Biohit Strategy for the Primary Prevention of Gastric Cancer: GastroPanel® for Detection of Acid-Free Stomach and Its Protection by Acetium® Capsules

Summary

Atrophic gastritis (AG) has a dual etiology: 1) *Helicobacter pylori* (Hp) infection, or 2) autoimmune mechanism (autoimmune type of AG; AAG). Hp-infection and AG/AAG are the two most important risk factors of gastric cancer (GC). Severe AG/AAG results in **acid-free stomach** colonized by Hp and other bacteria, producing **acetaldehyde** (Group I human carcinogen; IARC). Together with other conditions leading to a) acid-free stomach, e.g., chronic users of proton pump inhibitors (PPI), or b) increased exposure to acetaldehyde, e.g., cigarette smokers, alcohol intake, and ALDH2 enzyme mutations, AG/AAG-patients are at high-risk for GC. Both Hp, AG/AAG, and acid-free stomach can be diagnosed by non-invasive serological biomarker test (GastroPanel®, Biohit Oyj, Finland). GastroPanel® test also detects **high-acid output** predisposing to GERD (gastro-esophageal reflux disease) that bears an increased risk for Barrett's esophagus and esophageal cancer (ESC).

There is **no vaccine** against *Helicobacter pylori*, and **no specific therapy** for AG/AAG. Acetium® Capsule is a novel and **safe** (side effect-free) **anti-carcinogenic** formulation, designed for stomach protection by **eliminating acetaldehyde in** acid-free stomach**.** With the combined use of GastroPanel® test and Acetium® Capsule, one can reach an early diagnosis of these high-risk conditions and protect the stomach against acetaldehyde exposure. This **Biohit strategy** could offer, for the first time, a real opportunity for **the primary prevention** not only of the substantial (>1 million annual new cases) global cancer burden due to GC, but also of the **significant global comorbidity** associated with AG/AAG and acid-free stomach. Confirmatory evidence can only be obtained by extensive implementation of this **screen-and-prevent** strategy: 1) risk group detection by GastroPanel® and 2) stomach protection by Acetium® Capsule.

Background

The pathogenesis of gastric cancer (GC) is well established. Most GCs develop through Correa Cascade, initiated by *Helicobacter pylori (Hp*) infection and progressing through different stages of atrophic gastritis (AG/AAG) and intestinal metaplasia (IM) to invasive GC (1-16). In this process, AG/AAG has a key role, leading to acid-free stomach. This is turn is colonized by Hp (and other bacteria) that produce acetaldehyde, classified as Group I human carcinogen by IARC (17-20). Together with other conditions leading to a) acid-free stomach (e.g. chronic users of PPI medication) or b) conditions predisposing the subjects to increased exposure to acetaldehyde (e.g. cigarette smokers, alcohol intake, ALDH2 enzyme mutations), the AG/AAG-patients are at high-risk for GC (2-20), well over 1 million new cases being diagnosed each year (1).

A huge global morbidity is preventable by the Biohit strategy

Globally, 1) the **patients at risk for AG**, and 2) those subjected to **increased exposure to acetaldehyde** constitute an enormous disease burden. Apart from being at increased risk for GC, these patients are likely to develop multiple serious comorbidities (2-20).

Patients at risk for AG

Included in this category, are i) **elderly people**, ii) those with **autoimmune disease**, as well as iii) **patients infected with *Hp*** (17-20).

The age-specific prevalence of AG increases with age, approaching 10% among people over 70 years (21,74). According to conservative estimates, there are over **500 million** people suffering from AG (mostly asymptomatic) worldwide (1,18,20). In patients with autoimmune thyroid disease (AITD) or type I diabetes mellitus (DM1), the prevalence of AG or autoimmune AG (AAG) is increased up to 3- to 5-fold (22-29). Given that the *Hp*-prevalence exceeds 80% in countries with the largest populations (30), the best estimates suggest that 50% of the word population (i.e., > **3.5 billion**) are carriers of *Hp*-infection (31-33). Although *Hp* itself is not directly carcinogenic, AG is the single most potent risk factor of GC (30-33). In 5-10% (up to 350 million)

of *Hp*-infected patients, AG is moderate or severe, and the risk of GC increases in parallel with the severity of AG, up to 90-fold in patients with severe AG both in the corpus and antrum (31-34).

In addition to increasing the risk of GC, AG is associated with a wide variety of clinical sequels, many of which causing **significant comorbidity** particularly among elderly people (35,36,74). In acid-free stomach, absorption of vitamin-B12, iron, calcium, zinc and some drugs is impaired (35,36). **Iron deficiency anemia** and **osteoporosis** are the clinically most relevant consequences of iron and calcium malabsorption, respectively (35), present in 20–40% of patients with AG/AAG (21), whereas pernicious anemia (PA) due to **vitamin-B12 deficiency** can be diagnosed in up to 15–25% of these patients (37). Early detection of vitamin-B12 deficiency is the prerequisite for effective prevention of its potentially **serious neurological complications**, including Alzheimer's disease, peripheral neuropathy, depression and dementia (35,36,38,39).

People subjected to increased exposure to acetaldehyde
In this category, the most important risk groups include i) cigarette smokers ii) alcohol drinkers, iii) carriers of ALDH2 mutation, and iv) chronic users of PPI medication (17-20).

According to conservative estimates, there are **1.1 billion** regular smokers worldwide (40-47). Acetaldehyde is the major carcinogenic substance in cigarette smoke, predisposing cigarette smokers to acetaldehyde exposure in oral cavity and in upper gastrointestinal tract (17-20,48,49). The same applies to alcohol intake, because acetaldehyde is the first metabolite of alcohol, and also produced in the stomach from ethanol by local microbial oxidation (17-20,50).

Another well-known condition that increases the risk of acetaldehyde exposure is a **point mutation in ALDH2-gene**, resulting in deficient activity of the acetaldehyde metabolizing enzyme (ALDH2) (51,52). Carriers of this ALDH2 mutation comprise some **500 million** people, mostly residing in Asia. When drinking alcohol, the upper digestive tract mucosa of ALDH2-deficients is exposed via saliva to about 2-times and via gastric juice, up to 5–6 times higher acetaldehyde concentrations than in persons with active ALDH2-enzyme (51,52). Due to this increased local acetaldehyde exposure, the risk of ALDH2-deficient alcohol drinkers for oral, pharyngeal, ESC and GC is many-fold compared to alcohol drinking ALDH2-actives (17-20,50-52).

Another risk group are the **chronic users of PPI-medication**. The global number of PPI-users is most likely far above **700 million** people, and constantly increasing. According to two recent meta-analyses, chronic use of PPI-medication is associated with an increased risk of GC (53,54). A denominator in common with AG and PPI-use is acetaldehyde, endogenously formed from ethanol (17-20,50-52). Interestingly, the highest gastric juice acetaldehyde concentrations have been measured in ALDH2-deficient PPI-users (55).

GastroPanel® test reveals all the risks associated with AG and acid-free stomach
As a response to an unmet need of a non-invasive, inexpensive test (56-58), Finnish biotechnology company Biohit Oyj developed a simple blood test based on a panel of serum pepsinogen I (PGI) and II (PGII), gastrin-17 (G-17) and Hp IgG antibodies (IgG-Hp) using ELISA technique (GastroPanel® test), proposed as the first-line diagnostic test for dyspeptic symptoms and for screening of the risk conditions of GC (59,60).

The interpretation of GastroPanel® test is made by GastroSoft® application that distinguishes eight biomarker profiles that define specific structural abnormalities and functional disturbances of the stomach (61-64). These distinct profiles include: 1) normal profile; 2) high acid output; 3) low acid output; 4) superficial *Hp*-associated gastritis, with three options (active *Hp*-infection; successful *Hp*-eradication; failed *Hp*-eradication); 5) atrophic gastritis of the corpus (AGC); 6) atrophic gastritis of the antrum (AGA); 7) atrophic gastritis of the antrum and corpus (AGpan); and 8) the effect of PPI medication (61-66). Taken together, GastroPanel® test diagnosis the grade and topography of AG, and in addition, discloses the status of gastric acid output. Noteworthy, it is not only the acid-free stomach that is a risk condition (for GC), but **also high**

acid output bears an increased risk for ESC, by predisposing to **GERD** (gastro-esophageal reflux disease), erosive esophagitis and Barrett's esophagus (7,15,16,64).

In GastroPanel®, the *Hp* IgG ELISA is complemented by the other three biomarkers which are sensitive indicators of mucosal inflammation (66). This 4-marker panel makes GastroPanel® **the most comprehensive *Hp*-test**, devoid of the known shortcomings (false negative and false positive results) of the conventional *Hp*-tests (UBT, SAT) (66-70).

GastroPanel® is an ideal non-invasive test for diagnosing i) the patients at increased risk for GC, irrespective whether due to *Hp*-induced AG or AAG, as well as for monitoring ii) all those with acid-free stomach exposed to carcinogenic acetaldehyde due to any reasons (smokers, alcohol intake, ALDH2 mutation, chronic PPI users) (64,65,71-75).

Acetium® Capsule – an anti-carcinogenic formulation for protection of acid-free stomach
The **carcinogenic agent** in common to all the risk conditions discussed above is **acetaldehyde**, classified as Group I human carcinogen by IARC in 2009 (17). Apart from *Helicobacter* itself, which is capable of synthesizing acetaldehyde, **other bacteria** colonizing in **acid-free stomach**, are an abundant source of this carcinogenic substance (18-20). **It is the acid-free stomach (due to any cause listed above) that predisposes these subjects to increased acetaldehyde exposure with increased risk of GC** (18-20,50-52).

According to **the Biohit strategy**, all these special groups of patients should be 1) closely monitored by GastroPanel® to **disclose the patients at risk,** to be examined by endoscopy; and 2) all those with acid-free stomach (irrespective its cause) should be administered Acetium® capsules for life-long protection of their stomach mucosa (50-52,66-72).

Acetium® capsules are highly effective in eliminating acetaldehyde in acid-free stomach
The well-known reaction whereby L-cysteine (a semi-essential amino acid) eliminates the toxicity of acetaldehyde by covalent binding to form a stable 2-methylthiazolidine-4-carboxylic acid (MTCA)(76), was exploited by Biohit Oyj in its innovation of **Acetium® Capsule** (77). The novelty of this formulation of slow-release L-cysteine is based on the local elimination of carcinogenic acetaldehyde in the stomach (18-20,50-52,77). The efficacy of this Acetium® formulation has been conclusively demonstrated in three clinical trials in Finland (78), Sweden (79), and Japan (55).

Elimination of acetaldehyde in subjects with acid-free stomach
In a placebo-controlled, double-blind study, Acetium® Capsules effectively eliminated ethanol-derived acetaldehyde in the gastric juice of patients with AG (78). For several hours, the mean acetaldehyde level in gastric juice remained 2.6-times higher with placebo than with L-cysteine ($p=0.005$) (78). These data confirm that Acetium® Capsules effectively decrease acetaldehyde in an acid-free stomach during alcohol exposure.

Elimination of acetaldehyde in patients with AG
In the second study, slow-release L-cysteine decreased gastric juice acetaldehyde by a max. 87% at 60 min and the decline persisted for up to two hours (79). These results implicate that i) an exposure of gastric mucosa to acetaldehyde is decreased by a mean of 68% ($p<0.0001$) with Acetium® Capsules and this effect continues for at least two hours; ii) MTCA remains stable in the gastric juice for up to three hours (79).

Acetaldehyde elimination, ALDH2 mutation and PPI-treatment
The third clinical trial confirmed that Acetium® Capsule (2 x 100 mg) reduced the gastric juice acetaldehyde levels significantly (67%, 3-fold) also in PPI-treated individuals with either active or deficient ALDH2 enzyme (55). This study in Japan, confirmed that the acetaldehyde-eliminating effect of Acetium® Capsules persisted for 2 hours after intake (55).

The combined use of GastroPanel® and Acetium® Capsules- a unique opportunity for the primary prevention of a major global cancer burden

Some cancers are known to be preventable. In most cases, one can achieve only secondary prevention by using population-based screening programs to detect cancer precursor lesions that can be effectively treated. However, primary prevention, i.e., prevention of cancer development by any type of intervention, is rarely possible for any type of human cancer (1,8,43). That would necessitate an early detection of the risk factors and their effective elimination before the carcinogenic process has progressed even to the stage of cancer precursor lesions.

Theoretically, the combined use of 1) **GastroPanel® test** for i) targeted screening for early detection of the risk conditions of GC, and 2) **Acetium® Capsules** administered for elimination of acetaldehyde on daily basis for life-long, might offer, for the first time, such an opportunity for the primary prevention of GC. As an extra bonus, this strategy should help alleviating the substantial comorbidity associated with AG and acid-free stomach, affecting half of the world population. In addition, a systematic screening by GastroPanel® would result in substantial **savings in health care costs**. As an example, modelled for Finland, (a country with 5.5 million people), a systematic GastroPanel® screening of 10 age-groups (50–60-year-old) would result in savings of over 800 million euro in the life-time costs otherwise spent in the management of these subjects according to the current practices (80).

At present, this evidence is circumstantial, i.e., based on acceptance of the simple concept that elimination of the key carcinogenic substance prevents the future cancer of it. How well this hypothesis holds true in real life remains to be seen and depends entirely on the extent of the clinical implementation of this suggested strategy: a combined use of risk group screening (by GastroPanel®) and protection of the high-risk stomach by the anti-carcinogenic formulation (Acetium® Capsule) (81).

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