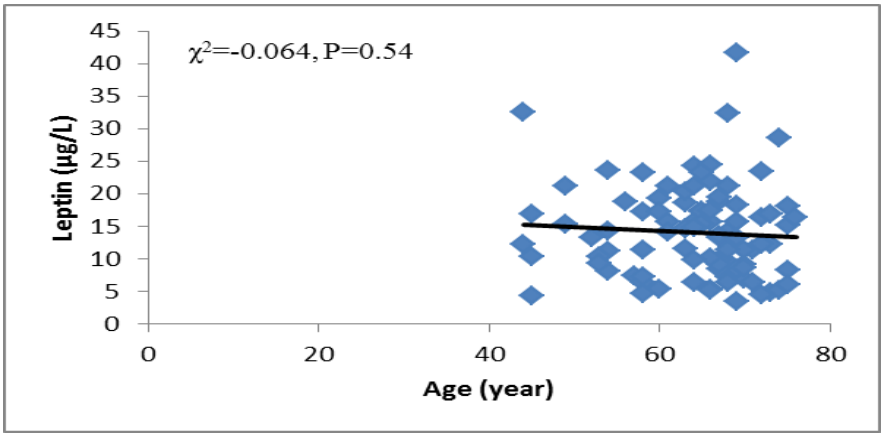

Figure 3: Correlation between leptin levels and age

DISCUSSION

Recent studies have demonstrated that leptin exhibits similar effects to cholecystokinin cytoprotective activity against acute gastric lesions due to the influence of ethanol or high doses of aspirin and indomethacin [6, 7]. Gastroprotective effect was connected with mRNA and protein expression of leptin in gastric mucosa. In our study we investigated the peculiarities of serum leptin levels in patients with chronic gastric lesions due to the influence of therapeutic doses of non-selective NSAIDs. We demonstrated that the serum leptin level was increased in patients with erosive changes of gastric mucosa that can be considered as gastroprotective effect. According to literature data, leptin accelerates the gastric ulcer healing mechanisms involving the upregulation of transforming growth factor and increases nitric oxide production due to upregulation of constitutive NO synthase (cNOS) and inducible NOS (iNOS) in the ulcer area [16].

According to our data leptin correlates significantly with BMI and it is higher in women vs men. This finding is similar to other reports [10, 17, 18]. In our study we didn't observe correlation between serum leptin level and age, although Roper et al. could not verify these results [19]. These controversies might be due to limited number of participants and the mean age of H. pylori infected patients was significantly lower compared to patients in our study.

During the recent years in the developed countries there is a steady increase in the number of people having obesity or overweight. According to modern opinions one of the causes of this tendency can be associated with the alteration of endogenous microbiota. Nowadays the disappearance of H. pylori is proved documentary. Moreover, the reduction of the frequency of occurrence of H. pylori was preceded by the number of people with overweight and obesity. Stomach produces leptin and is the main place of the ghrelin production. In recent time there is more and more data that H. pylori influences on their production leading to the changes of energy metabolism and further overweight and even obesity. At the same time H. pylori increases the level of pH of the stomach leading to the atrophy of GM. According to our data H. pylori colonization is associated with reduced serum leptin levels, independent of BMI that is similar to the results of the scientists from USA who showed that serum leptin level is significantly lower in Hp-positive patients [20]. Thus, we can consider that H. pylori influences on leptin homeostasis. However, we cannot offer a clear explanation for this finding. We suppose that it is connected with the alteration of gastric leptin production due to injuries of gastric mucosa and consequently leptin producing cells, leading to decline of circulating leptin level. Our findings may help in better understanding of the pathogenesis of NSAIDs-gastropathy which in future may lead to the development of more effective treatments and to avoid side effects from the most widespread drugs-NSAIDs.

REFERENCES

[1] Ma Z, Gingerich RL, Santiago JV, et al. Clin Chem 1996; 42: 942-946.
[2] Guilmeau S, Buyse M, Bado A. Curr Opin Pharmacol 2004; 4: 561-566.
[3] Francois F, Roper J, Goodman AJ, et al. Gut 2008; 57: 16-24.
[4] Sobhani I, Bado A, Vissuzaine C, et al. Gut 2000; 47: 178-183.

[5] Hemmasi G, Zamani F, Khonsari M, Sohrabi M, Abdollahi N, Ajdarkosh H. Middle East J Dig Dis 2013; 5 (3): 158-162.
[6] Konturek PC, Brzozowski T, Sulekova Z, et al. J Physiol Pharmacol 1999; 50 (4): 587-595.
[7] Konturek PC, Brzozowski T, Sulekova Z, et al. Eur J Pharmacol 2001; 23: 414 (1): 87-97.
[8] Shiotani A. Miyanishi T, Uedo N, Iishi H. Helicobacter 2005; 10: 373-378.
[9] Lankarani KB, Moghadami M, Masoumpoor M, Geramizadeh B, Omrani GR. Dig liver Dis 2004; 36:717-721.
[10] Zhang J, Ding SG, Yang XL, Wang Y, Zhang HJ. Beijing Da Xue Xue Bao 2010; 42(5): 543-546.
[11] Hemmasi G, Zamani F, Khonsari M, Sohrabi M, Abdollahi N, Ajdarkosh H. Middle East J Dig Dis 2013; 5 (3): 158-162.
[12] Jun DW, Lee OY, Lee YY, Choi HS, Kim TH, Yoon BC. Dig Dis Sci 2007; 52: 2866-2872.
[13] Kinkhabuala A, Roper J, Shak J, et al. Gastroenteol 2007; 132: 208.
[14] Pacifico L, Anania C, Osborn JF, Ferrara E, Schiavo E, Bonamico M et al. Helicobacter 2009; 14: 54-60.
[15] Khudur S, Jameel Dr, Karhoot J, et al. Al-Kindy Col Med J 2011; 7 (2): 74-77.
[16] Fallahi S, Nabavizadeh F, Sadr S, et al. J Stress Physiol Biochem 2011; 7 (4): 301-310.
[17] Sandelli LJ. Arthritis Rheumatol 2009; 60 (10): 2858-2860.
[18] Iwamoto J, Takeda T, Sato Y, Matsumoto H. Arthritis 2011: 1-6.
[19] Roper J, Francois F, Shue PL et al. J Clin Endocrinol Metab 2008; 93: 2350-2357.
[20] Azuma T, Suto H, Ito Y, et al. Gut 2001; 49: 324-329.