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CURRENT OPINION

Importance of atrophic gastritis in diagnostics and prevention of gastric cancer: Application of plasma biomarkers

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Introduction

The treatment of *Helicobacter pylori* infection is a key issue in the prevention of gastric cancer. Treatment of all infected subjects is the ultimate strategic goal even though it has not been reached anywhere so far, and, for many reasons, may be a target that will also be difficult to attain in the future. In clinical practice, gastric cancers appear in patients who have undergone *H. pylori* treatment, which suggests that this treatment as a strategy of cancer management may not be enough, and that it is not comprehensive – simple eradication of *H. pylori* may not prevent all gastric cancers. It is conceivable that the failures in cancer prevention occur particularly in patients with atrophic gastritis in whom a cancer or precancer lesions already exist and are quite frequent, and in whom the treatment of *H. pylori* may be a procedure that has come too late. This pool of patients may be significant, particularly among the elderly in populations where the *H. pylori* gastritis is common.

Despite the fact that atrophic gastritis is the most important, independent risk factor (risk condition) for gastric carcinoma identified so far [1,2], it has received little attention in clinical practice. Cancer risk rises exponentially with grade and extent of atrophic gastritis, and is found approximately 45 to 90-fold in patients with severe atrophic gastritis compared with the cancer risk in subjects with a healthy stomach (no gastritis nor atrophy, nor metaplasia) [2]. In addition, with few exceptions, atrophic gastritis develops only in subjects with *H. pylori* infection, suggesting that the cancer issue in atrophic gastritis is an intimate part of the cancer issue in *H. pylori* gastritis in general, and vice versa. On average, half of the people infected with *H. pylori* will develop atrophic gastritis of some degree or type during their lifetime [3–6].

At the time of endoscopy of subjects with moderate or severe atrophic gastritis, a careful biopsy sampling, and biopsy microscopy of all, even minimal, mucosal alterations will reveal gastric cancer or its precursor lesions (adenoma, dysplasia/intramucosal neoplasia) in up to 5% of patients [7,8]. In addition, invasive gastric carcinoma, if diagnosed at "asymptomatic" stage (no alarming or specific symptoms) in patients with atrophic gastritis, is "early" and curable in 70–80% of cases [7]. These data suggest that the focusing of diagnostic and therapeutic efforts to "asymptomatic" patients "at risk" would improve the results in the management of gastric carcinoma.

Atrophic gastritis is a fairly common lesion, and even though the prevalence of *H. pylori* gastritis has markedly decreased over the past few decades in developed populations, *H. pylori* gastritis still occurs in 30–70% of people in the elderly age groups in which gastric cancer remains a clinical problem [9]. The fear of malignancy strongly guides clinical practices and decision-making, whereby an immediate gastroscopy is recommended in elderly people (more than 45–55 years of age) with dyspeptic symptoms by most of the international and local consensus statements. In Finland, atrophic gastritis of moderate or severe degree is found in up to 10% of asymptomatic subjects or dyspeptic outpatients over 50 years of age [7].

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Despite the central role of atrophic gastritis as a major risk factor for gastric carcinoma, its diagnosis, and its grading and proper assessment are done poorly or not at all in clinical practice. For example, no tests for atrophic gastritis are performed, and gastroscopy without adequate biopsy samples from the antrum and corpus is a common practice in many countries, including many centres in the US. This implies that atrophic gastritis, and even ongoing *H. pylori* infection in these patients, must often be missed.

Atrophic gastritis markedly changes gastric physiology and acid output

Atrophy is defined as a loss of normal mucosal glands. This loss means failures in secretory functions and physiology of the gastric mucosa. Atrophy in the corpus results in low output of acid, whereas atrophy in the antrum results in impairments in the output of gastrin-17. In atrophic gastritis, the feedback loop controlling acid and pepsin secretions via the gastrin link is broken, resulting in varying degrees of hypochlorhydria, or even achlorhydria, and in hypo- or hypergastrinaemia, depending upon whether the antrum is atrophic or not. The histological grade of atrophic corpus gastritis has a strong negative correlation with acid output, and also with serum/plasma levels of pepsinogen I (or ratio of pepsinogen I to pepsinogen II) (Figure 1). Advanced atrophic corpus gastritis and loss of the feedback inhibition of antral G cells by low intragastric acidity results in hypergastrinaemia, and the gastrin-17 levels in serum may even be some hundreds of pmols per litre in some subjects if the antrum is normal (atrophic gastritis is restricted to the corpus).

Atrophy is followed by and/or accompanied by the appearance of metaplastic glands in atrophying mucosa (i.e. pseudopyloric metaplasia with or without intestinal metaplasia (IM)). Metaplastic glands do not secrete acid or gastrin-17 but express properties of intestinal and colonic mucosa to varying extent. With progression of atrophy, the metaplastic glands and epithelium may appear more and more immature, which is shown as a shift from IM of complete ("small-bowel type") type to IM of immature and incomplete types ("colon type"). This shift is considered to reflect an increasing risk of cancer in atrophic gastritis [10]. The hypochlorhydric or achlorhydric stomach allows colonization of bacteria other than *H. pylori*, some of which may produce mutagenic and carcinogenic substances [1,11].

In addition to a decrease in acid output, atrophic corpus gastritis results in impairment of intrinsic factor secretion (Figure 2) that is needed for proper absorption of dietary vitamin B_{12} in the small intestine [12]. Intrinsic factor is secreted from oxyntic (corpus/fundic) cells and this secretion is reduced in atrophic gastritis, as is acid secretion. Subsequently, all subjects with moderate or severe corpus atrophy are at risk for B_{12} malabsorption, and half of these subjects have decreased (B_{12} vitamin 170–220 pmol/l in serum) or severely low (lower than 170 pmol/l) levels of vitamin B_{12} in serum at the time of diagnosis of atrophic gastritis, i.e. levels

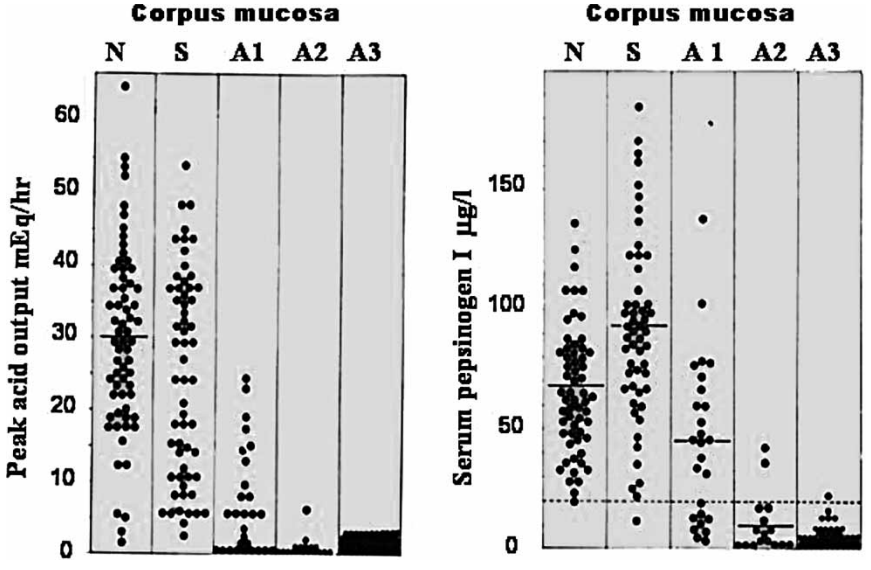

Figure 1. Peak acid output and serum pepsinogen I in different grades of atrophic corpus gastritis in patients with overt pernicious anaemia and in their 1st-degree relatives. Data from the study of Varis & Isokoski (Ann Clin Res 1981;13:133–8); data presented with the permission of the authors. Abbreviations: N = normal and healthy corpus mucosa; S = non-atrophic ("superficial") gastritis; A1 = mild atrophic gastritis; A2 = moderate atrophic gastritis; A3 = severe atrophic gastritis in corpus.

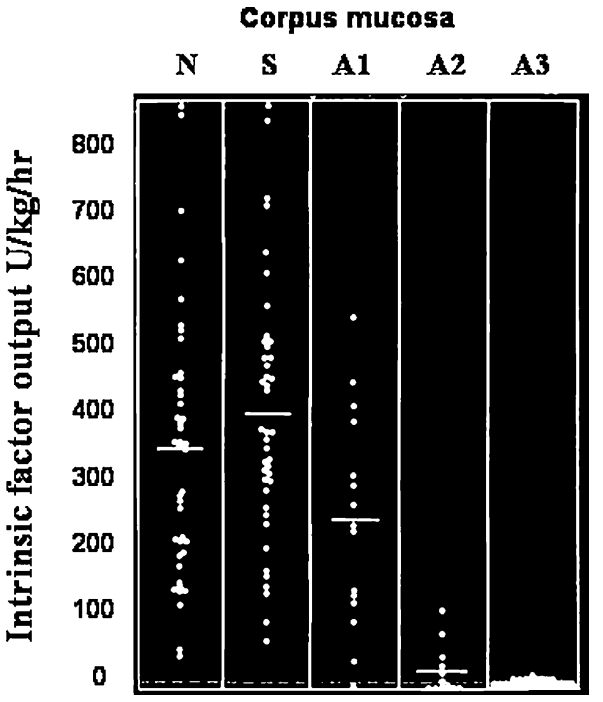

Figure 2. Intrinsic factor output in units per kilogram fat-free body-weight per hour (U/kg/FFB/h) in relation to grade of atrophic corpus gastritis in patients with overt pernicious anaemia and in their 1st-degree relatives. From the study by Varis & Isokoski (Ann Clin Res 1981;13:123–29); data presented with the permission of the authors. For abbreviations see Figure 1.

that are frequently associated with hyperhomocysteinaemia (serum homocysteine >15 μmol/l) [12]. Vitamin B_{12} is a necessary co-factor of methionine synthase, which plays a key role in the methylation of homocysteine to methionine in every cell, but in nerve and brain cells in particular [13].

Atrophic gastritis may heal after treatment of *H. pylori*

A common misunderstanding is that atrophic gastritis, particularly atrophic gastritis in the corpus and fundus, is autoimmune in origin and not related to *H. pylori*. Studies in Finland and Italy show the opposite to be the case and suggest that *H. pylori* is the major coexisting or causal factor, and that an on-going *H. pylori* infection can be demonstrated by serological tests in at least 70–80% of cases with advanced atrophic gastritis in the corpus/fundus [14–16]. The presence of an on-going *H. pylori* infection means that there is also an on-going risk of the progression of atrophic gastritis to more severe stages [17–21]. After treatment of *H. pylori* infection, however, the antibodies and chronic inflammation will disappear over a few months, and, along with these events, gastric function also tends to improve over some years [22]. According to some endoscopic and biopsy follow-up studies, there is also improvement in atrophic gastritis and intestinal metaplasia, which improve slowly but surely after the *H. pylori* eradication, possibly as a function of the square of the *H. pylori* negative time [22–28]. Although the available diagnostic techniques are not able to make a distinction between an improved function of the remaining parietal and chief cells and the actual histological recovery and re-growth of the lost cellular elements, the elimination of inflammation seems to allow a return of the function of gastric mucosa even at a very late stage of atrophic gastritis, resulting at least in partial restoration of the normal intragastric environment.

Atrophic gastritis, not age, is the risk factor for gastric cancer

Cancer risk is low in subjects with healthy stomachs, also in older age groups.

In multifactorial analyses, which include atrophic gastritis as a parameter in a model, age is not an independent risk factor for gastric carcinoma even though cancer incidence increases exponentially with age [2]. The common denominator for gastric carcinoma, and for the "ageing stomach", is atrophic gastritis; i.e. the prevalence of atrophic gastritis increases with age. This explains one-third of the gastric carcinoma risk in general [2]. As a risk factor for gastric carcinoma, atrophic gastritis of the antrum and corpus is independent and, in multifocal atrophic gastritis (atrophic gastritis occurs in both antrum and corpus), the joint risk is the multiplicand of the marginal risks [2]. Cancer risk increases exponentially with grade and extent of atrophic gastritis, and is highest when severe atrophic gastritis occurs in the whole stomach (severe panatrophy; severe multifocal atrophic gastritis) (Figure 3). Some estimates indicate that the cumulative risk, i.e. the probability of contracting gastric carcinoma within the next 10 years in the age groups from 50–54 to 70–74 years varies from 2% to 9% and from 8% to 32% in severe antral atrophic gastritis and from 0% to 5% and from 4% to 17% in severe corpus atrophic gastritis in males and females, respectively [2].

Among gastric carcinoma patients, normal and healthy gastric mucosa is quite rare. The proportion of gastric carcinoma patients with healthy gastric mucosa does not increase with age as might be expected if the age itself were an independent risk factor for cancer. In contrast, the proportion of patients with healthy stomachs is even slightly higher in younger cancer patients compared with those in the older age groups (Table I). In developed countries where the incidence of gastric carcinoma is low, 10–20% of the gastric carcinoma patients have a normal and healthy gastric mucosa by

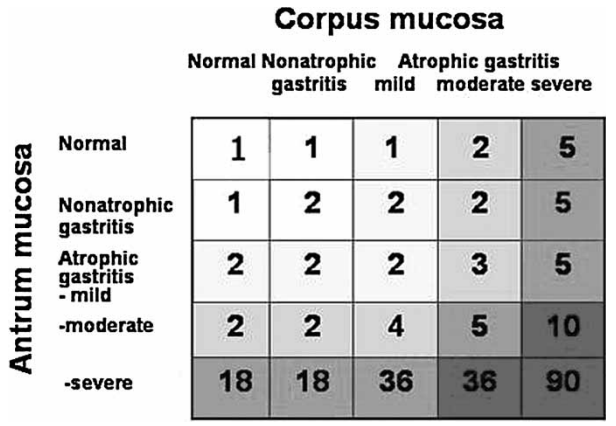

Figure 3. Risk (odds) of gastric cancer in different phenotypes of atrophic gastritis as compared with cancer risk in subjects with normal and healthy stomach mucosa (Normal/Normal). Data are modified from the study by Sipponen et al. [2]. Risk stages (0–IV) of gastric cancer according to Rugge & Genta (Gastroenterology 2005;129:1807–8) are indicated in the squares with different shading.

histology. In practice, this implies that, in order to find one cancer case even in the older age groups among subjects with normal and healthy stomachs in Western populations, several thousand gastroscopies would be needed. In addition, gastric cancer among patients with "healthy" stomachs may be familial, and related to inherited critical gene errors that are not a result of carcinogenic cascades of *H. pylori* infection or atrophic gastritis. Furthermore, most of the cancers in normal gastric mucosa are of diffuse, signet ring cell type and appear often at a young age (under 50 years of age).

Because the cancer risk is related strongly to the presence, grade and extent of atrophic gastritis, a decision to perform gastric cancer screening by gastroscopy based on age only may be neither wise nor productive. Instead, in all age groups, these decisions could be based on more accurate risk assessments; i.e. on the assessment of the presence or absence of atrophic gastritis. In addition to gastroscopy and biopsy histology, the risk assessments can be made easily and non-invasively using serum/plasma biomarkers for gastritis and atrophic gastritis. The application of biomarkers as a diagnostic tool may give new opportunities for rationales in diagnosis of atrophic gastritis, and in assessments of gastric cancer risk.

Recommendations for use of biomarkers in assessing atrophic gastritis and gastric cancer risk

First, we will provide our recommendations for the use of biomarkers in the diagnosis of atrophic gastritis and in the assessments of gastric cancer risks, and we will then present the rationale for these recommendations.

There is no doubt that a consultation by a specialist and urgent diagnostic testing such as endoscopy (gastroscopy, colonoscopy, laparoscopy, etc.) and other relevant clinical investigations (ultrasound, laboratory tests, etc.) are indicated for patients with severe abdominal complaints such as bleedings (low Hb), severe weight loss, etc. Biomarkers may be useful among patients with milder symptoms, or in screening of "asymptomatic" people.

Because *H. pylori* infection is a necessary causative factor in the majority of cases of gastric cancer, eradication of the infection will very likely reduce the incidence of gastric cancer. All patients with ongoing *H. pylori infection* should therefore undergo therapy to eradicate the infection. In addition to these efforts in cancer prevention, we recommend that due consideration should be given to the subjects with advanced precancerous conditions in which the possibility of a coexisting cancer or precancer lesion is high, and in whom the *H. pylori* eradication may be too late regarding cancer prevention, and, furthermore, in whom an endoscopy should be considered, or in whom it would be wise to assess whether any surveillance is indicated [29]. This is accomplished readily and non-invasively by testing for the presence and severity of atrophic gastritis by means of serum/plasma biomarkers.

Table I. Gastric cancer in different age groups. Association of cancer with normal and healthy underlying gastric mucosa, and with non-atrophic and atrophic gastritis. The sample of gastric cancer patients (714 patients) was collected in Southern Finland in the 1980s. The histology-based knowledge of the status of antral and corpus mucosa was available from 206 patients, on whom the present analysis is based.

Age group years	No. of cancer patients	Healthy, normal gastric mucosa; no. (%)	Non-atrophic gastritis; no. (%)	Atrophic gastritis of any grade or type; no. (%)
<50	34	5 (15)	28 (82)	1 (3)
50–59	33	3 (9)	15 (45)	15 (45)
60–69	57	6 (11)	19 (33)	32 (56)
70–79	60	1 (2)	10 (17)	49 (82)
80–	22	1 (5)	2 (9)	19 (86)
Total	206	16 (8)	74 (36)	116 (56)

In adopting serum/plasma biomarkers for the assessment of atrophic gastritis and cancer risks, our recommendations are, irrespective of the age of the patient, and including also the patients/subjects in the older age groups: (A) no *H. pylori* infection with a healthy stomach mucosa (all biomarkers are normal). Gastroscopy does not provide significant additional information as there is essentially no risk of gastric cancer in these cases. (B) non-atrophic gastritis with *H. pylori* infection (only the *H. pylori* test is abnormal). Again, gastroscopy would rarely be of significant diagnostic value and all non-malignant *H. pylori*-related disease would be easily cured along with eradication of the *H. pylori* infection; (C) atrophic gastritis with or without active *H. pylori* infection (tests for atrophy are abnormal irrespective of whether the *H. pylori* test is normal or abnormal). For these patients, one should consider consultation with a gastroenterologist as gastroscopy is advisable irrespective of whether the atrophic gastritis is *H. pylori* positive or not. Eradication of *H. pylori* is recommended for those with *H. pylori* infection.

In Western countries more than 50% of patients with uninvestigated dyspepsia in primary care practice fall into category A. At most, 10–20% fall into category C. The rationale for treatment of *H. pylori* in category B is to prevent gastritis from developing into atrophic gastritis, and also to heal and prevent the development of peptic ulcerations that are frequent, sometimes life-threatening, complications of the *H. pylori* gastritis. The goal in category C is to seek to identify those patients with an increased risk of gastric carcinoma, and to be able to treat the coexisting neoplasias at a curable stage.

Serology in the diagnosis of *H. pylori* gastritis in the elderly

In general practice, breath tests and antigen stool tests are commonly used in the diagnosis of *H. pylori* infection. These direct tests resolve the question of whether the patient has an *H. pylori* infection. They are, however, unable to answer the question of whether the patient has atrophic gastritis, and whether the patient is therefore at particular risk of gastric neoplasias. Nor can these direct tests, also including biopsy urease tests, provide reliable evidence to show whether the gastric mucosa is normal and healthy. A negative breath test does not rule out the possibility that the stomach is severely diseased, and that the patient might not have, for example, severe atrophic gastritis. The direct tests often give false negative results regarding the *H. pylori* status, particularly in patients with atrophic gastritis and intestinal metaplasia, obviously because of the reduction in *H. pylori* load in the gastric mucosa [30–33]. This low colonization of bacteria is also the cause of common false negative results of breath tests, or of antigen stool tests, in subjects under treatment with proton-pump inhibitors (PPIs) [34–37]. *H. pylori* serology is independent of these confounding influences, and the serological tests may be the most reliable *H. pylori* tests in the elderly age groups in which atrophic gastritis and hypochlorhydric stomach are common. In fact, if one relies only on the direct *H. pylori* tests among old people, the risk of false negative test results tends to be highest exactly among the subjects with the highest risk of cancer [38].

Treatment of *H. pylori* infection prevents the progression of gastritis

Active inflammation of gastric mucosa disappears within some days, and chronic inflammation within some months, after successful treatment of *H. pylori* [39,40]. A recent consensus statement suggests that the *H. pylori* eradication in pre-atrophic gastritis will decrease the gastric cancer risk, as the treatment is associated with improvement or normalization of the structure and function of the gastric mucosa, and with prevention of the progression of gastritis into atrophic gastritis [41]. This conclusion is based on studies from molecular biology, animal experiments, and on available clinical trials [41,42].

Treatment of *H. pylori* is assumed to stop the "carcinogenic cascades", as it reduces inflammation and leads to restoration of acid secretion [29]. However, it is not clear whether the eradication would do more than delay the progression of overt precancer lesions (adenoma, dysplasia, intramucosal neoplasia) to advanced forms of malignancy. In fact, some recent trials have suggested that cancers appear post-treatment in patients with atrophic gastritis in particular. A recent prospective and controlled study from China by Wong et al. [43] on 988 people showed that a significant number of cancers appeared after treatment of *H. pylori* in those with precancerous conditions or lesions, such as atrophic gastritis, IM or dysplasia but not in those with non-atrophic gastritis alone. This emphasizes the fact that the approaches used to improve gastric cancer management, in addition to active treatment of *H. pylori*, should also include the identification and treatment of patients with coexisting cancerous or precancerous lesions and conditions.

In populations with a high incidence of gastric carcinoma, the prevalence of atrophic gastritis is also high, and overt intramucosal neoplasias (precancerous lesions such as adenoma, dysplasia or intramucosal neoplasia) are prevalent as well.

Therefore, the strategies for management of *H. pylori*-infected patients in high risk countries should, in our opinion, include three elements: 1) primary prevention of gastric carcinoma by early treatment of *H. pylori* infection in all subjects with non-atrophic gastritis (preferably before the development of atrophic gastritis); 2) identification (biomarker screening) and *post hoc* endoscopic and biopsy examination of patients (subjects) with atrophic gastritis; and 3) treatment of *H. pylori* infection in all patients with atrophic gastritis in order to trigger the healing and improvement of the gastric mucosa.

Early diagnosis and treatment is an efficient strategy to achieve better results in the management of gastric cancers

In Finland, about 22,000 "asymptomatic" men, between the ages of 50 and 65 years and who were also smokers were actively screened for pepsinogen I (PGI) levels and the results showed that 9% (approximately 2000 men) of the men had advanced (moderate or severe) atrophic corpus gastritis [7], of whom approximately 70% had concomitant and ongoing *H. pylori* infection, detected by serology. Endoscopy with multiple biopsies from all abnormal endoscopically visible mucosal lesions was carried out in 1344 of these men, these procedures revealing 63 cases of cancer or neoplastic lesions (definite dysplasias of high or low grade). Of these cases, 18 were overt cancers (4 invasive advanced cancers; 7 invasive "early" cancers; 7 dysplasias/mucosal neoplasias of high grade). All these cancer cases were operated on surgically or endoscopically. During a 5-year follow-up, 4 of the 18 patients died of gastric carcinoma, all of whom had advanced cancer. None of the 14 patients with "early" cancer died of malignancy during the 5-year follow-up period. The 18 cancer cases found by active screening amounted to 15% of all gastric cancers that appeared in the study cohort within 5 years after the pepsinogen screening.

Corresponding population-based screening projects in Japan with pepsinogens as biomarkers have provided similar or even higher yields of early, curable cancers than in the screening described above from Finland [59]. This indicates that the active screening of atrophic gastritis with serum/plasma pepsinogens in the older age groups (45–50 years or more) followed by "*post hoc*" careful diagnostic endoscopy and biopsy microscopy is a tool towards increasing the successes of gastric cancer management.

Biomarkers are a useful non-invasive tool to diagnose atrophic gastritis, even in primary care

The assays of serum/plasma pepsinogen I and II, or pepsinogen I/pepsinogen II ratio, in addition to gastrin-17, are easy tools for assessment of the presence or absence of atrophic gastritis, even in clinical settings where an endoscopy is not available. If the maximal information is the goal of the testing, the minimum set of biomarker assays would be the completion of the *H. pylori* test with the assays of serum/plasma levels of pepsinogen I and II, (i.e. testing of pepsinogen I/II ratio), and gastrin-17 [44–48]. A scheme on the behaviour of these biomarkers in different types and grades of atrophic gastritis is presented in Figures 3 and 4. The biomarkers provide a diagnosis of atrophic gastritis with 83% and 95% sensitivity and specificity, respectively, compared to endoscopy and gastric biopsy microscopy [45].

There is a long list of studies that confirm the usefulness and application of the pepsinogen I or pepsinogen I/II ratio in the diagnosis of atrophic corpus gastritis [48–63]. Inclusion of a serum/plasma assay of fasting gastrin-17 widens the diagnostic possibilities [41,42]. Gastrin-17 in serum/plasma is dependent on intragastric acidity but also on the number of G cells in the antral mucosa. Fasting gastrin-17 is low in subjects with hyperacid

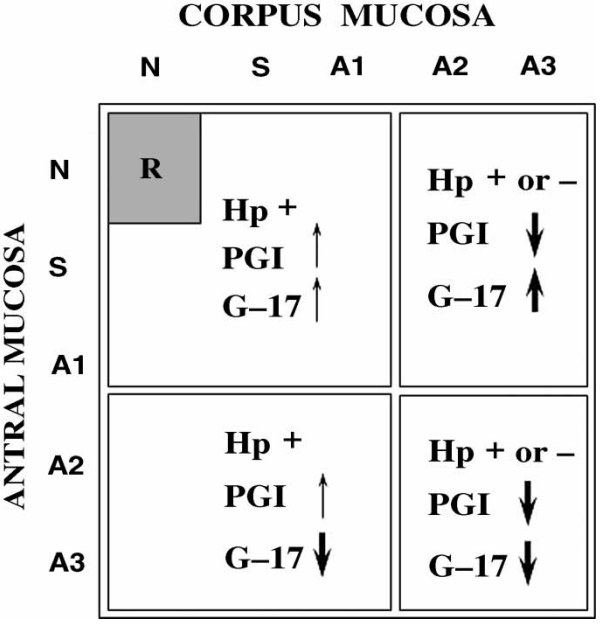

Figure 4. Scheme on the behaviour of biomarkers (pepsinogen I, gastrin-17 and *H. pylori* antibodies) in serum or plasma in different phenotypes of atrophic gastritis in relation to their normal levels in subjects with normal and healthy gastric mucosa (R). Measurement of the ratio of pepsinogen I to pepsinogen II can replace the pepsinogen I assay.

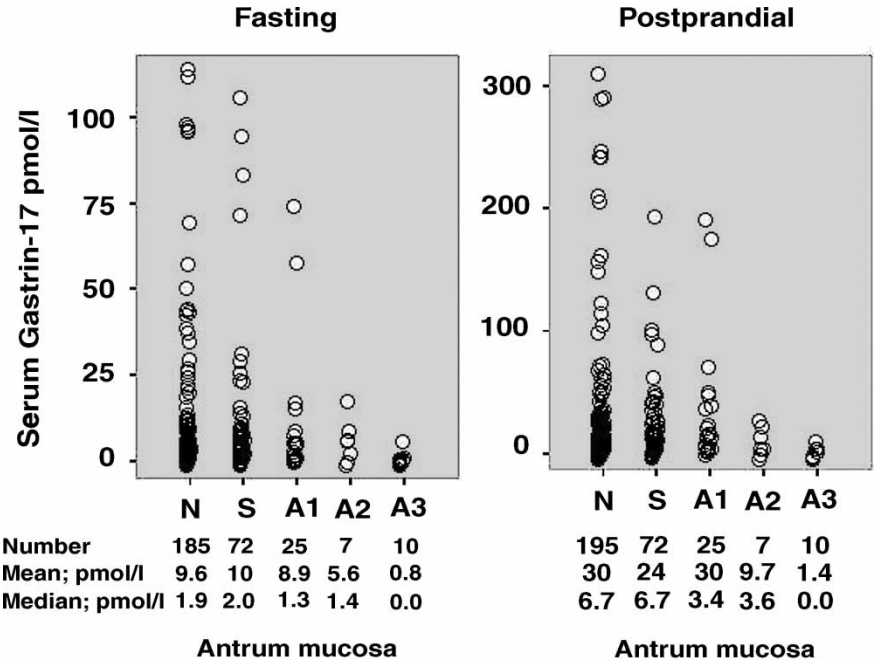

Figure 5. Serum levels of gastrin-17 (both fasting and postprandial) in relation to grade of atrophic gastritis in the antral mucosa. Abbreviations: N = normal and healthy antral mucosa; S = non-atrophic ("superficial") gastritis; A1 = mild atrophic gastritis; A2 = moderate atrophic gastritis; A3 = severe atrophic gastritis in antrum. Data modified and recalculated from the study by Sipponen et al. [56].

stomachs (often lower than 1–2 pmol/l) [64] but the serum levels also decrease along with an increasing grade of atrophic antral gastritis; i.e. along with the loss of antral glands (loss of G cells) (Figure 5). Thus, the gastrin-17 assay provides the possibility to diagnose atrophic gastritis that is restricted to the antrum, and, furthermore, to identify those patients with severe panatrophy (severe multifocal atrophic gastritis) in which both plasma pepsinogen I (or pepsinogen I/II ratio) and gastrin-17 are low. In contrast, the pepsinogen I, or pepsinogen I/II ratio, is low but gastrin-17 is high in those with atrophic gastritis limited to the corpus alone (Figure 4).

Biomarkers continue to be an area of active investigation and recent observations suggest that, in addition to pepsinogens and gastrins, changes in other peptide hormones secreted from gastric mucosa are potentially useful and that they could be applied as biomarkers for atrophic gastritis. For example, in a recent study by Suzuki et al. [65] it is suggested that plasma ghrelin might be one such biomarker. The plasma levels of this peptide correlated well with the serum levels of pepsinogen I as well as the pepsinogen I/II ratio in patients with atrophic gastritis

Conflict of interest

Dr. Pentti Sipponen is a scientific advisor and member of scientific board of Biohit Company, Helsinki, Finland. This material is based on work supported in part by the Office of Research and Development Medical Research Service, Department of Veterans Affairs, and by Public Health Service grant DK56338, which funds the Texas Gulf Coast Digestive Diseases Center, Dr. Graham has received grant support and/or free drugs or urea breath tests from Meretek, Jannsen/Eisai and TAP, and Biohit for investigator-initiated and investigator-controlled research. In addition, Dr. Graham is a paid consultant for Otsuka Pharmaceuticals and a member of the Board of Directors of Meretek, Diagnostics, the manufacturer of the [^{13}C]-urea breath test. Dr. Graham also receives royalities from the Baylor College of Medicine patent covering the serologic test, HM-CAP.

References

[1] Correa P, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, et al. Gastric precancerous process in a high risk population: cohort follow-up. Cancer Res 1990;50: 4737–40.

[2] Sipponen P, Kekki M, Haapakoski J, Ihamäki T, Siurala M. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. Int J Cancer 1985;35: 173–7.

[3] Valle J, Kekki M, Sipponen P, Ihamäki T, Siurala M. Long-term course and consequences of *Helicobacter pylori* gastritis. Results of a 32-year follow-up study. Scand J Gastroenterol 1996;31:546–50.

[4] Trey G, Marks IN, Louw JA, Jaskiewicz K, Sipponen P, Novis BH, et al. Changes in acid secretion over the years. A 30-year longitudinal study. J Clin Gastroenterol 1997;25: 499–502.

[5] Maaroos HI, Vorobjova T, Sipponen P, Tammur R, Uibo R, Wadström T, et al. An 18-year follow-up study of chronic gastritis and *Helicobacter pylori* association of CagA positivity with development of atrophy and activity of gastritis. Scand J Gastroenterol 1999;34:864–9.

[6] Kuipers EJ, Pals G, Pena AS, van Uffelen CW, Kok A, Westerveld BD, et al. *Helicobacter pylori*, pepsinogens and gastrin: relationship with age and development of atrophic gastritis. Eur J Gastroenterol Hepatol 1996;8:153–6.

[7] Varis K, Sipponen P, Laxen F, Samloff IM, Huttunen JK, Taylor PR, et al. and the Helsinki Gastritis Study Group. Implications of serum pepsinogen I in early endoscopic diagnosis of gastric cancer and dysplasia. Scand J Gastroenterol 2000;35:950–6.

[8] Varis K, Sipponen P, Laxen F, Samloff IM, Huttunen JK, Taylor PR, et al. and the Helsinki Gastritis Study Group. Implications of serum pepsinogen I in early endoscopic diagnosis of gastric cancer and dysplasia. Scand J Gastroenterol 2000;35:950–6.

[9] Sipponen P, Helske T, Järvinen P, Hyvärinen H, Seppälä K, Siurala M. Fall in the prevalence of chronic gastritis over 15 years: analysis of outpatient series in Finland from 1977, 1985, and 1992. Gut 1994;35:1167–71.

[10] Filipe MI, Munoz N, Matko I, Kato I, Pompe-Kirn V, Jutersek A, et al. Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. Int J Cancer 1994; 57:324–9.

[11] Väkeväinen S, Mentula S, Nuutinen H, Salmela KS, Jousimies-Somer H, Färkkilä M, et al. Ethanol-derived microbial production of carcinogenic acetaldehyde in achlorhydric atrophic gastritis. Scand J Gastroenterol 2002;37: 648–55.

[12] Sipponen P, Laxen F, Huotari K, Härkönen M. Prevalence of low vitamin B12 and high homocysteine in serum in an elderly male population: association with atrophic gastritis and *Helicobacter pylori* infection. Scand J Gastroenterol 2003;38:1209–16.

[13] Bolander-Gouaille C. Focus on homocysteine and the vitamins involved in its metabolism. Berlin: Springer Verlag; 2002.

[14] Sande N, Nikulin M, Nilsson I, Wadström T, Laxen F, Härkönen M, et al. Increased risk of developing atrophic gastritis in patients infected with CagA+*Helicobacter pylori*. Scand J Gastroenterol 2001;36:928–33.

[15] Aromaa A, Kosunen TU, Knekt P, Maatela J, Teppo L, Heinonen OP, et al. Circulating anti-*Helicobacter pylori* immunoglobulin A antibodies and low serum pepsinogen I level are associated with increased risk of gastric cancer. Am J Epidemiol 1996;144:142–9.

[16] Annibale B, Negrini R, Caruana P, Lehner E, Crossi C, Bordi C, et al. Two-thirds of atrophic body gastritis have evidence of *Helicobacter pylori* infection. Helicobacter 2001; 6:225–33.

[17] Kokkola A, Rautelin H, Puolakkainen P, Sipponen P, Farkkila M, Haapiainen R, et al. Positive result by serology indicates active *Helicobacter pylori* infection in patients with atrophic gastritis. J Clin Microbiol 1998;36:1808–10.

[18] Karita M, Noriyasu A, Teramukai S, Matsumoto S. Atrophic progression induced by *H. pylori* infection is correlated with a changing pepsinogen I value and associated with the development of gastric cancer. Dig Dis Sci 2004;49:1615–20.

[19] Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, et al. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. Int J Cancer 2004;109:138–43.

[20] Kitahara F, Shimazaki R, Sato T, Kojima Y, Morozumi A, Fujino MA. Severe atrophic gastritis with *Helicobacter pylori* infection and gastric cancer. Gastric Cancer 1998;1:118–24.

[21] Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001; 345:784–9.

[22] Kokkola A, Sipponen P, Rautelin H, Härkönen M, Kosunen TU, Haapiainen R, et al. The effect of *Helicobacter pylori* eradication on the natural course of atrophic gastritis with dysplasia. Aliment Pharmacol Ther 2002;16:515–20.

[23] Ohkusa T, Miwa H, Nomura T, Asaoka D, Kurosawa A, Sakamoto N, et al. Improvement in serum pepsinogens and gastrin in long-term monitoring after eradication of *Helicobacter pylori*: comparison with *H. pylori*-negative patients. Aliment Pharmacol Ther 2004;1(20 Suppl):25–32.

[24] Ito M, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, et al. *Helicobacter pylori* eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther 2002;16:1449–56.

[25] Borody TJ, Andrews P, Jankiewicz E, Ferch N, Carroll M. Apparent reversal of early gastric mucosal atrophy after triple therapy for *Helicobacter pylori*. Am J Gastroenterol 1993;88: 1266–8.

[26] Ruiz B, Garay J, Correa P, Fontham ET, Bravo JC, Bravo LE, et al. Morphometric evaluation of gastric antral atrophy: improvement after cure of *Helicobacter pylori* infection. Am J Gastroenterol 2001;96:3281–7.

[27] Kokkola A, Sipponen P, Haapiainen R, Rautelin H, Karjalainen-Lindsberg ML, Puolakkainen P. Development of Barrett's esophagus after "spontaneous" healing of atrophic corpus gastritis. Helicobacter 2003;8:590–3.

[28] Mera R, Fontham ETH, Bravo LE, Piazuelo MB, Comargo MC, Correa P. Long-term follow-up of patients treated for *Helicobacter pylori* infection. Gut 2005;54:1536–40.

[29] Graham D, Shiotani A. The time to eradicate gastric cancer is now. Gut 2005;54:735–8.

[30] Kokkola A, Rautelin H, Puolakkainen P, Sipponen P, Färkkilä M, Haapiainen R, et al. Diagnosis of *Helicobacter pylori* infection in patients with atrophic gastritis: comparison of histology, ^{13}C-urea breath test, and serology. Scand J Gastroenterol 2000;35:138–41.

[31] Karnes WE Jr, Samloff IM, Siurala M, Kekki M, Sipponen P, Kim SW, et al. Positive serum antibody and negative tissue staining for *Helicobacter pylori* in subjects with atrophic body gastritis. Gastroenterology 1991;101:167–74.

[32] Salomaa-Räsänen A, Kosunen TU, Mattila J, Sarna S, Rautelin H. Age-dependent accuracy of *Helicobacter pylori* antibody assays for adults, with special emphasis on atrophic gastritis. Clin Diagn Lab Immunol 2004;11:1185–8.

[33] Kokkola A, Kosunen TU, Puolakkainen P, Sipponen P, Härkönen M, Laxen F, et al. Spontaneous disappearance of *Helicobacter pylori* antibodies in patients with advanced atrophic corpus gastritis. APMIS 2003;111:619–24.

[34] Perri F, Ricciardi R, Merla A, Piepoli A, Gasperi V, Quitadamo M, et al. Appropriateness of urea breath test: a prospective observational study based on Maastricht 2000 guidelines. Aliment Pharmacol Ther 2002;16:1443–7.

[35] Graham DY, Opekun AR, Hammoud F, Yamaoka Y, Reddy R, Osato MS, et al. Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. Am J Gastroenterol 2003;98:1005–9.

[36] Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, Bloemena EC, Sandell M, Nelis GF, et al. Atrophic gastritis during long-term omeprazole therapy affects serum vitamin B_{12} levels. Aliment Pharmacol Ther 1999;13:1343–6.

[37] Murakami K, Sato R, Okimoto T, Watanabe K, Nasu M, Fujioka T, et al. Influence of anti-ulcer drugs used in Japan on the result of [^{13}C]-urea breath test for the diagnosis of *Helicobacter pylori* infection. J Gastroenterol 2003;38: 937–41.

[38] Watabe H, Mitsushima T, Yamaji Y, Okamoto M, Wada R, Kokubo T, et al. Predicting the development of gastric cancer from combining *Helicobacter pylori* antibodies and serum pepsinogen status: a prospective endoscopic cohort study. Gut 2005;54:764–8.

[39] Valle J, Seppälä K, Sipponen P, Kosunen T. Disappearance of gastritis after eradication of *Helicobacter pylori*: a morphometric study. Scand J Gastroenterol 1991;26:1057–65.

[40] Franceschi F, Genta RM, Sepulveda AR. Gastric mucosa: long-term outcome after cure of *Helicobacter pylori* infection. J Gastroenterol 2002;37(Suppl 13):17–23.

[41] Malfertheiner P, Sipponen P, Naumann M, Moayyedi P, Mégraud F, Xiao SD, et al. and the *H. pylori*-Gastric Cancer Task Force. *Helicobacter pylori* eradication can prevent gastric cancer. Am J Gastroenterology. In press.

[42] Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev 1997;6:639–42.

[43] Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al. and the China Gastric Cancer Study Group. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187–94.

[44] Sipponen P, Ranta P, Helske T, Kääriäinen I, Mäki T, Linnala A, et al. Serum levels of amidated gastrin-17 and pepsinogen I in atrophic gastritis: an observational case-control study. Scand J Gastroenterol 2002;37:785–91.

[45] Väänänen H, Vauhkonen M, Helske T, Kääriäinen I, Rasmussen M, Tunturi-Hihnala H, et al. Non-endoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. Eur J Gastroenterol Hepatol 2003;15:885–91.

[46] Pasechnikov VD, Chukov SZ, Kotelevets SM, Mostovov AN, Mernova VP, Polyakova MB. Possibility of non-invasive diagnosis of gastric mucosal precancerous changes. World J Gastroenterol 2004;10:3146–50.

[47] Sipponen P, Valle J, Varis K, Kekki M, Ihamäki T, Siurala M. Fasting levels of serum gastrin in different functional and morphologic states of the antrofundal mucosa. An analysis of 860 subjects. Scand J Gastroenterol 1990;25:513–9.

[48] Varis K, Kekki M, Härkönen M, Sipponen P, Samloff IM. Serum pepsinogen I and serum gastrin in the screening of atrophic pangastritis with high risk of gastric cancer. Scand J Gastroenterol 1991;186:117–23.

[49] Broutet N, Plebani M, Sakarovitch C, Sipponen P, Megraud F and the Eurohepygast Study Group. Pepsinogen A, pepsinogen C, and gastrin as markers of atrophic chronic gastritis in European dyspeptics. Br J Cancer 2003;88:1239–47.

[50] Knight T, Wyatt J, Wilson A, Greaves S, Newell D, Hengels K, et al. *Helicobacter pylori* gastritis and serum pepsinogen levels in a healthy population: development of a biomarker strategy for gastric atrophy in high risk groups. Br J Cancer 1996;73:819–24.

[51] Di Mario F, Moussa AM, Caruana P, Merli R, Cavallaro LG, Cavestro GM, et al. "Serological biopsy" in first-degree relatives of patients with gastric cancer affected by *Helicobacter pylori* infection. Scand J Gastroenterol 2003; 38:1223–7.

[52] Korstanje A, den Hartog G, Biemond I, Lamers CB. The serological gastric biopsy: a non-endoscopical diagnostic approach in management of the dyspeptic patient: significance for primary care based on a survey of the literature. Scand J Gastroenterol 2002; Suppl 236:22–6.

[53] Farinati F, Di Mario F, Plebani M, Cielo R, Fanton MC, Valiante F, et al. Pepsinogen A/pepsinogen C or pepsinogen A multiplied by gastrin in the diagnosis of gastric cancer? Ital J Gastroenterol 1991;23:194–6.

[54] Dinis-Ribeiro M, Yamaki G, Miki K, Costa-Pereira A, Matsukawa M, Kurihara M. Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. J Med Screen 2004;11:141–7.

[55] Mardh E, Mardh S, Mardh B, Borch K. Diagnosis of gastritis by means of a combination of serological analyses. Clin Chim Acta 2002;320:17–27.

[56] Borch K, Axelsson CK, Halgreen H, Damkjaer Nielsen MD, Ledin T, Szesci PB. The ratio of pepsinogen A to pepsinogen C: a sensitive test for atrophic gastritis. Scand J Gastroenterol 1989;24:870–6.

[57] Kiyohira K, Yoshihara M, Ito M, Haruma K, Tanaka S, Chayama K. Serum pepsinogen concentration as a marker of *Helicobacter pylori* infection and the histologic grade of gastritis; evaluation of gastric mucosa by serum pepsinogen levels. J Gastroenterol 2003;38:332–8.

[58] Bodger K, Wyatt JI, Heatley RV. Variation in serum pepsinogens with severity and topography of *Helicobacter pylori*-associated chronic gastritis in dyspeptic patients referred for endoscopy. Helicobacter 2001;6:216–24.

[59] Miki K, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. Am J Gastroenterol 2003;98:735–9.

[60] Dinis-Ribeiro M, da Costa-Pereira A, Lopes C, Barbosa J, Guilherme M, Moreira-Dias L, et al. Validity of serum pepsinogen I/II ratio for the diagnosis of gastric epithelial dysplasia and intestinal metaplasia during the follow-up of patients at risk for intestinal-type gastric adenocarcinoma. Neoplasia 2004;6:449–56.

[61] Urita Y, Hike K, Torii N, Kikuchi Y, Kanda E, Sasajima M, et al. Serum pepsinogens as a predicator of the topography of intestinal metaplasia in patients with atrophic gastritis. Dig Dis Sci 2004;49:795–801.

[62] Kitahara F, Kobayashi K, Sato T, Kojima Y, Araki T, Fujino MA. Accuracy of screening for gastric cancer using serum pepsinogen concentrations. Gut 1999;44:693–7.

[63] Shiotani A, Iishi H, Uedo N, Kumamoto M, Nakae Y, Ishiguro S, et al. Histologic and serum risk markers for noncardia early gastric cancer. Int J Cancer 2005;115:463–9.

[64] Sipponen P, Vauhkonen M, Helske T, Kääriäinen I, Härkönen M. Low circulating levels of gastrin-17 in patients with Barrett's esophagus. World J Gastroenterol 2005;11: 5988–92.

[65] Suzuki H, Masaoka T, Hosoda H, Nomura S, Ohara T, Kanagawa K, et al. Plasma ghrelin concentration correlates with the levels of serum pepsinogen I and pepsinogen I/II ratio: a possible novel and non-invasive marker of gastric atrophy. Hepatogastroenterology 2004;51:1249–54.