

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effects of different metabolic states and surgical models on glucose metabolism and secretion of ileal L-cell peptides: a study protocol for a cross-sectional study
<b>AUTHORS</b>	Celik, Alper; Dixon, John; Pouwels, Sjaak; Celik, Bahri; Karaca, Fatih; Santoro, Sergio; Gupta, Adarsh; Ugale, Surendra

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Nicola Basso Sapienza-Università di Roma
<b>REVIEW RETURNED</b>	26-Oct-2015

<b>GENERAL COMMENTS</b>	I am not sure whether the general reader of BMJ Open will be interested in reading a protocol for a clinical study. Besides this it is a wellwritten protocol.
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<b>REVIEWER</b>	Jodok Fink University of Freiburg, Department of Surgery
<b>REVIEW RETURNED</b>	17-Nov-2015

<b>GENERAL COMMENTS</b>	<p>The manuscript describes a study protocol of a "single centre cross sectional study". With the aim to evaluate serum levels of the intestinal hormones PYY and GLP-1, these hormones will be investigated in non-surgical and surgical patients. The surgery group includes 4 different metabolic operations, each representing a group of 30 patients. The non-surgical group includes obese and non-obese individuals with and without type 2 diabetes. The primary endpoint of the study is the area under the curve after PYY and GLP-1 measurements.</p> <p>Introduction The introduction contains known and correct facts about obesity surgery and intestinal hormones. However, each sentence seems so stand somewhat separate from the next. Therefore it is very hard to read.</p> <p>The "gap to be filled" is certainly the most important part of any introduction. However, the authors cannot demonstrate the need for this study, although the study itself is, without doubt, very interesting as we are indeed lacking knowledge of the physiological and postoperative levels of gut hormones.</p> <p>Inclusion criteria The authors define two groups of diabetic patients. However, the state of type 2 diabetes is poorly characterized. "Type 2 diabetes no longer than 3 years" is the only criteria mentioned. This leaves</p>
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	<p>patients with 200 IE insulin need with a HbA1c of 11% as well as patients with only one oral anti-diabetic agent and a normal HbA1c to be included. This will certainly be a large source of variation</p> <p>In the surgical group, type 2 diabetes is not defined at all. Again, this will produce a large variation that is not due to the issue intended to study. Furthermore, there is a huge change in body weight and body composition and a large amount of intestinal adaption between 6 months and 2 years after any metabolic operation. Why did the authors not include patients 6 months after any of these operations. That could be easily done and would produce far better results.</p> <p>Discussion</p> <p>The discussion contains a large section on GIP, which is not subject of this study. Furthermore, the discussion restates parts of the introduction.</p> <p>Overall, the idea of the study is certainly of interest for the scientific society. However, inclusion criteria should be defined more sharply. The manuscript is very hard to read in general and could be shortened immensely.</p>
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<b>REVIEWER</b>	Bethany Cummings Cornell University, USA
<b>REVIEW RETURNED</b>	08-Dec-2015

<b>GENERAL COMMENTS</b>	<p>The paper by Celik et al. describes the study protocol for the assessment of post-prandial secretion of GLP-1, PYY and oxyntomodulin after several types of bariatric surgery or in several different metabolic states. This seems to be an ambitious study which aims to improve our understanding of gut hormone physiology and pathophysiology.</p> <p>Comments:</p> <ol style="list-style-type: none"> <li>1. Limitations of the study should include utilization of only a 2 day washout period for use of diabetes medications.</li> <li>2. The effect of various types of bariatric surgery and various types of metabolic statuses on gut hormone secretion have been heavily studied. The introduction and discussion sections should be edited to clarify this and expand upon how this new study will improve upon what is already published.</li> <li>3. There are problems with units in the methods (aliquoting of 300ml?) and in table 1 units are not provided.</li> <li>4. The authors state that oxyntomodulin will be measured but do not provide methods for this.</li> </ol>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Nicola Basso

Institution and Country: Sapienza-Università di Roma, Italy

I am not sure whether the general reader of BMJ Open will be interested in reading a protocol for a clinical study. Besides this it is a well-written protocol.

Thank you for your very positive words about our manuscript. We think that it is interesting and of use for readers of BMJ Open to read how we conducted a physiological study like ours.

Reviewer: 2

Reviewer Name: Jodok Fink

Institution and Country: University of Freiburg, Department of Surgery

The manuscript describes a study protocol of a "single centre cross sectional study". With the aim to evaluate serum levels of the intestinal hormones PYY and GLP-1, these hormones will be investigated in non-surgical and surgical patients. The surgery group includes 4 different metabolic operations, each representing a group of 30 patients. The non-surgical group includes obese and non-obese individuals with and without type 2 diabetes. The primary endpoint of the study is the area under the curve after PYY and GLP-1 measurements.

## Introduction

The introduction contains known and correct facts about obesity surgery and intestinal hormones. However, each sentence seems to stand somewhat separate from the next. Therefore it is very hard to read.

An English native speaker has adjusted the introduction, to increase readability and understanding.

The "gap to be filled" is certainly the most important part of any introduction. However, the authors cannot demonstrate the need for this study, although the study itself is, without doubt, very interesting as we are indeed lacking knowledge of the physiological and postoperative levels of gut hormones.

In our opinion, the comparative aspect of our study is necessary because current knowledge is lacking in terms of gut hormone level differences in conventional and surgical models. Especially in newer surgical techniques like Mini Gastric Bypass and the Diverted Sleeve Gastrectomy less is known about the gut hormone levels. An additional paragraph is added to the introduction to elucidate this matter.

## Inclusion criteria

The authors define two groups of diabetic patients. However, the state of type 2 diabetes is poorly characterized. "Type 2 diabetes no longer than 3 years" is the only criteria mentioned. This leaves patients with 200 IE insulin need with a HbA1c of 11% as well as patients with only one oral anti-diabetic agent and a normal HbA1c to be included. This will certainly be a large source of variation. In the surgical group, type 2 diabetes is not defined at all. Again, this will produce a large variation that is not due to the issue intended to study. Furthermore, there is a huge change in body weight and body composition and a large amount of intestinal adaption between 6 months and 2 years after any metabolic operation. Why did the authors not include patients 6 months after any of these operations. That could be easily done and would produce far better results.

In both the surgical group and the non-surgical group the inclusion criteria have been sharpened and rewritten. Secondly it is true that there are huge changes occurring in the first two years, but in our experience (in Turkey, The Netherlands, Brazil and India) weight profiles are the most instable in the first six months after surgery, which also includes a hypothetically 'instable' gut hormone profile. In other words we wanted to make a comparison between different surgical and conservative models and therefore a stable situation is necessary, especially in the surgical models.

## Discussion

The discussion contains a large section on GIP, which is not subject of this study. Furthermore, the discussion restates parts of the introduction.

The first part of the discussion is a summary of our research questions and hypotheses. Secondly, GIP is included in the discussion to explain its role as an antagonist of the effects of GLP-1 and PYY. This is basically the foregut-hindgut imbalance.

Overall, the idea of the study is certainly of interest for the scientific society. However, inclusion criteria should be defined more sharply. The manuscript is very hard to read in general and could be shortened immensely.

An English native speaker has checked the manuscript and the inclusion criteria are defined more sharply in the revised manuscript.

Reviewer: 3

Reviewer Name: Bethany Cummings

Institution and Country: Cornell University, USA

The paper by Celik et al. describes the study protocol for the assessment of post-prandial secretion of GLP-1, PYY and oxyntomodulin after several types of bariatric surgery or in several different metabolic states. This seems to be an ambitious study, which aims to improve our understanding of gut hormone physiology and pathophysiology.

Comments:

1. Limitations of the study should include utilization of only a 2-day washout period for use of diabetes medications.

This has been added to the limitations section

2. The effect of various types of bariatric surgery and various types of metabolic statuses on gut hormone secretion has been heavily studied. The introduction and discussion sections should be edited to clarify this and expand upon how this new study will improve upon what is already published.

As stated earlier, the comparative aspect of our study is necessary because current knowledge is lacking in terms of gut hormone level differences in conventional and surgical models. An additional paragraph is added to the introduction to elucidate this matter.

3. There are problems with units in the methods (aliquoting of 300ml?) and in table 1 units are not provided.

Units are added to the legend of table 1. 'Aliquoting of 300 ml' was a typing error, and this has been corrected in the revisional manuscript.

4. The authors state that oxyntomodulin will be measured but do not provide methods for this.

This is a typing error (due to revisions of our earlier protocol). This has been corrected in the revisional manuscript.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Jodok Fink University of Freiburg
<b>REVIEW RETURNED</b>	06-Jan-2016

<b>GENERAL COMMENTS</b>	<p>The authors have addressed all mentioned points of the reviewers. The introduction now contains a very large “gap to be filled” part. Especially in the first sections the authors explain the need for this study.</p> <p>The authors altered the inclusion criteria to now add a HbA1C above 7 and “stable medication” for the diabetic patients. This however leaves my initial remark basically unchanged. Still this leaves a very large source of variation. And what does “stable medication” mean? Furthermore, the authors responded that they were interested in a stable incretin condition and that they therefore included a period from 6 months to 2 years. However that was exactly the point I tried to address. Especially in a time from 6-12 months, still a lot of changes occur.</p> <p>I think the study is of high interest to the scientific society as we lack comparative studies of both healthy and diabetic as well as surgical and non-surgical individuals. Even more it is important to very well define subjects included. It will be interesting so see the results.</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Jodok Fink

Institution and Country: University of Freiburg

Please state any competing interests or state ‘None declared’: None declared

The authors have addressed all mentioned points of the reviewers. The introduction now contains a very large “gap to be filled” part. Especially in the first sections the authors explain the need for this study.

The authors altered the inclusion criteria to now add a HbA1C above 7 and “stable medication” for the diabetic patients. This however leaves my initial remark basically unchanged. Still this leaves a very large source of variation. And what does “stable medication” mean?

Stable medication means that first of all patients did not change (or the doctors of the patients did not change medication) for 6 months or longer. This has been corrected and added to the manuscript

Furthermore, the authors responded that they were interested in a stable incretin condition and that they therefore included a period from 6 months to 2 years. However that was exactly the point I tried to address. Especially in a time from 6-12 months, still a lot of changes occur.

It is indeed true that in 6-12 months a lot of changes occur, but in our experience these are much gradual changes than in the first 6 months. Secondly in terms of weight loss, the first 6 months the delta weight loss is the highest.

I think the study is of high interest to the scientific society as we lack comparative studies of both healthy and diabetic as well as surgical and non-surgical individuals. Even more it is important to very well define subjects included. It will be interesting so see the results.

Thank you for your positive interest in our study