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Real-Time Gastric Juice Analysis to Rule Out the Presence of Autoimmune Gastritis: A Case-Control Study

Emanuele Dilaghi[a] Gianluca Esposito[a] Irene Ligato[a]
Alessandro Del Forno[b] Roberta Elisa Rossi[c] Cesare Hassan[d, e]
Bruno Annibale[a] Angelo Zullo[b]

[a]Department of Medical-Surgical Sciences and Translational Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy; [b]Gastroenterology and Digestive Endoscopy, "Nuovo Regina Margherita" Hospital, Rome, Italy; [c]Gastroenterology and Endoscopy Unit, IRCCS Humanitas Research Hospital, Milan, Italy; [d]Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Italy; [e]Humanitas Clinical and Research Center-IRCCS, Endoscopy Unit, Rozzano, Italy

Keywords
Autoimmune gastritis · Gastric juice analysis · pH value · Precancerous lesions

Abstract

Background: Autoimmune gastritis (AIG) is an infrequent disease predisposing to both neuroendocrine tumours and cancer. This study aimed to evaluate whether pH measurement of gastric juice allows accurate exclusion of the presence of AIG in real time so that gastric mucosa sampling on normal-appearing mucosa may be avoided. ***Methods:*** This study enrolled patients diagnosed with AIG and matched controls (ratio 1:5) who underwent upper endoscopy with standard gastric mucosa sampling and real-time, gastric juice pH assessment. A threshold of pH less than 4.5 was adopted as cut-off to rule out the presence of a feature of AIG. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall accuracy, positive likelihood ratio (LR+), and negative likelihood ratio (LR–) were calculated. ***Results:*** Data of 40 patients (M/F: 19/21; mean age: 58 years, range: 18–89) with AIG and 212 matched controls were evaluated. Among AIG patients, the feature of atrophy/metaplasia of the oxyntic mucosa was staged as mild in 9 cases, moderate in 9, and severe in the remaining 22 patients. Gastric juice analysis showed a pH value >4.5 in 29 (72.5%) patients and 12 (5.7%) controls. Sensitivity, specificity, accuracy, PPV, NPV, LR+, and LR– were 73% (95% CI = 0.57–0.84), 94% (95% CI = 0.90–0.97), 71% (95% CI = 0.64–0.74), 95% (95% CI = 0.93–0.97), 91% (95% CI = 0.87–0.95), 12.9 (95% CI = 7.19–23.03), and 0.29 (95% CI = 0.18–0.48), respectively. The histological assessment of false-negative cases showed the presence of only mild-moderate atrophy of oxyntic mucosa in 6 (54.5%) cases, and severe in the others. ***Conclusions:*** Our data found that real-time pH evaluation of gastric juice allows ruling out AIG with a very high NPV, but further studies are needed.

karger@karger.com
www.karger.com/pjg

Correspondence to:
Angelo Zullo, angelozullo66@yahoo.it

Análise em tempo real do suco gástrico para exclusão de gastrite autoimune - estudo caso-controlo

Palavras Chave
Gastrite auto-imune · Avaliação do suco gástrico · pH · Condições pré-malignas

Resumo

Introdução: A gastrite auto-imune (GAI) é uma condição rara que aumenta o risco de tumores neuroendócrinos e cancro gástrico. Este estudo teve como objetivo avaliar se a medição do pH do suco gástrico permite excluir em tempo real, com acuidade, a presença de GAI, de modo a evitar a realização de biópsias quando os aspetos endoscópicos são normais. ***Métodos:*** Foram incluídos doentes com GAI e controlos emparelhados (rácio 1:5) que realizaram endoscopia digestiva alta com biópsias gástricas padronizadas e medição do pH do suco gástrico em tempo real. O valor de pH <4,5 foi definido como *cut-off* para exclusão de GAI. Foram calculadas a sensibilidade, especificidade, valores preditivos positivos (VPP) e negativos (VPN), acuidade e rácios de verosimilhança (LR). ***Resultados:*** Foram avaliados os dados de 40 doentes com GAI (M/F 19/21; idade média 58 anos, intervalo 18–89) e de 212 controlos emparelhados. Nos doentes com GAI a atrofia/metaplasia intestinal na mucosa oxíntica em foi classificada como leve em 9 casos, moderada em 9 e grave nos restantes 22 doentes). A análise do suco gástrico mostrou um pH >4.5 em 29 (72.5%) dos doentes com GAI (vs. 5.7% nos controlos). A sensibilidade, especificidade, acuidade, VPP, VPN, LR+ and LR- foram de 73% (95% CI = 0.57–0.84), 94% (95% CI = 0.90–0.97), 71% (95% CI = 0.64–0.74), 95% (95% CI = 0.93–0.97), 91% (95% CI = 0.87–0.95), 12.9 (95% CI = 7.19–23.03), e 0.29 (95% CI = 0.18–0.48), respetivamente. A avaliação dos falsos negativos mostrou a presença de atrofia ligeira/moderada em 6 casos (54.5%) e severa nos restantes. ***Conclusão:*** Este estudo sugere que a medição do pH do suco gástrico em tempo real pode ser uma ferramenta promissora para excluir a GAI, embora sejam necessários estudos adicionais.

Introduction

Autoimmune gastritis (AIG) is a chronic, inflammatory disease characterized by progressive atrophy – with or without intestinal metaplasia – and enterochromaffin-like cell hyperplasia of gastric oxyntic mucosa (acid-secreting gastric compartment), sparing the antral mucosa [1, 2]. This condition increases the risk of both neuroendocrine tumours and cancer development in the stomach [3–5]. AIG is usually suspected when either iron or B_{12} deficiency anaemia develops, due to the reduction of gastric acid and intrinsic factor secretion, respectively [6]. Moreover, it is searched for at endoscopy in patients with positive serology to parietal cell autoantibodies, generally screened in patients with other autoimmune diseases, such as autoimmune thyroiditis or type 1 diabetes mellitus [6]. However, some patients with AIG complain of dyspeptic or even gastro-oesophageal reflux symptoms, so AIG may be also diagnosed at gastric biopsies performed during routine endoscopy [7]. According to current guidelines, standard sampling of gastric mucosa should be accomplished in 90% of appropriate upper endoscopies to search for *Helicobacter pylori* infection and gastric precancerous lesions, that is, atrophy and intestinal metaplasia, including AIG [8, 9]. However, these conditions are present in only a minority of patients with normal-appearing gastric mucosa, so the histological results are often clinically unrewarding. Indeed, an AIG prevalence as low as 1.9% was reported in a serology study in the USA [10], and 2.7% in three large endoscopic series from Italy, Australia, and Tunisia [11–13].

The interest towards gastric juice analysis during routine endoscopy has been renewed by the marketing of EndoFaster®, a device that performs a real-time evaluation of both ammonium and H^+ concentrations in the gastric juice, allowing to accurately rule out *H. pylori* and extensive atrophy involving antral and gastric body mucosa [14, 15]. Indeed, negative predictive values of gastric juice analysis as high as 97% on more than 2,000 patients were reported in a recent systematic review [16]. However, no specific data on EndoFaster® performance in AIG patients are available. Therefore, we designed this study to assess whether gastric juice analysis allows accurate exclusion of the presence of AIG in real time so that gastric mucosa sampling on normal-appearing mucosa may be safely and conveniently avoided.

Materials and Methods

Patients

This retrospective study was performed on data prospectively collected in a specific database where information of consecutive adult patients who underwent gastric juice analysis at upper endoscopy was registered. For this study, data of all patients diagnosed with AIG were retrieved and compared to those of matched controls enrolled in the

Fig. 1. The EndoFaster® device.

same database. Inclusion criteria were (a) histologically proven AIG; (b) no use of proton pump inhibitor therapy in the last 2 weeks before endoscopy; (c) absence of *H. pylori* at histology; (d) no previous therapy for *H. pylori* infection. These criteria were adopted to appropriately exclude present or past *H. pylori* infection potentially triggering atrophy/intestinal metaplasia development on gastric mucosa, in order to study only patients with true AIG. For each case, data of 5 controls matched for gender and age (±2 years) and with the same inclusion criteria, but without AIG, were recovered.

Endoscopic Procedures

All patients underwent upper endoscopy with standard (2 antral, 1 *incisura angularis*, 2 gastric body) biopsies on gastric mucosa, according to the updated Sydney system [17]. AIG was diagnosed when glandular atrophy (with or without intestinal metaplasia) with enterochromaffin-like cell hyperplasia was confined to the oxyntic mucosa, and a feature of normal antral mucosa was confirmed at histology [1]. During endoscopy, gastric juice analysis was performed by EndoFaster® (manufacturer: NISO Biomed S.r.l, Turin, Italy; distributor: Waldner Tecnologie Medicali, Trento, Italy). In detail, the device was interposed between the endoscope and the suction system, without causing any discomfort to the patient (Fig. 1). During endoscopy, lumen washing was avoided until the stomach was reached and at least 3 mL of gastric juice was aspirated. The device performs a real-time (within 90 s) gastric juice evaluation of pH values and ammonium concentrations, to suspect atrophic gastritis and *H. pylori* infection, respectively [16]. A threshold of pH less than 4.5 was adopted as cut-off to rule out the presence of atrophy involving the oxyntic mucosa and, then, a feature of AIG [16]. Informed consent was obtained for all the procedures. Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required, and no funds were received, the Investigational Review Boards waived formal approval for this retrospective analysis on medical records.

Table 1. Distribution of patients based on EndoFaster results (positive when pH >4.5) and histological feature of autoimmune gastritis (AIG)

	AIG positive	AIG negative	Total
EndoFaster positive	29	12	41
EndoFaster negative	11	201	212
Total	40	213	253

Statistical Analysis

Frequencies, percentages, and mean values with their 95% confidence intervals were calculated for all observations. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), accuracy, positive likelihood ratio, and negative likelihood ratio were calculated, and Fagan's nomogram accordingly was designed.

Results

Overall, data of 40 patients (M/F: 19/21; mean age: 58 years, range: 18–89) diagnosed with AIG and 212 matched (102/120; mean age: 59 years, range: 19–92) controls were evaluated. Among AIG patients, the feature of atrophy/metaplasia on the oxyntic mucosa was staged as severe in 22 (55%) cases, moderate in 9 (22.5%), and mild in the remaining 9 (22.5%) patients. Gastric juice analysis showed a pH value >4.5 in 29 (72.5%) patients and 12 (5.7%) controls. Sensitivity, specificity, positive predictive value, NPV, and the overall accuracy were 73% (95% CI = 0.57–0.84), 94% (95% CI = 0.90–0.97), 71% (95% CI = 0.64–0.74), 95% (95% CI = 0.93–0.97), and 91% (95% CI = 0.87–0.95), respectively, while the positive likelihood ratio value was 12.9 (95% CI = 7.19–23.03), and the negative likelihood ratio was 0.29 (95% CI = 0.18–0.48). Distribution of patients according to EndoFaster® results and AIG feature is provided in Table 1, and Fagan's nomogram in Figure 2 [2]. Data regarding the 11 false-negative cases are provided in Table 2. As shown, the histological assessment showed the presence of mild-moderate atrophy of oxyntic mucosa in 6 (54.5%) cases, and severe in the remaining 5 cases.

Discussion

Upper endoscopy is largely performed in routine practice for diagnostic, therapeutic, and follow-up purposes [9, 18]. However, the rate of inappropriate

examinations in open-access setting was >20%, with values reaching 61.7% in some series [19]. According to current guidelines, standard gastric biopsies should be performed during routine endoscopy to search for both *H. pylori* infection and precancerous lesions on gastric mucosa, namely atrophy and intestinal metaplasia [8, 9]. AIG, characterized by atrophy and/or metaplasia confined in the oxyntic mucosa of the stomach and increased risk of developing both type I NET and adenocarcinoma in the stomach [1, 2], is a quite infrequent condition. Indeed, a prevalence rate of less than 3% was reported in endoscopic studies performed in different geographic areas [11–13], and ranging between 3% and 9% in serological studies only on Scandinavian populations where the incidence of disease is particularly high [6].

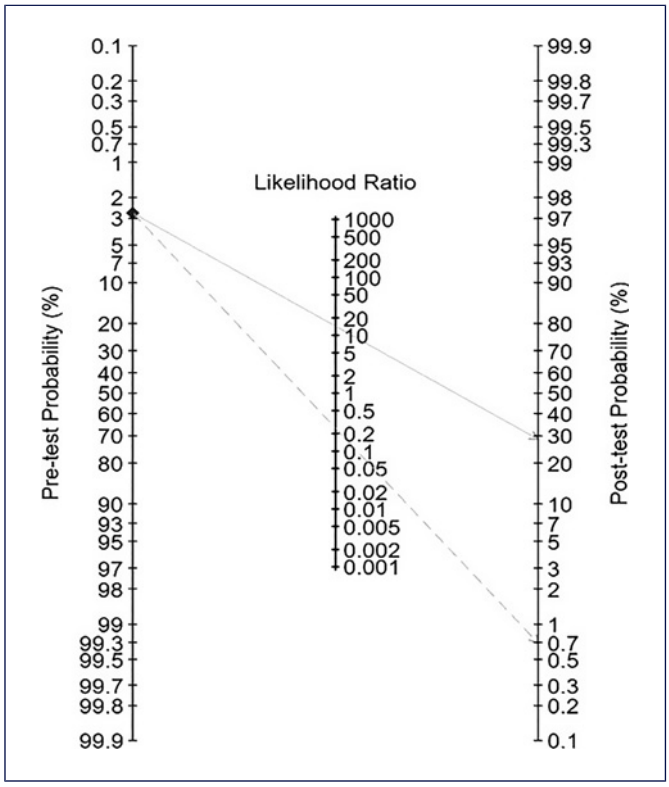

Fig. 2. Fagan's nomogram. The pretest probability indicated in the nomogram was that calculated in endoscopic studies.

Although generally suspected in patients with anaemia (micro- or macrocytic) or with parietal cell autoantibody seropositivity, AIG may be unexpectedly detected at histological assessment of gastric mucosa of patients with dyspepsia, particularly subtype postprandial distress syndrome or even with gastro-oesophageal reflux symptoms [7]. Can the gastric juice analysis be useful to avoid useless biopsies on normal-appearing mucosa without missing AIG? To achieve this purpose, a test with a very high NPV is needed. Real-time pH measurement in gastric juice with EndoFaster® was found to accurately rule out the presence of extensive atrophy/metaplasia involving both antral and gastric body mucosa [16]. To our knowledge, this is the first study on the accuracy of such a device in AIG patients. Our data found that by performing gastric juice analysis it is possible to rule out the presence of AIG with an NPV as high as 95%, so that only 5 patients in every 100 cases with negative EndoFaster® testing would be eventually overlooked for AIG. Of note, we observed that only mild-moderate atrophy on the oxyntic mucosa was present in more than half of patients with false-negative results at pH measurement. Therefore, it could be speculated that the patchy reduction of appropriate acid-secreting gastric glands revealed at histological assessment could be insufficient to markedly impair acid secretion detectable by pH measurement. On the other hand, the diagnosis of mild atrophy on gastric mucosa could represent an over-reporting, when considering that

Table 2. Patients with histological feature of AIG and normal pH values in gastric juice

Gender	Age, years	Gastric pH	Histology
F	46	3.5	Severe atrophy with intestinal metaplasia
F	53	1.3	Mild atrophy with focal intestinal metaplasia
F	66	1.7	Moderate atrophy with intestinal metaplasia
F	44	1.6	Mild atrophy without intestinal metaplasia
M	75	3.2	Severe atrophy with intestinal metaplasia
M	66	1.3	Moderate atrophy with intestinal metaplasia
F	18	2.6	Severe atrophy with intestinal metaplasia
F	60	2.6	Mild atrophy without intestinal metaplasia
M	63	1.6	Severe atrophy with intestinal metaplasia
M	40	1.6	Mild atrophy with focal intestinal metaplasia
F	65	2.8	Severe trophy with intestinal metaplasia

gastric biopsy specimens are not routinely oriented in clinical practice [20] and that interobserver agreement for atrophic gastritis among expert pathologists is only 0.73 [21]. Therefore, an even better performance of EndoFaster® in this setting could be foreseeable. On the other hand, beyond reducing useless biopsies in a negative test, a positive EndoFaster® result would alert the endoscopist to take standard biopsies on antral and gastric body mucosa. Indeed, despite it is recommended that gastric biopsies should be taken in >90% of endoscopies [8, 9, 22], the routine biopsy rate was quoted as low as 23% in a recent Italian study [23].

In the past, a pH 4 cut-off was proposed to rule out atrophy/metaplasia involving gastric oxyntic mucosa, because only few patients with this histological condition showed a pH value of gastric juice lower than 4 [24, 25]. However, a pH 4.5 cut-off was adopted in successive studies to disclose severe hypochlorhydria due to diffuse atrophy on gastric mucosa and, therefore, we cautionarily used the latter cut-off to rule out AIG [14, 15, 26].

Besides pH measurement, gastric juice analysis with EndoFaster® was found to be highly accurate in simultaneously excluding *H. pylori* – namely a type I carcinogen for gastric cancer according to the IARC [27]– by assessing ammonium concentration [16]. Therefore, it is clearly evident the advantage in contemporary discarding *H. pylori* infection and precancerous lesions by real-time gastric juice analysis with EndoFaster®. Moreover, avoiding foreseeable negative gastric biopsies in a definite portion of patients through the gastric juice analysis was found to distinctly reduce the environmental impact of upper endoscopy [28].

Some limitations of the study should be considered. The sample size is quite small, so our findings need to be confirmed in a larger, multicentre study. Although a standard biopsy sampling is routinely performed in our centre, the retrospective design of the study prevents specifically verification of the quality of endoscopic procedures or biopsies protocol in all cases. Finally, we excluded subjects with ongoing PPI use or presence of *H. pylori* infection, two conditions quite frequently encountered in routine practice.

Conclusions

Our data found that real-time pH evaluation of gastric juice allows ruling out AIG with a very high NPV, so that biopsies may be avoided on normal-appearing gastric mucosa. However, our results need to be confirmed in different settings.

Statement of Ethics

Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required, and no funds were received, the Investigational Review Boards of Nuovo Regina Margherita Hospital waived formal approval for this retrospective, cross-sectional study performed in clinical practice. Patients signed informed consent for both procedure and anonymous use of their data for scientific purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Angelo Zullo and Gianluca Esposito conceived the study and were responsible for the study design, statistical analysis, and drafting of the manuscript. Emanuele Dilaghi, Irene Ligato, and Gianluca Esposito were responsible for data and patient collection in each participant centre. Roberta Elisa Rossi, Cesare Hassan, and Bruno Annibale provided critical revision of the manuscript with important intellectual support. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data are available following reasonable inquiries directed to Angelo Zullo.

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