Gastric Atrophy Reversible or Irreversible after *Helicobacter pylori* Eradication – An Open Question

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Gastric atrophy (GA) and intestinal metaplasia (IM) may eventually develop in the course of chronic gastritis. Whether GA and IM are preneoplastic lesions as defined by some [1, 2] or rather a preneoplastic condition suggested by others [3] is more of a semantic nature. Both, GA and IM are undisputed indicators of a further increased risk for gastric cancer as compared with chronic gastritis in the absence of these abnormalities. GA and IM have been described to represent an obligatory transitional step in the cascade of chronic gastritis progressing to intestinal type gastric cancer [4]. With the discovery of *Helicobacter pylori*, this infection has become the established starting point of chronic gastritis and the pathways involved in gastric carcinogenesis have become better focused since. GA and IM have maintained their allocation as essential intermediate steps in intestinal-type gastric cancer development and are therefore important alterations of the gastric mucosa usually defined in the context of risk gastritis.

Chronic active gastritis induced by *H. pylori* is completely reversible and the gastric mucosa can be restored to normal by successful *H. pylori* eradication unless GA or IM have become apparent [5–7]. The question whether also GA and IM are reversible following *H. pylori* eradication has been a controversial issue ever since and many conflicting results have been reported in the literature [8, 9]. Reasons for this in addition to methodological aspects have been the inclusion of heterogeneous populations of

patients on and off drugs, inconsistent eradication therapies, numbers of biopsies and different biopsy sampling sites.

In the meta-analysis presented in this issue of *Digestion* by Wang et al. [10], the application of strict criteria has allowed to include 12 studies considered relevant and methodologically adequate extrapolated from over 2,000 citations dealing with this contentious issue. Important thereby is the exclusion of patients with intake of drugs other than for *H. pylori* eradication such as NSAIDs.

The total number of patients considered in the meta-analysis is 2,658 and the key finding is that *H. pylori* eradication leads to a significant improvement of GA in the gastric corpus while it has no effect on antral atrophy or on IM at any location. At first glance the finding on the reversibility of GA in the gastric corpus appears the most relevant observation as it indicates a chance for *H. pylori* eradication to interrupt the potential evolution to gastric cancer even in an advanced stage of chronic gastritis. Theories related to GA and associated hypochlorhydria as well as to GA offering the homing to stem cells that give rise to malignant clones in the atrophic gastric mucosa are better substantiated in gastric carcinogenesis than a specific role of IM [11–13].

In the meta-analysis, however, the degree of GA is not mentioned and this is crucial as only extensive GA impacts on gastric function (i.e. hypochlorhydria). IM is considered to be a bystander and an indicator of the sur-

rounding milieu with increased gastric cancer risk, and does not change after *H. pylori* eradication according to this meta-analysis. Although not directly involved in gastric carcinogenesis IM would be a better marker to indicate the reversibility or persistence of the preneoplastic condition since IM is a well-defined cell type while GA is subject to considerable interobserver variation among pathologists. On the other side, it cannot be ignored that IM may often be missed from the 'Sydney' biopsy sites and therefore many more biopsies are required for making IM a reliable marker [14].

The reversibility of GA at least in some of the studies is the best available evidence in supporting the concept that *H. pylori* eradication is worth even in advanced severe gastritis. The meta-analysis does not answer the question whether other factors have a possible impact on GA reversibility following *H. pylori* eradication. The more meaningful clinical aspect is not the reversibility but the arrest of progression of mucosal preneoplastic changes following *H. pylori* eradication. Several studies have indeed demonstrated a halt in the progression of gastric atrophic changes over a variable period of time [15–17] and this in fact holds true also for IM over a 5-year period [18]. Others have shown that some of the patients with preneoplastic changes (GA + IM) progressed to gastric cancer in spite of successful *H. pylori* eradication [2, 18].

The current definition of the point of no return beyond which eradication cannot prevent progression is not set, as even in a subset of patients with gastric cancers in early stage, *H. pylori* eradication conferred protection from metachronous gastric cancer [19].

The degree and extent of atrophy which still might be reversible or can at least be arrested in its further progression, although critical, has not been addressed in the meta-analysis. GA has been described by conventional histology only from randomly taken biopsies and in spite of the consistent grading according to the Sydney system the data obtained are not suitable to indicate the extent of

atrophy. Here the inclusion of a functional parameter such as pepsinogen 1 that reflects the status of the oxyntic mucosa will add important value to future studies. The meta-analysis proves shortcomings in our knowledge on this important issue, which is intimately related to the prevention of gastric cancer in advanced chronic gastritis by *H. pylori* eradication. Of the 12 articles included only 6 reported an atrophy assessment in the gastric corpus before and after *H. pylori* eradication and only 3 showed an improvement of GA in the corpus mucosa. Reversibility of the antrum atrophy was reported in only 3 of the 12 articles and was not significant. To note, this is contradictory when compared to a previous meta-analysis [15] and this is based on just one additional individual study which had not been available in the previous analysis.

The conclusion from the meta-analysis is that IM persists and so does GA in the antrum, but there is a significant improvement of GA in the corpus. As the main message, the meta-analysis lends support to the fact that *H. pylori* eradication is beneficial also in GA in the corpus and supports guidelines to eradicate *H. pylori* in this condition [20–22]. As we do not know who on an individual basis will benefit from regression of GA or at least will have no further progression in clinical practice, the individual patient with GA even after *H. pylori* eradication needs to be controlled in regular follow-ups. The recent Dutch trial alerts to this strategy with data of a 1.7% annual incidence of gastric cancer originating from atrophic gastritis [23]. This may be even higher in some regions of the world.

I cannot subscribe to the conclusion made by the authors who, based on their findings, recommend *H. pylori* eradication for those with GA in corpus. I would rather state that even in the presence of GA *H. pylori* eradication is still of value, but stress the point that *H. pylori* eradication should whenever possible be performed before the development of GA and IM.

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