

REVIEW

Is *Helicobacter pylori* the primary cause of duodenal ulceration?

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Abstract *Helicobacter pylori* infection may not be the primary cause of duodenal ulceration in cases not associated with non-steroidal anti-inflammatory drugs, but may be a secondary complication. In developing countries with a uniformly high prevalence of *H. pylori* infection there are marked regional differences in the prevalence of duodenal ulcer (DU). In some countries, especially those with a low prevalence of *H. pylori*, 30–40% or more patients with DU may be *H. pylori* negative. The absence of *H. pylori* infection in early cases of DU is also reported. In DU patients with antral *H. pylori* infection, duodenal colonization by *H. pylori* may often be absent. After complete *H. pylori* eradication, recurrence of DU within 6 months in some reports is as high as 20%. The evidence suggests that high acidity and reduced duodenal mucosal resistance remain the primary causes of DU and that *H. pylori* infection, when present, results in chronicity. Reduced mucosal resistance results in duodenal gastric metaplasia which permits colonization of the duodenum with *H. pylori* from the antrum. Therefore, whatever causes reduced mucosal resistance may be the primary factor and evidence suggests that this cause may be diet related. This would explain the enigma of regional variations in DU prevalence unrelated to *H. pylori* prevalence.

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Key words: aetiology, diet, duodenal ulcer, *Helicobacter pylori*, prevalence.

INTRODUCTION

While the role of *Helicobacter pylori* eradication in the healing of duodenal ulcer and its effect on reduced recurrence rate is well supported, there is accumulating evidence that *Helicobacter pylori* infection may be only a secondary factor and not the primary cause of duodenal ulceration. This concept is supported by the following observations:

GEOGRAPHICAL DISTRIBUTION IN DEVELOPING COUNTRIES

Despite the high, universal prevalence of *H. pylori* infection in developing countries there are reports of marked regional or ethnic differences in duodenal ulcer prevalence. The prevalence of duodenal ulcer is higher in the moister, southern areas of India, China and the West Coast of Africa, and lower in the drier northern areas.^{1–5} Duodenal ulcer is twice as common in the Indian pop-

ulation of Fiji than in Fijians although the prevalence of *H. pylori* infection is similar.^{6,7}

These differences in the prevalence of duodenal ulcer are not explained by the corresponding differences in the prevalence of the more toxic CagA and VacA *H. pylori* strains.

PREVALENCE OF *HELICOBACTER PYLORI*-NEGATIVE DUODENAL ULCERATION

If patients on non-steroidal anti-inflammatory drugs are excluded, there are now 15 reports of a 30–75% prevalence of *H. pylori*-negative duodenal ulcer patients^{8–24} (Table 1). The prevalence appears to be higher in areas where the overall prevalence of *H. pylori* infection is relatively low.²⁵ Jyotheeswaran *et al.*, from Greater Rochester, New York, reported a 48% prevalence of *H. pylori*-negative duodenal ulcers in white patients and 15% in non-white patients, with an overall negative

Table 1 Endoscopy reports of *Helicobacter pylori*-negative duodenal ulcer (DU)

| Author | Place | Year | % <i>H. pylori</i> -negative DU |
|---|-------------------------------|------|---------------------------------|
| Oshowo ⁸ | UK, London | 1999 | 30 |
| Jones ⁹ | UK, Manchester | 1986 | 41 |
| Maher ¹⁰ | USA, Rochester | 1987 | 43 |
| Jyotheeswaran <i>et al.</i> ¹¹ | USA, Rochester | 1998 | 39 |
| Greenberg <i>et al.</i> ¹² | USA, Harvard | 1997 | 40 |
| Gislason <i>et al.</i> ¹³ | USA, Baltimore | 1997 | 30 |
| Fenger <i>et al.</i> ¹⁴ | Greenland (Inuit) | 1997 | 50 |
| Mirghani <i>et al.</i> ¹⁵ | Sudan, Khartoum | 1994 | 38 |
| Kontou and Katelaris ¹⁶ | Australia, Sydney | 1997 | 32.5 |
| Uyub <i>et al.</i> ¹⁷ | Malaysia, N. Peninsular | 1994 | |
| | Malayans | | 72 |
| | Non Malayans | | 14 |
| Petersen <i>et al.</i> ¹⁸ | USA, N. Carolina | 1996 | 26 |
| Lanza <i>et al.</i> ¹⁹ | USA, Houston | 1996 | 30 |
| Bruno <i>et al.</i> ²⁰ | USA, military hospital | 1997 | 75 |
| Sprung and Apter ²¹ | USA, Florida | | |
| | Retrospective | 1998 | 68 |
| | Prospective | 1998 | 69 |
| Dres Pest <i>et al.</i> ²³ | Argentina | 1996 | 33 |
| | Early DU | | 59 |
| | Chronic DU | | 22 |
| Parsonnet ²⁴ | All countries (meta-analysis) | 1998 | 40 |
| Sprung and Gano ²² | USA, Florida (retrospective) | | 52 |

prevalence of 39%.¹¹ Parsonnet conducted a meta-analysis of available reports which gave the overall prevalence of *H. pylori*-negative duodenal ulcers as 40%.²⁴ These reports suggest that *H. pylori* infection is not a necessary prerequisite of duodenal ulceration.

EARLY CASES OF DUODENAL ULCERATION MAY BE *HELICOBACTER PYLORI* NEGATIVE

Dres Pest *et al.* reported that only 41% of patients with the first attack of duodenal ulceration were *H. pylori* positive compared with 78% of chronic patients.²³ This suggests that initially some early duodenal ulcer patients may be free from *H. pylori* infection and acquire it later.

LOW PREVALENCE OF *HELICOBACTER PYLORI* COLONIZATION OF THE DUODENUM IN DUODENAL ULCER PATIENTS

A widely held concept is that colonization of areas of duodenal gastric metaplasia in the duodenum by *H. pylori* is the cause of mucosal damage and ulceration. There are five reports, however, of low prevalence of duodenal colonization by *H. pylori* in duodenal ulcer patients with positive antral infection (31, 32, 34, 48

and 67.5%).^{23,26-29} Dres Pest *et al.* reported no colonization at all in patients with their first attack.²³ Thus, *H. pylori* colonization of the duodenum may not be a necessary factor in the development of duodenal ulceration.

DUODENAL ULCER RECURRENCE AFTER *HELICOBACTER PYLORI* ERADICATION

There are several reports giving a duodenal ulcer recurrence rate in patients not on non-steroidal anti-inflammatory drugs, of 6–10%, 6–24 months after complete *H. pylori* eradication.^{18,19,30} Recently, however, Laine *et al.* from North America, reported a 20% recurrence rate at 6 months after eradication in a meta-analysis of seven reported trials that strictly fulfilled rigid criteria.³¹ This suggests that factors other than *H. pylori* infection are involved in the genesis of duodenal ulceration, particularly in areas such as North America where the overall prevalence of *H. pylori* infection is not high.

DISCUSSION

These findings suggest that *H. pylori* infection may not be a primary cause of duodenal ulceration, that ulceration does occur independently of such infection and even that the infection may be acquired subsequently resulting in chronicity of the ulceration. This supports

a return to the concept that the initial cause of duodenal ulceration is a combination of an increased output of acid together with an inability of the duodenal mucosa to cope with the presenting acid load. The response to this inability is the development of duodenal gastric metaplasia. These factors alone may lead to breakdown of the mucosa and duodenal ulceration.³²⁻³⁷ If there is *H. pylori* infection of the antrum, colonization of the duodenum may contribute to this breakdown and ulceration, but such colonization can only occur if there is pre-existing metaplasia. In some cases, *H. pylori* infection of the antrum may be acquired after the initial duodenal ulceration has occurred. As with infected wounds elsewhere, the infection can contribute to the chronicity of the ulcer and its resistance to healing.

Thus, *H. pylori* infection may be only a secondary factor in duodenal ulceration and the other factors of high acid output and reduced duodenal mucosal resistance resulting in gastric metaplasia remain the primary cause. There is evidence suggesting that the reduced mucosal resistance may be related to the absence of protective lipids in the staple diet.³⁸⁻⁴⁵ This would explain the regional differences in the prevalence of duodenal ulcer in developing countries where the overall prevalence of *H. pylori* is high.

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