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Review article

SERUM PEPSINOGEN I AND PEPSINOGEN II AS NON-INVASIVE BIOMARKERS FOR THE DIAGNOSIS OF CHRONIC ATROPHIC GASTRITIS

Zornica Gorcheva[1], Valeriya Racheva[2], Mirela Vasileva[3]
1)Clinic of Internal Diseases, St. Marina University Hospital, Medical University, Pleven, Bulgaria
2)Department of Clinical Laboratory, St. Marina University Hospital, Medical University, Pleven, Bulgaria
3)Department of Imaging Diagnostic, St. Marina University Hospital, Medical University Pleven, Bulgaria.

ABSTRACT:

Atrophic gastritis, intestinal metaplasia and dysplasia of the gastric mucosa are major risk factors for the development of an intestinal type of gastric cancer. The selection of patients with such lesions could help with early detection and improve better the prognosis. Esophagogastroscopy is the "gold standard" in detecting gastric cancer and precancerous lesions of the stomach. However, this examination is invasive, expensive, and cannot serve as a screening method. Measurement of serum levels of pessinogen I and pessinogen II is used in high-risk populations in Europe and Asia as a non-invasive marker for the diagnosis of chronic atrophic gastritis. A serum pepsinogen I level ≤ 70ng/ml and pepsinogen I/pepsinogen II ratio ≤ 3 are accepted in many countries as values that most accurately identify patients with advanced atrophic gastritis. On the other hand, the differences in the analytical methods used to determine the level of pepsinogens make the interpretation of results and diagnostic validation difficult.

Keywords: pepsinogen, chronic atrophic gastritis, intestinal metaplasia, gastric cancer,

BACKGROUND

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. The prognosis is poor, with an average 5-year survival of less than 20%, as most patients are diagnosed at an advanced stage. Detection of early forms and precancerous lesions is crucial and significantly improves the prognosis. Diagnosing the disease at an early stage is challenging. Many patients are asymptomatic in the early stages, and the advanced form of the disease is diagnosed relatively late [2, 3]. From early to advanced stages, gastric cancer (GC) progression is a long process, which can be influenced as early as the precancerous lesion stage [4]. Chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) are recognized as high-risk conditions, against the background of which gastric carcinoma may develop. CAG and IM are considered precancerous lesions [5, 6, 7]. The interstitial type of gastric adenocarcinoma represents the final stage of a sequence described as the Correa cascade [8, 9]. This process begins with the onset of inflammation in the gastric mucosa. Subsequent stages progress through the development of non-atrophic chronic gastritis (without glandular loss), followed by multifocal atrophic gastritis, intestinal metaplasia (complete and incomplete type), dysplasia (mild grade and severe grade), and end up with the appearance of early gastric carcinoma [10, 11, 12]. The basis of the cascade is the onset of chronic atrophic gastritis and subsequent intestinal metaplasias, against the background of which dysplasia and intramucosal carcinoma would develop [10, 13].

Current studies have shown that patients with severe gastric atrophy, extensive intestinal metaplasia, and dysplasia are at increased risk of GC [14]. According to a large meta-analysis by Chen et al., eradication of Helicobacter pylori does not reduce the risk of GC for these patients. Therefore, high-risk groups need to be identified and followed up using appropriate methods [15].

Esophagogastroduodenoscopy (EGD) with biopsy is the "gold standard" for screening and diagnosing gastric cancer and precancerous lesions. However, the test is invasive, expensive, and cannot be applied in routine practice. On the other hand, some biomarkers in serum may be used for a non-invasive assessment of gastric atrophy [16, 17]. Serum pepsinogens may be employed as predictors of gastric atrophy in screening for patients with suspected precancerous lesions [18].

The aim of this review is to summarise the data for pepsinogens as non-invasive biomarkers for the diagnosis of chronic atrophic gastritis.

REVIEW RESULTS

An electronic search was performed on Pub Med database. We used 'serum pepsinogen', 'atrophyc gastritis', 'intestinal metaplasia', 'gastric precancerous lesion' as keywords. The studies had to be in English, published from

1993 to 2022, be meta-analyses or systematic reviews. All the patients with CAG, IM and GC presented in the studies had to be histologically confirmed. We found 34 studies that met these criteria.

Pepsinogens

Michael Samloff was the first to suggest using pepsinogen as a "serologic biopsy of gastric mucosa" in 1982 [19]. Pepsinogen (PG) is an inactive precursor of pepsin, which is transformed into an active enzyme under the influence of hydrochloric acid. PG includes two pepsin proenzymes, of which 99% are released into the gastric lumen and 1% into the circulation. Hence, they can be measured as indirect markers of changes in the gastric mucosa [20]. The two isozymogenes - pepsinogen I (PgI) and pepsinogen II (PgII), are produced in different stomach parts. Most of PgI is produced in the chief cells of the fundic glands, and smaller quantities are manufactured in their parietal cells. The production of PgII, however, takes place in various types of glands of the stomach and Brunner's glands of the duodenum.

Regarding these processes, the atrophy of the gastric body and the disappearance of chief and decreased parietal cells, there occurs a decrease in PgI levels, while PgII levels remain relatively stable [21]. At the same time, the presence of inflammatory changes in the gastric lining, most commonly due to a Helicobacter pylori infection, can increase both PgI and PgII levels. Furthermore, in the case of Helicobacter pylori gastritis, due to the progression of atrophic gastritis from the gastric antrum to the gastric body, PgI values progressively decrease as the chief and parietal cells are damaged. In contrast, PgII values may increase due to inflammation originating in the antrum and spreading to the upper gastric compartments [22, 23]. Because of all these changes, together with the PgI and PgII values, the ratio between the two isoenzymes serum PG I/II ratio is used in the diagnostic algorithm [24].

In 2004, Ribeiro et al. published data from a meta-analysis, suggesting measuring serum pepsinogen levels as a screening method to identify patients with precancerous lesions and GC [23]. The analysis included 296,553 participants from 27 population-based studies and 4358 selected patients from 15 studies. The authors aimed to validate the measurement of PgI and PgII as a screening method for gastric cancer and precancerous lesions by identifying patients with CAG and associated lesions. The researchers placed the results from the studies into three groups: PgI ≤ 70ng/ml, sPGr ≤ 3; PgI ≤ 50ng/ml, sPGr ≤ 3; PgI ≤ 30ng/ml, sPGr ≤ 2. Respectively, the sensitivities were 77%, 68%, and 52% for the given groups. The positive predictive values (PPV) ranged between 0.77% and 1.25%, and the negative predictive values (NPV) were between 99.08% and 99.90%. Based on the analysis, Ribeiro et al. suggested that values of Pg1 ≤ 70ng/ml and sPGr ≤ 3 were positive for HAG and values of PgI ≤ 50ng/ml and sPGr ≤ 3 as positive for dysplasia. Regarding gastric cancer, the sensitivity was 77.3%, and the specificity was 73.2%. In conclusion, the authors proposed that the definition of the "pepsinogen test" [PgT] should include the PgI values and the PgI/PgII ratio.

In 2005, Lomba - Viana et al. initiated a cross-sectional study and a prospective cohort study [25]. The authors aimed to investigate serum PgI and sPgr values in asymptomatic patients in northern Portugal. They studied 13 118 individuals aged 40 to 79 years. The patients were divided into two groups: one including those with positive tests (PgI ≤ 70 ng/ml) and another - the remainder with negative results (PGr ≤ 3). Of the 446 patients with positive tests, 274 agreed to undergo EGD and be followed up for five years. Of the negative ones, 240 patients were randomly selected, and the same protocol was applied. Biopsies were taken from all patients for Helicobacter pylori testing. The authors concluded that the risk for GC increased when patients were positive for PgT, regardless of Helicobacter pylori infection and absence of symptoms. For GC detection, PgT showed a sensitivity of 67% and a specificity of 47%. The positive predictive value was 2%, and the negative predictive value was 99%. It is noteworthy that in three patients with GC, the test was false-negative, one with a diffuse type and two with interstitial carcinoma, according to Lauren's classification [13]. None of the patients mentioned that they had used proton pump inhibitors (PPIs), and many studies have shown that using PPIs leads to changes in parietal cell function and secretion. Furthermore, in cases of diffuse gastric carcinoma, PgT may be negative, as this type does not follow the Correa cascade, does not develop in association with atrophic gastritis (AG), and is related to other etiological and genetic factors.

Several other large meta-analyses confirmed the data suggesting that low PgI and sPGr levels have an inverse correlation with the risk of developing intestinal-type GC [25]. The authors of a meta-analysis, including 1520 patients with GC and 2265 with AG, reported a significant heterogeneity between the method of PG serum testing, making the interpretation of the results difficult. ELISA is the most commonly used method, but some investigators use radioimmunoassay, chemiluminescent assay, immunoturbidimetry, or the latex agglutination test [25].

By comparing three methods of PG testing, Marcis et al. wanted to investigate the diagnostic accuracy of PGT in clinical practice. They studied patients with histological confirmed AG (50 positives and 755 negatives) for moderate and severe AG [26]. Three different methods were used: two ELISA tests (Biohit, Finland and Vector Best, Russia) and a latex agglutination test (Eiken, Japan). The results obtained using these methods for detecting severe corpuscular atrophy varied: 44-76% for sensitivity, 62.6 - 93.1% for specificity, and 63.1 - 90.3% for overall accuracy. These data show differences in absolute values, even between the two ELISA methods, which cannot be explained by different laboratory principles, e.g., latex agglutination test and ELISA. In addition, the diagnostic value of PgT depends on the cut-off value. Values such as PgI ≤ 70 and PGr ≤ 3 are widely used in many studies, although they refer to Asian countries, mainly Japan [14].

A study on 284 patients with dyspeptic complaints

was conducted in 14 European countries, aiming to test the role of serum pepsinogen levels as a diagnostic test for the severity of multifocal atrophic gastritis [18]. The results Broutet N. et al. reported were as follows: 65.0% sensitivity and 77.9% specificity, with a cut-off point of 5.6. Different cut-off values were published by Kim et al. In 95 patients studied, the serum pepsinogens levels were significantly lower in patients with AG and MI, and cut-off pointsd" 3.5 with the highest specificity and sensitivity were used [27].

Another meta-analysis published in 2015, including 30,000 patients from 13 different Eastern and Western countries, aimed to evaluate the accuracy of pepsinogens in diagnosing AG and GC [14]. According to the results obtained by Huang Y. et al., PGT showed 69% sensitivity and 73% specificity in diagnosing GC of the intestinal type, and 69% sensitivity and 88% specificity in diagnosing HAG. However, the authors reported a limiting factor they associated with the heterogeneity of the studies in terms of diagnostic methods and the different cut-off values for these methods. Furthermore, only two of the studies were conducted in European countries, which may be a limiting factor from a geographical and ethnic point of view. Therefore, for the test to be used routinely, ESGE recommends in the MAPS Guideline 2019 that it be locally validated for individual populations [28].

An interesting feature regarding the severity of atrophy and PG values was demonstrated by a study of 186 patients with early gastric neoplasms who were about to undergo endoscopic submucosal dissection [29]. Patients meeting criteria for serologic atrophy, sPG I/II<3 and PgI<70 ng/ml, were more often in the group with severe atrophy [61%] than those with the mild form (18%). In addition, 58 of 186 patients (31.2%) were found to have Helicobacter pylori, with a higher percentage (63.3%) having severe atrophy. Although Helicobacter pylori was investigated by rapid urease test and histologically with standard staining, there may have been an underestimation of the infection as it is known to clear spontaneously after a long period of contamination.

Kikuchi et al. observed similar data, in which PgI and sPGr levels decreased in the Helicobacter pylori (HP)-positive group as early as 2000 [30]. Ito et al. reported data suggesting that the atrophy improved, and regression of IM was observed after the eradication of CP [31]. This led to increased levels of PgI and sPGr. In a study on 3572 symptomatic patients, Yuan et al. published data showing that patients with active infection had higher levels of PgII and lower levels of sPG I/II than uninfected patients [32]. Similar data have been published by other teams: Tu H et al. [33] and Shan JH et al. [34]. Different cut-off values for HP positive and negative patients were also suggested by Tong et al. [35]. In a prospective study of asymptomatic individuals, they measured serum PG level and analyzed the correlation with endoscopic and histological findings and KP status. They concluded that PG levels significantly ($p < 0.01$) decreased in the group with severe AG compared with the group with mild atrophy and no atrophy. They found different cut off values of PGr for the HP (+) and HP (-) groups, i.e. $PGr \leq 6.28$ and $PGr \leq 4.28$, respectively. The AUC curve values approached 0.850, indicating a good predictive value of the enzymes as a marker for severe atrophy. The use of different cut-off values may increase the diagnostic accuracy of PGT in front of the investigators.

The relevance of other factors such as gender, age, weight, and certain risk factors (alcohol, cigarettes) to PG levels is controversial. Huang et al. published data from a study of 6596 "healthy" patients. The study showed that PG values decreased with age and were higher in men than in women [36]. Regarding alcohol use and smoking, a study on 1992 asymptomatic patients found no significant difference [37]. Zhang et al. published the results of a study on 2568 healthy individuals and found no statistically significant age- and sex-related values of PGr. However, they reported a slight PgI and PgII increase with age in both sexes [38]. On the other hand, age has been shown to be a risk factor for GC development [20]. Further studies on healthy populations are needed to report the effect of these factors on PG values.

CONCLUSION

Serum pepsinogens are reliable markers for detecting AG, especially the moderate and severe forms with MI, which are considered precancerous conditions. Low levels of PgI and sPGr correlate with the severity of gastritis and can be non-invasive markers to assess the risk of the intestinal type of GC. Using PGT can identify patients who are at risk and require endoscopic investigation. Validation may be necessary, taking into consideration the specificity of some geographical regions and ethnic factors.

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Address for correspondence:
Zornica Gorcheva
Department of Therapeutic Care, Faculty of Heath Care, Medical University Pleven
25A, Mayor Gortalov str., Pleven, Bulgaria.
E-mail: zornica.gorchev@gmail.com