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Randomized, double-blind, placebo-controlled trial to evaluate the effect of *Helicobacter pylori* eradication on glucose homeostasis in type 2 diabetic patients☆

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Abstract *Background and aims:* Literature data suggest an association between *Helicobacter pylori* infection and glucose homeostasis. However, a causative link between them has not been demonstrated yet. The aim of this study is to investigate the effect of *H. pylori* eradication on glucose homeostasis in patients with type 2 diabetes.
Methods and results: A randomized, double-blind, placebo-controlled trial was conducted to investigate the effect of *H. pylori* eradication on glucose homeostasis in 154 patients with type 2 diabetes and who tested positive for *H. pylori* infection (mean age (SD), 63.1 (8.1) years). Subjects were assigned to *H. pylori* eradication treatment or placebo. Metabolic and inflammatory parameters were measured in all subjects at baseline and 4 weeks after the treatment. *H. pylori* eradication led to an improvement in glucose homeostasis, measured by HOMA-IR ($p < 0.001$) and K_{ITT} ($0 = 0.041$), due to the decrease in fasting insulin levels ($p = 0.004$). The results also showed that lower levels of inflammatory parameters were present after eradication.
Conclusion: To our knowledge this is the first randomized, double blind, controlled study where the effect of *H. pylori* eradication on glucose homeostasis in subjects with type 2 diabetes has been investigated. Our findings demonstrate that *H. pylori* eradication improves glucose homeostasis in patients with type 2 diabetes through a decrease in pro-inflammatory factors. Trial registration number: ACTRN12609000255280 (https://www.anzctr.org.au/).

☆ Trial registration no. ACTRN12609000255280 registered 13 may 2009.

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Introduction

It is known that HP is a causative agent of many gastrointestinal conditions, stomach cancer and extragastric manifestations [1–5], such as coronary heart disease [6–9] and inflammation [10–12]. Literature data also suggest an association between *Helicobacter pylori* infection and glucose homeostasis. However, a causative link between them has not yet been demonstrated. Conflicting *in vivo* results have been published on this possible relationship between HP and type 2 diabetes [13,14]. Some publications have shown no correlation between HP infection and glucose homeostasis [15–17], whereas others have reported that HP infection significantly contributes to promoting insulin resistance [18,19]. Furthermore, the seroprevalence risk of HP infection among patients with diabetes is still controversial. Although recent data have demonstrated that HP infection leads to an increased rate of incidence of diabetes in a prospective cohort study of individuals aged over 60 years [20], other studies have verified no prevalence of HP infection in either diabetic or non-diabetic subjects, nor when subjects were chosen with upper gastrointestinal symptoms [21]. Other viruses and bacteria have been related to diabetes. The exposure to infections has been considered a potential cause of increased activity of the innate immune system. Healthy men exposed to common pathogens such as herpes virus type I and II, enteroviruses and Clamidia pneumoniae showed increased fat mass and insulin resistance. Specifically, the higher the serum levels of inflammatory markers, the lower the insulin sensitivity and the greater the exposure to these pathogens [22,23]. Also HP can cause active chronic inflammation by activating neutrophils and monocytes, inducing different mediators regulating the release of leukocytes [3,24] and, consequently, the accumulation of reactive oxygen species (ROS) [25]. Considering that HP has one of the highest frequencies of exposure among bacterial infections in the general population, these findings confirm the importance that HP infection may have in triggering the innate immune system. Epidemiological studies investigating the impact of pathogenic burden on diabetes and, in particular, of HP on diabetes [26] have been limited; thus, our purpose was to evaluate any potential glycemic benefits of HP eradication on patients with type 2 diabetes.

Starting with the findings from these studies, we aimed to evaluate whether the eradication of HP could modify glucose homeostasis in type 2 diabetic subjects.

Methods

Study design

The study design was a randomized double-blind controlled trial (Fig. 1), which was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000255280).

Briefly, the diabetic subjects were defined as HP positive or negative by urea breath test (UBT). The HP positive subjects were randomized in two different groups of treatment. Four weeks after treatment, the presence of HP infection was assessed again in all subjects. Insulin resistance and metabolic parameters were measured in all subjects at baseline and at 4 weeks after the end of treatment.

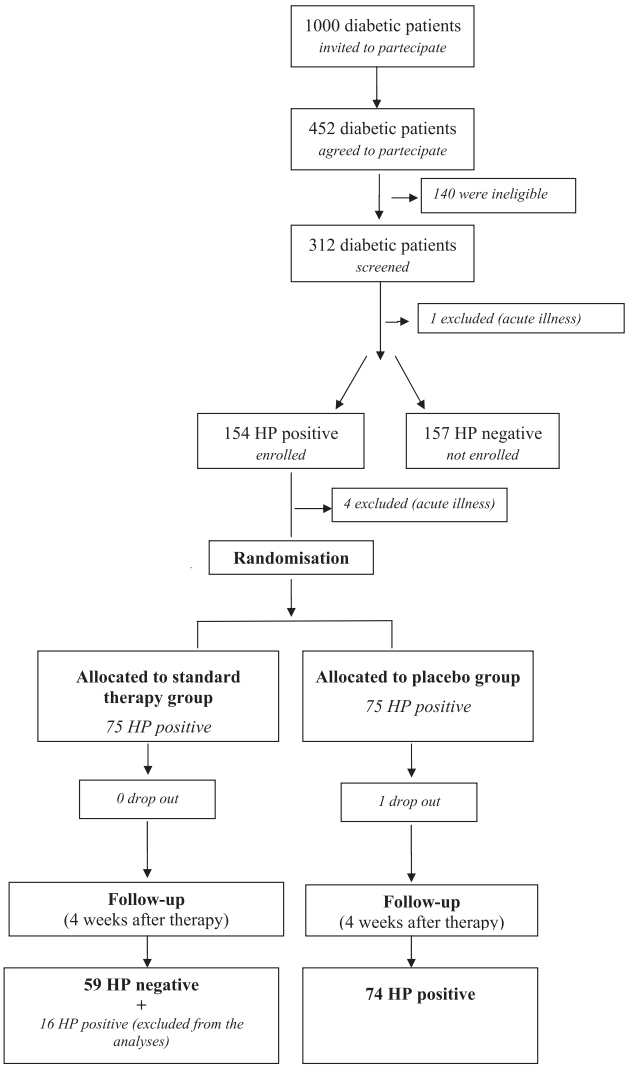

Figure 1 Flow chart of the study.

The study was conducted at the Metabolic Diseases and Diabetology Unit of the National Institute of Health and Science on Aging (INRCA), Ancona, Italy. Diabetic subjects were selected from a larger population of subjects afferent routinely to our outpatient centre for the prevention and care of diabetes. All experimental procedures and written informed consent, obtained from all subjects, were reviewed and approved by the Ethics Committee of our Institute in accordance with the principles expressed in the Declaration of Helsinki.

Patients

A random selection of 1000 men and women with type 2 diabetes and registered at our outpatient diabetes centre