Endocrine tumors of the pancreas and gastrointestinal tract
van Eeden, S.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 5

COMPARISON BETWEEN SEROLOGY, ENDOSCOPY AND HISTOLOGY IN THE DIAGNOSIS OF ADVANCED GASTRIC BODY ATROPHY: A STUDY IN A DUTCH PRIMARY COMMUNITY

André Korstanje, Susanne van Eeden¹, G.Johan A. Offerhaus¹, Frans L. Waltman², Gijsbert den Hartog³, Freek W.C. Roelandse⁴, John H.M. Souverijn⁴, Izak Biemond⁵, Cornelis B.H.W. Lamers⁵.

General practice, ‘s-Gravenpolder, The Netherlands
¹Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands
²Department of Internal Medicine, Oosterschelde Hospital, Goes, The Netherlands
³Department of Gastroenterology, Rijnstate Hospital, Arnhem, The Netherlands
⁴Department of Clinical Chemistry, Leiden University Medical Center, Leiden, The Netherlands
⁵Department of Gastroenterology, Leiden University Medical Center, Leiden, The Netherlands.

Submitted
Abstract

Gastric body atrophy (GBA) is a precursor lesion of gastric cancer. Little is known about the value of serological screening for GBA in a primary health care community. The relation between serological findings, endoscopical and histological GBA changes was studied in a sample of the general population.

Consecutive adults (n=997) were serologically screened for GBA in a Dutch family practice; 34 subjects had serological GBA, defined as hypergastrinemia (>100ng/l), hypopepsinogenemia A (<17μg/l) and a low pepsinogen A/C ratio (<1.6). Two years later, 25 subjects of this group, agreed in serological retesting and further investigation with gastroscopy and biopsy for assessment according to the Sydney system.

At serological retesting 20 of 25 subjects fulfilled the criteria of GBA again. Histological examination of the corpus biopsies showed advanced GBA in 18 of 24 subjects (75%, 1 subject had no corpus biopsies) and 17 of 19 (89%) subjects with repeated positive serology. After disclosure of serology results, re-examination of the biopsies revealed GBA in the 2 patients with initially insufficient evidence of GBA as well, giving a concordance of 100% (19/19). One subject with normal serum gastrin at retesting had both antral and body atrophy giving a concordance between serological and histological GBA of 95% (19/20). No adenomatous polyps, tumors or dysplastic alterations were found. Macroscopic features observed during gastroscopy were of no value in the assessment of atrophy.

Identification by serology of subjects with chronic atrophic body gastritis in population-based screening and prevention studies in primary care is adequately possible and useful in selecting subjects for endoscopy.

Introduction

Chronic atrophic gastritis is a chronic inflammation of the stomach accompanied by loss of the specialized glandular cells. Atrophy leads to thinning of the mucosa and is a common denominator in all pathological processes that cause severe mucosal damage. The development of chronic atrophic gastritis is a multifactorial process, involving microbiological factors like Helicobacter pylori infection, unidentified host and environmental factors, or autoimmunity directed against gastric glandular cells. The autoimmune form of gastritis is typically located in the body, whereas the type induced by chronic injury or infection is located more often in the antrum. The loss of the glandular structures can be accompanied by metaplasia. A large number of studies point to the importance of chronic gastritis in the evolution of such gastritis towards mucosal atrophy, intestinal metaplasia, dysplasia and finally gastric adenocarcinoma. Early identification of patients with atrophic gastritis might give opportunities in modifying the risk of gastric cancer, which is nowadays the second leading cause of cancer-related mortality worldwide, having a very poor clinical prognosis. Histological examination is the most reliable way to determine atrophic gastritis, but this is not done routinely. Its principal use is to rule out cancer rather than to deter-
mine the presence and extent of atrophic gastritis. The by far preferential diagnostic instrument to screen for atrophic gastritis is a “serum biopsy”, i.e. measuring serum pepsinogen A and C and serum gastrin as functional markers of the gastric mucosa.\textsuperscript{9,10} Low serum pepsinogen A (PgA) and a low pepsinogen A/C ratio in combination with elevated serum gastrin, are considered useful predictors of gastric body atrophy (GBA). Several studies have shown the diagnostic potential of non-invasive, serological biomarkers for atrophic gastritis.\textsuperscript{11-14} Taking into account the underlying aetiology of chronic atrophic gastritis, serological testing for \textit{H. pylori}\textsuperscript{2-4,10} and parietal cell antibodies has an additional diagnostic value.\textsuperscript{10,14}

Apart from predisposing to gastric cancer, gastric body atrophy can also lead to vitamin B\textsubscript{12}-deficiency. This occurs in both autoimmune corpus gastritis and in the more common multifocal pangastritis that involves corpus and antrum and usually results from \textit{H. pylori} infection. This can already exist for a long time as a clinically latent entity with possible irreversible cell damage to the nervous system.\textsuperscript{5,15} Early detection of vitamin B\textsubscript{12}-deficiency is therefore important and timely supplementation is indicated to prevent pernicious anemia and neurological sequelae. It is likely that a significant number of patients suffering from vitamin B\textsubscript{12}-deficiency caused by atrophic gastritis remain undiagnosed and untreated and that, with regard to public health, it would be important to identify these patients in time.\textsuperscript{16} Despite the apparent importance of the diagnostic potential of serological methods, so far no studies have been conducted in general practice to determine the significance of serology in the screening for atrophic body gastritis. The purpose of the present study was to evaluate the value of the serological markers of atrophy, i.e. blood pepsinogen and gastrin levels, to predict histological GBA in a community-based family practice in The Netherlands. Additionally, attention was paid to the relation between macroscopic endoscopical findings and histomorphological mucosal changes. Furthermore, we determined the prevalence of \textit{H. pylori} infection on the basis of serological tests and histological examination and the prevalence of autoimmunity in gastric atrophy.

\textbf{Patients and methods}

\textbf{Study population}

In a period of 2 years a total of 997 adults, consecutively entering the primary health care system because of common medical problems, volunteered in serological screening for GBA in the general practice of one of us (AK) in ‘s-Gravenpolder, a rural village in the South-West of The Netherlands. Exclusion criteria were age <18 years and current pregnancy. The participants were asked to donate a fasting blood sample and to fill in a questionnaire on the frequency and severity of gastric symptoms during the preceding 3 months, past gastric diseases and the use of stomach- and/or antibiotic drugs. Examination of the whole group revealed serological GBA in 34 persons (3.4\%, 15 M, 19 F; mean age 67
years, range 28-91). Two years later, 25 of the 34 subjects (12 M, 13 F; mean age 67 years) agreed in undergoing upper gastrointestinal endoscopy after an over-night fast, combined with serological retesting of the markers of atrophy, of anti-H.pylori- and autoimmune antibodies. The remaining 9 subjects were not biopsied for the following reasons: 3 persons had deceased, 2 persons had moved out of the region, 2 persons were not able to undergo endoscopy because of serious comorbidity and 2 persons refused further investigation. The study was performed according to the declaration of Helsinki and all participants gave informed consent before entering the study.

**Serological examination**

All obtained serum samples were tested by well-validated radioimmunoassays for levels of pepsinogen A (PgA), pepsinogen C (PgC) and gastrin. Our validated criteria for advanced serological GBA, corresponding to pentagastrin refractory achlorhydria or severe hypochlorhydria (peak acid output <5 mmol/hr) expressed in the level of the serum markers, were defined as a serum concentration of PgA <17 μg/l, a PgA/C ratio < 1.6 and an accompanying serum concentration of gastrin >100 ng/l. H. pylori serology was performed by a validated enzyme immuno-assay using specific immunoglobulin G against *H. pylori*. The results were expressed as the absorbance index (AI): serum with an AI >0.32 IgG *H. pylori* antibody was considered evidence of *H. pylori*-infection. Additionally, all serum samples were tested for parietal cell- and intrinsic factor autoantibodies using commercially available kits, respectively Autoscreen 1, Scimedx Corporation, Denville, NJ 07834, USA and Genesis Diagnostics Ltd, Little Port, UK. Serum vitamin B12 concentration was tested by Immulite® 2000 Vitamin B12, Diagnostic Products Corporation, Los Angeles, CA 90045-5597, USA.

**Endoscopic Examination**

Patients fasted for at least 9 hours before the examination. Gastroscopy was performed in the usual manner using Olympus video-endoscopy equipment. Endoscopic characteristics and appearances of gastric mucosal inflammation were recorded for each subject according to the Sydney System, Endoscopic division. The following characteristics were scored: normal mucosa with its pink colour, with uniform smoothness and lustre, versus endoscopic characteristics of inflammation e.g. 1. edema - 2. erythema - 3. friability - 4. exudates - 5. flat erosions - 6. raised erosions - 7. rugal hyperplasia - 8. rugal atrophy - 9. visibility of vascular pattern - 10. intramural bleeding spots - 11. nodularity. After maximum air insufflation at the end of examination, the corpus was examined for the presence of rugae. The grade of the various macroscopic features was scored as absent, mild, moderate or severe.
CHAPTER 5

Biopsy collection
Biopsy samples were obtained using a standard pinch-biopsy forceps. Antral and fundic biopsy specimens were systematically collected as follows: 6 biopsies from the mid antrum, about 2 cm pre-pyloric from the anterior and posterior antral wall, 4 for histological examination, 2 for culture; 6 biopsies from the mid body, about 5 cm distal of the gastro-esophageal junction from the anterior and posterior body wall, also 4 for histological examination and 2 for culture. Biopsies for histology were fixed in 10% buffered formalin.

Histological Examination
All biopsies from each subject were routinely fixed in 10% buffered formalin and embedded in paraffin blocks. Five micron sections were hematoxylin and eosin stained and examined by 2 expert gastrointestinal pathologists (SvE & GJAO) according to the updated Sydney classification system. Additional immunostaining was performed with antibodies against gastrin, chromogranin and *H. pylori* to identify gastrin producing G-cells, enterochromaffin-like cells and *H. pylori*, respectively. The diagnosis of chronic atrophic gastritis was based on the full spectrum of the updated Sydney System scores, i.e. chronic inflammation, activity, glandular atrophy, intestinal metaplasia and absence or presence of *H. pylori*, systematically applied to the biopsy specimens. Chronic inflammation was evaluated on the basis of an increase of mononuclear cell infiltration of the lamina propria. Activity of gastritis was defined according to the presence or absence of intra-epithelial granulocytes. Gastric atrophy refers to the loss of the deeper specialized glands, i.e. in the body the parietal cells and secondly the chief cells. The loss of the glandular structures can be accompanied by metaplasia. All histopathological issues were semiquantitatively graded as absent, mild, moderate or severe. The biopsy specimens were reviewed by the 2 above mentioned experienced pathologists. In case of disagreement the pathologists discussed the case to reach consensus.

Results
Retesting of serum markers of atrophy
Retesting of the markers of atrophy, undertaken 2 years after the initial screening and immediately before endoscopy, revealed serological gastric body atrophy in only 20 of 25 subjects (Table 5.1). The 5 “drop-out” subjects showed the follow

Table 5.1 Serological, endoscopical and histological characteristics in 25 primary healthcare subjects with focus on gastric atrophy. * no corpus biopsy specimens, ** no antrum biopsy specimens, ?* too small biopsy specimens, no optimal diagnosis, PgA=pepsinogen A, PgA/C ratio =ratio pepsinogen A/pepsinogen C, GBA=gastric body atrophy, GAA= gastric antral atrophy, + = mild, ++ = moderate, +++ = severe
Comparison between serology, endoscopy and histology

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Gastrin</th>
<th>PgA</th>
<th>PgA/C ratio</th>
<th>Gastrin retest</th>
<th>PgA retest</th>
<th>PgA/C ratio retest</th>
<th>GBA after retest</th>
<th>GBA after retest</th>
<th>GBA after retest</th>
<th>GBA after retest</th>
<th>GBA after retest</th>
<th>GBA after retest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1760</td>
<td>2</td>
<td>0.3</td>
<td>1664</td>
<td>1</td>
<td>0.3</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1245</td>
<td>2</td>
<td>0.1</td>
<td>1269</td>
<td>2</td>
<td>0.2</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>12</td>
<td>1.4</td>
<td>86</td>
<td>17</td>
<td>2.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>3100</td>
<td>2</td>
<td>0.3</td>
<td>2212</td>
<td>1</td>
<td>0.3</td>
<td>+</td>
<td>*</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>239</td>
<td>3</td>
<td>0.3</td>
<td>123</td>
<td>3</td>
<td>0.4</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>193</td>
<td>9</td>
<td>0.5</td>
<td>134</td>
<td>25</td>
<td>1.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2885</td>
<td>7</td>
<td>0.6</td>
<td>933</td>
<td>8</td>
<td>0.9</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>184</td>
<td>16</td>
<td>0.6</td>
<td>68</td>
<td>16</td>
<td>0.7</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>1995</td>
<td>1</td>
<td>0.1</td>
<td>764</td>
<td>1</td>
<td>0.1</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>1750</td>
<td>5</td>
<td>0.4</td>
<td>534</td>
<td>2</td>
<td>0.2</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>2300</td>
<td>2</td>
<td>0.1</td>
<td>2086</td>
<td>0</td>
<td>0.1</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>1960</td>
<td>2</td>
<td>0.3</td>
<td>1352</td>
<td>1</td>
<td>0.4</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>1391</td>
<td>13</td>
<td>0.6</td>
<td>1791</td>
<td>3</td>
<td>0.3</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>156</td>
<td>14</td>
<td>1.2</td>
<td>59</td>
<td>17</td>
<td>3.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>940</td>
<td>7</td>
<td>0.4</td>
<td>77</td>
<td>9</td>
<td>5.3</td>
<td>-</td>
<td>-</td>
<td>**</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>137</td>
<td>5</td>
<td>0.4</td>
<td>116</td>
<td>3</td>
<td>0.7</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>324</td>
<td>7</td>
<td>0.3</td>
<td>628</td>
<td>9</td>
<td>0.8</td>
<td>+</td>
<td>+++</td>
<td>?*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>593</td>
<td>3</td>
<td>0.3</td>
<td>552</td>
<td>3</td>
<td>0.7</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>486</td>
<td>7</td>
<td>0.3</td>
<td>459</td>
<td>5</td>
<td>0.3</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>418</td>
<td>2</td>
<td>0.5</td>
<td>146</td>
<td>6</td>
<td>1.3</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>1775</td>
<td>6</td>
<td>0.7</td>
<td>2257</td>
<td>1</td>
<td>0.3</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>492</td>
<td>15</td>
<td>0.8</td>
<td>1179</td>
<td>14</td>
<td>0.8</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>259</td>
<td>2</td>
<td>0.1</td>
<td>159</td>
<td>4</td>
<td>0.3</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>488</td>
<td>4</td>
<td>0.3</td>
<td>1284</td>
<td>6</td>
<td>0.5</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25</td>
<td>438</td>
<td>7</td>
<td>1.0</td>
<td>284</td>
<td>11</td>
<td>0.8</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

61
CHAPTER 5

ing serological characteristics: 1 subject (no. 8) had normal gastrin after retesting with low PgA and a low PgA/C ratio, thus no longer fulfilling the serological criteria of GBA. The remaining 4 subjects showed normal serum pepsinogens and normal gastrin after retesting. Two of these persons (nos. 3 and 14) had borderline test results in the first round and the other 2 individuals (nos. 6 and 15) had an unexplained conversion to normal levels of the serum markers (Table 5.1).

Histopathologic findings

As expected after serological retesting, 4 individuals with normal serology (nos. 3, 6, 14, 15) had no evidence of histological body atrophy, but only modest aspecific chronic inflammation. One subject (no. 8), with normal gastrin and low PgA with a low A/C ratio, thus partially fulfilling the criteria of serological body atrophy, had antral and body atrophy in the biopsies, so making the serological profile false negative.

Moderate to severe body atrophy was found in 17 of 20 subjects with repeated serological GBA. With regard to the other 3 subjects: from one subject (no. 4) only antrum biopsy specimens and no corpus biopsies were available; the second person (no. 23) had severe H. pylori gastritis, preventing optimal grading of atrophic changes and the third subject (no. 17) had aspecific inflammation with atrophy that was difficult to recognize.

Because of the discrepancy between serological and histological results in the 2 subjects and the outspoken atrophy profile in the retest “serum biopsy”, the biopsies were reviewed and showed the presence of body atrophy after all, also in these 2 serologically atrophic subjects (nos. 17 and 23).

Antral biopsies showed atrophic changes in 8 of 23 subjects. One subject had no antrum biopsies (no. 15), another subject had inadequate antral biopsies for optimal histopathological investigation (no. 17). H. pylori was identified in the biopsies of 7 (35%) of 20 persons with GBA. Eleven GBA subjects showed evidence of ECL-cell hyperplasia in the corpus biopsy specimens. None of the investigated subjects showed evidence of gastric dysplasia or malignancy.

Serological results related to histological findings

On the basis of the serological findings after retesting and histological reviewing, all 19 persons showed histological GBA. One histological GBA-subject with a normal serum gastrin level at retesting, therefore only partially fulfilling the serological GBA criteria (false-negative), had developed antral intestinal metaplasia in addition to GBA (no. 8 in table 5.1), giving a concordance between serological and histological GBA of 95% (19/20).

Endoscopic diagnoses

In 8 subjects (40%) of the group of 20 individuals with repeated serological GBA, moderate to severe atrophic gastritis of the corpus was diagnosed endoscopically, based on the presence of a vascular pattern in a slightly distended stomach with
Comparison between serology, endoscopy and histology

absent or flattened folds. In 2 of those 8 persons also atrophic gastritis of the antrum was found endoscopically. Greyish patches, histologically corresponding to intestinal metaplasia, were found in 2 of the 8 subjects. In 10 of the remaining 12 subjects, an erythematous exudative gastritis was diagnosed. Finally, 2 subjects had a flat erosive gastritis.

The 5 “drop-out” subjects without serological body atrophy showed the following endoscopical appearances: person nos. 3, 6 and 8 erythematous exudative, no. 14 mild atrophic and no. 15 flat erosive.

Endoscopic features related to histological findings

The endoscopic diagnosis of body atrophy, made in 8 of 20 subjects, was confirmed histologically in 6 of them. One subject had no corpus biopsies and the other person (no. 14) had only modest chronic inflammation in the corpus biopsies. The absence of folds and presence of visible vessels, as gastroscopic atrophy features, had only a positive predictive value in the diagnosis of body atrophy, but the absence or presence of visible vessels had no diagnostic value in antrum atrophy. In 4 persons with normal endoscopic features the biopsies showed mild to severe corpus atrophy and a normal to mild antrum atrophy.

The 11 subjects with macroscopic erythematous exudative gastritis had the following histological diagnoses: 6 showed moderate to severe body atrophy and 5 had a normal histological appearance. The remaining 2 individuals with macroscopic flat erosive gastritis showed advanced body atrophy and a modest chronic body gastritis, respectively. Biopsies of greyish patches confirmed the endoscopical diagnosis of intestinal metaplasia. Overall, there appeared to be a very weak correlation between endoscopic and histological findings.

<table>
<thead>
<tr>
<th>Anti PC &amp; IF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ ve</td>
<td>- ve</td>
</tr>
<tr>
<td><strong>Anti-H. pylori</strong></td>
<td></td>
</tr>
<tr>
<td>+ ve</td>
<td>4</td>
</tr>
<tr>
<td>- ve</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 5.2** Anti- H. pylori and autoimmune serology in 20 histological gastric body atrophy subjects. Anti-H. pylori=antibodies to Helicobacter pylori, Anti-PC= antibodies to parietal cells, Anti-IF=antibodies to intrinsic factor, + ve=positive, - ve=negative
H. pylori- and autoimmune serology in GBA-patients

H. pylori serology was positive in 12 (60%) of the 20 histologically identified GBA persons. 11 (55%) of 20 GBA subjects had antibodies to parietal cells and/or antibodies to intrinsic factor (1 person had only antibodies to intrinsic factor); 4 persons had both antibodies to H. pylori and to parietal cells (20%). One female person was seronegative for H. pylori, parietal cells and intrinsic factor. She appeared to have an IgG AI 0.29, so near the serological cut off point, indicating an extinguished H.pylori-infection (Table 5.2).

After retesting, it is worth noting that a H.pylori-seroconversion of 2 subjects (no. 14 and 25) had taken place in the elapsed 2 years, respectively from H.pylori seropositive to negative and the reverse way in the other patient. Patient no. 14 showed also the abovementioned conversion from serological body atrophy to a normal profile.

Vitamin B12 deficiency

The levels of all histological GBA persons ranged from 53 to 399 pmol/l. Eight (40%) subjects of 20 histological GBA persons had low (<120 pmol/l) serum vitamin B12 levels. The distribution of H. pylori and autoimmunity in our GBA-subjects with vitamin B12-deficiency is shown in table 5.3.

History of gastric complaints

Analysis of the questionnaires of the 20 subjects with histological GBA on the frequency and severity of any epigastric pain, heartburn, nausea, belching and acid regurgitation, showed that 11 persons (55%) never had stomach complaints, 4 (20%) seldomly, 3 (15%) sometimes and 2 persons (10%) often. None of the
Comparison between serology, endoscopy and histology

Sex (M/F) 11/9
Median age at diagnosis (yrs) 68 (range 31-93)

History of complaints

<table>
<thead>
<tr>
<th>Complain</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>11 subjects (55%)</td>
</tr>
<tr>
<td>Seldom</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Often</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

Positive H. pylori serology 12 (60%)
Positive H. pylori histology 7 (35%)
Autoimmunity 11 (55%)
(antibodies-parietal cells & intrinsic factor detectable)
H. pylori & autoimmunity positive 4 (20%)

Vitamin B₁₂ level <120 pmol/l 8 (40%) (range <53-399)
Median serum gastrin level (ng/l) 882 (range 68-2257)
Median pepsinogen A level (μg/l) 5 (range 0-14)

Table 5.4 Characteristics and functional findings at diagnosis of 20 subjects with histological gastric body atrophy.

Discussion

The value of serology for the histological diagnosis of gastric body atrophy was assessed in a Dutch general practice. To our knowledge, this is the first study in which the diagnostic value of the gastric serum biopsy is investigated in a primary health care setting. Although serological gastric investigation is already more than 2 decades generally accepted as a diagnostic non-invasive tool, it has never got appropriate attention in primary care. Most of the currently available data, regarding the prevalence of chronic atrophic gastritis in the general population, are obtained from endoscopic studies of hospital outpatients with dyspeptic problems, referred to Gastroenterology Departments. The addi-
tional value of our study is that we enrolled a large number (997) of adult subjects, consecutively entering the general practice for common health questions, so we were able to screen a representative sample of the general indigenous Dutch population.

In the present study the result of serological retesting, 2 years after the initial serological screening, is noteworthy. In the evaluative group of 25 individuals for endoscopy, only 20 subjects appeared to be sero-atrophic at retesting. Retesting is advisable in cases of borderline test results and when a substantial interval in time elapses between screening and follow up investigation. Serological results are most reliable immediately before endoscopy because of certainty that the target group of subjects has an empty stomach. Moreover, because the serological and histological biopsies are taken at the same time, the mutual comparison is more reliable. The serum biopsy is a biologic parameter and consequently liable to variability. Taking into account the dynamics of gastritis, progress (patient no. 8) and also regress (patient no. 14) of atrophic gastritis can be reported.

Considering the histological examination after serological retesting, all 19 subjects with serological GBA and corpus biopsies, showed histological GBA, giving a concordance of 100%. However, 1 subject with normal serum gastrin at retesting, therefore only partially fulfilling the serological atrophy criteria (false-negative), had antral atrophy with intestinal metaplasia in addition to GBA (patient no. 8), giving a concordance between serological and histological GBA of 95% (19/20). In fact, this was the single subject among 20 individuals with GBA who had serological evidence of extended antral atrophy. The rarity of serologically extended antral atrophy in subjects with GBA is in agreement with a study by Bins et al. in factory workers and their spouses, who reported a single case with normal gastrin pointing to antral atrophy in one of 14 subjects with pentagastrin-refractory achlorhydria.22

Furthermore, our study confirms that macroscopic diagnoses with regard to atrophy as observed during endoscopy are of limited value. Only 6 of 20 patients with gastric atrophy were identified. The remaining 14 atrophy-patients had variable diagnoses, mainly erythematous exudative gastritis but also flat erosive gastritis and even a normal appearance. Except for the absence of rugae and the presence of visible vessels in the fully insufflated stomach, as signs of moderate to severe atrophic corpus gastritis, macroscopic features observed during gastroscopy appeared to have a very weak correlation with histological findings. This is in accordance with most previous studies and it must be emphasized that the ultimate diagnosis of atrophic gastritis should be based on histological examination of the gastric mucosa.19,21,23

Gastric atrophy is the endpoint of chronic active gastritis, mainly caused by *H. pylori* infection3,4,24 or gastric autoimmunity associated with pernicious anemia.25 Therefore in our GBA group we investigated the prevalence of *H. pylori* infection and autoantibodies to parietal cells and intrinsic factor. It is reported that PgA is upregulated in *H. pylori*-infected patients compared with *H.
Comparison between serology, endoscopy and histology

pylori-uninfected patients. Consequently, the serological finding of a low serum PgA level and a low PgA/C ratio in a H. pylori infected patient is strongly indicative of gastric body atrophy. H. pylori was identified histologically, using hematoxylin and eosin and immunohistochemical stains, in 7 (35%) of the 20 individuals with GBA while H. pylori serology was positive in 12 (60%) subjects. Routine biopsy sampling may underestimate the true prevalence of H. pylori infection in diffuse atrophic gastritis. Therefore serological testing of H. pylori infection in gastric atrophy is warranted in such patients. Apart from that, considering the natural course of H. pylori antibodies and gastric mucosal histology in patients with advanced atrophic gastritis, H. pylori antibodies disappear spontaneously within 10 years in almost one fourth of patients with advanced atrophic corpus gastritis. The disappearance of H. pylori antibodies is accompanied by no or only a mild improvement of the gastric mucosa. The conversion to seronegativity found in 1 subject in this study may belong to the category of spontaneous disappearance of H. pylori antibodies and the conversion to seropositivity in another person may point to a de novo infection or recrudescence. Regarding the autoimmune pathogenesis of gastric body atrophy, in this primary care study 11 (55%) of 20 persons with serological atrophy at retesting had antibodies to parietal cells and/or antibodies to intrinsic factor. In the current study all 20 patients with histologically proven atrophy had either antibodies to H. pylori (60%) or to parietal cell and intrinsic factor (55%), which is in agreement with the etiology of gastric atrophy. Four (20%) patients had both H. pylori and autoimmune antibodies which matches with several studies on a possible role of H. pylori in the development of autoimmune gastritis. One patient was seronegative overall but had an IgG AI to H. pylori of 0.29, just below the serological upper limit, pointing to H. pylori-infection in the past, a so-called serological scar. According to the histological diagnosis of gastric body atrophy, our study revealed vitamin B12-deficiency in several participants: 8 (40%) subjects of the group of 20 GBA patients showed a low serum vitamin B12 level under the reference value, 7 of them were previously unknown with a deficiency. Adequate substitution has been started by now. In the causal distribution in our study population autoimmunity dominates over H. pylori (table 5.3). Because of the evident hypergastrinemia in advanced GBA, attention was also paid to the prevalence of enterochromaffin-like cell (ECL) hyperplasia in the corpus biopsies. Gastrin has a tropic effect on the ECL cells of the oxyntic mucosa, stimulating their function and proliferation. ECL-cell hyperplasia in the gastric corpus is a common feature in diffuse chronic atrophic gastritis restricted to the fundus, with or without associated pernicious anemia and in H. pylori-related multifocal chronic atrophic gastritis. In our study 11 of the investigated subjects with GBA had ECL-cell hyperplasia. There was no evidence of development from hyperplastic ECL cells into carcinoid tumors. This study in a Dutch general community confirms previously reported data showing that a high serum gastrin and a low serum pepsinogen A, together with
a low pepsinogen A/C ratio, are good predictors of the presence of atrophic body gastritis as a cancer-prone lesion. A reliable serological test to detect GBA is important for population-based screening and prevention studies. The serological gastric biopsy has the advantage that it reflects the status of the whole stomach. However, histological investigation remains essential for the ultimate management of gastric diseases and is the reference standard in the detection of atrophic gastritis. Actually, serological and histological methods may be complementary in the diagnostic assessment of atrophic gastric pathology. In the absence of widespread screening recommendations in primary care, the early detection and prevention of gastric cancer will depend on individual forward-thinking practitioners. In recent years, much evidence now indicates that first-degree relatives of patients with gastric cancer carry an increased risk of developing atrophic body gastritis in the presence of H. pylori infection. Finally, our study confirms that there is no relation between atrophy and gastric complaints. None of the subjects with GBA had gastric complaints severe enough to consult a doctor or to use drugs. So, the only way to detect subjects with gastric atrophy, with focus on people at risk, is screening with a serum biopsy.

This study was performed in a group of subjects, selected from a large cohort on the basis of serological evidence of GBA. However, it can not be excluded that there are subjects with histological GBA among the subjects who did not fulfill the serological criteria of GBA. In conclusion, this study in a community-based family practice emphasizes the diagnostic value of gastric serology for general practitioners. A serological gastric biopsy can be used as a reliable non-invasive screening-instrument in basic health care centers in selecting patients for further invasive investigation for chronic atrophic body gastritis and should be recommended in the assessment of subjects at risk for gastric cancer.

References


Comparison between serology, endoscopy and histology


