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Research Article

EFFECT OF HELICOBACTER PYLORI ERADICATION ON SERUM LEVELS OF GHRELIN AND LEPTIN

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ABSTRACT

Background And Aim: Helicobacter pylori may interact with gastric tissue disturbing the regulation of ghrelin and leptin hormones. This study aimed at evaluating the effect of Helicobacter pylori eradication on serum levels of ghrelin and leptin in Egyptian patients.
Methods: Forty Egyptian patients with positive H. pylori infection who were selected from those presented with dyspepsia were included. All were subjected to stool antigen test, pre-meal serum ghrelin and leptin levels and calculation of body mass index (BMI) before and 12 weeks after H. pylori eradication therapy.
Results: Eradication was successful in 80% and failed in 20%. The mean serum ghrelin level was highly significantly increased after treatment in H. pylori eradicated group (P=0.005), while it was non-significantly increased in failed-eradication group (P=0.71). There was no significant difference in mean serum leptin level before and after H. pylori treatment in both eradicated and non-eradicated groups (P=0.55 and 0.325 respectively). BMI was highly significantly increased in all patients after treatment regimen in both eradicated and non-eradicated groups (P=0.009 and 0.018 respectively).
Conclusion: Serum ghrelin and BMI were significantly increased following H. pylori eradication. Thus, eradication therapy for H. pylori infection is crucial for appetite improvement and weight gain in dyspeptic patients.

INTRODUCTION

The gastric epithelial cells express both ghrelin and leptin and their receptors. Inflammation can modify their production [1, 2]. Helicobacter pylori infection colonizes the human stomach and may interact with the host tissue affecting the regulation of ghrelin and leptin [3, 4].

Ghrelin is a polypeptide hormone which is mainly produced by the gastric entero-endocrine cells (oxyntic cells) and is activated into acylated ghrelin; by the enzyme ghrelin O-acyl-transferase (GOAT) in gastric mucosa; before secretion to the blood stream. It is a potent appetite stimulator in addition to its anti-inflammatory and regulatory effect on gastrointestinal motility and acid secretion [5]. Serum ghrelin concentration increases during fasting and decreases after eating. It decreases energy expenditure and promotes weight gain [6, 7].

Alterations in ghrelin regulation following H. pylori eradication may reflect the extent of baseline gastric inflammation. Plasma levels of acyl-ghrelin may be significantly elevated post- H. pylori eradication, and its variation may reflect the severity of atrophic gastritis [8]. Previous studies reported the occurrence of long-term weight gain; in addition to changes in baseline acyl-ghrelin values and changes in BMI following H. pylori eradication [9].

Leptin is produced primarily by adipocytes. It reduces appetite and increases energy utilization [10]. Reflecting the observed weight gain, both pre-meal and post-meal serum leptin levels were significantly elevated after H. pylori eradication and differed significantly from baseline values [11].

This study aimed at evaluating the effect of Helicobacter pylori eradication on serum levels of ghrelin and leptin in Egyptian patients.

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PATIENTS AND METHODS

This prospective cohort study was conducted on 40 Egyptian patients with positive H. pylori infection who were selected from those presenting with dyspepsia (epigastric pain and heart burn). They were presented to Internal Medicine and Tropical Medicine Departments and outpatient clinics at Ain Shams University Hospital, during the period from January 2015 to December 2015.

Informed written consent was obtained from each patient prior to inclusion. The study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients who received proton pump inhibitors, H. pylori eradication therapy or antibiotics in the previous 4 weeks, those with recent corticosteroid or non-steroidal anti-inflammatory drug (NSAIDS) use; alcoholic gastritis; intra-abdominal malignancies such as lymphoma or gastric carcinoma; chronic liver disease as well as those with any other co-morbidity were excluded.

All included patients were subjected to the following:

1- Complete clinical evaluation.
2- Laboratory investigations:

a. Complete Blood Count (CBC).
b. Liver profile: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total and direct bilirubin and INR.
c. Renal profile: creatinine and blood urea.
d. Fasting and two hours post prandial blood sugar.
e. H. pylori status determination: Immunocard (ImmunoCard STAT ® HpSA - Meridian Bioscience, Inc.) was used to assess H. pylori antigen in morning stool samples at the time of diagnosis and 4 weeks after eradication. Immunocard is a rapid immune-chromatographic test for the qualitative detection of H. pylori antigen in human stool. It is based on monoclonal H. pylori antibodies and a lateral flow chromatography technique.
f. Pre-meal (12 hours-fasting) serum ghrelin and leptin levels before and 12 weeks after H. pylori eradication.

Five mL of venous blood was drawn aseptically from each patient, 2 mL was placed in an EDTA Vacutainer (Becton Dickinson and Company, Franklin Lakes, New Jersy) tubes for performing complete blood cell count and 3 mL was collected in plain Vacutainers for chemistry analysis and serum ghrelin and leptin assessment. A complete blood picture using Coulter counter (T660; Beckman Coulter, Brea, CA) with differential count was done. ALT, AST, creatinine, blood urea nitrogen and fasting blood glucose were assessed on Synchron CX-9 Pro auto analyzer (Beckman Instruments Inc.; Scientific Instruments Division, Fullerton, CA 92634, 3100, USA).

Serum ghrelin was assayed before and 12 weeks after H. pylori eradication using a commercially available sandwich Enzyme Linked Immunosorbent Assay (ELISA) kit (RayBio® Human Ghrelin ELISA Kit. Catalog #: ELH-GHRL) according to the manufacturer's instructions. Briefly, sera and standards were added to plates coated with an antibody specific for human ghrelin and incubated at room temperature, color develops in proportion to the amount of ghrelin bound. Optical density was determined using a Stat Fax 2100 microplate reader (Awareness Technology INC, USA) at 450 nm.

Serum Leptin levels were assayed before and 12 weeks after H. pylori eradication using a commercially available standard sandwich Enzyme Linked Immunosorbent Assay (ELISA) kit (BOSTER BIOLOGICAL TECHNOLOGY Co., Ltd. Catalog No. EK0437), according to the manufacturer's instructions. Briefly, sera and standards were added to plates coated with an antibody for leptin. The density of colour is proportional to the human leptin amount of sample captured in plate, optical density was determined using a Stat Fax 2100 microplate reader at 450 nm.

3- H. pylori eradication therapy:
Patients were given a 14-days twice-daily regimen (amoxicillin 1000 mg, clarithromycin 500 mg, and a proton pump inhibitor (PPI); omeprazole 20 mg, or esomeprazole 40 mg).

Then after that, they were given a 14-days once-daily proton pump inhibitor (PPI) (omeprazole 40 mg) to complete 28 days of eradication therapy.

4- Body weight and height were determined for all patients to calculate body mass index (BMI) before eradication and 12 weeks after eradication of H. pylori [calculated as: BMI=weight (kg)/height $(m)^2$].

Statistical analysis

The collected data were coded, tabulated, and statistically analysed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0.

Continuous variables were compared using the T-test, and pair wise analyses were performed using non- parametric tests (Wilcoxon's signed rank test, Mann-Whitney U tests. Categorical variables were compared using the Chi- square test with Yates' correlation or Fisher's exact test. Spearman correlation coefficient was calculated for the relationship of leptin and ghrelin levels to BMI.

P value < 0.05 was considered statistically significant and $P < 0.01$ as highly significant.

RESULTS

The current prospective cohort study was conducted on 40 Egyptian patients with dyspepsia (epigastric pain and heart burn) that were proved to be H. pylori positive by stool antigen test. They were 14 males (35%) and 26 females (65%). Their mean age was 34.5 ± 9.902 years (range: 19-53 years).

Before receiving eradication therapy for H. pylori, the mean body mass index (BMI) of included patients was 26.2 ± 1.824 kg/m^2. Their mean baseline serum ghrelin and leptin levels were 3412 ± 1673 and 3533 ± 682 pg/ml respectively.

All included patients received a regimen for H. pylori eradication in the form of proton pump inhibitors (PPIs), amoxicillin and clarithromycin. Eradication was successful in 32 patients (80%) and failed in 8 patients (20%). There was no significant relation between either patient age or gender and

status of H. pylori eradication (P-value =0.828 and 0.489 respectively).

The mean serum ghrelin level (pg/ml) was significantly increased following treatment of H. pylori infection (the mean serum ghrelin level before treatment was = 3412 ± 1673 in comparison to 3599 ± 1627 after treatment, P-value = 0.049). However, there was no significant difference in mean serum leptin level (pg/ml) before and after H. pylori treatment (the mean serum leptin level before treatment was = 3533± 682 in comparison to 3689 ± 607 after treatment, P-value = 0.38).

Table (1) shows comparison between serum ghrelin level before and after treatment regimen in relation to H. pylori eradication status. The mean serum ghrelin level was highly significantly increased after treatment in H. pylori eradicated group (P-value= 0.005), while it was non-significantly increased after treatment in failed eradication group (P-value = 0.71).

However, the mean serum leptin level was non-significantly affected by treatment in both eradicated and non-eradicated H. pylori patients (P-value= 0.55 and 0.325 respectively) **(Table 2).**

Table (3) shows that body mass index (BMI) (kg/m^2) was highly significantly increased in all patients after treatment regimen of H. pylori in both eradicated and non-eradicated groups (P-value = 0.009 and 0.018 respectively).

Tables (4, 5) show non-significant correlations between each of serum ghrelin and leptin levels before and after treatment with all patients' parameters.

Table 1 Serum ghrelin (pg/ml) before and after treatment regimen in relation to H. pylori eradication status.

	Serum Ghrelin Before Treatment			Serum Ghrelin After Treatment				
	Mean	±	SD	Mean	±	SD	t	P-value
Eradicated	3284	±	1641	3599	±	1643	-3.264	0.005*(HS)
Failed Eradication	3641	±	1587	3688	±	1522	-0.408	0.710 (NS)

HS: highly significant, NS: non- significant.

Table 2 Serum leptin (pg/ml) before and after treatment regimen in relation to H. pylori eradication status.

	Serum Leptin Before Treatment			Serum Leptin After Treatment				
	Mean	±	SD	Mean	±	SD	t	P-value
Eradicated	3554	±	726	3683	±	625	-0.611	0.550 (NS)
Failed Eradication	3453	±	551	3714	±	614	-1.174	0.325 (NS)

NS: non- significant.

Table 3 Body Mass Index (BMI) before and after treatment regimen in relation to H. pylori eradication status.

	BMI (kg/m^2)							
	Before Treatment			After Treatment				
	Mean	±	SD	Mean	±	SD	t	P-value
Eradicated	26.313	±	1.662	26.694	±	1.780	-2.990	0.009* (HS)
Failed Eradication	25.750	±	2.630	26.289	±	2.723	-4.688	0.018* (HS)

HS: highly significant.

Table 4 Correlation of serum ghrelin levels before and after treatment with all patients' parameters.

	Serum ghrelin before treatment (pg/ml)		Serum ghrelin after treatment (pg/ml)	
	r	P-value	r	P-value
Age (years)	0.026	0.914	-0.027	0.910
Serum Leptin before treatment (pg/ml)	-0.067	0.778	0.181	0.444
Serum Leptin after treatment (pg/ml)	0.177	0.456	0.147	0.537
Weight before treatment (Kg)	-0.159	0.504	-0.129	0.586
Weight after treatment (Kg)	-0.151	0.526	-0.122	0.609
Height (m)	-0.191	0.419	-0.163	0.493
BMI before treatment (Kg/m^2)	-0.129	0.588	-0.150	0.528
BMI after treatment (Kg/m^2)	-0.061	0.799	-0.029	0.902
Hb (g/dl)	-0.045	0.852	-0.141	0.553
Serum Creatinine (mg/dl)	0.075	0.753	-0.336	0.148
ALT (u/l)	-0.156	0.512	-0.454	0.064
AST(u/l)	-0.328	0.158	-0.412	0.071
Total bilirubin (mg/dl)	0.140	0.556	-0.104	0.662
INR	-0.104	0.662	0.170	0.473
Serum Albumin (mg/dl)	0.033	0.890	0.049	0.838

BMI: body mass index, Hb: haemoglobin, ALT: alanine transaminase, AST: aspartate transaminase, INR: international normalised ratio.

Table 5 Correlation of serum leptin levels before and after treatment with all patients' parameters.

	Serum leptin before treatment (pg/ml)		Serum leptin after treatment (pg/ml)	
	r	P-value	r	P-value
Age (years)	0.022	0.926	0.164	0.491
Weight before treatment (Kg)	0.111	0.641	0.098	0.682
Weight after treatment (Kg)	0.111	0.640	0.172	0.467
Height (m)	0.035	0.885	0.112	0.639
BMI before treatment (Kg/m^2)	0.164	0.490	0.042	0.860
BMI after treatment (Kg/m^2)	0.132	0.579	0.140	0.555
Hb (g/dl)	-0.059	0.804	-0.144	0.545
S. Creatinine (mg/dl)	-0.213	0.366	-0.265	0.259
ALT (u/l)	-0.246	0.297	-0.105	0.659
AST (u/l)	-0.052	0.828	-0.207	0.381
Total bilirubin(mg/dl)	-0.019	0.938	0.138	0.561
INR	0.044	0.855	0.017	0.943
Serum Albumin (mg/dl)	0.025	0.916	-0.193	0.416

BMI: body mass index, Hb: haemoglobin, ALT: alanine transaminase, AST: aspartate transaminase, INR: international normalised ratio.

DISCUSSION

Helicobacter pylori is a gram negative bacterium that infects the stomach causing chronic gastritis. It is a major cause of peptic ulcer disease and is classified by World Health Organization as one of the gastric carcinogens. Some infected individuals may have dyspeptic symptoms, however, a substantial proportion of them are asymptomatic [12].

Previous studies reported that gastric colonization with H. pylori has a significant effect on serum leptin levels [3] and on both gastric and plasma levels of ghrelin [13]. In the current study, we investigated the impact of H. pylori eradication on serum leptin and ghrelin levels in a cohort of H. pylori positive Egyptian patients as well as the impact of H. pylori eradication on BMI of these patients.

In the current study, 35% of the forty recruited participants were males and 65% were females. Among the studied patients, 32 patients (80%) responded to H. pylori eradication regimen and 8 (20%) had failed eradication.

There was no significant relation between either patient age or gender and status of H. pylori eradication. There was a significant increase in serum ghrelin level 12 weeks following H. pylori eradication, while there was a non-significant difference regarding serum leptin levels before and after eradication. This was in agreement with *Kawashima et al.* [8] and *Gunji et al.* [14].

Boltin and Nivy [15] reported that weight gain following H. pylori eradication is partially explained by increased gastric expression of ghrelin and plasma ghrelin level.

However, there is a considerable controversy between the results of different studies regarding the effect of H. pylori eradication on plasma ghrelin level. *Nweneka and Prentice* [16], in their meta-analysis, found that the majority of previous studies reported that H. pylori infection reduced plasma ghrelin level; other studies reported increased ghrelin level after eradication of H. pylori infection and some studies reported no differences in plasma ghrelin levels before and after eradication. It seems that the relation between H. pylori infection and plasma ghrelin level is complex one and many factors may have a role, such as H. pylori strain, severity of gastritis and gastric atrophy, long duration of infection and duration of follow up after H. pylori eradication.

It has been previously reported that H. pylori infection directly acts on mechanisms controlling ghrelin production by oxyntic cells through release of cytotoxins, lipopolysaccharides and other noxious agents and this is prominent with long duration of infection. If plasma ghrelin levels are followed up shortly after eradication of H. pylori there may be little or no difference but significantly increased levels are detected after longer duration (6 months) from eradication [13, 17].

In the current study, serum leptin levels did not differ significantly before and after H. pylori eradication. This was consistent with results of *Azuma et al.* [18] and *Jun et al.* [19].

On the contrary, *Vitale et al.* [20] reported that H. pylori infection can increase plasma leptin levels thus affecting appetite and promoting occurrence of dyspeptic symptoms. These contradictory results regarding serum leptin level and its affection by H. pylori infection can be explained by the fact that there is another major source of leptin; the adipose tissue cells which are not affected by H. pylori gastritis; so plasma leptin is not largely affected by H. pylori eradication. In addition, some differences in follow up period after eradication and demographic characteristics of different studies can explain these contradictory results.

Another important finding in our study is the significantly increased body mass index (BMI) 12 weeks after H. pylori eradication. This may be attributed to improved appetite and ameliorated dyspeptic symptoms as bloating and early satiation likely due to increased ghrelin level or increased acylated ghrelin which is the metabolic active form of ghrelin from the inhibitory effect of H. pylori infection on the gastric enzyme ghrelin O-acyl-transferase (GOAT) [5].

Boltin and Nivy [15] reported that weight gain following H. pylori eradication is poorly understood phenomenon and probably results from interacting between multiple factors including plasma and gastric ghrelin levels.

H. pylori eradication in our study population was not significantly related to any of laboratory parameters. This means that other clinical factors are more important determinants to response to H. pylori eradication as resistance pattern to antibiotics used in eradication regimen and the patient compliance to continue the eradication regimen inspite of side effects. It has been previously reported that H. pylori eradication is necessary in symptomatic patients and this has many benefits regarding gastrointestinal and extra-gastrointestinal aspects. Improved ghrelin level (gastric and plasma) is substantial benefit that related to improved appetite and weight gain in the treated dyspeptic patients [21].

CONCLUSION

Serum ghrelin level and BMI were significantly increased following H. pylori eradication. Thus, eradication therapy for H. pylori infection is crucial for appetite improvement and weight gain in dyspeptic patients.

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