Helicobacter pylori Interference with Micronutrients and Orally Administered Drugs: A New Mechanism Explaining its Role in Extragastric Disorders

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Abstract: There is an increasing evidence that *Helicobacter pylori* may interfere with gastrointestinal metabolism of micronutrients and drugs such as iron, cobalamin, thyroxine and levodopa, with relevant clinical effects.

In this review we examine the strength of the causal association and the plausible pathophysiologic mechanisms underlying these adverse effects.

Key Words: *Helicobacter pylori*, iron, cobalamin, thyroxine, levodopa, malabsorption, gastritis, gastric acidity.

INTRODUCTION

Helicobacter pylori (*H. pylori*) a gram negative microorganism discovered by Warren and Marshall in 1982 [1], is now recognized as the main etiologic agent of gastritis, peptic ulcer disease and gastric cancer in man [2]. It is the only organism able to colonize the hostile acidic environment of the stomach for its ability to produce the enzyme urease, that hydrolyzes urea and produces ammonia which in turn buffers external acid and creates a suitable pH niche [3].

Although the organism is non-invasive, several reports have claimed an association between its presence and disorders outside the gastro-intestinal tract: cardiovascular, neurological, endocrine, and haematological diseases, allergy and diabetes and its complications [4]. Two main mechanisms have been advocated to explain these associations: the ability of *H. pylori* to induce a chronic systemic inflammatory state and the strong humoral immunologic response induced by its presence in the stomach [4].

In recent years, increasing evidence has been accumulated that *H. pylori* induced perturbations of the gastrointestinal environment may interfere with the metabolism and/or the absorption of micronutrients and drugs, and that these alterations may be reverted by eradication treatment. This means that we now have the potential to treat several disorders linked to micronutrients malabsorption and to improve the efficacy of orally administered drugs, simply with one week course of antibiotic therapy, which is the treatment able to eliminate the organism in the vast majority of the cases.

Probably, the most important pathophysiologic mechanism underlying the malabsorption of drugs and micronutrients is related *H. pylori* gastritis and its consequences on gastric acid secretion. In fact, all infected subjects develop gastritis; however, on the basis of the gastric site and the severity of gastritis, the consequences on gastric acid secretion may be quite different. In the vast majority of cases there is the development of mild gastritis, involving both the antrum and the corpus of the stomach, without any impairment of gastric acid secretion. Some patients, however, develop inflammation largely confined to the antral region (so called "antrum-predominant gastritis"), associated with excessive acid secretion [5]. In a minority of cases, gastritis may involve exclusively the acid-secreting corpus region, leading to hypochlorydria [6]. Drugs and micronutrients affected by changes of gastric acid secretion may thus be adsorbed with reduced efficiency.

In this review we will examine the malabsorption of micronutrients and drugs which may have the most relevant clinical consequences.

H. PYLORI AND IRON

Iron deficiency in humans results in impairments in immune, cognitive and reproductive functions, as well as in decreased work performance. It develops through three stages: 1. iron depletion, 2. iron deficient erythropoiesis, and 3. iron-deficiency anemia (IDA). Epidemiologic analyses suggest an association between *H. pylori* infection and iron deficiency. In fact, a recent nationwide survey, performed in the US [7] found that *H. pylori* infection was associated with decreased serum ferritin levels (percent change -13.9%, 95% confidence interval (CI): -19.5, -8), with IDA prevalence (prevalence odds ratio (POR) 2.6, 95% CI: 1.5, 4.6), and with a 40% increase in the prevalence of iron deficiency (POR 1.4, 95% CI: 0.9, 2.0). Several mechanisms may be responsible for the above reported associations Fig. (**1**): A) *H. pylori* invariably induces gastritis with frequent neutrophil infiltration; there are therefore in the stomach increased levels of neutrophil-derived lactoferrin which binds iron; since *H. pylori* outer membrane has a lactoferrin binding receptor, the complex iron/lactoferrin is picked up by the bacterium for its own growth. Given the very rapid turn-over of *H. pylori*, the bacterial iron stores are rapidly lost in the stools together

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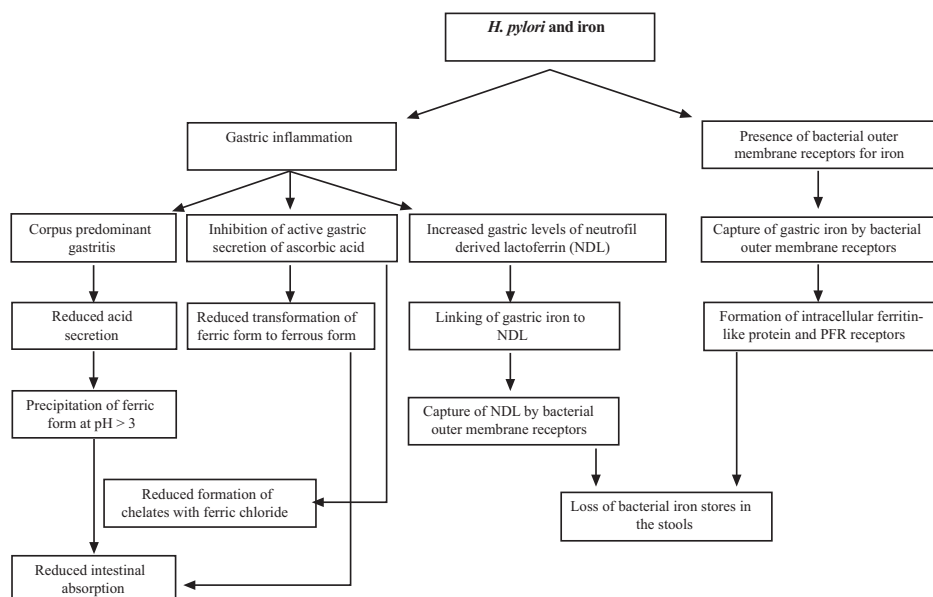
Fig. (1).

with the dead bacteria. This mechanism could explain why an iron supply is no longer available for hemopoiesis, but only enhances *H. pylori* proliferation [8]; B) *H. pylori* may cause iron deficiency by competing with the host for available food iron. Iron is in fact an essential growth factor for *H. pylori* which is equipped with iron-repressible outer membrane proteins responsible for iron uptake and with pfr and napA intracellular ferritin-like proteins involved in iron storage [9].

Perhaps, the most important mechanism linking *H. pylori* infection with iron deficiency may be represented by changes in the gastric environment induced by the infection.

In Western countries, about 80% of dietary iron is in the non haemic ferric form, and it needs an acidic intragastric pH to be reduced to the ferrous form and be absorbed [10]. At a critical intragastric pH>3, the reaction is impaired [11]. In addition to low intragastric pH, the presence of an appropriate concentration of ascorbic acid, which is actively secreted from plasma into the gastric juice [12, 13], is also needed [14, 15]. Ascorbic acid may also play a role in iron absorption even in the adverse condition of an intragastric pH>3, since it is able to form chelates with ferric chloride, which is stable at relatively high pH values [11]. It has been demonstrated that ascorbic acid is reversibly depleted in the gastric juice of patients with *H. pylori* gastritis [16-18].

The causal role of *H. pylori* in the induction of these alterations is strengthened by the positive effect of eradication therapy on the intragastric levels of ascorbic acid, on the reversal of gastric acid hyposecretion and on the concomitant improvement of iron deficiency [19-21].

H. PYLORI AND COBALAMIN

Cobalamin is obtained exclusively from the diet, with animal proteins being the primary source [22]. The clinical features of cobalamin deficiency involve the blood, the gastrointestinal tract, and the nervous system. The hematologic manifestations are almost entirely the result of megaloblastic anemia, although very rarely purpura may appear, due to thrombocytopenia. The gastrointestinal manifestation effects reflect the effect of cobalamin deficiency on the rapidly proliferating gastrointestinal epithelium, responsible for diarrhea and malabsorption. The neurologic manifestations are characterized by demyelination, followed by axonal degeneration and eventual neuronal death. Signs and symptoms include numbness and paresthesia in the extremities, weakness, and ataxia.

Peptic digestion in an acidic environment is required to release cobalamin from food proteins and to allow the binding to R proteins. Excess cobalamin binds to another cobalamin-binding protein, intrinsic factor. When cobalamin bound to R proteins and/or intrinsic factor passes into the duodenum, pancreatic proteases degrade the R proteins, release cobalamin, and allow for cobalamin binding to intrinsic factor. Intrinsic factor–bound cobalamin is then absorbed in the terminal ileum by specific intrinsic factor/cobalamin receptors found on the enterocytes. In the absence of intrinsic factor, less than 2% of ingested cobalamin is absorbed compared with 70% absorption when intrinsic factor is present.

There are several epidemiologic studies linking *H. pylori* infection to cobalamin deficiency [23, 24]. Support to an interference of *H. pylori* infection on vitamin B12 metabolism is given by the clinical studies showing that eradication of the micro-organism may induce normalization of serum vitamin B_{12} levels, anemia, and macrocytosis [25, 26]. Since long term *H. pylori* infection may impair various gastric functions such as acid/pepsin secretion [27], critical to split vitamin B12 from food binders and for its subsequent transfer to R binder in the stomach, the diminished acid secretion which may be caused by *H. pylori* gastritis may lead to a

failure in the absorption of food-bound vitamin B12 Fig. (**2**). Furthermore, *H. pylori*- induced gastritis could cause a secretory dysfunction of the intrinsic factor, contributing further to cobalamin malabsorption [28] Fig. (**2**). *H. pylori* may be linked to food cobalamin malabsorption by another indirect mechanism: indeed, gastric acid hyposecretion linked to corpus-predominant gastritis may induce bacterial overgrowth in the gastrointestinal tract, which can result in bacterial binding of cobalamin and decreased absorption [29] Fig. (**2**). Thus, decreasing the anaerobic load with a regimen of broad-spectrum antibiotics may improve food-cobalamin malabsorption and contribute to treat cobalamin deficiency in addition to *H. pylori* eradication. In fact, small studies have reported that treatment of patients with a regimen of antibiotics, including tetracycline, can increase food-cobalamin absorption and correct low serum vitamin B_{12} levels [30, 31].

In addition to food-cobalamin deficiency, it has recently been suggested that *H. pylori* infection may be linked to pernicious anemia [32].

Pernicious anemia has a prevalence of approximately 3% in the white population older than 60 years [33, 34]. It is a disease of unknown etiology characterized by chronic atrophic gastritis (predominantly affecting the parietal cells in the body of the stomach), decreased acid secretion, and autoimmune manifestations including a high prevalence of antibodies directed against parietal cells and/or intrinsic factor. How could *H. pylori* be linked to this disorder? At a first glance, epidemiologic studies seem to be contradictory for a role of the organism, since a decreased prevalence of the infection has been reported in patients with pernicious anemia in comparison to controls [35, 36]. It should be noted, however, that *H. pylori* prevalence may change with the gastrointestinal tract's microenvironment. An *H. pylori* seror-eversion rate of more than 6% per year has indeed been reported in patients with pernicious anemia [32]. Thus, *H. pylori* may be eliminated in patients with pernicious anemia, as the achlorhydria creates a hostile environment for *H. pylori* growth and colonization. This suggests that patients with *H. pylori* infection develop chronic atrophic gastritis, increased parietal cell loss, food-cobalamin malabsorption, and, ultimately, pernicious anemia if the *H. pylori* infection remains untreated and the gastritis progresses Fig. (**2**).

H. pylori may be involved in the pathogenesis of pernicious anemia *via* antigenic mimicry. *H. pylori*, like many other bacteria, is effective at inducing host cellular and humoral immune responses that may cross react with host cellular antigens [37]. Antibodies directed against the H^+,K^+-adenosine triphosphate protein, the most common autoantigen in pernicious anemia, have been found in high titers in patients with *H. pylori* infection [38,39]. *H. pylori* infection also produces a gastric cellular immune infiltrate consisting of macrophages and activated T lymphocytes [40]. Thus, a strong host immune response against *H. pylori* could produce the destructive pangastritis changes observed in patients with classic pernicious anemia [37]. Host differences in major histocompatibility complex or other immunostimulatory genes might then explain why only a minority of patients with *H. pylori* infection develop cobalamin malabsorption and cobalamin deficiency.

A relevant consequence of *H. pylori*- induced cobalamin deficiency may be represented by the development of hyperhomocysteinemia. In fact, homocysteine is formed within cells from the demethylation of methionine, a sulfurated essential amino acid derived from dietary proteins [41,42]. There are two main pathways for reducing homocysteine concentrations. Through the first, the acquisition of the methyl group (2CH3) from the donor methyltetrahydrofolate, homocysteine is re-methylated back to methionine. In the second, the so-called transsulfuration pathway, homocysteine and serine are condensed to form cystathionine and water. This leads to the formation of cysteine, which is reutilized or eventually excreted in the urine. Because remethylation is effective at low homocysteine concentrations, this pathway regulates fasting levels of homocysteine [41,42]. As described above, the development of *H. pylori* related atrophic gastritis leads to reduced vitamin B12 absorption due to the disruption of the previously described physiologic mechanisms, resulting in hyperhomocysteinemia. Indeed, deficiency in vitamin B12 and folate is probably the most common cause of the hyperhomocysteinemia [27]. Folic acid and vitamin B12 are required for remethylation of homocysteine, and even subclinical deficiency of these vitamins can increase plasma homocysteine levels [43] Fig. (**2**). Homocysteine impairs the production of nitric oxide and thrombomodulin by endothelial cells, causes endothelial denudation with subsequent platelet and fibrin deposition; and produces oxygen free radicals, hydrogen peroxide, and lipid peroxidation, with subsequent foam cell formation and smooth muscle cell proliferation [44] Fig. (**2**). Hyperhomocysteinemia is a well-established independent risk factor for the development of atherosclerosis-related diseases since it causes vascular endothelial damage [45]. Several studies have suggested an association between *H. pylori*-related atrophic gastritis and hyperhomocysteinemia [27, 28, 46, 47]. Therefore, *H. pylori* induced hyperhomocysteinemia may be one of the causal mechanisms underlying the reported association between infection and overt atherosclerotic disorders.

H. PYLORI AND DRUG MALABSORPTION

This is an entirely new and exciting chapter in the history of *H. pylori* related disorders. Two studies, published in 2006 suggest that the infection may have relevant adverse effects on pharmacokinetics of orally administered drugs used for the treatment of important disorders such as goiter and Parkinson's disease. It is very likely that several other orally administered drugs, whose intestinal absorption may be influenced by perturbations of gastric environment, will show in the next future an interaction with the presence of *H. pylori* in the stomach. We report here in detail the available evidence on the interference of the organism on thyroxine and levodopa pharmacokinetics.

H. pylori and Thyroxine

Thyroxine is a widely used orally administered drug for the treatment of several thyroid disorders, especially those related to hypothyroidism [48]. An inhibitory role of *H. pylori* infection was shown in a recent elegant study by Centanni *et al*. [49]. They obtained evidence for this inhibitory role in three different ways:
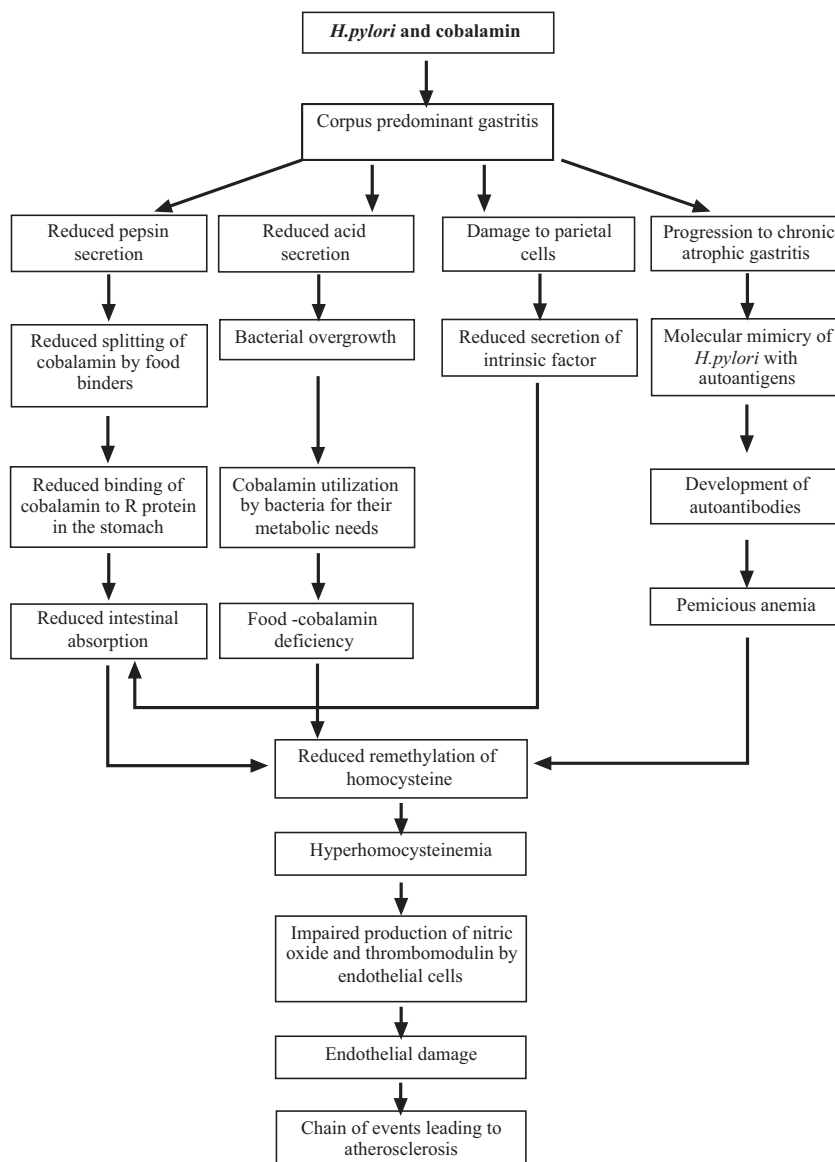
Fig. (2).

1. Evaluation of daily thyroxine requirement needed to achieve pre-established low levels of thyrotropin (0.05 to 0.20 mU per liter) in patients with or without infection. For this purpose, they studied three different subgroups of patients:

a) 53 patients with *H. pylori* related non atrophic gastritis; b) 29 patients with *H. pylori*- related atrophic gastritis; c) 135 patients without gastritis and *H. pylori* infection (reference group)

All patients were followed for at least 30 months. During follow-up, all patients with *H. pylori* infection showed a significantly higher increase in thyroxine requirement in comparison to the reference group, the maximal increase being observed in those with *H. pylori*-related atrophic gastritis.

2. Effect on thyroxine requirement of newly diagnosed *H. pylori* infection. During follow-up, 11 patients belonging to the reference group showed evidence of *H. pylori* infection. When the infection was diagnosed, a sharp increase in serum thyrotropin was observed, before thyroxine treatment was changed.

3. Effect of *H. pylori* eradication. The above reported 11 patients were treated with antibiotics in order to eradicate the infection. After treatment, a low level of serum thyrotropin was re-established in all patients, at a slightly higher median dose of thyroxine.

Taken together, these findings strongly support a role of the microorganism in thyroxine pharmacokinetics. The exact pathogenetic mechanism, however, remains elusive. The

authors speculate that the low levels of acid secretion induced by *H. pylori*- related atrophic gastritis may alter the ionization status and the conformational characteristics of the thyroxine molecule and thus alter the efficiency of intestinal absorption of the hormone. This hypothesis, however, do not fully explain the data. In fact, an interference with intestinal thyroxine absorption was observed also in patients with non atrophic gastritis, which is generally associated with normal or even increased acid secretion (50); furthermore, an impact on thyroxine need was observed soon after the detection of infection, before the development of chronic gastritis and related changes on gastric environment. A direct effect of the organism on thyroxine, perhaps mediated by ammonia production, cannot therefore be excluded Fig. (**3**).
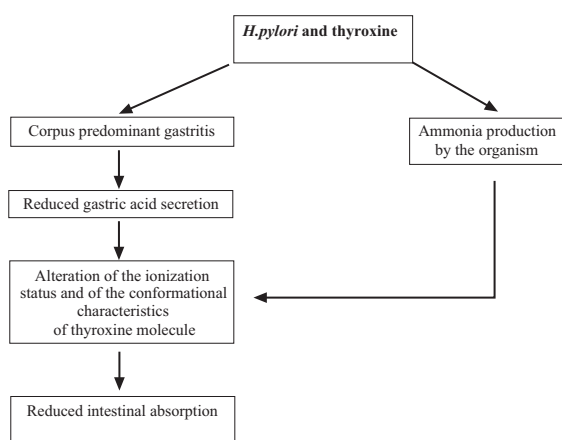

Fig. (3).

H. pylori and Levodopa

Levodopa is widely recognized as the most effective oral medication for relieving the signs and symptoms of Parkinson's disease (PD). However, after a honeymoon period of months to years, when PD symptoms are remarkably and predictably relieved by levodopa, complications begin to appear. Among the most troubling of these adverse effects there are motor fluctuations consisting of re-emergence of symptoms appearing at progressively shorter intervals after scheduled dosages of medication (wearing off), wide swings in extent of benefit from successive dosages, and, perhaps most disturbing for patients, episodes of sudden and substantial loss of benefit seemingly unrelated to the timing and amount of levodopa dosing ("random offs"). The development of these motor fluctuations is related to the progressive loss of viable dopaminergic cells in the brain coupled with erratic delivery of levodopa across the blood-brain barrier. In the early stages of PD, there are sufficient numbers of intact dopaminergic cells to take up exogenously administered levodopa, store it as dopamine, and release it under neural control during periods of time when levodopa delivery has temporarily failed, thereby preventing "off" episodes. With disease progression, more neurons die and this buffering capacity is lost with a temporary loss of clinical benefit in case of any aberration in the continuous availability of levodopa. Irregularity in levodopa delivery to the brain is common in

PD and impaired gastrointestinal transit or absorption of the drug are among its major causes.

Orally administered levodopa must pass through the pylorus to the duodenum where it is absorbed. Because gastric motility is impaired in advanced PD, levodopa tablets can remain stagnant in the stomach, preventing or delaying any clinical effect. Once reaching the duodenum, absorption can be impaired by local structural or inflammatory pathology. A variety of strategies have been attempted to surmount these transit and absorption problems, including pharmacologic formulations to enhance levodopa passage through the pylorus, liquified suspensions of levodopa tablets, direct delivery of levodopa to the duodenum through an enteral tube, and the use of prokinetic drugs. None of these techniques has been entirely effective or entirely acceptable to patients. Indeed, unexplained intestinal levodopa malabsorption has been reported in more than 15% of PD patients with declining efficacy and response fluctuations after chronic administration of the drug [51]

H. pylori might affect levodopa bioavailability through several mechanisms: 1) degradation of the drug, as observed with anaerobic bacteria [52], sharing many metabolic pathways with *H. Pyroli* [53]; 2) disruption of mucosal integrity of duodenum [54], site of levodopa absorption [55]; 3) local production of reactive oxygen species [56], which may inactivate the drug [57]. Furthermore, perturbations of gastric acidity, such as gastric acid hypersecretion, may reduce levodopa solubility and absorption [58]. In a recent work from our group [59], we evaluated whether *H. pylori* infection may interfere with the availability of levodopa, performing a series of experiments to explore the possible underlying pathophysiologic mechanisms.

In order to assess the role of the infection, we studied the effects of *H. pylori* eradication in *H. pylori*-positive, motor-fluctuating patients with PD on levodopa. Seventeen patients were given an *H. pylori* eradication treatment, and 15 of them were *H. pylori*-negative by study end. A sharp increase in levodopa absorption was observed at 2 weeks and 3 months, after both single and repeated administrations of levodopa. The *H. pylori* eradication group had also a marked improvement in clinical disability and 'on-time' duration. On the basis of these findings, we felt that the infection had probably an inhibitory role on intestinal absorption of levodopa. At this point, the first question was: could this role be mediated by the increased local oxidative stress linked to *H. pylori* infection? To answer this question, we performed the same evaluations that we have done in patients treated with eradication therapy, in 17 patients treated with allopurinol, a drug that does not eradicate *H. pylori*, but that may antagonize its oxidant effects [60]. No beneficial effect was obtained with the administration of this drug, and we therefore concluded that the adverse effect of *H. pylori* on levodopa absorption was probably not mediated by oxidative damage. A second question was: may the damage be linked to a direct degradation of levodopa moiety by the infecting organism? In order to address this question, we compared the changes over time of levodopa concentrations in 6 liquid cultures contaminated with *H. pylori* and in 6 non contaminated cultures to which the same quantity of levodopa had been added (Pietroiusti *et al*, unpublished data). The findings of the ex-

periment, illustrated in Fig. (**4**), showed no evidence of important differences in the degradation rate of the drug between contaminated and non contaminated cultures. Thus, also the answer to the second question was: "no".
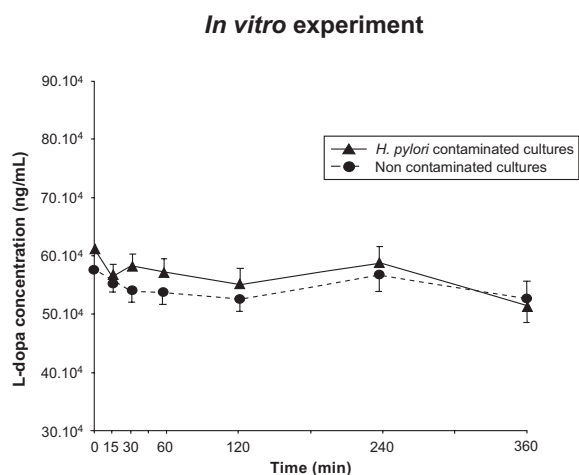
In vitro experiment

Fig. (4).

The third question was: may perturbations in acid secretion induced by *H. pylori* be of pathogenetic relevance? The key determinant of the effect of infection on gastric acid secretion is represented by the severity and distribution of *H. pylori*- induced gastritis. Gastritis that is largely confined to the antral region is associated with excessive acid secretion [5]. In contrast, gastritis that involves the acid secreting corpus region leads to hypochlorydria [6]. Interestingly, these abnormalities may be reverted after *H. pylori* eradication [61]. Thus, in order to obtain an indirect but reliable index of the effect of *H. pylori* infection in our patients, we analyzed the type and intensity of gastritis: we found that antrum predominant gastritis (associated with acid hypersecretion) was present in the majority of our patients. Since increased secretion of gastric acid may impair levodopa absorption [58] we concluded that this mechanism could explain the adverse effects of the infection on levodopa pharmacodynamics observed in our patients Fig. (**5**).

The final question was: may mucosal alterations induced by *H. pylori* at the site of intestinal absorption of levodopa play a role? Also in this case the answer was: probably yes. The drug is in fact actively absorbed at the duodenum level [55], and *H. pylori* is able to induce inflammatory changes at this site [54], possibly impairing active levodopa absorption. We found a strict relation between reversal of duodenal inflammatory changes associated with *H. pylori* eradication, and improvement in levodopa absorption, supporting the hypothesis that *H. pylori* related changes in the duodenum may alter active drug absorption Fig. (**5**).

Other mechanisms not explored in our study may concur to explain the observed findings. For example, gastrointestinal motility alterations, as frequently found in levodopa treated PD patients [62], may allow bacterial overgrowth even in the stomach. [63]. These bacteria, generally able to metabolize neutral amino acids [64] might in turn directly
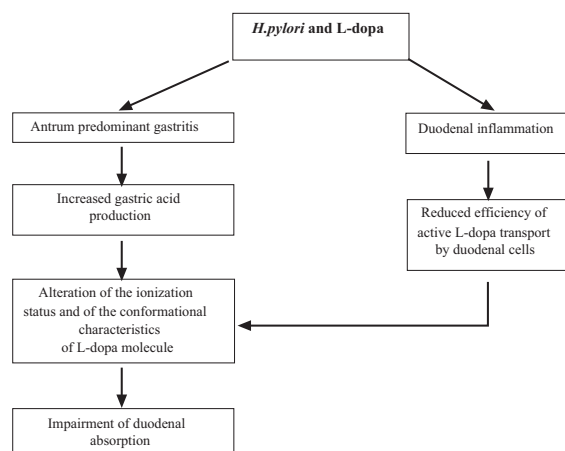

Fig. (5).

affect levodopa intestinal absorption and their elimination, due to anti-*H. pylori* antibiotic treatment, could induce a better levodopa adsorption. However, this hypothesis needs to be properly tested in future studies.

In conclusion, growing evidence is raising on the role that *H. pylori* infection may have on the intestinal absorption of several substances, included commonly used drugs, that may be altered for the changes of gastroduodenal environment due to the infection. The potential effect on human health may be impressive, and probably mostly unexplored. On the other hand, the possibility to eliminate this organism with a relatively short course of antibiotic therapy, open new perspectives for the improvement of several conditions unresponsive until now to the usual medical treatment.

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