Introduction

Stomach cancer is the fourth most frequently observed malignant disease in the world and is the second most frequent cause of cancer death [1, 2]. When the distribution of cancer cases in men and women (respective incidences, 3.96 and 2.12 per 100,000) is examined according to respective organs, stomach cancer ranks second [3, 4].

Stomach cancer has a multifactor etiology, being influenced by a number of genetic, environmental and predisposing factors. Among the predisposing factors, chronic atrophic gastritis is the most important, and its incidence increases with age [5, 6]. The most common type of gastric cancer, the intestinal type, is usually preceded by chronic atrophic gastritis [6, 7]. Because precursor lesions and most of the early stomach cancers are asymptomatic, and because a clear diagnosis can be made only via biopsy, most stomach cancers are not diagnosed until the late stages, leading to increased morbidity and mortality [2]. Gastritis serology is therefore of crucial importance in population-based screening and prevention studies [6, 7].

The gold standard for the diagnosis of gastric atrophy is the histological study of biopsies obtained during an upper gastrointestinal (GI) endoscopy, an invasive method that is too complicated for use in population screening. It would be better to obtain knowledge of the frequency and natural history of gastric mucosal atrophy by non-invasive strategies applicable to an asymptomatic population because this would allow prevention strategies to be tested and would lead to more effective diagnoses of the progression to (early) gastric cancer [2].

Conclusions:
Localizing in the pylorus and cardia via this method is difficult, we believe that posing lesion for stomach cancer. Although the diagnosis of stomach cancers predictor of stomach cancer and atrophic gastritis, the most important predisposing factors, chronic atrophic gastritis will be decreased.

Key Words: Gastritis, Pepsinogen, Stomach cancer

Usefulness of Serum Pepsinogen Levels as a Screening Test For Atrophic Gastritis and Gastric Cancer

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Abstract

Objective: The purpose of our study was to research the applicability of measuring serum pepsinogen I (PG I) and PG I/pepsinogen II (PG II) ratios as screening tests for atrophic gastritis, which is the most important predisposition for stomach cancer.

Materials and Methods: We measured serum pepsinogen levels in non-specific gastritis, atrophic gastritis and gastric cancer using a radioimmunoassay method. We included in this study 30 healthy control, 30 non-specific gastritis, 30 atrophic gastritis and 50 gastric cancer cases.

Results: The serum PG I level was statistically higher in the control group and in the patient group with chronic non-specific gastritis compared to the patient groups with chronic atrophic gastritis and stomach cancer (p<0.05). The best cut-off values for diagnosing stomach cancer using serum PG I and PG I / PG II ratios were found to be <25 ng/ml for PG I and <3.0 for PG I / II. The same cut-off values were also most effective for the patients with atrophic gastritis.

Conclusions: Serum pepsinogen screening was shown to be a practical predictor of stomach cancer and atrophic gastritis, the most important predisposing lesion for stomach cancer. Although the diagnosis of stomach cancers localized in the pylorus and cardia via this method is difficult, we believe that the detection of early-stage cancers that develop following chronic atrophic gastritis in particular will be possible, and therefore the morbidity and mortality of stomach cancer will be decreased.

Key Words: Gastritis, Pepsinogen, Stomach cancer

Özet

Amaç: Bu çalışmada amacımız serum pepsinojen I (PG I) ve PG I / pepsinojen II (PG II) düzeylerinin mide kanser ve onun en önemli predispozan faktörü olan atrofik gastrit ile ilişkisini incelemektir.

Gercek ve Yöntem: Çalışmamızda sağlıklı kontrol 30, nonspesifik gastritli 30, atrofik gastritli 30 ve mide kanserli 50 hastada serum pepsinojen düzeylerini radioimmunoassay yöntemi ile ölçtük.

Bulgular: Çalışmamız sonucunda serum PG I düzeyleri atrofik gastrit ve mide kanseri olgularında sağlıklı kontrollere göre düşük bulundu. Mide kanseri ve atrofik gastrit tanıları için kullanılabilecek en iyi sınır değerler PG I için <25 ng/ml, PG I / II için <3.0 olarak tespit ettik.

Sonuç: Serum pepsinojen taramasının, mide kanserinin en önemli predispozan lezyonu olan atrofik gastrit ve mide kanserinin pratik bir göstergesi olduğunu gösterdi. Her ne kadar pilor ve kardiyada lokalize mide kanserlerinin tanısı bu yöntemle zor olası dahi, özellikle atrofik gastrit izleyen mide kanserlerinin erken dönemde tespiti mümkün olabilecektir ve böylece mide kanserlerinin mortalite ve morbiditesinin azaltacağını düşündükuz.

Anahtar Kelimeler: Gastrit, Mide kanseri, Pepsinojen

Introduction

Stomach cancer is the fourth most frequently observed malignant disease in the world and is the second most frequent cause of cancer death [1, 2]. When the distribution of cancer cases in men and women (respective incidences, 3.96 and 2.12 per 100,000) is examined according to respective organs, stomach cancer ranks second [3, 4].

Stomach cancer has a multifactor etiology, being influenced by a number of genetic, environmental and predisposing factors. Among the predisposing factors, chronic atrophic gastritis is the most important, and its incidence increases with age [5, 6]. The most common type of gastric cancer, the intestinal type, is usually preceded by chronic atrophic gastritis [6, 7]. Because precursor lesions and most of the early stomach cancers are asymptomatic, and because a clear diagnosis can be made only via biopsy, most stomach cancers are not diagnosed until the late stages, leading to increased morbidity and mortality [2]. Gastritis serology is therefore of crucial importance in population-based screening and prevention studies [6, 7].

The gold standard for the diagnosis of gastric atrophy is the histological study of biopsies obtained during an upper gastrointestinal (GI) endoscopy, an invasive method that is too complicated for use in population screening. It would be better to obtain knowledge of the frequency and natural history of gastric mucosal atrophy by non-invasive strategies applicable to an asymptomatic population because this would allow prevention strategies to be tested and would lead to more effective diagnoses of the progression to (early) gastric cancer [2].
There are two main types of pepsinogen (PG), namely PG I (PG A) and PG II (PG C). Both of these types are produced in the essential cells in the stomach corpus and fundus and in mucous cervical cells. Unlike PG A, PG C is also produced in the Brunner glands in the proximal duodenum and in the pyloric glands in the antrum [8]. Serum pepsinogen levels reflect the morphological and functional status of the stomach mucosa, so they serve as markers of chronic atrophic gastritis [9]. Low levels of serum PG A and PG A / PG C are observed in patients with atrophic gastritis, peptic ulcer disease, intestinal metaplasia, dysplasia, gastric polyps, and gastric cancer [8].

The purpose of our study was to research the applicability of serum pepsinogen concentrations as a screening test for atrophic gastritis, which is the most important predisposition for stomach cancer.

Materials and Methods

A total of 110 patients from the Atatürk University Faculty of Medicine, Department of Internal Diseases, Clinic of Gastroenterology were included in the study. Of these, 30 patients were diagnosed with chronic nonspecific gastritis via endoscopy and histopathology, 30 with chronic atrophic gastritis, and 50 with stomach cancer. All other gastritis types other than chronic atrophic gastritis were assessed as nonspecific gastritis.

A control group consisting of 30 healthy volunteers, who had no dyspeptic complaints and who were determined to have normal gastric mucosa via endoscopy and histopathology, was also included in the study.

All of the patients and control group members were informed about the study. Signed informed consent forms were received from those who participated in the study.

Antrum, corpus, and fundus biopsies were collected from the control, atrophic gastritis, and nonspecific gastritis groups. Endoscopy was performed using an Olympus brand video endoscope. Lesion and mucosa biopsies were collected from the group with stomach cancer.

After biopsy materials had been examined in the pathology laboratory, the patients diagnosed with normal stomach mucosa, chronic nonspecific gastritis, atrophic gastritis, and stomach cancer were chosen for inclusion in the study.

Blood was taken from members of the patient and control groups after fasting for 12 hours. Sera were collected by centrifugation at 4,000 rpm for 5 min. Each serum sample was stored in two individual tubes and stored at -80 °C until analysis. Prior to the measurement of the serum pepsinogen I and pepsinogen II levels, serum samples were thawed in a refrigerator at 4 °C for 12 hours and then were brought to room temperature.

Serum pepsinogen I and II levels were measured with a radioimmunoassay (RIA) method using pepsik I (p2564) and pepsik II (p2224) commercial kits (DiaSorin Biomedica Saluggia, Italy).

Table 1. Median levels of serum PG I, PG II, and PG I / II ratio according to gender and gastric histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>n (M/F)</th>
<th>PG I (ng/liter)</th>
<th>PG II (pg/liter)</th>
<th>PG I / II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic nonspecific gastritis</td>
<td>30 (15/15)</td>
<td>28.79±3.68</td>
<td>8.39±0.87</td>
<td>3.43±0.42</td>
</tr>
<tr>
<td>Chronic atrophic gastritis</td>
<td>30 (15/15)</td>
<td>17.87±4.77</td>
<td>7.87±0.76</td>
<td>2.27±0.63</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>50 (17/33)</td>
<td>19.89±6.43</td>
<td>7.92±0.94</td>
<td>2.51±0.68</td>
</tr>
<tr>
<td>Control</td>
<td>30 (15/15)</td>
<td>22.91±1.82</td>
<td>6.28±0.48</td>
<td>3.65±0.38</td>
</tr>
</tbody>
</table>

M: male, F: female, PG I: pepsinogen I, PG II: pepsinogen II
negative predictive value, and correctness rate in the patients with stomach cancer were 95%, 82%, 0.93, 0.98 and 0.88, respectively.

When a serum PG I level of <20 ng/ml and a serum PG I / PG II level <3.0 were collectively taken as the cut-off values, the specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate in the patients with stomach cancer were found to be 98%, 60%, 0.95, 0.98 and 0.74, respectively.

When <25 ng/ml was taken as the serum PG I limit value, 42 (84%) of the 50 patients with stomach cancer could be discriminated. At this cut-off, the specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate in the patients with stomach cancer were 95%, 82%, 0.93, 0.98 and 0.88, respectively.

When a serum PG I level of <20 ng/ml and a serum PG I / PG II level <3.0 were collectively taken as the cut-off values, the specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate in the patients with stomach cancer were found to be 98%, 60%, 0.95, 0.98 and 0.74, respectively.

When <25 ng/ml was taken as the serum PG I limit value, 40 (80%) of the 50 patients with stomach cancer could be identified. At this cut-off, the specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate in the patients with stomach cancer were 56%, 80%, 0.60, 0.56 and 0.67, respectively.

When a serum PG I level of <25 ng/ml and a serum PG I / PG II level of <3.0 were collectively taken as the cut-offs, the specificity, sensitivity, positive predictive value, negative predictive value and correctness rate in the patients with stomach cancer were 98%, 82%, 0.97, 0.98 and 0.90, respectively.

When a serum PG I level of <25 ng/ml and a PG I / PG II level <3.0 were taken as the cut-offs, 9 (18%) of the 50 patients with stomach cancer could not be identified. Among these patients, cancer was localized in the corpus in one patient, in the pylorus in three patients, and in the cardia in five patients. Among the five stomach cancers localized only in the cardia and the three stomach cancers localized only in the pylorus, none could be determined using the PG I cut-off of <25 ng/ml and the serum PG I / PG II cut-off <3.0.

**Discussion**

The observations from this study suggest the progression from acute gastritis to chronic gastritis to atrophic gastritis and finally to intestinal metaplasia, dysplasia, and cancer. As in other cancers, it is difficult to identify the cause of the disease due to the long latency period between the beginning of a tumor and the actual diagnosis, a period that can last for decades [11]. At present, despite the increased information about gastric carcinogenesis, the number of gastric cancers diagnosed in the early stages is still very low. Noninvasive methods are allowing more stomach cancer cases to be diagnosed in the early stages. In our study, the potential of serum PG I and PG I / PG II levels was investigated as a screening strategy for early stages of stomach cancer.

At present, no study has directly examined whether a pepsinogen screening method can reduce gastric cancer mortality. The single use of pepsinogen tests is by no means sufficient for stomach cancer screening; however, it provides a valuable measure for selecting a population that needs further screening with endoscopy [12-15]. Serum pepsinogen was introduced for cancer screening to identify individuals with extensive atrophic gastritis [16]. In our study, the serum PG I and PG I / PG II levels of the control group and patients with chronic nonspecific gastritis were higher than those of patients with chronic atrophic gastritis and stomach cancer. We were able to determine serum PG I level and PG I / PG II cut-off values whose sensitivity and specificity were the most effective for discriminating patients with chronic atrophic gastritis and stomach cancer. As cut-off values, levels lower than 20 and 25 ng/ml were optimal for serum PI, and lower than 3.0 was optimal for PG I / PG II ratio. The best cut-
off values for diagnosing stomach cancer using serum PG I and PG I / PG II levels were found to be <25 ng/ml for PG I and <3.0 for PG I / PG II. The corresponding specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate were 98%, 82%, 0.97, 0.98 and 0.90, respectively. The same optimal cut-off values were identified for the patients with atrophic gastritis, with the specificity, sensitivity, positive predictive value, negative predictive value, and correctness rate of 100%, 90%, 1.00, 1.00 and 0.68, respectively. Kitara et al., in a study of a screening test in patients with stomach cancer, found the specificity and sensitivity for stomach cancer to be 84.6 and 73.5, respectively, when a serum PG I level cut-off of <70 ng/ml and a serum PG I / PG II ratio cut-off of <3.0 were used [17]. In a study carried out by Yoshihara et al., a significant relationship was determined between atrophic gastritis and low levels of serum PG I and PG II and between atrophic gastritis and stomach cancer. With a PG I cut-off of <50 ng/ml and a serum PG I / PG II ratio cut-off of <3.0, the authors were able to discriminate cases of atrophic gastritis. They found a significant relationship between low serum PG I / PG II ratios and the possibility of stomach cancer occurrence and adenoma in both men and women.

There is a known relationship between Helicobacter pylori infection and atrophic gastritis and stomach cancer. However, because a positive test for H. pylori is already prevalent in the local population, H. pylori was not taken into consideration in the study [18]. Similarly, in the current study, the population from which the test subjects were drawn also tests highly positive for H. pylori; consequently, we also did not take the presence of H. pylori into consideration in our study [11]. In our study, the serum PG I and PG I / PG II ratios were determined to be low at a statistically significant level in the patients with chronic gastritis and with stomach cancer compared to the control group. In the previous studies, no cut-off values were demonstrated to be related to serum PG I level and PG I / PG II ratios. In similar studies on this subject, different cut-off values were used, and the sensitivity and specificity were reported to range from 74.3-93% and 68.4-100%, respectively [8,19-22]. The current study shows that cut-off values for the serum PG I level <25 ng/ml and the serum PG I / PG II ratio <3.0 would be convenient and meaningful for stomach cancer and atrophic gastritis screening.

Using these recommended cut-off values, 9 (18%) of 50 patients with stomach cancer were not detected in the current study. Among these patients, cancer was localized in the corpus in one patient, in the pylorus in three patients and in the cardia in five patients. These cut-off values also failed to detect five stomach cancers localized only in the cardia and three stomach cancers localized only in the pylorus. In the study carried out by Kitahara and colleagues [17], they stated that it was difficult to determine the serum pepsinogen level and rates of stomach cancers that originated from the pyloric gland region, as was seen in our study. Therefore, the serum PG I level and the sensitivity and specificity of PG I / PG II ratios may be more useful as screens for non-cardia stomach cancers.

In conclusion, serum pepsinogen screening was shown to be a practical predictor of stomach cancer and atrophic gastritis, the most important predisposing lesion leading to stomach cancer. Although the diagnosis of stomach cancers localized in the pylorus and cardia via this method is difficult, we believe that the detection of early-stage cancers developing after chronic atrophic gastritis in particular will be possible, and therefore the morbidity and mortality of stomach cancer will be decreased. Further studies are needed to clarify the pathogenesis of gastric cancer and to establish screening methods for groups at high risk for this cancer.

Conflict of interest statement The authors declare that they have no conflict of interest to the publication of this article.

References