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Duodenal ulcer treated with *Helicobacter pylori* eradication: seven-year follow-up

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Summary

The long-term benefits of *Helicobacter pylori*-eradication treatment (HET) in *H pylori*-associated duodenal ulcer are unclear. We followed up patients with duodenal ulcers from a trial of *H pylori* eradication in 1985–86.

63 of 78 patients (81%) were reviewed clinically and had upper gastrointestinal endoscopy with gastric antral biopsy. Of 35 patients previously rendered *H pylori* negative, 32 (92%) remained *H pylori* negative after 7·1 years (mean). All patients initially *H pylori* positive remained infected, unless HET was given in the interim. Duodenal ulceration was found in 20% (5 out of 25) of patients remaining *H pylori*-positive, compared with 3% (1 of 38) of *H pylori*-negative patients ($p < 0.05$).

The reduction of duodenal ulcer relapse obtained from *H pylori* eradicaton in *H pylori*-associated duodenal ulcer extends to at least 7 years after treatment, and is likely to be due to freedom from *H pylori* infection. However, duodenal ulcer may recur in patients rendered *H pylori* negative, due to factors other than reinfection with *H pylori*.

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Introduction

The association between gastric *Helicobacter pylori* colonisation and duodenal ulcer (DU) is well established,[1] and many studies have shown that eradication of *H pylori* reduces DU recurrence.[2,3] Most of these studies have followed patients for 2 years or less, and little is known of the outcome over longer periods. Borody's group found that 97% of patients rendered *H pylori* negative remained negative by C^{14}-urea breath test after 4 years of follow up;[4] earlier work suggested that patients remaining *H pylori* negative were free from DU relapse for up to 4 years, though small numbers were involved.[5] Although eradication of *H pylori* is clearly important in the short term, *H pylori*-eradication treatment (HET) would be more valuable if its effect was shown to extend over longer periods. We determined the long-term outcome of HET in a cohort of patients who took part in the earliest controlled trial of HET in duodenal ulcer,[6] after which some were *H pylori* positive and others negative.

Patients and methods

100 patients were enrolled in a prospective double-blind trial of HET in 1985 and 1986, in which endoscopic appearances and *H pylori* status were recorded over 12 months.[6] At the end of the trial, patients returned to the care of their general practitioner. These patients were traced through hospital records, their general practitioner, or by telephone. Patients who were contactable were approached to undergo clinical examination and upper-gastrointestinal endoscopy with antral biopsy.

Medical attendances for DU-related symptoms and results of relevant investigations were recorded and corroborated from case

Initial *H p* status	Current *H p* status	
	Positive	Negative
Positive (n=28)	23	5*
Negative (n=35)	2	33†

*All 5 received *H pylori* eradication therapy.
†One patient had documented *H pylori* reinfection at 5 years, received *H pylori* eradication therapy, and is now *H p* negative.

Table 1: **Current *H pylori* (*H p*) status compared with *H p* status at the end of the initial study**

records. Upper gastrointestinal endoscopy was done by a gastroenterologist blinded to details of the patient's past medical history and 3 gastric antral biopsies were taken.

Relapse of DU was defined as current—active DU at follow-up endoscopy; proven—relapse proven by endoscopy or barium meal in the period between studies; and clinical—relapse during the intervening period as judged by the patient's history (symptoms identical to previous DU symptoms and which were considered consistent with DU disease), whether confirmed by investigation or not, and excluding asymptomatic relapses detected at follow-up endoscopy.

Formalin-fixed paraffin-embedded sections of gastric antral biopsies were examined for the presence of inflammation and *H pylori* with haematoxylin and eosin, and Giemsa stains. Sections were examined by an experienced histopathologist blinded to the patient's details. The *H pylori* status of the patient was defined histologically as $Hp+$ or $Hp-$. The study was approved by the Ethics Committee of Royal Perth Hospital.

Results

Of 100 patients in the original study,[6] 78 were available for follow-up and 63 (81%) agreed to clinical review and endoscopy 5·1–7·6 years (mean 6·5) later. There were 44 males and 19 females (mean age of 53, range 24–83). Of the remaining 22 from the original study, 14 were uncontactable, 4 had died, and 3 were unfit for endoscopy. 1 patient had undergone total gastrectomy for Zollinger Ellison syndrome.

Initial *H pylori* status of the 63 patients is compared with current *H pylori* status in table 1. Patients who were initially $Hp-$ include a group of patients who completed the initial study by Marshall et al[6] and a group who failed treatment, were withdrawn from the study and after subsequent HET were shown to be $Hp-$ during the following 12 months. 32 of 35 patients (92%) initially $Hp-$ remained $Hp-$ up to 7·1 years (mean) (range 6·1–7·9) follow-up after eradication of *H pylori*. 1 patient initially $Hp-$ was found to have $Hp+$ chronic antral gastritis without DU after 5 years at a time of clinical relapse; he received HET and was $Hp-$ at follow-up endoscopy 2 years later. 2 other patients initially $Hp-$ became $Hp+$, and both had documented DU relapse, although one was associated with non-steroidal anti-inflammatory drug (NSAID) use. 28 patients were $Hp+$ at the end of the initial trial. 23 of these remain $Hp+$ and 5, all of whom received further HET in the interim, have been rendered $Hp-$.

At follow-up endoscopy (table 2), active DUs were present in 5 of 25 (20%) patients currently $Hp+$ in contrast to 1 of 38 (3%) $Hp-$ patients (χ^2 5·28; $p<0·05$) (current relapse). Proven relapse occurred in 9 of 26 (35%) $Hp+$ patients and 3 of 37 (8%) $Hp-$ patients (χ^2 6·97; $p<0·01$). One patient who was $Hp+$ at the end of the initial study had an endoscopically-proven DU accompanied by gastric antral *H pylori* after 5 years, received HET, and is currently $Hp-$. He is included in the $Hp+$ group for analysis of proven and clinical relapse, despite being currently $Hp-$. Of patients with proven relapse, 9 had DUs documented endoscopically and 3 by barium meal. Clinical relapse occurred in 11 of 26 (42%) $Hp+$ patients compared with 8 of 37 (22%) patients who were $Hp-$ at follow up (χ^2 3·1; $p<0·10$).

H pylori status	Current DU relapse	Proven DU relapse	Clinical DU relapse
Hp+	5 (n=25)	9 (n=26)	11 (n=26)
Hp−	1 (n=38)	3 (n=37)	8 (n=37)
p	<0 05	<0 01	<0 1

DU=duodenal ulcer. For definitions of relapses see text.
One patient currently *H p−* had proven DU relapse accompanied by persistence of *H pylori* 4 8 years after the initial study; hence he was *H p+* in the proven and clinical groups for statistical analysis. "n" = number with specified *H pylori* status.

Table 2: **Incidence of duodenal ulcer relapse compared with *H pylori* status at time of relapse**

3 patients received maintenance H2-receptor antagonists during the intervening years (2 currently $Hp+$ and the $Hp-$ patient who had an active DU at follow-up endoscopy). 6 patients received further HET when symptoms of DU recurred after completion of the initial study. Only 2 of these 6 patients had DU confirmed by endoscopy or barium meal. Use of NSAIDs accompanied clinical DU relapse in 3 patients (2 currently $Hp+$ and 1 $Hp-$).

Discussion

This is the first long-term study of the natural history of *H pylori* infection and DU after *H pylori* eradication. Others have shown, either in small numbers or in studies without endoscopy, that reinfection is uncommon up to 4 years post-eradication;[4,5] our data confirm this and extend the period of observation further. Given that 3 of 35 previously $Hp-$ patients became reinfected over a total of 248 post-eradication patient years, this gives an annual reinfection rate of 1·2% (95% confidence intervals 0–4·8%), which is slightly higher than previously-reported estimates of up to 0·64%.[4,7,8] The absence of spontaneous loss of *H pylori* over this time is also consistent with other reports.[9] A criticism of our study might be that 37 of the 100 patients treated in the original trial could not be followed up and that this might bias our results; however, 21 of these 37 were $Hp-$ at the end of the initial study, a similar proportion to that in the remaining 63 patients who were followed up.

A major benefit of HET is the reduction in DU recurrence; this has been shown over a 2-year follow up,[2] and in small numbers of patients up to 4 years.[5] The value of HET would be greater still if the risk of DU relapse was reduced indefinitely. This propostion is supported by our study which shows a significantly lower long-term relapse rate in patients rendered $Hp-$ compared with those who remain $Hp+$. Inaccuracies exist in documenting relapse rates in the ways described in our study. In particular, there may be underestimates because of clinically-silent DU disease. Indeed, of the 6 patients found to have an active DU at follow up endoscopy, 2 had no symptoms. The relatively low incidence of proven DU relapse in $Hp+$ patients in our study (35% over 6·5 years) presumably reflects the absence of surveillance endoscopy over that time period. Clinical relapse as defined in our study, although subject to inaccuracies of diagnosis, is of importance when examining the cost effectiveness of HET. Clinical relapse occurring in the intervening period between studies occurred in 42% of $Hp+$ patients compared with 22% of $Hp-$ patients ($p<0·1$). Some of these relapses may have been due to non-ulcer dyspepsia, reflux, or other diseases. When a patient has frequent relapses of DU, traditional practice is to choose between

repeated courses or long-term maintenance with H2-receptor antagonists. Our findings suggest that HET is an alternative which may result in reduced costs and be used increasingly as less complex HET regimens with fewer side effects are developed.

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Ischaemic heart disease and low birth weight: a test of the fetal-origins hypothesis from the Swedish Twin Registry

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Summary

Twins constitute a population with lower than average birth weight for reasons that are not a consequence of social disadvantage.

The hypothesis that ischaemic heart disease (IHD) is linked to low birth weight was tested by analysing whether or not 8174 female and 6612 male Swedish twins had a higher mortality compared to the general Swedish population. The association between adult body height and IHD mortality was also analysed in a nested case-control study among monozygotic and dizygotic twins. Ischaemic heart disease mortality was not higher among twins (women: relative risk [RR] 0·99; 95% confidence limits [CL] 0 89–1·10; men: RR 0·85; CL 0·79–0·92). However, the shorter twin in a twin pair was more likely to die of heart disease than the taller (odds ratio [OR] 1·15, CL 1 03–1·25).

We suggest that postnatal influences may well be as important as prenatal influences in producing any effect on ischaemic heart disease mortality and that the type of growth retardation in utero experienced by twins may not constitute a risk for ischaemic heart disease in adulthood.

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Introduction

It has been suggested that the origins of ischaemic heart disease (IHD) are to be found in a suboptimal intra-uterine environment which leads to growth retardation of the fetus.[2] Twins have a lower than average birth weight, although their development is thought to be similar to that of single pregnancies until the third trimester[2,3] and are on average 900 g lighter than single children at birth.[4] At 38-weeks gestation the average twin weighs less than a tenth-percentile single child, and over 90% of twins fall below median weight for single children.[5] It has been suggested that "a slight reduction in birth weight (of twins) may reflect severe prenatal growth restriction".[6] Campbell and Samphier pointed out that "if twin-birth weights are referred to singleton standards, all individual twins are identified as growth retarded or light for dates".[7] It seems therefore justifiable to look at twins as individuals who during the third trimester experience retarded growth and, compared to single children, a suboptimal intra-uterine environment.

Results from studies of IHD mortality in relation to birth weight in Hertfordshire and Sheffield, UK[8,9] showed the greatest risk in the lowest birth weight category ($\leqslant$2·5 kg). In both studies this risk was estimated to be 27% above that of the average risk for all men included. Twins would on average fall into the lowest birth-weight category, as defined by those two studies. If there is a linear association between birthweight and ischaemic heart disease, as suggested,[10] one would expect IHD mortality among twins to be greater by this degree. Low average birth weight among twins is not a consequence of social disadvantage. The use of twins to study the association between low birth weight and IHD has the advantage of avoiding one of the concerns expressed about studies of single births in which low birth weight is likely to be associated with social disadvantage, thus giving rise to the potential for socio-economic confounding of the relationship between birth weight and adult mortality.[11]