

BMJ Open Effects of different metabolic states and surgical models on glucose metabolism and secretion of ileal L-cell peptides: protocol for a cross-sectional study

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ABSTRACT

Introduction: Obesity and type 2 diabetes mellitus are increasing worldwide, reaching pandemic proportions. The understanding of the role of functional restriction and gut hormones can be a beneficial tool in treating obesity and diabetes. However, the exact hormonal profiles in different metabolic states and surgical models are not known.

Methods and analysis: The HIPER-1 Study is a single-centre cross-sectional study in which 240 patients (in different metabolic states and surgical models) will receive an oral mixed-meal tolerance test (OMTT). At baseline and after 30, 60 and 120 min, peptide YY and glucagon-like peptide 1 levels and glucose and insulin sensitivity will be measured. The primary end point of the study will be the area under the glucagon-like peptide 1 and peptide YY curves after the OMTT. Secondary study end points will include examination of the difference in plasma levels of the distal ileal hormones in subjects with various health statuses and in patients who have been treated with different surgical techniques.

Ethics and dissemination: An independent ethics committee, the Institutional Review Board of Istanbul Sisli Kolan International Hospital, Turkey, has approved the study protocol. Dissemination will occur via publication, national and international conference presentations, and exchanges with regional, provincial and national stakeholders.

Trial registration number: NCT02532829; Pre-results.

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are increasing worldwide, reaching pandemic proportions.¹ Diet, exercise and medication remain the cornerstones for the treatment of T2DM. However, apart from studies demonstrating promising results in some developed countries, the long-term success rates of lifestyle and drug modifications are disappointing.² Even with an impressive

Strengths and limitations of this study

- The study will provide new insights into gut hormone profiles in different metabolic states and surgical models.
- The study will also provide insights into glucose metabolism and insulin resistance and their correlation with gut hormones.
- This study is limited to four surgical procedures: sleeve gastrectomy, mini gastric bypass, sleeve gastrectomy with ileal transposition, and sleeve gastrectomy with transit bipartition.
- This is a single-centre study performed in a Turkish metabolic surgery clinic with a specific patient population, which may limit generalisability of the study results.
- Only a 2-day washout period will be used for diabetes medication.

armamentarium of medication, adequate long-term glycaemic control is difficult, and overly tight glycaemic control introduces a proportionate risk of hypoglycaemia; furthermore, targets have been modified because of the high risk of cardiovascular events.³ Moreover, diabetes medication can promote weight gain, which in turn exacerbates obesity issues.^{4 5}

In cases where classic surgical strategies prove to be inadequate, broad gastrointestinal (GI) surgical methods offer new alternatives to treating obesity and T2DM.⁶ In severely obese patients, bariatric surgical options produce significant sustained weight loss, improvement in obesity-related comorbidities, and reduction in long-term mortality.⁷ Currently, bariatric surgery is considered to be appropriate for individuals with a body mass index (BMI) >35 kg/m² and serious obesity-related comorbidities, including T2DM. Surgical procedures involving intestinal bypass exert particularly large

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effects on diabetes.⁸ Mounting evidence indicates that these remarkable effects result from not only weight loss but also weight-independent antidiabetic mechanisms.⁹ Consequently, conventional bariatric procedures and new experimental GI operations are being explored for management of patients with T2DM who are overweight or class I obese (BMI 30–35 kg/m²).

Many physiological mechanisms proposed to explain the improvement in glucose metabolism, insulin metabolism and β -cell function following surgery include:^{10–14}

- A. Major diet restriction early after surgery
- B. Hepatic insulin sensitivity recovery early after surgery
- C. Increase in incretin hormone (glucagon-like peptide 1 (GLP-1)) caused by rearrangements in the GI tract
- D. Earlier blockage of glucagon secretion caused by GLP-1
- E. Less hunger and early satiety (changes in ghrelin, GLP-1, peptide YY (PYY) and oxyntomodulin)
- F. Recovery of β -cell function by incretin stimulation
- G. Weight-loss-induced reduction in β -cell gluco- and lipo-toxicity.

Evidence gaps to be filled

The complete mechanisms of glucose and insulin metabolism and the changes after metabolic surgery remain poorly understood. The variable levels of incretin stimulation (especially GLP-1) and improved glycaemic control in those with diabetes have been shown after various bariatric techniques.^{10–13} PYY(1–36) is also synthesised and released from specialised enteroendocrine cells called L-cells found predominantly within the distal GI tract (hindgut) and is then cleaved by the enzyme, dipeptidyl peptidase-4, to give the active form, PYY(3–36).¹⁵ In our study, we will measure the active PYY (3–36) to better document the effects of the active form of PYY for eight groups. Measurement of serum PYY in ‘no surgery’ and ‘surgery’ groups will give us the pattern of PYY stimulation in different groups. Since all eight groups will be tested with the standard oral mixed-meal tolerance test (OMTT), the effect of macronutrients on the PYY peak will be overcome.¹⁶ The ‘ileal brake’ term can be considered a summary of GLP-1 and PYY actions on the gut, including reduction in gastric emptying and delay in intestinal transit, and can be used as a tool for treatment of people with obesity and related conditions. We must add that they also act on both the peripheral and central nervous systems, concentrating at the arcuate nucleus of the hypothalamus, which plays a key role in the regulation of appetite. Batterham *et al.*¹⁷ reported the effects of PYY(3–36) on rats, and the following year documented the effects on humans,¹⁸ and found that basal levels of PYY in obese compared with normal-weight subjects were lower. There was also a blunted postprandial PYY rise, suggesting that a lack of endogenous PYY secretion may be implicated in the development of obesity. In our study, we expect to see different patterns of serum PYY levels, which should better explain the role of PYY in the eight different

groups. GLP-1 is secreted from distal intestinal L-cells along with PYY and oxyntomodulin in response to a meal. However, little is known about the levels of distal intestinal L-cell hormones in healthy individuals, different disease states, and different body compositions. Also, the difference in the baseline values and activities of these hormones after different surgical techniques has not been extensively studied. The present study will provide insight into the physiology of these gut hormones and their relation to glucose metabolism after metabolic surgery. Secondly, this study will provide insight into differences between gut hormone levels in different metabolic states and after different surgical procedures, which will be necessary for our understanding of physiological aspects of these gut hormones.

SPECIFIC AIMS

We plan to test our hypothesis, and thereby accomplish the objective of this application, by pursuing the following specific aims.

Aim 1: To measure and compare the levels of GLP-1 and PYY in non-obese healthy volunteers versus obese diabetic patients versus obese non-diabetic subjects versus non-obese diabetic patients with administration of a standardised OMTT at baseline, 30, 60 and 120 min.

Hypothesis 1: There will be increasing levels of GLP-1 and PYY response to an OMTT in individuals across the diabetes-obesity spectrum, from those who are obese diabetics followed by non-obese diabetics, obese non-diabetics and healthy non-obese non-diabetics.

Aim 2: To measure and compare the levels of GLP-1 and PYY in patients who have undergone sleeve gastrectomy (SG) versus mini gastric bypass (MGB) versus sleeve gastrectomy with ileal transposition (SIT) versus sleeve gastrectomy with transit bipartition (STB) after administration of OMTT at baseline, 30, 60 and 120 min.

Hypothesis 2: There will be increasing levels of GLP-1 and PYY after an OMTT in patients who have undergone an SG, followed by MGB, SIT and STB.

Aim 3: To analyse the response of insulin and glucose after an OMTT in relation to the type of surgery.

Hypothesis 3: There will be marked improvements in glycaemic control and insulin activity in techniques involving bowel anastomosis, compared with SG.

In this study, we aim to analyse the baseline levels and 30, 60 and 120 min postprandial activities of GLP-1 and PYY in no surgery and surgery groups (defined below). This will be the initial evaluation of a durability study that is planned for a minimum of 5 years follow-up.

METHODS

This cross-sectional study will be performed at the Metabolic Surgery Clinic in Istanbul. Inclusion will be performed by the physician researcher after written informed consent. The study consists of a non-surgical and a surgical group.

Sample size calculation and statistical analysis

The study is fashioned as a cross-sectional analysis and it will be an institutional review board (IRB)-approved prospective study. Sample size calculation is based on the formula of Kelsey. The sample size will be 120 subjects in the surgical group and 120 subjects in the non-surgical group (which means 30 subjects in each subgroup) based on a significance level of 5%, a power of 80% and a mean decrease in fasting glucose level (post-operative) of 35%.^{19 20}

In total, 240 patients will be included in this study (box 1). Continuous variables will be presented as mean \pm SD, and categorical variables as frequency with percentages. Statistical analysis will be performed by repeated measurement analysis of variance and one-way analysis of variance.

In all tests, values of $p < 0.05$ will be considered significant. SPSS (V.20.0) will be used to prepare the database and for statistical analysis.

Non-surgical group

Study population

We will be studying 120 subjects (aged 30–60 years) in the non-surgical groups.

Inclusion criteria

- A. For healthy subjects (group NS-A): No known disease, no previous surgery, glycated haemoglobin (HbA1c) $< 5.7\%$, BMI $< 25 \text{ kg/m}^2$ ($n=30$)
- B. For diabetic obese (group NS-B): Type 2 diabetes diagnosis at least longer than 3 years; under stable medical treatment (no changes in medication or insulin dosage have been made in the last 6 months); HbA1c $> 7\%$; weight stability, defined as no significant change (5%) within the last 3 months; BMI $> 30 \text{ kg/m}^2$ ($n=30$)
- C. For diabetic non-obese (group NS-C): Type 2 diabetes diagnosis at least longer than 3 years; under stable medical treatment (no changes in medication or insulin dosage have been made in the last 6 months); HbA1c $> 7\%$; weight stability, defined as no significant change (5%) within the last 3 months; BMI $< 30 \text{ kg/m}^2$ ($n=30$)

- D. For obese non-diabetics (group NS-D): HbA1c $< 5.7\%$; no signs and history of type 2 diabetes; BMI $> 30 \text{ kg/m}^2$ ($n=30$).

Exclusion criteria

- A. Insulin/islet antibody and glutamic acid decarboxylase antibody positivity, plasma fasting C-peptide $< 1 \text{ ng/mL}$
- B. Liver cirrhosis, severe renal failure, collagen diseases, severe endocrinopathies, blindness
- C. Heart failure, acute myocardial infarction, stroke or transient ischaemic attack, unstable angina pectoris
- D. History of malignancy or malignant neoplasm, severe inflammatory complications, neurological or cardiovascular
- E. Pregnancy
- F. Any conditions that, as decided by the head of the study, could represent a risk to the patient or could affect the protocol results.

Recruitment of the subjects

The subjects for this non-surgical arm of the study will be recruited from the websites of surgical and medical associations and formally announced in the meetings. The study will also be promoted in national organisations. Interested candidates will be directed to study personnel who will provide study-related information and screen the patients for initial eligibility. Patients who agree to stop their antidiabetic medications 2 days before evaluation will be enrolled in the study.

Surgical group

Identification of study population

In the surgical group there will be four different types of surgery. Age- and sex-matched patients who have undergone laparoscopic sleeve gastrectomy (group SG), mini gastric bypass (group MGB), SG with ileal transposition (group IT) or SG with transit bipartition (group TB), not less than 6 months previously but within the last 2 years, will be enrolled. The primary methodology of the study is to achieve an adequate number of patients via an announcement through the website of the Turkish Metabolic Surgery Foundation and divide the patients according to the mentioned categories.

In the surgical groups, we expect a change in hormones by proximalising an intestinal limb and as a consequence activating the entero–insular axis. Similarly, as observed in morbidly obese subjects after bariatric surgery, changes will be stable in the long term. Based on observations in morbidly obese and T2DM morbidly obese subjects, we expect a great reduction in or disappearance of insulin resistance and improvement in β -cell function, represented here by variables obtained from a mathematical model applied to OMTT data (fasting insulin secretion, total insulin secretion, β -cell glucose sensitivity, rate sensitivity and potentiation factor) with consecutive improvement in clinical T2DM symptoms and the other components of the metabolic syndrome.

Box 1 Overview of study groups and outcomes measured

Non-surgical groups ($n=120$)

1. Healthy volunteers ($n=30$)
2. Obese diabetics ($n=30$)
3. Obese non-diabetics ($n=30$)
4. Non-obese diabetics ($n=30$)

Surgical groups ($n=120$)

5. Sleeve gastrectomy (SG, $n=30$)
6. Mini gastric bypass (MGB, $n=30$)
7. SG with ileal transposition (IT, $n=30$)
8. SG with transit bipartition (TB, $n=30$)

To assess the characteristics of distal ileal hormones, we will perform an OMTT and analyse the variables in box 2. The exclusion criteria will be the same as in the non-surgical group.

Inclusion criteria

- Patients with type 2 diabetes who have undergone an SG, an MGB, an SIT or an STB more than 6 months ago, but within the last 2 years, with steady weight profile (weight stability is defined as no significant change (5%) within the last 3 months)
- Preferably not taking any kind of antidiabetic drugs or will agree to stop all antidiabetic drugs 2 days before evaluation
 - With either a reduction in HbA1c (compared with preoperative value) and/or reduction in insulin and/or reduction in antidiabetic drugs
- Absence of or resolved comorbidities (dyslipidaemia, hypertension, neuropathy, retinopathy, cardiovascular disease, stroke events or lower extremity amputation)
- Possibility to participate in the quadruplicate measurement protocol.

Recruitment of subjects

The subjects for this non-surgical arm of the study will be recruited from the websites of surgical and medical associations and formally announced in the meetings. The study will also be promoted in national organisations. Interested candidates will be directed to study personnel who will provide study-related information and screen the patient for initial eligibility. Patients who agree to stop their antidiabetic medication 2 days before evaluation will be enrolled in the study.

Intervention

OMTT, a standard mixed-meal tolerance test (350 kcal, consisting of 55% carbohydrate, 25% protein and 20% fat), is going to be performed on each participant. Venous blood samples will be collected at the fasting stage and at 30, 60 and 120 min after the OMTT via a

Box 2 Outcomes measured

- Baseline and 30, 60 and 120 min GLP-1 and PYY response to an OMTT
 - Baseline and 30, 60 and 120 min plasma insulin and glucose measurements
 - Fasting lipid profile: total cholesterol, HDL- and LDL-cholesterol and triglycerides
 - Liver profile: AST, ALT and GGT
 - Body weight, BMI, waist and hip circumference
- ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, γ -glutamyltransferase; GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OMTT, oral mixed-meal tolerance test; PYY, peptide YY.

Table 1 Oral mixed-meal tolerance test (OMTT) protocol

Time (min)	Yellow lavender with gel separator	Na2EDTA	K2 2xK2EDTA +DPP IV inhibitor	Volume
0	7	3	6	16
30	7	3	6	16
60	7	3	6	16
120	7	3	6	16

Yellow lavender with gel separator: serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, γ -glutamyltransferase (all in μ U/L).
Na2EDTA: HbA1c (mmol/mol).
2xK2EDTA+DPP IV inhibitor: glucagon like peptide-1 (GLP-1 in pmol/l); peptide YY (in pg/mL).

catheter localised in the antecubital vein. All blood samples will be drawn according to the OMTT protocol (table 1).

Analytical procedures

All the blood samples will be collected according to the aforementioned OMTT protocol. Blood samples collected into ice-chilled tubes containing K2EDTA (spray-dried) tubes treated with dipeptidyl peptidase-4 inhibitor (BD Cat No: 366473 vacutainer P700) will be used for PYY and GLP-1 determinations. The tubes will be kept on ice until centrifuged at +4°C for 20 min at 4000 g. Plasma will be separated and immediately frozen at -20°C in aliquots of 30 mL and kept until analysis. Serum separated by gel-containing yellow lavender tubes for the analysis of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and γ -glutamyltransferase (GGT), and whole blood samples collected into Na2EDTA for HbA1c analysis will be used. Plasma glucose will be monitored from the plasma obtained from fluoride/oxalate tubes (grey lavender). Plasma insulin will be measured from plasma obtained from Na2EDTA tubes. Liver function tests (SGOT, SGPT and GGT) and HbA1c will have a single measurement during fasting. Plasma insulin levels and plasma glucose levels will be measured during fasting and 30, 60 and 120 min after the OMTT.

Outcomes measured

During the patient visit, a complete medical history and physical examination will be performed. Body weight, waist and hip circumference, and BMI will be measured and recorded. The following outcomes (box 2) will also be measured.

A. Plasma PYY will be measured by a commercial ELISA kit from Biovender Research and Diagnostics Products 'Human PYY ELISA' (Cat No: RSCYK080R) with a competitive enzyme immunoassay (EIA) using a combination of highly specific antibody to human PYY and a biotin-avidin affinity system. The EIA kit shows 100% cross-reactivity with human PYY(3-36) and human

PYY(1–36), and shows less than 0.003% cross-reactivity with human and rat neuropeptide Y, which have a similar amino acid sequence to human PYY.

Test principle. This EIA kit for determination of human PYY in samples is based on a competitive EIA using a combination of highly specific antibody to human PYY and a biotin–avidin affinity system. Labelled antigen is added to the wells of a plate coated with rabbit anti-human PYY antibody, standard or samples to produce a competitive immunoreaction. After incubation and plate washing, horseradish peroxidase (HRP)-labelled streptavidin is added to form an HRP-labelled streptavidin-biotinylated antigen–antibody complex on the surface of the wells.

B. Plasma total GLP-1 will be measured with a commercial ELISA kit (EIA-5095; DRG) with a two-site ‘sandwich’ technique with two selected GLP-1 antibodies.

Test principle. This ELISA is designed, developed and produced for the quantitative measurement of GLP-1 (7–36) and GLP-1(9–36) in plasma samples. The assay uses the two-site ‘sandwich’ technique with two selected GLP-1 antibodies. Assay standards, controls and test samples are directly added to wells of a microplate coated with streptavidin. Subsequently, a mixture of biotinylated GLP-1-specific antibody and an HRP-conjugated GLP-1-specific antibody is added to each well. After the first incubation period, a ‘sandwich’ immunocomplex of ‘streptavidin–biotin antibody–GLP-1 (7–36)/(9–36)–HRP-conjugated antibody’ is formed and attached to the wall of the plate. The unbound HRP-conjugated antibody is removed in a subsequent washing step. For the detection of this immunocomplex, each well is then incubated with a substrate solution in a timed reaction and then measured in a spectrophotometric microplate reader. The enzymatic activity of the immunocomplex bound to GLP-1 (7–36)/(9–36) on the wall of the microtitre well is directly proportional to the amount of total GLP-1 in the sample.

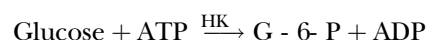
- ▶ **Sensitivity** The sensitivity of this total GLP-1 ELISA, as determined by three times the SD above zero standard on 12 replicate determinations, is ~0.6 pmol/L.
- ▶ **Specificity** This bioactive GLP-1(7–36) assay is specific for GLP-1(7–36). It is expected that this assay will not detect the following peptides:
 - GLP-1(7–36) 100%
 - GLP-1(9–36) 100%
 - GLP-1(9–37) <0.1%
 - GLP-1(7–37) <0.1%
 - GLP-1(1–36) <0.1%
 - GLP-2 <0.1%
 - Glucagon <0.1%

C. Liver function tests (SGOT, SGPT and GGT) will be measured by the IFCC Enzymatic Assay in a Cobas 6000 (Roche Diagnostics).

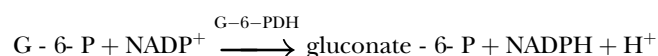
D. HbA1c will be measured by the turbidometric assay, Tina-quant HbA1c Gen.3, in a Cobas 6000 based on measurement of the antipolyhapten complex.

E. Plasma insulin levels will be measured by an electrochemiluminescence immunoassay in a Cobas 6000 based on a sandwich assay. For quality control, PreciControl Multimarker or PreciControl Universal will be used.

F. Plasma glucose levels will be measured by an enzymatic reference method with hexokinase. Hexokinase catalyses the phosphorylation of glucose to glucose 6-phosphate (G-6-P) by ATP.



Glucose-6-P dehydrogenase (G-6-PDH) oxidises G-6-P in the presence of NADP to gluconate 6-phosphate. No other carbohydrate is oxidised. The rate of NADPH formation during the reaction is directly proportional to the glucose concentration and is measured photometrically.



Primary end points

The primary end point as the key outcome measure of the study will be area under the GLP-1, PYY, glucose and insulin curves after the OMTT.

Secondary end points

Secondary study end points will include examination of the difference in plasma levels of the distal ileal hormones in subjects with various health statuses and in patients who have been treated by different surgical techniques.

Ethics and informed consent

An independent ethics committee, the Istanbul Sisli Kolan International Hospital Institutional Review Board, has approved the study protocol. Oral and written informed consent will be obtained from the patients before inclusion. This study will take place in the Metabolic Surgery Clinic, Sisli, Istanbul, Turkey and the inclusion of patients will take place between October 2015 and March 2016.

Informed laboratory personnel will perform the OMTT, as well as measurements of PYY and GLP-1.

Research nurses will collect the necessary data (from patient charts) and will store them on a secure hard drive. These hard drives will be collected and stored at the Metabolic Surgery Clinic in Istanbul.

Adverse events

Although the OMTT is considered safe, serious adverse events possibly related to it will be reported to the ethics committee.

Dissemination plan

We expect that the results of this study will help us to understand the physiology regarding the enteric gut hormones and the improvement in glucose metabolism

and insulin sensitivity after bariatric and metabolic surgery. The results will also give us insight into how to select patients for specific bariatric surgical procedures. We expect the study to have international appeal because of the increasing interest in gut hormone physiology and its correlation with patient outcomes (in terms of improvement/remission of type 2 diabetes after surgery). For end-of-study knowledge dissemination, we intend to publish in medical, health services and/or public health journals. More importantly, we plan to present and discuss the results of our study at national and international congresses focusing on surgery and endocrinology.

DISCUSSION

In this study we have three main hypotheses. (1) There will be increasing levels of GLP-1 and PYY response to an OMTT in individuals across the diabetes–obesity spectrum, from those who are obese diabetics followed by non-obese diabetics, obese non-diabetic and healthy non-obese non-diabetics. (2) There will be increasing levels of GLP-1 and PYY after an OMTT in patients who have undergone an SG followed by those who have had an MGB, SIT or STB. (3) There will be marked improvements in glycaemic control and insulin activity after techniques involving bowel anastomosis, compared with SG. To our knowledge, this is the first study that aims to extensively research glucose metabolism and secretion of ileal L-cell peptides in different metabolic states and surgical models.

There is increasing evidence that gut hormones play an important role in the neuroendocrine physiology of hunger and satiety. As pointed out by Santoro²¹ and Celik *et al.*^{19 20} there is need for a change in the current practice of bariatric/metabolic surgery. For such changes, we need to focus on functional restriction, the proximal and distal gut imbalance, and the role of gut hormones such as PYY and GLP-1.^{19 21}

One of the important hormones in the proximal gut is glucose-dependent insulinotropic polypeptide (GIP). It is known to be a counteractive hormone that produces an insulin response, but, instead of decreasing the secretion of glucagon, it enhances it.²¹ Abnormally high levels of GIP are present (mainly a proximal gut product) in obese and diabetic patients.²² Any kind of dietary restriction will lead to significant decreases in GIP levels.²³ GIP is a hormone that is obesogenic and insulinotropic, and strategies to block GIP production are beneficial for these patients.^{24 25}

In contrast, the distal gut hormones (eg, GLP-1 and PYY) or their agonists, are beneficial for obese and diabetic patients. Either way, blocking the hormonal activity of the proximal gut and increasing the activity of the distal gut is beneficial. Surgical procedures support these findings.²⁰ Because of the scarcity of literature on the production of these hormones in different metabolic states and surgical models, a total of eight groups

will be compared with each other (see [box 1](#)), to gain more insight into the physiology of glucose and hormone metabolism.

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Contributors AC, JBD: initial idea. AC, JBD, SP, BOC, FCK, SS, AG, SU: drafting and finalising of the manuscript.

Competing interests JBD is supported by an NHMRC Senior Research Fellowship. He has consultancies with Apollo Endosurgery, Bariatric Advantage and Novo Nordisk, serves on the Scientific Advisory Board OPTIFAST (Nestle Australia), has received speaker's fees from iNova Pharmaceuticals, Eli Lilly, Biogen Idec, Abbott Australasia, and Merck Sharp and Dohme, and received course director fees from Quadrant Healthcom for the MISS meeting. His research institution has received funding from NHMRC Project Grants, RACGP, Allergan Inc, Nestle Australia, ResMed and BUPA. SS is on the Ethicon Advisory Board.

Patient consent Obtained.

Ethics approval The Istanbul Sisli Kolan International Hospital Institutional Review Board.

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