

## 혈중 렙틴치와 운동이상형 기능성 소화불량증과의 관계

아주대학교 의과대학 소화기내과학교실

한종대·이광재·김진홍·조성원

### The Relevance of Plasma Leptin Levels to Dysmotility-Like Functional Dyspepsia

Jong Dae Hahn, M.D., Kwang Jae Lee, M.D., Jin Hong Kim, M.D. and Sung Won Cho, M.D.

*Department of Gastroenterology, Ajou University School of Medicine, Seoul, Korea*

**Background/Aims:** Leptin is known to be related to both appetite and gastric motility. However, little is known about the clinical implication of leptin in functional dyspepsia (FD). The aim of this study was to investigate the association of the plasma leptin levels with dysmotility-like FD. **Methods:** 42 patients with dysmotility-like FD and 14 healthy controls were enrolled. The gastric emptying time (GET) was measured using a radiolabeled solid meal, and plasma leptin levels were determined before and 30 min after the test meal with using a commercially available radioimmunoassay kit. **Results:** The mean preprandial and postprandial leptin levels of the patient group were not significantly different from those of the control group. The leptin levels were not significantly correlated with the GET of the patient group. Those levels did not differ between the delayed gastric emptying and normal emptying subgroups. **Conclusions:** The plasma leptin levels are not altered in dysmotility-like FD patients and they are poorly correlated with the gastric emptying time, suggesting that leptin does not seem to play a significant role in the pathogenesis of dysmotility-like FD. (**Kor J Neurogastroenterol Motil 2006;12:157-160**)

**Key words:** Functional dyspepsia, Gastric emptying, Leptin

### INTRODUCTION

Leptin is an anorexigenic hormone secreted mainly by adipose tissue.<sup>1</sup> Leptin secretion is known to be less affected by meals.<sup>2</sup> In contrast to ghrelin, leptin transmits satiety signals to appetite-regulatory regions in hypothalamus and reduces appetite.<sup>3</sup> In addition, leptin has been shown to delay gastric emptying.<sup>4</sup> Thus, leptin is considered to antagonize the action of ghrelin.

Delayed gastric emptying is a major pathophysiological mechanism underlying symptoms in functional dyspepsia (FD).<sup>5-8</sup> Dyspeptic symptoms presented in patients with FD are mainly related to eating. Since leptin has been found to be

associated with eating behavior and gastric motility or emptying, it is plausible that this hormone might be implicated in the pathophysiology of FD. Therefore, we hypothesized that alteration of plasma leptin levels might be related to dysmotility-like dyspepsia or delayed gastric emptying. We investigated whether plasma leptin levels are altered in patients with dysmotility-like FD and the levels are associated with gastric emptying time and dyspeptic symptoms.

### MATERIALS AND METHODS

#### Study subjects

42 FD patients with dysmotility-like symptoms were enrolled in this study. FD was diagnosed by Rome II criteria.<sup>9</sup> Main dyspeptic symptoms included fullness, bloating, nausea or early satiety. During the screening period, organic causes were excluded and symptoms were assessed with the questionnaire. 14 healthy volunteers participated in this study as well. They were matched by age, sex ratio and body mass index (BMI).

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책임저자: 이광재, 경기도 수원시 영통구 원천동 산5 (442-731)  
아주대학교병원 소화기내과학교실  
Tel: (031) 219-6939, Fax: (031) 219-5999  
E-mail: kjleemd@hotmail.com

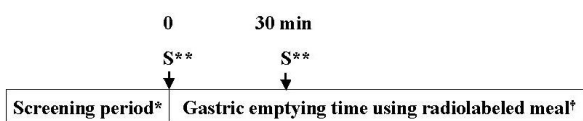
None of the study participants had diabetes and history of abdominal surgery, and was taking any medications. Control subjects had no symptoms and history of gastrointestinal diseases.

The protocol was approved by the Institutional Review Board of the Ajou University Hospital and all subjects were provided written informed consent with a complete description of the study. This study was performed in accordance with Helsinki Declaration.

### Gastric emptying study

After an overnight fast, subjects took a test meal consisting of two pieces of white bread with one egg to which 2mCi of <sup>99m</sup>Tc colloid were added, and 200 mL liquid yogurt (523 kcal, carbohydrate 69 g, protein 19 g, and fat 19 g). The test meal was consumed within 10 minutes. Immediately after ingestion of the meal, scintigraphic imaging was obtained, using a dual head gamma-camera (MS-2, Siemens Medical System Inc., IL, USA). Images were acquired in supine position every 15 minutes for 120 minutes. After the examination, the region of interest was set around the stomach, and the counts were measured. The mean of the total stomach counts of anterior and posterior images was used to calculate gastric half-emptying time. Data were processed and corrections for radioactive decay were performed. Gastric half-emptying time was defined as the time at which 50% of the radiolabeled material had left the stomach.

### Measurements of plasma leptin levels



\*Excluding organic causes and scoring dyspeptic symptoms

\*\*Sampling of blood for determination of leptin levels

\*Standardized solid meal labeled by <sup>99m</sup>Tc Tin-Colloid (523 kcal, carbohydrate 69g, protein 19g, and fat 19g)

**Fig. 1.** Study design showing the time of blood sampling and gastric emptying test. Immediately after ingestion of the radio-labeled test meal, scintigraphic images were acquired in order to assess gastric emptying time. During the gastric emptying test, two times of blood sampling for the measurement of plasma leptin levels were done immediately before and 30 minutes after the test meal.

During the gastric emptying test, two times of blood sampling were done immediately before and 30 minutes after the test meal (Fig. 1). Blood samples were drawn into tubes containing EDTA (1 mg/mL) and aprotinin (500 U/mL), and then centrifuged at 4°C to obtain plasma. Plasma was stored at -70°C until assayed. Plasma leptin concentrations were measured with a commercially available RIA kit (LincoResearch Inc., St. Charles, MO) using <sup>125</sup>I-labeled human leptin tracer and the double-antibody/polyethylene glycol technique. The lower limit of detection was 0.5 ng/ml, and the mean intra- and interassay coefficients of variation were 5.4% and 6.3%, respectively.

### Statistical analysis

All values are presented as mean ( standard deviation (SD). Student's t-test or the Mann-Whitney U-test was performed for comparison of age, gastric emptying time, hormone levels, and body mass index between the groups. Using Pearson's chi-square test or the Fisher's exact test when cell counts were sparse, sex ratio, *H. pylori* infection and delayed gastric emptying were compared between the two groups. Pearson correlation coefficient was used to assess the strength of the linear association between the hormone level and gastric emptying time. SPSS version 11.5 (SPSS Inc., Chicago, IL, U.S.A.) was used for all statistical calculations. The p value below 0.05 was considered to be statistically significant.

## RESULTS

### Clinical characteristics of the patient group

There were no significant differences in age, sex ratio, BMI, or the prevalence of *Helicobacter pylori* (*H. pylori*) infection between dysmotility-like FD patients and controls (Table 1).

The mean gastric half-emptying time was 133.5 min in the patient group, whereas it was 90.5 min in the control group (p<0.001).

### Plasma leptin levels

Immediately before the test meal, the mean plasma leptin level of patients was not different from that of controls

( $5.4 \pm 3.2$  vs.  $5.0 \pm 2.3$  ng/mL;  $p > 0.05$ ). Also at 30 min after the test meal, no significant differences in the leptin levels were observed between the two groups ( $5.2 \pm 2.7$  vs.  $4.7 \pm 2.1$  ng/mL;  $p > 0.05$ ). In both groups, the leptin levels were not significantly changed after the meal, compared with the preprandial levels ( $5.2 \pm 2.7$  vs.  $5.4 \pm 3.2$  ng/mL;  $p > 0.05$ ).

#### Relationship with gastric emptying

In the patient group, the preprandial and postprandial leptin levels showed poor correlation with gastric half-emptying time ( $R=0.07$  and  $R=0.16$  respectively;  $p > 0.05$ ). When delayed gastric emptying was defined as gastric half-emptying time  $<$  the control mean  $+2$  SD (110.7 min), the leptin level before the meal did not significantly differ between delayed gastric emptying and normal emptying subgroups ( $5.2 \pm 2.8$  vs.  $5.8 \pm 3.9$  ng/mL;  $p > 0.05$ ). Similarly, there was no significant difference in the postprandial leptin level between the two subgroups ( $5.0 \pm 2.5$  vs.  $5.5 \pm 3.1$  ng/mL;  $p > 0.05$ ).

## DISCUSSION

In the present study, we showed that plasma leptin levels were not altered in FD patients with dysmotility-like symptoms. As FD is a heterogeneous disorder associated with diverse pathophysiologic mechanisms, different pathophysiologic mechanisms may be involved in the genesis of symptoms in FD patients. It has been suggested that leptin may be involved in the genesis of early satiety.<sup>10</sup> Previous studies have shown that leptin plays a major role in the amount of food consumption. Recently, leptin and its receptors have been found in the human gastric mucosa. Actually, fasting plasma leptin levels were reported to be significantly higher in patients with dysmotility-like dyspepsia when compared to controls.<sup>11</sup> In that study, leptin levels were also significantly correlated with the presence of gastritis and *H. pylori* infection. Leptin may have a role in the pathogenesis of the dysmotility variety of non-ulcer dyspepsia through mechanisms other than *H. pylori* infection. However, we did not observe substantially higher plasma leptin levels in dysmotility-like FD patients. Individual leptin levels did not show significant correlation with gastric half-emptying time.

The influence of meal on leptin levels is controversial yet. Leptin was not significantly affected by meal in this study. The mechanism related to the regulation of leptin secretion remains to be investigated. It has been presumed that leptin may affect gastric motility through its effect on vagus nerve.<sup>12</sup> Actually, leptin has been shown to delay gastric emptying in animal studies.<sup>4</sup> However, in patients with dysmotility-like FD, we could not observe positive correlation between plasma leptin levels and gastric emptying time. In addition, there was no significant difference in plasma leptin levels between FD patients with normal gastric emptying and with delayed gastric emptying. Those findings may be attributable to two possibilities. One is that various factors, including the presence of *H. pylori* infection and gastritis, the intensity of infection, the severity of inflammation, sex and age, BMI, and the amount of adipose tissue might affect plasma leptin levels. Thus, unless all these factors would be considered, positive results are unlikely to be made. The other one is that delayed gastric emptying in dyspeptic patients may be related to heterogeneous causes. Although altered leptin levels may delay gastric emptying, its role in the pathogenesis of delayed gastric emptying found in patients with functional dyspepsia remains uncertain. It means more investigation is needed to see whether high plasma leptin levels may result in dyspeptic symptoms and delay gastric emptying in humans.

In our study, preprandial and postprandial leptin levels were not altered in dysmotility-like FD patients. Gastric half-emptying time was not well correlated with plasma leptin levels, both in the preprandial and in the postprandial period. In addition, leptin levels in patients with delayed gastric emptying were not different from those in patients with normal gastric emptying.

**Table 1.** Clinical characteristics of study subjects

	Patients	Controls
No.	42	14
Mean age, yr (range)	42 (19-66)	40 (32-50)
Sex ratio (M:F)	20:22	8:6
Body mass index (kg/m <sup>2</sup> )	$22.9 \pm 2.4$	$22.6 \pm 2.4$
H. pylori infection	25:17	7:7
Gastric half-emptying time (min)	$133.5 \pm 35.0^*$	$90.5 \pm 10.1$

\*  $P < 0.001$  compared to controls

Our findings of the present study suggest that leptin does not seem to play a significant role in the pathogenesis of dysmotility-like FD. Further investigation on the implication of leptin in gastric motor and sensory function is required.

## 요 약

**목적:** 렙틴은 식욕과 위의 운동과 관련이 있다고 알려져 있다. 그러나 기능성 소화불량증에서 렙틴의 임상적 의의에 대해서는 알려진 것이 거의 없다. 이에 저자 등은 혈중 렙틴치와 운동이상형 기능성 소화불량증과의 관계에 대해 알아보려고 하였다. **대상 및 방법:** 42명의 운동이상형 기능성 소화불량증 환자와 14명의 건강 대조군을 대상으로 방사선 동위원소를 이용한 위배출시간 검사를 시행하였고, 동시에 시험식 섭취 전과 30분 후에 각각 채혈을 시행하여 혈중 렙틴치를 측정하였다. **결과:** 식전 및 식후의 평균 혈중 렙틴치는 환자군과 건강 대조군간에 유의한 차이가 없었다. 환자군에서 식전 및 식후의 각각의 렙틴치는 위배출 시간과 유의한 상관성이 없었다. 위배출이 지연된 군과 정상인 군간에 식전 및 식후의 혈중 렙틴치에 유의한 차이가 없었다. **결론:** 운동이상형 기능성 소화불량증 환자에서 혈중 렙틴치는 정상 대조군과 차이가 없고, 위배출시간과 유의한 관련이 없어서 운동이상형 소화불량증을 유발하는데 중요한 역할을 하지 않는 것으로 보인다.

**색인단어:** 기능성 소화불량증, 위배출, 렙틴

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