Recovery of gastric function in patients affected by chronic atrophic gastritis using L-cysteine (Acetium®): one year survey in comparison with a control group

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Abstract. Background and aim: Chronic Atrophic Gastritis (CAG) is a precancerous condition for gastric cancer (GC) as single risk factor, being a consequence of a previous Helicobacter pylori (Hp) infection or based on autoimmune mechanisms. Achlorhydria plays an important role towards the formation of a class I carcinogen, acetaldehyde, after food intake. L-cysteine has been claimed to be able to bind in a covalent way acetaldehyde when administered at meals. Methods: In this study we enrolled two CAG groups of patients, one treated with 300 mg/daily of L-cysteine for one year, the other one untreated. We assessed gastric function lasting the one-year follow-up by using noninvasive surrogates, i.e. Pepsinogen I (PGI) and gastrin 17 (G17). Results: In the group of 77 CAG on therapy we found a statistically significant increase in PGI values and a decrease in G17 levels, in comparison with unchanged values in control group. Conclusions: L-cysteine seems able to provide a recovery in gastric function when administered in CAG patients and could be proposed as a possible therapy in such patients. (www.actabiomedica.it)

Keywords: Pepsinogen I, Gastrin 17, Chronic Atrophic Gastritis, L-cysteine, Acetaldehyde

Introduction

Chronic atrophic gastritis (CAG) is a precancerous condition for gastric cancer (GC) as single risk factor (1-7). Helicobacter pylori (H.p.) infection is claimed to be the etiological factor in the development of chronic gastritis leading, lasting the years in some subjects, to CAG and then GC. (8-12). A different mechanism to develop CAG is based on autoimmune response targeted against parietal cells and intrinsic factor, typically located only in the fundus and in the corpus (13-15). The risk of GC increases with the extension of Intestinal Metaplasia (IM) as well as the severity of CAG (16). Among the patients with severe atrophy in the antrum, this risk is higher than in healthy subjects and the risk increases consequently if severe atrophy is found either in both antrum and corpus (severe panCAG) (10, 11, 17, 18).

The prevalence of CAG and GC increases with increasing age and the risk for both diseases is highest among the subjects >45 years old (19, 20). The Correa’s cascade represents a most accepted sequence of events from normal mucosa to gastric cancer, a multi-step gastric carcinogenesis including the progression from normal mucosa through chronic non-atrophic gastritis, atrophic gastritis and intestinal metaplasia to intraepithelial neoplasia (previously called dysplasia) and finally to carcinoma (1). On one hand, this long-lasting process of carcinogenesis represents an opportunity to elaborate a screening strategy to identify early stage, i.e. precancerous condition, on the other hand a difficulty is represented by the fact that the majority of...
patients affected by CAG are asymptomatic or experiencing not specific manifestations like early satiation, epigastric fullness or bloating (13, 21-23).

The Updated Sydney System (USS) is the most widely accepted as sample protocol for diagnosis of CAG (24), being the OLGA (operative link for gastritis assessment) and/or OLGIM (operative link on gastric intestinal metaplasia) system, currently of reference for staging of gastritis (25, 26).

A proposed surrogate to investigate by non-invasive way both function and morphology of gastric mucosa is represented by serum pepsinogens (so called “serological biopsy”) (27).

Serum pepsinogens (PGI and PGII) were proposed in the diagnosis of gastric diseases in dyspeptic patients in general population (4, 28-30) and in selected patients (31). Moreover, Gastrin 17 (G17) has been proposed beside pepsinogens to verify the maintenance of negative feedback between acid and gastrin, critically modified in the picture of CAG, because of important modification in acid secretion (32-34). In particular, in body atrophic gastritis, in which atrophy leads to achlorhydria, G17 increases significantly, being the serological spectrum represented by low levels of PGI and high levels of gastrin (23).

Several meta-analyses (35-37) pointed out the properties of serum pepsinogens in the diagnosis of CAG, due to very high negative predictive value.

Based on the literature, pepsinogens were recommended by international experts for screening and diagnosis of CAG (10, 11).

In the literature the majority of studies documented an improvement of CAG and in some case of IM following H.p. eradication (38-41).

Di Mario by using serology, also demonstrated an improvement of the picture of CAG after H.p. eradication, lasting a four-year follow-up (42).

In 2009 IARC declared acetaldehyde as group 1 carcinogen equivalent to many others similar carcinogens (43). Acetaldehyde derives from the metabolism of ethanol through oxidation and it is an important downstream of tobacco smoke (44-46). The evidence for the carcinogenesis of acetaldehyde derives from several epidemiological studies on selected populations of alcohol drinkers and alcohol dehydrogenase (ADH) deficiency, as well as low aldehyde dehydrogenase activity (47). The accumulation of acetaldehyde in the saliva, in turn represents an increased risk for different upper gastrointestinal tract neoplasms (48, 49). In the mouth, it has been demonstrated the dissolution of acetaldehyde into the saliva during smoking (50). The carcinogenic effect of tobacco is mediated by noxious aldehydes in saliva at level of oral cavity and subsequently in the larynx, esophagus and stomach (51). Also stomach cancer is claimed to be dependent from the formation of acetaldehyde in gastric lumen trough to the role of local microbiota. In fact, some microbe strains of the saprophytic oral or intestinal microflora can exert ADH activity to induce acetaldehyde formation from ethanol by oxidation (52, 53). Patients affected by CAG show some changes in microbiome composition resulting in a presence of bacteria in gastric lumen producing both local ethanol and acetaldehyde from glucose metabolism (54). After assumption of ethanol, in this scenario, the production of both compounds has been described as a 5-fold increase (55).

Sprince et al. (56), demonstrated about forty years ago the properties of L-cysteine – a non-essential amino-acid – in order to avoid the toxicity of acetaldehyde by creating a covalent binding leading to the formation of a stable 2-methylthiazolidine-4-carboxylic acid (MTCA), which is a non-toxic compound cleared through feces and urine. (56, 57). Other studies focused on the protective role of ascorbic acid in prevention of precancerous condition such as atrophic gastritis (58). In the last decade, Salaspuro et al. (59) demonstrated that compounds slowly releasing L-cysteine locally in the oral cavity were able to successfully remove acetaldehyde from the saliva in alcohol and smokers’ consumers (59, 60). Several studies confirmed the properties of chewing gum containing L-cysteine of removing acetaldehyde from saliva in smokers (61, 62). Other studies demonstrated the capacity of L-cysteine to remove acetaldehyde also from gastric juice in achochlorhydic stomach after alcohol administration (63, 64). A recent study, after oral administration of 15% alcohol solution in a total dose of 0.3 g/kg by using L-cysteine capsules shows that the compound was able to eliminate ethanol-derived acetaldehyde from gastric juice of patients with atrophic gastritis and the persistence of the effect at least for 40 min (65).
Aim

This study was designed to evaluate the assessment of gastric function by means of serology (Pepsinogen I and Gastrin 17) in patients with diagnosis of CAG treated for 1 year with 300 mg of L-cysteine daily compared with a control group of CAG untreated patients.

Patient and methods

Data collection

Data were recovered from the database and medical records from one single medical center located in Northeast of Italy. We collected patients affected by CAG, diagnosed by endoscopy and histology. The biopsies were collected according to USS (24) and evaluated according to OLGA grading (25).

Patients with CAG were characterized, according with different etiology: autoimmune gastritis and/or post-Hp infection. Autoimmune gastritis was diagnosed by means of positivity of anti-parietal cell antibodies and corresponding histological criteria. Post-infectious atrophic gastritis was diagnosed by previous confirmation of Hp infection (see Hp status methods) All patients at baseline were Hp negative for at least two years and off PPI therapy in the last six months.

Patients with CAG were subdivided in two groups, according with the intake of L-cysteine (Acetium®, Biohit Helsinki, Finland) at dosage of 100 mg capsules during meals, three times a day for 1 year (Group 1) and subjects without therapy, except anti-acid or prokinetics when needed (Group 2). Clinical data (age, sex, etiology of CAG - autoimmune or Hp. related) as well as smoking habit and alcohol intake were collected for each patient. We choose the cut-off of 10 cigarettes/day to define smoking habit and ethanol 40gr/day for positive alcohol intake.

Group 1 included 77 patients (24 males 53 females, mean age 52.7 ± 11.2 ys.) whose gastritis etiology was autoimmune (30 pts.) or Hp.-related (20 pts.) gastritis. Table 1 summarized the epidemiological data.

In all patients of both groups a serological sample was obtained to measure levels of PG I and G 17 using Elisa method (Biohit. Helsinki, Finland). Normal values are reported as follow: PG I: 30-160 µg/L, G 17: 1-10 pg/L. PGI and G17 levels were measured at baseline and after 3, 6, 12 months.

Hp. status was assessed by means of three methods in each patient: 13C-urea breath test, histology of gastric mucosa (using hematoxylin and eosin with modified Giemsa), serology by IgG antibody (Elisa method; Biohit, Helsinki, Finland)

Inclusion criteria

Only Hp negative patients, investigated by UBT, serology and histology of gastric mucosa, were enrolled in the study; age: >18 ys. < 75 ys. old. Only patients who have a biopsy confirmed CAG with corpus restricted disease or with pan-atrophy according to the OLGA staging or Sydney system were included in the study. Some subjects of both groups had an history of Hp infection previously successfully eradicated (at least two years before).

Exclusion criteria

Patients who underwent previous upper gastrointestinal tract surgery; previous history of neoplasms; PPI therapy in the last year.

| Table 1. Demographics | Group 1 | Group 2 | p |
|-----------------------|--------|--------|---|
| Patients N°           | 77     | 50     | ns |
| Male                  | 24 (31.16%) | 14 (28.00%) | ns |
| Female                | 53 (68.83%) | 36 (72.00%) | ns |
| Mean age              | 52.7±11.2 ys | 50 ± 11.9 ys | ns |
| Age range             | 37-74 ys | 43-79 ys | ns |
| Smoking habit         | 14 (18,18%) | 9 (18,00%) | ns |
| Alcohol intake        | 19 (24,68%) | 11 (22,00%) | ns |
| Previous H.p.         | 47 (61.03%) | 20 (40.00%) | <0.001 |
| Autoimmune gastritis  | 30 (38.96%) | 30 (60.00%) | <0.001 |
| Group 1 CAG treated by L-cysteine (study group) | Group 2 untreated CAG (study group) |
**Study design**

Single center, controlled, not randomized study that included two populations: the first (Group 1) included 77 pts. affected by chronic atrophic gastritis (CAG) diagnosed by histology treated with L-cysteine capsules (100mg three times daily with meals) for 12 months compared to 50 CAG pts. as control group (Group 2) off therapy.

**Statistics**

Statistical analysis was performed with the SPSS (version 20.1) statistical software program for windows. Chi-squared and Wilcoxon tests for paired data were used when appropriate. Data were expressed as mean for quantitative variables. All p were two-tailed with statistically significance indicated by a value of p<0.05.

The study was performed in accordance with the declaration of Helsinki and approved by local Ethics Committee (Identifier: 92687).

**Results**

Table 2 summarized serological values of PGI and G17 at baseline, three, six and twelve months after entering the study, in both groups.

Serum levels of PGI and G17 in the two groups lasting 1 years of follow-up were reported in figures 1 and 2.

In treated patients (group 1), PGI levels increase from baseline lasting the follow-up period from 7.88 µg/L to 15.92 µg/L at twelfth month, in statistically significant manner (p<0.001). On the contrary, in control group (Group 2), PGI levels stay unchanged lasting the follow-up (baseline: 6.30 µg/L vs twelve months: 7.10 µg/L; p=ns) (Fig. 1).

Conversely, G17 values show a decrease from baseline: 30.31 pg/L to 19.23 pg/L at twelve months; p<0.001 in Group 1 opposite to Group 2, showing no significant modifications lasting the follow-up (baseline: 34.52 pg/L; twelve month: 32.15; p=ns) (Fig. 2).

We stratified all patients, treated and untreated, according with OLGA Grading, in different severity of CAG. The distribution of OLGA scores in Group 1 was: OLGA 1: 10 pts, OLGA 2: 18 pts, OLGA 3: 26 pts, OLGA 4: 23 pts and in Group 2 was: OLGA 1: 5 pts, OLGA 2: 11 pts, OLGA 3: 19 pts, OLGA 4: 15 pts.

We decide to group patients showing OLGA 1 and OLGA 2 in “OLGA Low-grade” and patients with OLGA 3 and OLGA 4 in “OLGA High-grade”.

Fig. 3 and 4 summarizing values of PGI and G17 from baseline to twelve months, according with the OLGA severity score.

Data showed the lowest levels of PGI in the group of “OLGA High-grade” in comparison with patients showing “OLGA Low-grade”, being this feature confirmed in both groups (treated and untreated).

Group 1 OLGA “Low-grade”: 10.2 µg/L vs 4.5 µg/L in “OLGA High-grade”;

|         | Baseline | 3 months* | 6 months** | 12 months*** | p          |
|---------|----------|-----------|------------|--------------|------------|
| **PGI** |          |           |            |              |            |
| Group 1 | 7.88 µg/L| 11.51 µg/L| 13.73 µg/L | 15.92 µg/L   | * <0.05    |
|         |          |           |            |              | **<0.01    |
|         |          |           |            |              | ***<0.001  |
| Group 2 | 6.90 µg/L| 7.20 µg/L | 6.80 µg/L  | 7.10 µg/L    | ns*        |
|         |          |           |            |              | **ns       |
|         |          |           |            |              | ***ns      |
| **G17** |          |           |            |              |            |
| Group 1 | 30.31 pg/L| 25.46 pg/L| 21.84 pg/L | 19.23 pg/L   | * <0.01    |
|         |          |           |            |              | **<0.001   |
|         |          |           |            |              | ***<0.001  |
| Group 2 | 34.52 pg/L| 35.48 pg/L| 35.8 pg/L  | 32.15 pg/L   | * ns       |
|         |          |           |            |              | **ns       |
|         |          |           |            |              | ***ns      |

*3 months vs baseline values; **6 months vs baseline values; *** 12 months vs baseline values; Group 1 CAG treated by L-cysteine (study group); Group 2 untreated CAG (control group)
ticular relevance as regards G17 in the group of OLGA “High-grade”: baseline 39.7 pg/L vs 21.8 pg/L.

Discussion

Until now, Cag is lacking a reliable therapy, being the only suggestion to provide adequate follow up for such condition, considered at risk to develop GC (1-4).

From a functional point of view CAG is characterized by a low level of chlorohydric acid (hypochloridria) or – in the most severe cases – achlorhydria, in turn related with increased risk to develop GC (10).

Group 2 OLGA “Low-grade” 11.3 μg/L vs 5.3 μg/L OLGA “High grade”; p<0.001

Conversely, the highest values of G17 were find in OLGA “High-grade”, both in Group 1 and Group 2: 39.7 pg/L and 35.6 pg/L, opposite to levels in OLGA “Low-grade”: Group 1: 18.2 pg/L, Group 2 16.7 pg/L; p<0.001.

Figures 3 and 4 summarizes the modifications of both PGI and G17 lasting follow-up in the two groups, according with OLGA severity score. Ones more, treated patients show a statistically significant modification from baseline to twelfth month, of
tients treated with L-cysteine, while the values of untreated CAG patients in control group remain unchanged, lasting the entire follow-up period. More important seems to be the critical decrease of G17 levels in treated patients from 30.31 pg/L at baseline to 19.23 at 12th month: in particular, in OLGA 3 and 4 groups, the decrease was from 39.7 pg/L at baseline to 21.8 at the end of follow-up. Interestingly, the major modification of both markers, PGI and G17, was observed after 3 months from the intake of L-cysteine.

The serological phenotype of body atrophic gastritis is represented by the picture of low levels of PGI (a surrogate of chlorohydric acid secretion) and high levels of G17 (due to negative feedback with acid) (23).

By using OLGA severity score, as expected, patients affected by OLGA 3 and 4 showed lowest levels of PGI and highest values of G17, in comparison with low severity scores (OLGA1 and 2).

The main result of the study is represented by a feature of a statistically increase of PGI levels in patients treated with L-cysteine, while the values of untreated CAG patients in control group remain unchanged, lasting the entire follow-up period. More important seems to be the critical decrease of G17 levels in treated patients from 30.31 pg/L at baseline to 19.23 at 12th month: in particular, in OLGA 3 and 4 groups, the decrease was from 39.7 pg/L at baseline to 21.8 at the end of follow-up. Interestingly, the major modification of both markers, PGI and G17, was observed after 3 months from the intake of L-cysteine.

**Figure 3.** PGI values according with OLGA grading

**Figure 4.** G17 values according with OLGA grading
and remain stable, lasting the other 9 months of follow-up, suggesting possibly a hypertrophy of gastric glands, stimulated by the compound, more than an increase “de novo” of the number of glands (hyperplasia).

As we know, achlorhydria plays a critical role in carcinogenetic mechanisms in gastric mucosa, being acetaldehyde the most important factor involved in such transformation from CAG to adenocarcinoma (44,45, 46). In this view the recovery of gastric secretion represented by an increase of PGI levels could be of importance in limiting acetaldehyde production into the stomach after food ingestion, and in particular alcohol beverages (52, 53).

Similarly, the decrease in G17 levels lasting one year follow-up period after daily administration of 300 mg of L-cysteine, is important, considering the role of the hormone as a growth factor involved in pre-neoplastic conditions and in NEN (10).

In literature is generally accepted that CAG represents an irreversible stage of change for gastric mucosa, but recently some authors hypothesized a possible recovery of CAG picture (10), being the debate at the present open. The increase in PGI levels coupled with the decrease in G17 values seems support the possibility of a recovery of CAG at least as regards gastric function.

To prove this assumption, we need the support of histology, before and last the treatment, which is lacking in the present study, being, probably one year of follow-up, a too short interval to observe modifications in gastric morphology. The main purpose to administered L-cysteine in CAG patient was based on the ability of the compound in binding in a covalent way acetaldehyde in achlorhydric stomach, proved in both experimental and clinical studies (56,57,59). The modifications of acetaldehyde levels in gastric juice, was not investigated in the present study, but the feature of a recovery of gastric function in subjects treated with L-cysteine was totally unexpected, and to our knowledge, never documented, until now, in a full paper.

Strength points: all patients entered the study were consecutively enrolled and histologically diagnosed to confirm CAG, according to OLGA severity score, following a standardize biopsy sampling. The control group (untreated patients) was recruited in same geographical area and diagnosed by same endoscopic and pathological team and was comparable as regards epidemiological factors.

The values of surrogate markers for gastric function (PGI and G17) were coherent at baseline with a picture of CAG, as well as the severity of OLGA scores and remain unchanged – as expected – in control group lasting all the follow-up period.

Weakness points: for sure the lack of histology to support the hypothesis of gastric function recovery following L-cysteine administration, represents the major weakness of the study and needs to confirm in next studies, hopefully based on a longest follow-up period (at least two years).

Additionally, we don't provide, in this study, any data on modifications in acetaldehyde values in gastric mucosa in both groups.

Conclusion

CAG is a precancerous condition in which – at present – the only suggestion is to propose a correct follow-up according to severity of picture. This study aimed to provide an indication of therapy for such patients by using L-cysteine - daily administered – based on the properties of this compound to bind in an irreversible way acetaldehyde in achlorhydric stomach and seems suggest a possible recovery in gastric function lasting therapy by using validated serologic markers.

Next studies are necessary to confirm these results by performing histology of gastric mucosa.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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