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Correlation between the expressions of leptin and its receptors (ObR,sObR) in gastric cancer

Mide kanserinde leptin ve reseptörlerinin (ObR, sObR) ekspresyonları arasındaki korelasyon

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Abstract: Objective: The expressions of leptin and its receptor (ObR) have been observed in human gastric cancer (GC) tissue. Leptin can promote the proliferation of GC cells. However, the correlation between leptin and ObR expressions in GC and the role of gastric ObR protein levels in patients with GC is still unclear. This study aimed to evaluate the relationship between leptin, gastric ObR protein and soluble leptin receptor (sObR) levels and whether their possible role of indicator in GC.

Methods: Serum leptin, gastric leptin and serum sObR concentrations were determined in 30 male patients with GC and 25 male dyspeptic subjects by enzyme linked immunosorbent assay. We analysed the expression of gastric ObR levels in endoscopically obtained biopsy samples by using Western Blotting method.

Results: Compared with controls, patients had lower serum leptin and higher gastric tissue leptin levels. sObR protein concentrations of patients were detected significantly higher, gastric ObR protein expression were lower than subjects in control group.

Conclusion: Leptin in gastric cancerous region and sObR in circulation are overexpressed in GC. Their expressions are associated with malignancy. Decreased leptin levels, induces the sObR signal in circulation. This negative feedback regulation is also seen in gastric tissue: increased gastric tissue leptin levels inhibits gastric ObR protein expression. Thus,leptin and ObR may be important indicators in GC.

Keywords: Gastric cancer, Leptin, ObR, sObR, Western blot

Özet: Amaç: Leptin ve reseptörünün (ObR) ekspresyonu, insan mide kanseri (GC) dokusunda gözlenmiştir. Leptin GC hücrelerinin çoğalmasını teşvik edebilir. Ancak, GC olan hastalarda leptin ve ObR ekspresyonu ile mide ObR protein düzeylerinin rolü arasındaki ilişki hala net değildir. Bu çalışma GC'de leptin, mide ObR protein ve çözünebilir leptin reseptör (sObR) düzeyleri arasındaki ilişkinin değerlendirilmesini amaçlamıştır.

Metod: Serum leptin, mide leptin ve serum sObR konsantrasyonları mide kanseri olan 30 erkek hasta ve 25 erkek dispeptik hastada enzimle bağlanmış immünosorbent yöntem ile tayin edildi. Mide ObR seviyeleri, endoskopik olarak elde edilen mide biyopsi örneklerinde Western Blot yöntemi kullanılarak incelendi.

Bulgular: Kontroller ile karşılaştırıldığında, hastaların daha düşük serum leptin ve daha yüksek gastrik doku leptin düzeyleri vardı. Hastaların sObR protein konsantrasyonları anlamlı derecede yüksek saptandı, mide ObR protein ekspresyonları kontrol grubundaki bireylere göre daha düşükolarak bulundu.

Sonuç: GC'de kanserli bölgede leptin ve dolaşımda sObR aşırı eksprese edilmektedir. Ekspresyonları,kanser ile ilişkilidir. Azalmış leptin düzeyleri, dolaşımdaki sObR sinyalini indükler. Bu negatif geri besleme düzenlemesi ayrıca

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mide dokusunda da görülür: artmış gastrik doku leptin düzeyleri, mide ObR protein ekspresyonunu inhibe eder. Böylece, leptin ve ObR, GC'de önemli belirteçler olabilir.

Anahtar Kelimeler: Mide kanseri, Leptin, ObR, sObR, Western blot

1 Introduction

Gastric cancer (GC) is the fourth most common malignancy worldwide, with nearly 1 million cases per year. GC is also the second leading cause of cancer-related death annually. Carcinomas of the stomach constitutes 90–95% of malignant neoplasms. About 90–95% of GC are adenocarcinomas [1,2]. GC is about two times more common in men than in women. In our country; Turkey, GC is 8.72% of all cancers in men. The average age of patients at diagnosis was 56 [3,4].

Most patients present with advanced-stage disease. Although surgery is the only potential curative treatment, the overall survival results remain poor due to the high risks of recurrence, so scientists developed new aggressive adjuvant therapies. Palliative chemotherapy is usually the only treatment option for patients with advanced GC. Maintenance chemotherapy is an evolving concept in medical oncology and can be administered with the same drug(s) in the initial regimen or with an alternative agent [5]. But there is still a need for the identification of *new biochemical markers* in the treatment of patients with GC.

Leptin is a 16 kDa weighing peptide hormone, discovered by Zhang and his colleagues in 1994, secreted from adipocytes, affects hypothalamus by negative feedback mechanisms, decreases nutrient uptake and increases energy expenditure [6,7]. Similar to cytokines, leptin is a hormone containing 167 amino acids. It is encoded in (7q31) ob /ob human genome located on the long arm of chromosome 7 [8,9]. Although leptin is mainly expressed in adipose tissue; it is shown to be secreted by gastric epithelium, placenta, skeletal muscle, bone marrow, pituitary gland and mammary gland, too [10–15].

Leptin exposes its hormonal effects by binding to ob-specific transmembrane receptor called ObR. Using an expression cloning strategy in mice, leptin receptors were identified as diabetes (db) gene products by Tartaglia *et al*. Leptin receptors are included in the class 1 cytokine family [16]. Leptin receptor gene is fastened alternatively to create at least 6 different isoforms (ObRa - ObRf). All isoforms have an identical extracellular ligand binding domain with 816 amino acids from the amino terminal, but the intracellular domain in C – terminal differs [17]. ObRb, is the only long-form having an intracellular domain with residue 302 amino acids, while others have shorter (32–97 amino acids) [18].

As Bado and colleagues previously demonstrated in rats [19], the human leptin receptor has been shown in gastric mucosa, too [20]. Sobhani and co-workers have shown the human stomach expressing the long form of leptin receptor by immunoblot method in their study [20].

Endogenous gastric leptin, acts as a gastrointestinal hormone via autocrine and/or paracrine ways in the gastrointestinal tract. Leptin plays an important role in the physiological activity of digestion, the protection of gastric mucosal cells, nutrition, the regulation of gastric acid secretion and gastric hormones, the modulation of intestinal transport and controlling short time-meal size [21].

Recent evidence suggest that leptin has several functions, all play a role in tumor development and progression, including stimulation of tumor cell growth, migration, invasion and enhancement of angiogenesis [22]. Bidirectional expression of leptin and ObR could be a tumor specific phenomenon in the transformation of intestinal metaplasia to adenocarcinoma and intestinal type gastric tumor [23].

Soluble leptin receptor (sObR) is the main leptin binding activity in plasma and has helped us to understand the regulation of biological activities of leptin in vivo. Decreased leptin levels, induces the sObR signal in circulation as a negative feedback regulation.

Many studies showed that leptin signals manages a variety of physiological functions in various peripheral tissues [24]. sObR is also available in these tissues. Acute sObR induction temporarily inhibits the leptin signal in these areas [25].

The expressions of leptin and its receptor (ObR) have been observed in human GC tissue. Leptin can promote the proliferation of GC cells. However, the correlation between leptin and ObR expressions in GC and the role of gastric ObR protein levels in patients with GC is still unclear. This study aimed to evaluate the relationship between leptin, gastric ObR protein and sObR levels and whether their possible role of indicator in GC.

2 Materials and Methods

2.1 Patients

Serum leptin, gastric leptin, gastric ObR protein and serum sObR protein concentrations were determined in 30 male patients who were admitted to Gastroenterology Depart-

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ment in Kayseri Erciyes University Faculty of Medicine. These patients were suspected of GC without symptoms of clinical metastasis and referred for upper gastrointestinal endoscopy. They were diagnosed as gastric adenocarcinoma in histopathological examination. 25 male dyspeptic subjects, in terms of body mass index similar to patients' group, were included to the study as a control group. The study was approved by Kayseri Erciyes University Faculty of Medicine Human Ethics Committee (approval number: 09/147). All samples were obtained with written informed consent of the patients prior to their inclusion. None of the participants had undergone gastrointestinal surgery. Secondary malignancy, hepatitis B and hepatitis C infection, hypertension, diabetes mellitus and other metabolic diseases were the exclusion criterions.

Biopsy samples were endoscopically obtained from patients' cancerous region of the gastric tissue for the analysis of gastric tissue ObR protein and leptin levels. Normal gastric tissue biopsy samples were also taken from just adjacent to the cancerous region of patients' stomach and they were called as control 1. Dyspeptic subjects' normal endoscopic gastric corpus biopsies were called as control 2.

2.2 Serum leptin and sObRprotein concentrations

After 12 hours fasting, on the day of endoscopy, venous blood samples were drawn between 08.00 and 09.00 a.m. They were centrifuged for 10 minutes at 2000 rpm and serum was separated and stored at -80°C until the assay.

Serum leptin, gastric leptin and sObR protein concentrations were assessed by commercial enzyme linked immunosorbent assay kits (BioVendor; Czech Republic), based on the protocol provided by the manufacturer.

2.3 Measurement of gastric mucosal levels of leptin

Biopsy samples were obtained endoscopically, homogenized in phosphate-buffered saline (PBS). By centrifugation at 10 000 g for 10 minutes, homogenate supernatants were obtained and assayed for total protein by modified Lowry method. Aliquots of the supernatants were frozen at -80 until the assay. Gastric leptin contents were measured by a commercial enzyme linked immunosorbent assay kit (BioVendor Research and Diagnostic Products; Brno, Czech Republic). The concentrations of leptin were expressed in ng/mg protein.

2.4 Gastric ObR protein levels

As described previously, the amount of protein in the tissues were measured and the highest protein content of patients' tumor tissue, normal gastric tissue and gastric tissue proteins of the control group were separated by 8% SDS-PAGE (20 µg total protein) electrophoresis. Subsequently proteins were transferred to nitrocellulose paper by Western blotting method. They were incubated with polyclonal anti-leptin receptor antibodies and determined by electrogenerated chemiluminescence (ECL) detection system.

2.5 Statistical analysis

Statistical analysis was done by using the SPSS version 17 (Statistical Package for Social Science; Chicago, IL, USA). The results of groups with normal distribution are presented as mean±SD, and the median was use to present results that showed abnormal distribution. To deter¬mine significant differences between the groups, t-test for data with normal distribution and Mann-Whitney U test for data with non-normal distribution were used. The p values ≤0.05 of the obtained results was accepted as statistically significant.

3 Results

3.1 Patient demographics

Our study population consisted of 30 men in patients' group with a mean age of 64.26±9.84. The control group consisted of 25 healthy men with a mean age of 42.32±13.89. There were no significant differences in these groups in body mass index (BMI) status (24.77±3.61 and 25.87±2.85 respectively).

3.2 Serum concentrations of leptin and gastric adenocarcinoma status

The patients' serum leptin levels were measured significantly lower than the levels of control group. The difference between the median values of serum leptin in these two groups (2.22 and 4.63 ng/mL respectively) were found statistically significant ($p<0.05$) (Table 1).

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Table 1: Comparison baseline characteristics/findings between patients and the control group.

Baseline characteristics/findings	Gastric adenocarcinoma	Control	*P* value
Number	30	25	
Sex (M)	30	25	
Age	64.26±9.84	58.32±13.89	NS
BMI (Body mass index)			NS
<24.9	19	8	
25–29.9	10	14	
30–34.9	1	3	
35–39.9	–	–	
>40	–	–	
Histological type†			
MA	4	–	
PA	19	–	
SRC	4	–	
UC	3	–	
Stage			
II	4		
III	15	–	
IV	3	–	
Distant metastasis			
M0	27	–	
M1	3	–	
Leptin (ng/mL)	2.22‡ (0.76; 7.01)	4.63‡ (2.75; 6.25)	0.027
sObR (ng/mL)	35.63‡ (24.91; 54.29)	26.39‡ (19.22; 33.05)	0.01

†Histological type: MA: Moderately differentiated adenocarcinoma; PA: Poorly differentiated adenocarcinoma; SRC: Signet ring cell carcinoma; UC: Undifferentiated. ‡Mann-Whitney test. Data are median and interquartile range (25%; 75%). NS: Non significant.

Table 2: Gastric mucosal levels of leptin.

	Gastric adenocarcinoma	Control 1	Control 2	*P* value
Number	30	30	25	0.45
Gastric leptin (ng/mL)	26.45‡ (16.21; 56.93)	21.79‡ (12.88; 34.91)	20.37‡ (12.93; 38.72)	

‡Mann-Whitney test. Data are median and interquartile range (25%; 75%). NS: Non significant.

3.3 Serum concentrations of sObRprotein and gastric adenocarcinoma status

Serum soluble leptin receptor concentrations of patients were measured higher than those of control subjects and the difference between median values of these two groups (35.63 and 26.39 ng/mL respectively) were found statistically significant (p<0.05) (Table 1).

In order to evaluate the correlation between levels of serum leptin and sObR, we performed Spearman's correlation analyse. Serum leptin and sObR concentrations were shown to be negatively correlated (correlation coefficient, r=0.800, p<0.05) in patients' but no correlation was shown in control group.

3.4 Gastric mucosal levels of leptin in relation to gastric adenocarcinoma status

Gastric leptin contents of tumor tissues in patients with gastric adenocarcinoma were higher than normal gastric tissues obtained adjacent to the cancerous region in patients and biopsies of control subjects (p<0.05) (Table 2).

3.5 Expression of ObR protein in gastric mucosa

Gastric ObR proteinexpression of tumor tissues in patients were decreased. Gastric ObR protein expression was higher in patients' and control subjects' normal gastric

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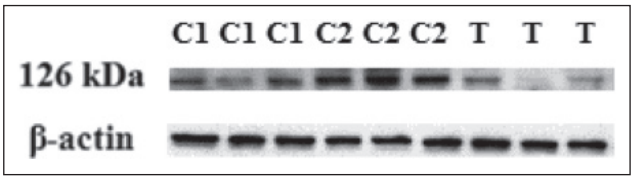


Figure 1: ObR protein expression. SDS-PAGE: C1; Normal gastric tissue biopsy samples from just adjacent to the cancerous region of patients' stomach. C2; Dyspeptic subjects' normal endoscopic gastric corpus biopsies. T; Patients' cancerous region of the gastric tissue.

tissues. ObR protein expression was shown as band 126 kDa (Figure 1).

4 Discussion

Gastric cancer is often found random and associated with further complications. The prognosis is poor and in many industrial countries, 5-year survival from diagnosis is only 10% [4].

Leptin is produced by adipose tissue, modulates feeding behavior and weight control as a hormone. Recently, stomach is defined as a major source of leptin that has various functions in the gastrointestinal tract: Leptin interacts with nervus vagus and cholecystokinin (CCK) to delay gastric emptying and has complex effects on intestinal motility. Leptin plays a major role in the control of body weight and also has growth factor like functions on epithelial cells. Leptin modulates the absorption of macronutrients from gastrointestinal tract, including differently in physiological and pathological conditions. In physiological conditions, exogenous leptin has been shown to reduce carbohydrate absorption and enhance the absorption of small peptides. It is noted that leptin increases the absorption of carbohydrates, protein and fat in certain pathological conditions. It is also reported that abnormal expression of leptin and leptin receptor may be associated with cancer development and progression [26].

It has been shown by immunoprecipitation and Western blotting analysis that leptin and the extracellular portion of leptin receptor bound together as protein compatibly. In the absence of this soluble receptor, leptin declines rapidly.

Gastric cancer is a rare but an important malignancy. The relationship between the development of cancer and leptin-a cytokine elevated in obese individuals- is investigated.It is also emphasized that leptin and its receptor may play a role in the development of gastric cancer. However, actual mechanism of the interaction between leptin and leptin receptor resulting in this way is not yet completely clarified.

In studies, generally, serum leptin levels of patients with gastrointestinal cancer are reported lower than those of controls [27,28].

Studies have attracted attention to the link between cancer development and a rising level of cytokine: leptin in obese individuals. And also there are rare studies mentioned about clinical correlations of leptin and stomach cancer [29].

There is no study indicating serum leptin levels of patients with gastric adenocarcinoma like ours. A single case-control study performed in our country has been reported. However, unlike our study, it was included only patients with metastatic cancer and significantly weight loss. In that study, leptin levels in patients with gastric cancer were found significantly lower than in controls parallel to the conclusion in our work [30].

Studies are mostly conducted in patients after major surgery or postoperative gastric tissue. However, surgical stress stimulates the synthesis of leptin from adipose tissue [31]. Unlike the others, in our study we evaluated biopsy samples obtained endoscopically at the time of first diagnosis.

As stated previously, leptin, which is thought to play a role in the pathogenesis of cancer, is a peptide hormone primarily secreted from adipocytes. sObR, regulates leptin functions but its association with cancer is unknown. One of the few studies conducted on this topic, a strong inverse relationship with colorectal cancer was found [32,33].

Importantly, it should be emphasized that, in another study, no significant difference was found aboutserum leptin concentrations of cancer patients and healthy control group with the same sex and similar BMI between 18.5–25 [32].

BMI and gender are the baseline characteristic factors of affecting serum leptin concentrations. Serum leptin concentrations are affected by changes in BMI and nutritional status in patients with cancer and serum leptin concentration is a potential parameter in the evaluation of nutritional status of these patients [32].

There is a gender difference in circulating leptin concentrations. Leptin levels in women is two to three times higher than men with the same BMI. A higher proportion of adipose tissue and increased production rate of leptin per unit mass of adipose tissue explain why women have higher circulating leptin levels than men. In order to exclude this gender factor, we chose only male participants created the patient and control groups in our study.

There were no significant differences in BMI levels measured between patient and control groups, so we eliminated another factor: BMI, affecting serum leptin concentration. In this case, the reason of this decrease in

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the level of serum leptin in patients, make us think about only cancer-related malnutrition.

Like other biological signaling pathways, leptin appears to regulate its own receptor and signaling. Decreased leptin levels, induces the sObR signal in circulation. Leptin receptor may act as a negative regulator of leptin activity. In this study, leptin levels were found decreased in cancer tissues and high circulating levels of leptin receptor were observed in these patients. So these results make us again think that soluble leptin receptor and leptin expression of tissues play a role in cancer progression. In a study conducted in recent years, 10 gastric cancer tissue samples and 96 control gastric mucosal leptin levels were examined by immunohistochemical staining. Leptin levels in tumor tissues were found significantly higher than normal gastric tissue samples as we found in our results [34]. Recent studies show that leptin and ObR levels of gastric cancer tissues are higher than normal tissues [35,36].

It is believed to be an important factor that gastric carcinogenesis is induced with the interaction between leptin and leptin receptor. Gastric leptin expression is increased in the presence of the gastric mucosa injury [37,38] and infection [39]. After the infection was eradicated, the reduction of gastric leptin expression suggests that leptin may play a role in the pathogenesis of gastric cancer [40]. Presence of leptin system's autocrine loop in the development of intestinal type gastric adenocarcinoma, has been recently reported by Zhao and co-workers [23]. Therefore, understanding the interaction between leptin and leptin receptor is beneficial in the management of gastric cancer and this receptor blockade may be a rational therapeutic strategy [25].

Basically, the primary purpose of the measurement of leptin and its receptors is to clarify the relationship with gastric cancer. In our study we compared tumor tissue leptin levels with two controls and we found tumor tissue leptin levels higher than the leptin levels of gastric tissues of healthy individuals and normal gastric mucosa samples of patients with gastric cancer. But interestingly, leptin receptor protein expression in tumor tissues were weaker than gastric tissues of controls' and patients' normal gastric tissue biopsies taken just adjacent to the tumor region. So, this result was interpreted as an indicator of negative correlation between gastric tumor leptin and receptor protein expression.

The present study has some limitations. There is a need for further studies evaluating leptin and its receptor levels with a larger number of patients with gastric adenocarcinoma and the relation between these parameters and the patients' outcome.

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Conflict of interest: None declared.

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