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(Article begins on next page)

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PEPSINOGEN II in GASTRITIS and *HELICOBACTER PYLORI* INFECTION

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Barchi A., Bricca L., Franzoni L., Rodriguez Castro K, Russo M.: data collection and analysis of the literature.

All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Abstract

Background and Aim: In the gastric mucosa, pepsinogen II (PgII) is produced/secreted by glands in the mucus-secreting antral and cardia compartments, but also by the chief cells and the oxyntic glands. Increasing PgII serum levels are associated with the whole spectrum of gastric inflammatory diseases, including gastritis induced by *Helicobacter pylori* (*H. pylori*). This review critically addresses the clinical value of PgII serology for assessing gastric mucosal inflammation, and as a marker of *H. pylori* status, in both naïve *H. pylori*-positive patients and after eradication therapy.

Results: A search in PubMed/Scopus records yielded 39 out of 1,190 published scientific studies meeting the selection criteria for this study. In the studies considered, PgII levels were significantly associated with non-atrophic gastric inflammatory lesions (p-values: 0.025-0.0001). *H. pylori*-positive patients had significantly higher PgII levels than *H. pylori*-negative individuals (p-values: 0.05-0.0001). While a significant drop in serum PgII levels is consistently reported in *H. pylori*-eradicated patients (p-values: from 0.05 to 0.0001), inconsistencies in the related negative and positive predictive values significantly lower the clinical reliability of PgII testing by comparison with other available non-invasive tests.

Conclusions: PgII serology may provide clinically useful information on gastric inflammatory diseases, particularly if they are non-atrophic. PgII serology is inconsistent, however, for the purposes of distinguishing patients whose *H. pylori* eradication therapy is successful from those who remain infected.

INTRODUCTION

Acid secretion is the distinctive function of the gastric mucosa¹. Hydrochloric acid is secreted by parietal cells (also known as oxyntic cells) that are located mainly (95%) in the oxyntic mucosa (fundus and body regions), and partly in the mucus-secreting antral mucosa (50%)^{2, 3}

Pepsinogens are aspartic proteinases synthesized/secreted by the gastric chief cells. They have a major role in the digestive process⁴. Pepsinogen I ([PgI]; pepsinogen A) is only produced/secreted by the chief cells of the oxyntic glands. As both parietal cells and chief cells are located within the oxyntic glands, PgI is considered a reliable proxy of the stomach's acid-secreting capacity, and ultimately as a consistent surrogate marker of maximal acid output. Pepsinogen II (also known as progastricsin [PGC], or pepsinogen C) is produced/secreted by glands in the mucus-secreting antral and cardia compartments, but also by the chief cells mainly included in the oxyntic glands.^{5, 6} Both pepsinogens are autocatalytically activated when the acidity level drops below pH 5, leading to the exposure of active site, and they are rapidly inactivated by the post-pyloric alkaline pH. While both pepsinogens are excreted mainly into the stomach lumen, very small amounts (about 1%) spread into the bloodstream, enabling their serological detection. A large body of literature has examined the reliability of serological assessments of PgI and PgII as a proxy of the gastric gland function, and on the clinical value of PgI, PgII and the PgI/II ratio as markers of gastric mucosa inflammation and atrophy (the latter consistently believed to be associated with gastric cancer risk).

This comprehensive review focuses on the clinical value of PgII as a serological marker of gastric inflammatory disease, and *H. pylori* gastritis, in particular. The following issues are critically addressed: (a) PgII serology in the setting of gastritis (be it atrophic or non-atrophic); (b) PgII and *H. pylori* status; and (c) PgII before and after successful or unsuccessful *H. pylori* eradication treatment.

MATERIALS & METHODS

A search for the available literature electively addressing PgII serology was conducted in the PubMed and Scopus databases up to December 31st 2020. The search included the following keywords: pepsinogen II, PgII, pepsinogen C, PgC, with “and” as a Boolean operator, in relation to atrophic gastritis, non-atrophic gastritis, gastritis activity, *H. pylori* status, *H. pylori* eradication, “and” PgII sensitivity, PgII specificity, and cut-off values. All scientific articles including the above-mentioned keywords were considered, whatever the method used to measure PgII levels (radioimmunoassay, ELISA or chemiluminescence). For each study, sensitivity and specificity values (with 95% confidence intervals [95% CI]) were both checked, together with positive and negative predictive values. Only scientific articles in English were considered. Studies lacking essential information that could not be obtained directly from the authors were also excluded.

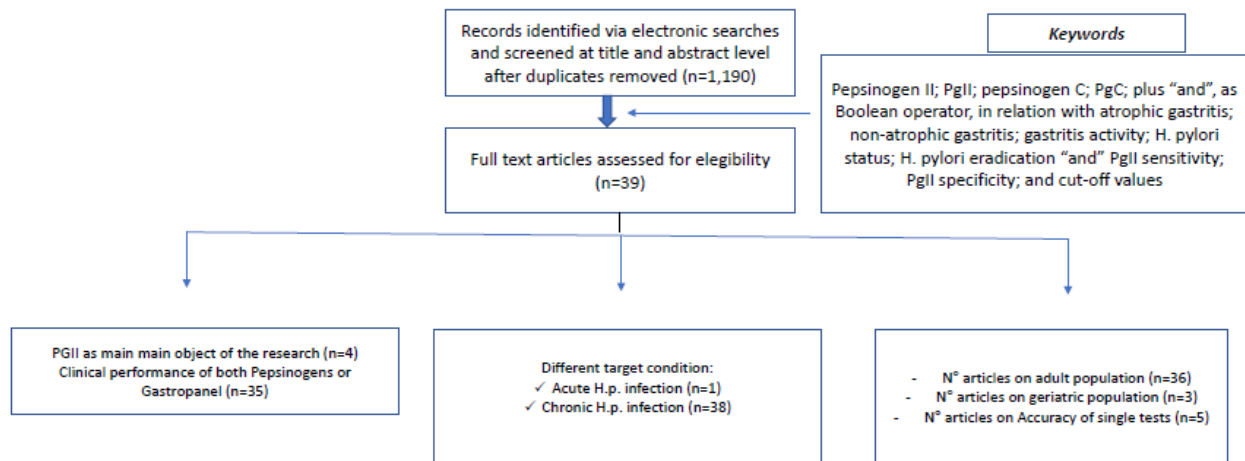
RESULTS

After removing duplicates, 1,190 records were identified, among which there were 35 full-text articles that included the sensitivity, specificity and cut-off values for the relationship between PgII levels and: i) gastritis; ii) *H. pylori* status; and iii) *H. pylori* eradication. In all but three of the studies^{7, 8, 9}, PgII was tested together with PgI and/or in

conjunction with other serological variables (anti-*Hp* antibodies, gastrin 17 [Gastropanel]) (Fig. 1).

Fig. 1

Flow chart of literature search and selection



Nella tavola PGII va corretto in PgII

- *PgII serology in patients with gastric inflammatory lesions (with or without mucosal atrophy)*

Table 1 summarizes the results obtained by 9 studies in which PgII levels were tested in different gastritis phenotypes (non-atrophic *versus* atrophic), and compared with those of healthy controls. One further study only considered patients with atrophic gastritis (not those with non-atrophic gastritis or healthy controls).

| Author (reference) | Year | Patients (n.) | PgII (micrograms/L) | | | | p value |
|----------------------------------|------|---------------|---------------------|------------------------|-------------------------------|------|---------|
| | | | Normal mucosa | Non-atrophic gastritis | Atrophic gastritis | IM | |
| Broutet ¹³ | 2003 | 222 | 8.7 | 12.5 | 14.5 | | 0.0001 |
| Germanà ¹¹ | 2005 | 287 | 9.0±8.0 | 15.7±10.4 | 13.9±10.1 | | nr |
| Sun ¹⁰ | 2007 | 841 | 7.4 | 12.8 | 13.0 | | nr |
| Haj-Sheykholeslami ²⁷ | 2008 | 294 | 6.6±2.8 | 13.9±9 | | | nr |
| He† ⁸ | 2011 | 1200 | 6.6 | 12.4 | 11.9 | 11.2 | 0.0001 |
| Syrianen ⁶³ | 2017 | | 9.5±4.6 | 17.3±10.1 | | | nr |
| Han‡ ⁶⁴ | 2018 | 107 | -- | -- | 13.9±6.7 "limited atrophy" | | 0.025 |

| | | | | | | | |
|-----------------------------|------|------|------------|--------------|---------------------------------|--|----|
| | | | | | 11.2±5.5 advanced atrophy | | |
| Crafa ¹² | 2020 | 266 | 5.8±2.4 | 14.1±8.2 | 7.3±3.6 | | nr |
| Kumar ²⁸ | 2020 | 210 | 12.77±7.53 | 13.97 ± 8.14 | | | |
| Miftahussurur ²⁶ | 2020 | 1206 | 8.5 | 14.2 † | | | nr |

In all cases, PgII levels were significantly higher in patients with non-atrophic gastritis (range: 12.4 to 17.3 [micrograms](#) /L) than in healthy controls (range: 5.8 to 12.7 [micrograms](#)/L). In three of the five studies comparing atrophic *versus* non-atrophic gastritis ^{8, 10, 11, 12, 13} higher PgII levels were associated with non-atrophic gastritis. In a large study by He and coworkers⁸, the status of the gastric mucosa was only assessed endoscopically¹⁴: patients with both non-atrophic and atrophic gastritis showed significantly higher PgII serum levels than controls ¹⁵. Taken together, the studies considered suggest that PgII is consistently associated with gastric inflammatory lesions (more than with atrophy). Such an association is in keeping with the results obtained by Kuipers *et al.*¹⁶, who found a significant direct association between the amount of inflammatory infiltrate (as assessed histologically) and PgII serum levels.

- *PgII serology by H. pylori status*

Table 2 shows the relationship between serum PgII levels and *H. pylori* status. Seventeen studies (4 from Japan ^{17, 18, 19, 20}; 2 from China ^{8, 21}; 1 from Korea ²²; 5 from Europe ^{7, 11, 12, 13, 23}; 1 from the USA ²⁴; 1 from South America ²⁵; 1 on populations of South and Southeast Asia ²⁶; 1 from Iran ²⁷; and one from India ²⁸) tested the clinical usefulness of PgII as a marker of active *H. pylori* infection.

Table 2: PgII levels by *H. pylori* status († gastric cancer patients; ‡ two weeks after acute *H. pylori* infection; Hp-ve: *H. pylori* negative patients; Hp+ve: *H. pylori* positive patients; nr: not reported in the publication)

| Author (reference) | Year | Patients (n.) | PgII in Hp-ve patients (micrograms /L) | PgII in Hp+ve patients (micrograms /L) | p values |
|----------------------------------|------|---------------|---|---|----------|
| Broutet ¹³ | 2003 | 266 | 8.45 | 15.5 | 0.001 |
| Di Mario ⁷ | 2004 | 313 | 8.6 ± 3.7 | 16.8 ± 7.4 | <0.001 |
| Germanà ¹¹ | 2005 | 287 | 8.9 ± 7.9 | 15.9 ± 1.0 | <0.001 |
| Nurgalieva ²⁴ | 2006 | 20 | 9.1±8.5 ‡ | 42±40 ‡ | 0.001 |
| Kim ²² | 2007 | 1,485 | 8.0 ± 5.8 | 17.5 ± 10.5 | < 0.001 |
| Haj-Sheykholeslami ²⁷ | 2008 | 481 | 9.8 ± 9 | 15.0 ± 9.9 | nr |
| He ⁸ | 2011 | 2,022 | 6.6 | 14.0 | < 0.0001 |
| Huang ²¹ | 2016 | 2,814 | 11.50 ± 7.45 | 18.09 ± 8.68 | <0.05 |
| Kumar ²⁸ | 2016 | 168 | 13.97 ± 8.14 † | 18.78 ± 12.63 † | 0.034 |
| Osumi ¹⁷ | 2017 | 650 | | 24.7±12.1 | |
| Kawamura ¹⁸ | 2019 | 45 | 24.7±13.1 | 16.3±8.6 | 0.08 |
| Kikuchi ¹⁹ | 2019 | | 6.70 | | |
| Syrianen ²³ | 2019 | 80 | 9.5 ± 4.6 | 17.3 ± 10.1 | <0.001 |
| Fernandez-Botran ²⁵ | 2020 | 203 | 8.2 | 17.8 | < 0.0001 |

| | | | | | |
|-----------------------------|------|-------|---------|----------|---------|
| Miftahussurur ²⁶ | 2020 | 1,309 | 9.3 | 17.9 | < 0.001 |
| Okuda ²⁰ | 2020 | 187 | 9.5 | 17.0 | < 0.01 |
| Crafa ¹² | 2020 | 246 | 5.2±2.4 | 14.1±8.2 | <0.001 |

In all but one ²⁹ of the studies, *H. pylori*-positive patients had significantly higher PgII levels (range: 6.6 to 13.9 [micrograms](#)/L in Hp-ve individuals versus 14.0 to 24.7 [micrograms](#)/L in Hp+ve cases). These features were basically consistent in various epidemiological contexts.

Focusing on the relationship between PgII and CagA status, in keeping with results previously obtained by Broutet et al¹³, Okuda *et al* recently confirmed that serum PgII levels were significantly higher in CagA-seropositive infection (PgII levels: 9.0 [micrograms](#)/L in CagA-negative individuals versus 15.3 [micrograms](#)/L in CagA-positive ones; p= 0.001). This difference retained a borderline significance even when cancer patients were considered²⁵.

- PgII serology in *H. pylori* eradication

Table 3 summarizes the results of the studies addressing the changes (if any) in patients' serum PgII levels after they had been given successful versus unsuccessful *H. pylori* eradication therapy.

Table 3: PgII levels before and after successful or unsuccessful *H. pylori* eradication therapy († patients cured of their *H. pylori* infection; ‡ Patients not cured of their *H. pylori* infection; nr= not reported in the publication)

| Author (reference) | Year | Patients (n.) | Serum PgII values (micrograms /L) | | | p value |
|-----------------------|------|------------------|--|---------------------------|--------------|---------|
| | | | Before eradication therapy | After eradication therapy | | |
| | | | | successful | unsuccessful | |
| Hunter ²⁹ | 1993 | nr | 13. 3±0.8 | 7.9±0.7 | 13.6±1.7 | 0.001 |
| Tanaka ³⁰ | 2004 | 9 | 21.9±3 | 10.3±2 | | 0.0001 |
| Plebani ³¹ | 1992 | 49 | Increased | Decreased | Unchanged | 0.001 |
| Pilotto ³² | 1996 | 88 | 21.58±1.97 | 14.34 ± 1.75 | 21.12±3.07 | 0 .001 |
| Plebani ³³ | 1996 | 192† | 18±1 | 8±1 | --- | 0.001 |
| | | 97‡ | 13±1 | --- | 13±1 | ns |
| Di Mario ⁷ | 2004 | 70 | 17.5±7.5 | 8.2±2.0 | 15.6±5.9 | <0.001 |
| Gatta ³⁴ | 2011 | 228 | 17 | 8 | 16 | <0.001 |
| Osumi ¹⁷ | 2017 | 650 | 24.7±12.1 | 7.5±3.5 | 23.3±12.2 | <0.05 |

Serum PgII levels (tested between 1 and 2 months after completing the eradication therapy) dropped significantly only in patients whose treatment was successful, whereas the other patients' PgII levels remained much the same as before. Notably, these results were consistent whatever the method used to measure PgII (radioimmunoassay or ELISA).

Table 4: Cut-off values, sensitivity, and specificity for PgII in assessing the success of *H. pylori* eradication therapy († population over >65 years old; nr= not reported in the publication; ‡ according to Youden's Index)

| Author (reference) | Year | Cut-off | Sensitivity % | Specificity % | Accuracy % |
|------------------------|------|--|---------------|---------------|------------|
| Hunter ²⁹ | 1993 | -25% | 82 | 62 | nr |
| Pilotto† ³² | 1996 | 5.1 micrograms /L ‡ | 59 | 62 | 60 |
| Di Mario ⁷ | 2004 | -25% | 93 | 91 | 93 |
| He ⁸ | 2011 | 10.25 micrograms /L | 71.6 | 70.1 | 70,7 |
| Gatta ³⁴ | 2011 | -22.7% | 100 | 96.6 | 98 |
| Osumi ¹⁷ | 2017 | -25% | 93.1 | 93.8 | 93.2 |

As for the PgII cut-off values for judging the success of *H. pylori* eradication therapy, most studies suggested a 23-25% decrease from a patient's PgII levels before the treatment. In an adult population, He⁸ established a cut-off at 10.25 µg /L, significantly higher than the one proposed by Pilotto *et al.* in a geriatric population based on Youden's index (5.1 µg /L)³². Depending on the cut-off adopted, the test's specificity ranged between 62% and 96.6%. Two studies reporting the positive (PPV) and negative (NPV) predictive values for PgII levels as an indicator of *H. pylori* eradication generated inconsistent results (PPV = 98-67.6%; NPV = 71-74%)^{7, 8}.

DISCUSSION

Based on what was known about functional gastric physiopathology, IM Samloff suggested in the early 1980s that serum pepsinogens (I and II) could be useful serological markers of various kinds of gastric mucosal damage³⁴. At around the same time, Ichinose and coworkers proposed a radioimmunoassay method for measuring serum pepsinogens driven by the same biological rationale³⁵. The promise of such non-invasive diagnostic procedures prompted a (possibly excessive) enthusiasm for the idea of a “serological biopsy”.³⁴

Over the years before *H. pylori* was discovered, PgII serology had been suggested as a non-invasive test potentially capable of providing clinically useful information on a variety of gastric diseases, including non-atrophic and atrophic gastritis, gastric polyps, and gastric cancer (GC).^{10, 16, 28, 36, 37, 38, 39, 40, 41, 42}

After the discovery of *H. pylori*, further studies proposed testing pepsinogens (Pgl and PgII) to identify patients harboring (advanced) atrophic gastritis, which had been widely recognized as the *H. pylori*-triggered field of cancerization in the so-called “epidemic” gastric cancer. A functional test for exploring the “efficiency” of the gastric mucosa thus came to be inappropriately perceived as revealing a “cancer marker”.

Far more studies on the clinical impact of testing serum pepsinogens have focused on Pgl (with 5,953 records, as opposed to 1,117 records for PgII), while PgII is largely tested “in support” of Pgl values (as in the Pgl/PgII ratio), as a marker of oxyntic atrophy^{43, 44, 45}. This review aims to restore serum PgII testing to its original (appropriate) clinical-biological role, examining both its clinical usefulness and its operative limitations.

In 2004, DY Graham⁴⁶ unequivocally documented seroconversion (from anti-Hp-negative to anti-Hp-positive, with a prevalence of 94% in 4 weeks), and the onset of gastric mucosal inflammation in a model of acute *H. pylori* infection in a group of volunteers. A significant increase in serum levels of PgII (but not Pgl) was also documented within the first two weeks of these volunteers becoming infected (PgII 9.1±8.5 µg /L at the baseline,

18±16 after 7 days [$p=0.008$], and 42±40 after 14 days [$p=0.001$]). These results are consistent with those obtained by Lorente and coworkers in an in vitro study showing that *H. pylori* (irrespective of the strain involved) promotes PgII secretion from human peptic cells via an intracellular pathway mediated by calcium and nitric oxide.⁴⁷

The present review likewise documented significantly higher serum PgII levels in gastritis patients who were infected with *H. pylori* (from 14.1 to 24.7 µg /L) than in those who were not (below 10 µg /L in all but three studies)^{8, 10, 17, 27, 35, 49}. As expected (given the association between *H. pylori* infection and mucosal inflammation), serum PgII levels were always significantly higher in the patients carrying the infection, regardless of the laboratory method used (colorimetric, radioimmunoassay, ELISA, chemiluminescence).^{10, 36, 37, 49, 50, 51, 52} The increase in PgII levels also correlated with the amounts of all the types of inflammatory cells involved in the histological phenotype of gastritis.¹⁶

PgII has also been proposed as a marker of successful *H. pylori* eradication therapy ever since 1992 (years before more sensitive/specific tests become available)³¹. Judging from the findings of the present review (Table 4), PgII serum levels drop significantly after *H. pylori* eradication therapy, but the reliability of serological testing as an indicator of successful eradication suffers from inconsistencies in its sensitivity and specificity. As a cut-off that can be safely assumed to indicate that eradication therapy has been successful, most studies suggest a 25% drop in PgII levels after the treatment^{7, 17, 29}. That said, the sensitivity and specificity values can vary considerably in adult populations (from 82% to 100%, and from 62% to 96.6%, respectively), reflecting the numerous situations that might potentially influence the results (Table 4). Much the same can be said of the results that emerged when PgII was tested in a selected population of geriatric patients.^{32, 53} The variability seen in how PgII levels respond to the eradication effort may plausibly have to do with the fact that the efficacy of the treatment in down-modulating or clearing the inflammatory lesions (and lowering PgII levels as a consequence) may not necessarily reflect a successful eradication of the infection^{54, 55, 56}. On the other hand, the successful eradication of *H. pylori* may not always be associated with patients' inflammatory lesions disappearing (and their serum PgII levels dropping)^{57, 58, 59, 60, 61}. Il giallo si avvolge su se stesso e dovrebbe essere più esplicito... vorrebbe dire qualcosa, ma senza arrivare al punto dolente ...in più a prima frase è lunga

Overall, the findings of the present review do not alter the skeptical conclusion reached by M. Tarek Al-Assi in 1999, who wrote: "Despite a significant fall in serum markers of *H. pylori* infection in the groups of successfully treated individuals, no marker (PgII among others) tested in this study approached the reported accuracy of the urea breath test"⁶².

In conclusion, this review supports the reliability of PgII as a marker of gastric mucosal inflammation, particularly in non-atrophic gastritis caused by *H. pylori* infection. A drop in PgII levels of at least 25% (within 2 months after completing eradication therapy) supports a down-modulation of a patient's inflammatory lesions. On the other hand, PgII is a considerably less reliable indicator of the success of *H. pylori* eradication therapy. Its clinical usefulness is further lessened by the availability of more sensitive and specific (and even less invasive) test methods. When coupled with PgI levels (and the PgI/PgII ratio, as in the ABC classification⁴⁴ and MAPS⁴⁵), then PgII levels are useful as a marker of both gastric inflammation and *H. pylori* infection. Mi pare che così non vada perchè non è mai stato discusso il Rapporto.

Forse meglio togliere la frase o rimodularla

The value of PgII in association with PgI testing ... ma toglierei anche questo

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