Scandinavian Journal of Gastroenterology, 2010; 45: 1036–1041

informa
healthcare

ORIGINAL ARTICLE

Prevalence of undiagnosed advanced atrophic corpus gastritis in Finland: an observational study among 4,256 volunteers without specific complaints

AINO TELARANTA-KEERIE[1], RITVA KARA[1], LEA PALOHEIMO[1], MATTI HÄRKÖNEN[2] & PENTTI SIPPONEN[3]

[1]*Biohit Oyj, Laippatie 1, Helsinki, Finland,* [2]*Department of Clinical Chemistry, Helsinki University Central Hospital, Helsinki, Finland, and* [3]*Repolar Oy, Espoo, Finland*

Abstract

Objective. The objective of this observational study was to estimate the prevalence of advanced atrophic corpus gastritis (ACG) among Finnish adult volunteers without specific complaints using a biomarker blood test. The objective also was to assess the feasibility and acceptance of the biomarker test among the volunteers. ***Materials and methods.*** GastroView® biomarker test (Biohit Oyj, Helsinki, Finland) was performed on mostly fingerprick blood samples from 4,256 volunteers (average age 56 years, range 18–92 years), independent of symptoms. GastroView® biomarker test was offered to citizens at public events during 2007–2009. The test consisted of the measurement of pepsinogen I and II levels (and ratio) and *H. pylori* IgG antibody level in plasma by ELISA. ***Results.*** Altogether 3.5% (150 individuals) of all 4,256 volunteers had ACG. In the age group of 70 or over, the prevalence of ACG increased to 8% (62 individuals). Altogether 19% (819 individuals) of all volunteers and 37% (56 individuals) of those with ACG had an ongoing *H. pylori* infection. In volunteers with ACG, the diagnosis was new in 95% (142 individuals), 5% (7 individuals) had received vitamin B12 supplementation and 13% (20 individuals) had received PPI medication according to a self-administered questionnaire; and 26% (39 individuals) reported gastrointestinal reflux like symptoms. ***Conclusions.*** This study shows that advanced ACG is a common disease among Finnish adults, and remains to be undiagnosed in most under the current healthcare practice. The biomarker test shows high feasibility and acceptance among the general public, and is simple to perform even in "field" conditions.

Key Words: *Atrophic, biomarker, corpus, fingerprick, gastritis, GER, Helicobacter pylori, PPI, vitamin B12*

Introduction

The diagnosis of gastric diseases in Finland is currently based on the use of proton pump inhibitors (PPIs), indirect *Helicobacter pylori* (*H. pylori*) tests (mostly urea breath test (UBT) or fecal antigen tests), and gastroscopy in dyspeptic patients over 50 years of age [1]. This practice may result in unnecessary examinations and treatments, and false negative results if relied on the UBT or fecal tests alone, but it may also leave significant gastric diseases undiagnosed [2]. One such significant disease is atrophic corpus gastritis (ACG). Patients with ACG are often asymptomatic and therefore do not seek, or are not referred to, any medical examinations.

ACG may be autoimmune in origin and limited to corpus and fundus alone, but it may also appear as multifocal atrophic gastritis (MAG; atrophic pangastritis), in which both antrum and corpus are atrophic [3–6]. This latter type of atrophic gastritis is always *H. pylori*-initiated and extends in proximal direction from antrum or angulus. MAG is the most prevalent

Correspondence: Aino Telaranta-Keerie, PhD, Lab21, 184 Cambridge Science Park, Cambridge CB4 0GA, United Kingdom.
E-mail: aino.telaranta-keerie@lab21.com

(Received 18 March 2010; accepted 18 April 2010)

ISSN 0036-5521 print/ISSN 1502-7708 online © 2010 Informa Healthcare
DOI: 10.3109/00365521.2010.487918

form of ACG worldwide, whereas the autoimmune type is prevalent in countries of the Northern Europe. However, it is possible that even the autoimmune form of ACG is an *H. pylori*-triggered disease in which the initial infection disappears when the corpus mucosa undergoes atrophy and causes hypoacidity. This is evidenced in follow-up studies, in which the signs of *H. pylori* infection gradually disappear as stomach hypoacidity and atrophy in corpus and fundus appear, and antral mucosa may even heal during this process [5,7].

H. pylori UBT or stool antigen tests may give false negative test results in patients with ACG [8–10]. This is because the atrophy is autoimmune in origin or, in cases with *H. pylori* infection, the load of bacteria in stomach is too small to provide a positive test signal in the UBT or stool antigen tests, resulting in false conclusions of the stomach health.

Achlorhydric or hypochlorhydric stomach caused by atrophic gastritis (both atrophic gastritis limited to corpus but particularly atrophic pangastritis) is the most important known risk factor for gastric cancer. ACG, irrespective of whether it is of autoimmune or *H. pylori* (MAG) origin, may result in malabsorption of vitamin B12, many micronutrients and medicines. These facts render atrophic gastritis an important disease to de diagnosed and recognized [11,12]. By contrast, when the stomach mucosa is normal, the risk of gastric cancer and other stomach disorders is practically negligible, independent of the patient's age or gastric symptoms [13]. This emphasizes the importance of the correct diagnosis of healthy and normally functioning stomach mucosa in clinical practice.

H. pylori gastritis without atrophy of the corpus mucosa (acid secretion is not impaired) in turn causes a high risk of peptic ulcer disease but a relatively small, even negligible risk of gastric cancer. Differentiation between these conditions (normal stomach mucosa vs. non-atrophic *H. pylori* gastritis or atrophic gastritis) is impossible based on symptoms, *H. pylori* tests or PPI trials alone [13,14]. Furthermore, a trial course of PPIs is obviously unnecessary if the patient's stomach is already hypochlorhydric or achlorhydric due to atrophic gastritis, and it may only delay correct diagnosis and treatment [2].

The aim of this observational study in a selected study population consisting of adult Finnish volunteers was to estimate the current prevalence of advanced (moderate and severe) ACG and non-atrophic *H. pylori* gastritis (*H. pylori* gastritis without concomitant corpus atrophy) in Finland using a blood biomarker test. Another aim was to assess the feasibility and acceptance of the biomarker test among the general public.

Methods

Study population

The study material consisted of blood samples from four subpopulations consisting of altogether 4,256 adult volunteers (Table I).

Measurement of pepsinogen I, pepsinogen II and *H. pylori* antibody levels in the EDTA plasma (GastroView® test; Biohit Oyj, Helsinki) was offered free of charge for subpopulations 1 and 2, and with charge for subpopulation 3. All volunteers were tested independently of whether they had symptoms or not.

The study subgroups were as follows: (1) the "Medical Conventions" – subpopulation consists of volunteers (doctors or other medical staff) who gave fingerprick samples at eight different Finnish Medical Conventions and Exhibitions (Helsinki 2007, 2 × Helsinki 2008, Helsinki 2009, Oulu 2008, Turku 2008, Kuopio 2008, Oulu 2008). Samples were taken at the Biohit Exhibition Stand during Convention opening hours. (2) Volunteering participants of Biohit Oyj General Meetings in 2007, 2008 and 2009. (3) Volunteers at several Biohit events held at various locations in Finland, where the biomarker test was offered to the general public. The events were advertised with small adverts in local newspapers or magazines, and/or on public notice boards. The events were held in 2008–2009. There was no overlap of people in different occasions of the blood sampling. All subjects were asked of previous GastroView® tests.

The number, average age and sex of the volunteers in each subpopulation are shown in Table I.

The use of the above study populations for scientific purposes has been approved by the Finnish Ministry of Social Affairs and Health (STM/4793/2008).

Methods

All plasma samples (from fingerprick or small venous EDTA blood) were tested using the GastroView® biomarker test (Biohit Oyj, Helsinki, Finland). The test consists of measurement of plasma pepsinogen I and pepsinogen II (PgI, PgII and PgI/PgII ratio) and *H. pylori* IgG antibodies (HpAb) by the ELISA method. Test results, together with a short interpretation of the results created by the GastroSoft® software and a note guiding the patient to contact his/her "family doctor" if the result indicated *H. pylori* gastritis or atrophic gastritis, were sent directly to the patients by mail.

Table I. Demographic data and prevalence of subjects with advanced atrophic corpus gastritis (ACG), with ongoing *H. pylori* infection without co-existing corpus atrophy, or with healthy stomach mucosa in the study populations (1–3).

Subpopulation	Total number of volunteers No. (%)	Average age (range) Years	Men/women No.	Healthy stomach mucosa No. (%)	*H. pylori* gastritis without advanced corpus atrophy No. (%)	Advanced ACG[1] No. (%)
Medical Conventions (1)	1,028 (100)	48 (19–92)	292/736	840 (82)	181 (18)	7 (0.7)
Biohit general meetings (2)	380 (100)	51 (21–84)	223/157	316 (83)	57 (15)	7 (1.8)
Sample collection events (3)	2,848 (100)	59 (18–91)	1,018/1,830	2,131 (75)	581 (20)	136 (4.8)
Total	4,256 (100)	56 (18–92)	1,533/2,723	3,287 (77)	819 (19)	150 (3.5)

[1]*H. pylori* positive or negative.

Interpretation of GastroView® results by GastroSoft®

The GastroSoft® software uses an algorithm that is based on the levels of PgI, PgII and HpAb in plasma as measured by GastroView®. When the results showed a low PgI level (<30 µg/l) and/or a low PgI/PgII ratio (<3), the GastroSoft® interpretation was "moderate or severe atrophic corpus gastritis". Cases fulfilling these criteria were considered to have advanced ACG. If PgI level and PgI/PgII ratio were normal but the volunteer had an elevated HpAb result (>30 EIU), this was interpreted as "non-atrophic *H. pylori* gastritis". When the levels of all the biomarkers were within their reference ranges (PgI >30 µg/l and PgI/PgII ratio >3, HpAb 30 EIU or below), the GastroSoft® interpretation was "healthy, normal stomach mucosa". An elevated HpAb level (>30 EIU) was always interpreted as indicating an ongoing *H. pylori* infection, with the exception of volunteers who had received *H. pylori* eradication treatment and had an elevated HpAb level close to the cut-off (>30 to <40 EIU). If PgII level in such an individual was ≤10 µg/l, GastroSoft® interpreted the result as a "successful eradication and absence of an ongoing *H. pylori* infection". If PgII level was >10 µg/l, the interpretation was "unsuccessful eradication and the presence of a still ongoing *H. pylori* infection" [15]. A specialist laboratory physician examined all reports provided by GastroSoft® before they were mailed to the volunteers.

Sensitivity and specificity of the GastroView® biomarker test

The test has a sensitivity of 82% (CI 95%: 70–93%) and specificity of 98% (CI 95%: 97–99%) in the diagnosis of moderate or severe atrophic gastritis compared to the "gold standard" method, histopathological biopsy microscopy [16,17]. The sensitivity and specificity of the test to diagnose a healthy stomach mucosa are 90% (CI 95%: 87–92%) and 90% (CI 95%: 86–93%), respectively [18]. In fact, the biomarker tests may in reality be more reliable than the endoscopical "gold standard" method [18]. Biopsy microscopy is sensitive to errors caused by biopsy sampling and subjective views or experience of the endoscopist and pathologists [18]. The GastroView® biomarker test, by contrast, is an objective non-invasive laboratory assay and can be easily performed on all patients, independently of clinical history and the presence or absence of any symptoms.

Self-reported questionnaire on clinical history

At time of sample collection, the following details were requested from the volunteers and recorded in a "self-reported questionnaire" by the laboratory technician: personal identification details; number and time of possible previous *H. pylori* eradication treatments; use of PPI medication in the recent history, and whether this use was regular ("every day" or "nearly every day") or occasional; the presence or absence of heartburn or acid regurgitation (indicating symptoms of gastrointestinal reflux; GER) in the recent history, and whether these symptoms were frequent ("every day" or "nearly every day") or occasional. Only self-reports of frequent GER-like symptoms and a regular and occasional use of PPIs were recorded as positive. In cases where a volunteer was unsure, the answers were recorded as negative. Additional, spontaneous comments from the volunteers such as previous diagnosis of atrophic gastritis, cancer history, vitamin B12 supplementation, etc., were also recorded.

Results

H. pylori infection is still common in the Finnish society. Among all the 4,256 volunteers (average

age 56 years, age range 18–92 years), 19% (819) had an ongoing non-atrophic *H. pylori* gastritis (Table I). Altogether 3.5% (150) of all 4,256 volunteers had advanced (moderate or severe) ACG (Table I). Of these 150 individuals, only eight had a previous diagnosis of atrophic gastritis, seven received vitamin B12 supplementation, one took "hydrochloride tablets" and one had undergone a surgery to remove gastric cancer. Six individuals self-reported a frequent prevalence of gastric cancer in their families.

The prevalence of ACG increased significantly with age, reaching 8% in age group 70 years or over (Table II). An interesting observation was that approximately 13% of the volunteers with ACG self-reported that they had recently been taking PPI medication (Table III). Approximately 35% of all volunteers, and 35% of the volunteers with a healthy stomach mucosa, self-reported recent heartburn and/or acid reflux symptoms. Also 26% of the volunteers with ACG self-reported same GER-like symptoms even though they had ACG, and subsequently a hypochlorhydric or even achlorhydric stomach according to the biomarker test. The difference of the prevalence of GER-like symptoms between healthy individuals and subjects with ACG (35 vs. 26%) was statistically (χ^2-test) significant ($p < 0.01$). However, the relatively high prevalence of GER symptoms in ACG subjects may also mean that the self-reported GER symptoms were not associated with real GER in up to two-thirds of the individuals.

Discussion

This observational "field" study shows that Finnish adults are interested in their stomach health and willing to get tested by the biomarker test on their own initiative, and even at their own cost. In all test occasions, queues of volunteers appeared, even though only small announcements in local newspapers or notice boards were used to inform the public of the test events. Physicians and other health professionals did not make an exception. Queues were formed at the sample collection booths also in Medical Conventions, during which altogether 1,028 volunteers belonging to the medical personnel wanted the test.

If *H. pylori* infection or ACG was detected in the test, the subject was referred to consult a physician. Decisions of possible additional laboratory tests and/or gastroscopy were asked to be made by the physician. In this study, no additional tests or surveillances were carried out. A follow-up study is planned to find out whether the instructions to consult a physician were followed-up, and what the findings were in – and conclusions from – the additional examinations.

In this "field" study, we found that it was easy to collect and analyze large numbers of stomach biomarker tests. A general trust in biomarker tests and the fact that only a small venous blood sample or a fingerprick sample was required were likely partial reasons for the good feasibility. Altogether 4,256 volunteers were tested, a number that can be estimated to be close to the yearly number of patients undergoing gastroscopy in large Finnish university clinics.

This study does not, of course, explain the exact motivations of the volunteers for wanting to get tested. However, the high number of volunteers is likely to reflect a worry that many people may feel about their stomach health, or a fear about serious stomach diseases – irrespective of the presence or absence of any specific abdominal complaints.

This study shows that a large number of adult Finns have an undiagnosed, advanced ACG, which will always result in hypochlorhydric or achlorhydric stomach due to atrophy of the acid-secreting oxyntic mucosa, irrespective of whether the ACG is of autoimmune or *H. pylori* origin [19]. ACG affects the health of elderly people in particular, and was observed in as high as 8% of people aged 70 or over. With the help of a simple extrapolation, it can be estimated that tens of thousands of people in Finland (population 5.3 million) must currently suffer from undiagnosed ACG, and consequently from a severely hypochlorhydric or achlorhydric stomach.

In a recent doctoral thesis from Finland, up to 32% of elderly people were observed to have an actual or latent vitamin B12 deficiency [20]. It is likely that a significant proportion of these individuals have an undiagnosed ACG and a consequent impairment in secretion of intrinsic factor, resulting in vitamin malabsorption as the basal cause of the vitamin B12 deficiency. Patients with atrophic gastritis are often asymptomatic and remain, therefore,

Table II. Prevalence of subjects with advanced atrophic corpus gastritis (ACG) by age in whole study populations.

Age group	Total number of volunteers	Advanced ACG	
		All	*H. pylori* positive
Years	No.	No. (%)	No. (%)[1]
<39	644	2 (0.3)	0 (0)
40–49	660	11 (1.7)	5 (45)
50–59	1,091	27 (2.5)	13 (48)
60–69	1,117	48 (4.3)	19 (40)
>70	744	62 (8.3)	19 (31)
Total	4,256	150 (3.5)	56 (37)

[1]% proportion of all the individuals with ACG.

Table III. Background information given by the volunteers in the self-reported study questionnaire.

Subgroup	All volunteers No. (%)	Previous *H. pylori* eradication treatment No. (%)	Proton pump inhibitor (PPI) medication No. (%)	Reflux symptoms No. (%)
All volunteers	4,256 (100)	659 (16)	1,086 (26)	1,499 (35)
Healthy stomach mucosa	3,287 (77)	467 (14)	878 (27)	1,151 (35)
H. pylori gastritis (no advanced atrophic corpus gastritis)	819 (19)	169 (21)	188 (23)	309 (38)
Advanced ACG[1]	150 (3.5)	23 (15)	20 (13)	39 (26)

[1]*H. pylori* positive or negative.

undiagnosed, and a deficiency of vitamin B12 may develop insidiously, easily remaining unnoticed by the doctor or the patient [21].

Extrapolation of the results of this study also allows us to estimate that thousands of Finnish people are currently prescribed PPI medication even though they have a hypochlorhydric or achlorhydric stomach due to ACG. In fact, 13% of subjects with ACG in this study self-reported taking PPIs before the biomarker test. By contrast, as high as 26% of subjects with ACG also self-reported GER-like symptoms. This may be an explanation for the relatively high proportion of subjects with ACG taking prescribed PPI medication.

The healthcare practice should be able to differentiate patients with atrophic gastritis from those with a "healthy stomach" for several reasons. One reason is that the patients with atrophic gastritis are to be referred to diagnostic gastroscopy and biopsy microscopy due to the cancer risk, whereas such an examination does not usually need to be prompted as the first choice in subjects with a healthy stomach mucosa [13]. According to the international consensus guidances, patients with a co-existing *H. pylori* infection and atrophic gastritis should also receive treatment for *H. pylori*, irrespective of whether the patient has stomach symptoms or not [22].

An acid-free or hypochlorhydric stomach is always colonized by various microbes, especially from oropharynx [23]. These microbes are able to produce potent carcinogens, including nitrosamines and acetaldehyde, which are classified by IARC as class I carcinogens [11,23]. A lack of the acid buffer in the stomach may also increase the risk of contracting intestinal and respiratory microbial infections [24]. Furthermore, the absorption of many essential micronutrients (including iron, calcium, magnesium and zinc) is impaired in ACG and hypochlorhydric stomach, and absorptions of many per oral medicines are altered in an unpredictable manner in such stomachs [13,25].

The presence of *H. pylori* antibodies with normal plasma levels of PgI and PgII, and normal ratio of PgI/PgII indicate "non-atrophic *H. pylori* gastritis". Such patients have a higher than an average risk of peptic ulcer disease [26,27], whereas only a small (but not negligible) risk of gastric cancer [13]. In these cases, *H. pylori* eradication and gastroscopy are optional according to the consensus statements [22], the choice of the intervention being dependent on symptoms, patient's wishes, physician's assessments and local resources [22]. Alarm symptoms always require prompt gastroscopy, in which cases all pre-gastroscopy laboratory tests (including all *H. pylori* tests) are useless, only wasting time and money. All clinically relevant information can be obtained from gastroscopy and biopsy histology.

When all biomarker test results are normal, the structure and function of the stomach mucosa is normal and healthy with very high probability [16,18]. A person with such a normal stomach mucosa has a very small, and in practice negligible, risk of any significant gastric disease including peptic ulcer diseases and gastric cancer [13]. In our opinion, an immediate gastroscopy among such subjects, independent of the patient's age and symptoms, would only be waste of time and resources. Gastroscopy in such cases would not provide any clinically important additional information [13]. Other medical examinations such as colonoscopy, abdominal US or fecal occult blood test, etc., are likely to be more useful and more cost-effective than a prompted gastroscopy.

The reliability of the used biomarkers to reflect properly the stomach mucosa and *H. pylori* infection has been validated in numerous studies around the world, and the tests are already used in the screening of individuals susceptible to cancer in Japan. In diagnosis of ACG, the PgI biomarker is commonly used, but the PgI/PgII ratio is relied more in Japan and Asia in general. In the present study, both of these biomarkers were taken into account.

Acknowledgement

GastroView® biomarker testing and sample collection was performed and funded by Biohit Oyj.

Declaration of interests: A. Telaranta-Keerie, L. Paloheimo and R. Kara work, or have recently worked, in the R&D, Sales and Marketing Departments of Biohit Oyj. M. Härkönen and P. Sipponen are scientific consultants and members of the Scientific Board at Biohit Oyj.

References

[1] Färkkilä M. Miten dyspepsiaa tulisi hoitaa? Duodecim 2004;120:2537–42.

[2] Salaspuro M. Ovatko "testaa ja hoida" – strategian haitat hyötyä suuremmat? Duodecim 2005;121:852.

[3] Correa P. *Helicobacter pylori* and gastric carcinogenesis. Am J Surg Pathol 1995;19(Suppl 1):S37–43.

[4] 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.

[5] Kekki M, Siurala M, Varis K, Sipponen P, Sistonen P, Nevanlinna HR. Classification principles and genetics of chronic gastritis. Scand J Gastroenterol 1987;141 (Suppl):1–28.

[6] 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.

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

[8] 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, 13C-urea breath test, and serology. Scand J Gastroenterol 2000;35:138–41.

[9] Gatta L, Vakil N, Ricci C, Osborn JF, Tampieri A, Perna F, et al. Effect of proton pump inhibitors and antacid therapy on 13C urea breath test and stool test for *Helicobacter pylori* infection. Am J Gastroenterol 2004;99:823–29.

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

[11] 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.

[12] 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.

[13] Sipponen P, Graham DY. Importance of atrophic gastritis in diagnostics and prevention of gastric cancer: application of plasma biomarkers. Scand J Gastroenterol 2007;42:2–10.

[14] Heikkinen M, Pikkarainen P, Eskelinen M, Julkunen R. GP's ability to diagnose dyspepsia based only on physical examination and patient history. Scand J Prim Health Care 2000;18:99–104.

[15] Di Mario F, Cavallaro LG, Moussa AM, Caruana P, Merli R, Maini A, et al. Usefulness of serum pepsinogens in *Helicobacter pylori* chronic gastritis: relationship with inflammation, activity, and density of the bacterium. Dig Dis Sci 2006;51(10):1791–5.

[16] 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.

[17] 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.

[18] Storskrubb T, Aro P, Ronkainen J, Sipponen P, Nyhlin H, Talley NJ, et al. Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: the Kalixanda study. Scand J Gastroenterol 2008;43:1448–55.

[19] Varis K, Isokoski M. Screening of type A gastritis. Ann Clin Res 1981;13:133–8.

[20] Loikas S, Koskinen P, Irjala K, Löppönen M, Isoaho R, Kivelä SL, et al. Vitamin B12 deficiency in the aged: a population-based study. Age Aging 2007;36:177–83.

[21] 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.

[22] Malfertheiner P, Mégraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. Gut 2007;56:772–81.

[23] 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.

[24] Martinsen TC, Bergh K, Waldum HL. Gastric juice: a barrier against infectious diseases. Basic Clin Pharmacol Toxicol 2005;96:94–102.

[25] Sipponen P, Härkönen M. Hypochlorhydric stomach – a risk condition for calcium malabsorption and osteoporosis? Scand J Gastroenterol 2010:45:133–8.

[26] Sipponen P, Varis K, Fräki O, Korri UM, Seppälä K, Siurala M. Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis. A clinical follow-up study of 454 outpatients. Scand J Gastroenterol 1990;25:966–73.

[27] Sipponen P, Seppälä K, Äärynen M, Helske T, Kettunen P. Chronic gastritis and gastroduodenal ulcer: a case control study on risk of coexisting duodenal or gastric ulcer in patients with gastritis. Gut 1989;30:922–9.