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May 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

**Title:** *Helicobacter pylori* infection in patients with selective IgE deficiency. RESEARCH REPORT

**Author:** Eli Magen, Menchem Schlesinger, Itzhak Ben-Zion, Daniel Vardy.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 10802

The manuscript has been improved according to the suggestions of reviewers. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Dr. Eli Magen, MD.

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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 10802

**Title:** Helicobacter pylori infection in patients with selective IgE deficiency

**Reviewer code:** 00199528

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-04-20 16:04

**Date reviewed:** 2014-04-28 14:40

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

the topic of the study is very interesting and it is evaluating the immunologic association between a rare disease of IgE deficiency and h. pylori infection. however, there is major statistical error. Authors want to design a "retrospective" case-control study. they compare endoscopic finding and response to eradication treatment in IgE deficient individuals with that IgE normal controls. however case-control studies should be done by clearly defining "case" and "control". in this study who is the "case"; individuals with low IgE, individuals with low IgE and dyspepsia or individuals with low IgE and dyspepsia and H. pylori positive by UBT. then controls should be chosen accordingly. if the case was 43 individuals with low IgE, then all 223 controls must be questioned for the dyspepsia and underwent UBT and/or endoscopy with H.pylori evaluation. other wise all the statistical test used are invalid. my comment is either to redefine the case and do statistical analysis accordingly or to report the data as a descriptive study.



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### Answer:

In our study the "Case" was defined as individuals with low IgE and dyspepsia and H. pylori positive by UBT. This is described in the "Patients and Methods/subjects" section of the manuscript: "the subjects aged  $\geq 12$  years old with serum total IgE of  $< 2$  kIU/L, with clinical symptoms of dyspepsia and a positive  $C^{13}$ -UBT were included in the Case group". Accordingly, the Control group was randomly sampled with a case-control ratio of twelve controls for each case (1:20) from the remaining subjects aged  $\geq 12$  years old, with serum total IgE of  $\geq 2$  kIU/L, clinical symptoms of dyspepsia and a positive  $C^{13}$ -UBT.

The Case group was consisted from **158** individuals with low serum total IgE, dyspepsia and a positive  $C^{13}$ -UBT, while **3160** subjects with serum normal or high total IgE, dyspepsia and a positive  $C^{13}$ -UBT were included in Control group (Table 1). As the study was retrospective, we have collected the relevant clinical data about dyspepsia, H. pylori evaluation and endoscopy from the electronic medical database and regretfully, we had no opportunity to question the subjects prospectively for the dyspepsia. 32 patients underwent endoscopy from the Case group, and 223 subjects from the Control group (Table 2). All these endoscoped subjects (from Case and Control groups) had clinical symptoms of dyspepsia (according the medical records – one of the inclusion criteria) and underwent UBT for H. pylori evaluation (were with a positive  $C^{13}$ -UBT).

The authors understand that the reviewer here probably implied the information bias characterized for any retrospective study, due to possible inaccurate clinical records and missing data. We have addressed this issue as a limitation of the study in the discussion section.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 10802

**Title:** Helicobacter pylori infection in patients with selective IgE deficiency

**Reviewer code:** 01433781

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-04-20 16:04

**Date reviewed:** 2014-05-05 21:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

The beneficial properties of IgE require elucidation. Selective IgE deficiency is defined as a significant decrease in the levels of IgE (<2.5 int.units/mL) in a patient whose other immunoglobulin levels, including IgG subclasses and IgA levels, are normal. It is a laboratory finding that does not necessarily equate to a clinical disorder. The prevalence depends upon the population under study. There is some evidence that IgE antibodies play a protective role against viral, parasitic, and bacterial infections in humans. This study by Eli Magen et al investigated the prevalence and clinical characteristics of Helicobacter pylori infection in dyspeptic patients with IgE deficiency. They found more H. pylori positive gastritis in patients with IgE deficiency compare to controls. Eradication rate for legacy triple therapy was statistically inferior in the IgE deficiency group compare to the control, but interestingly eradication rate was similar for Levofloxacin-based triple therapy in case and control group. This information could be of interest for clinicians regarding patients with IgE deficiency The manuscript is nicely presented, well structured, and the discussion and conclusions consistent with the results. Minor Comments: I got a lot of problems reading the paper because, especially in the last part, almost all spaces among the words are missing. I do not believe they are typing errors. Maybe something happened downloading the paper!!



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### Answer:

The authors would like to thank reviewer providing us with his positive response. Actually, we were also surprised by the fact, that eradication rate for a 14-day treatment with Amoxicillin 1 g b.i.d.; Clarithromycin 500 mg b.i.d., and Omeprazole 20 mg, b.i.d. triple therapy was statistically inferior in the IgE deficiency group compare to the control, but *H. pylori* eradication rate was similar for Levofloxacin-based triple therapy in case and control group. As for the problems in reading the paper in the last part, maybe there were some problems in downloading the paper from the WJG site.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 10802

**Title:** Helicobacter pylori infection in patients with selective IgE deficiency

**Reviewer code:** 00068278

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-04-20 16:04

**Date reviewed:** 2014-05-07 02:35

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Isolated IgE hypogammaglobulinemia is rare and its contribution to host defense is controversial. The authors investigated the prevalence of Hp infection among dyspeptic patients with/without IgE deficiency and evaluated response to eradication therapy. The topic is interesting but its presentation needs revision. 1-How many controls were sampled for each case, 10 or 20? a-In "subject" section, it was stated that "The Control group was randomly sampled with a case-control ratio of ten controls for each case (1:20) from the remaining subjects aged  $\geq 12$  years old, with serum total IgE of  $\geq 2$  kIU/L, clinical symptoms of dyspepsia and a positive C13-UBT. b-In results (demographic and laboratory characteristics of cases and controls): There were 158 subjects with IgED and control group included 1.500 subjects (1:9.5). In the following sentence, it was written that there were 718 dyspeptic subjects among 3.160 (158:3160=1:20) control group subjects (total IgE  $\geq 2$  kIU/L). What is the difference between 2 control groups? 2-The ratio of C13-UBT positivity in dyspeptic case group is not 20.5% (32:158) but is 74.4% (32:43). The ratio of C13-UBT positivity in control group is 31.1% (223:718), not 7.1% (223:3.160).



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### Answer:

Regretfully, there were some typographical errors in the manuscript:

- a. In the "subjects section", must be a case-control ratio of **twelve** controls for each case (1:20).
- b. In results (demographic and laboratory characteristics of cases and controls): There were 158 subjects with IgED and control group included **3160** subjects (1:20).

C13-UBT was positive in 32 (**74.4%**) dyspeptic subjects of Case group and in 223 (**31.1%**) dyspeptic patients of Control group ( $p < 0.001$ ).

The above mentioned typos were corrected in the manuscript.

We would like to thank the reviewer for his/her comments and suggestions for the manuscript. We believe that the comments have identified important errors, which required correction.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 10802

**Title:** Helicobacter pylori infection in patients with selective IgE deficiency

**Reviewer code:** 00506513

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-04-20 16:04

**Date reviewed:** 2014-05-07 11:43

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

This manuscript contains interesting observation. The authors describe that the correlation between IgE deficiency and H. pylori-related dyspepsia. However, it is unclear whether IgE deficient patients are compromised to H. pylori infection or easier to deteriorate dyspepsia, such as gastritis. If possible, rate of H. pylori infection in IgE-deficient patient group and other patient group should be presented. Setting denominators is inappropriate. Example 1: In Table 2, GE endoscopy findings, such as gastritis, should be expressed as relative values to number of subjects examined GE endoscopy, which is set as 100%. Example 2: In Table 1, HP positive dyspepsia should be expressed as relative values to number of patients with dyspepsia, which is set as 100%. p. 4, line 15 and 20: "all subjects ---,having performed serum total IgE measurement and 13C-urea breath test---": Is this true? According to the description in results section, a part of subjects examined 13C-urea breath test. p. 4, line 19: "ten controls" should be "twenty controls".



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### Answer:

We would like to thank the reviewer for his/her detailed comments and suggestions for the manuscript. We believe that the comments have identified important issues, which required improvement.

We agree with the reviewer, that it is unclear from our work, whether IgE deficient patients are compromised to H. pylori infection or easier to deteriorate dyspepsia, such as gastritis. Unfortunately, we had no possibility to check the rate of H. pylori infection in IgE-deficient patient group and Control group. We understand that this is an important limitation our retrospective study. To answer to this question, a prospective study should be done. We have addressed this issue as a limitation of the study in the discussion section.

Regretfully, there were some typographical errors in the manuscript:

In the "subjects section", must be a case-control ratio of **twelve** controls for each case (1:20). In results (demographic and laboratory characteristics of cases and controls): There were 158 subjects with IgED and control group included **3160** subjects (1:20). The typos were corrected in the manuscript.

As suggested, in Table 2, GE endoscopy findings, such as gastritis, has been expressed as relative values to number of subjects examined GE endoscopy, which is set as 100%.

As suggested, in Table 1, HP positive dyspepsia has been expressed as relative values to number of patients with dyspepsia, which is set as 100%. C13-UBT was positive in 32 (**74.4%**) dyspeptic subjects of Case group and in 223 (**31.1%**) dyspeptic patients of Control group ( $p < 0.001$ ).