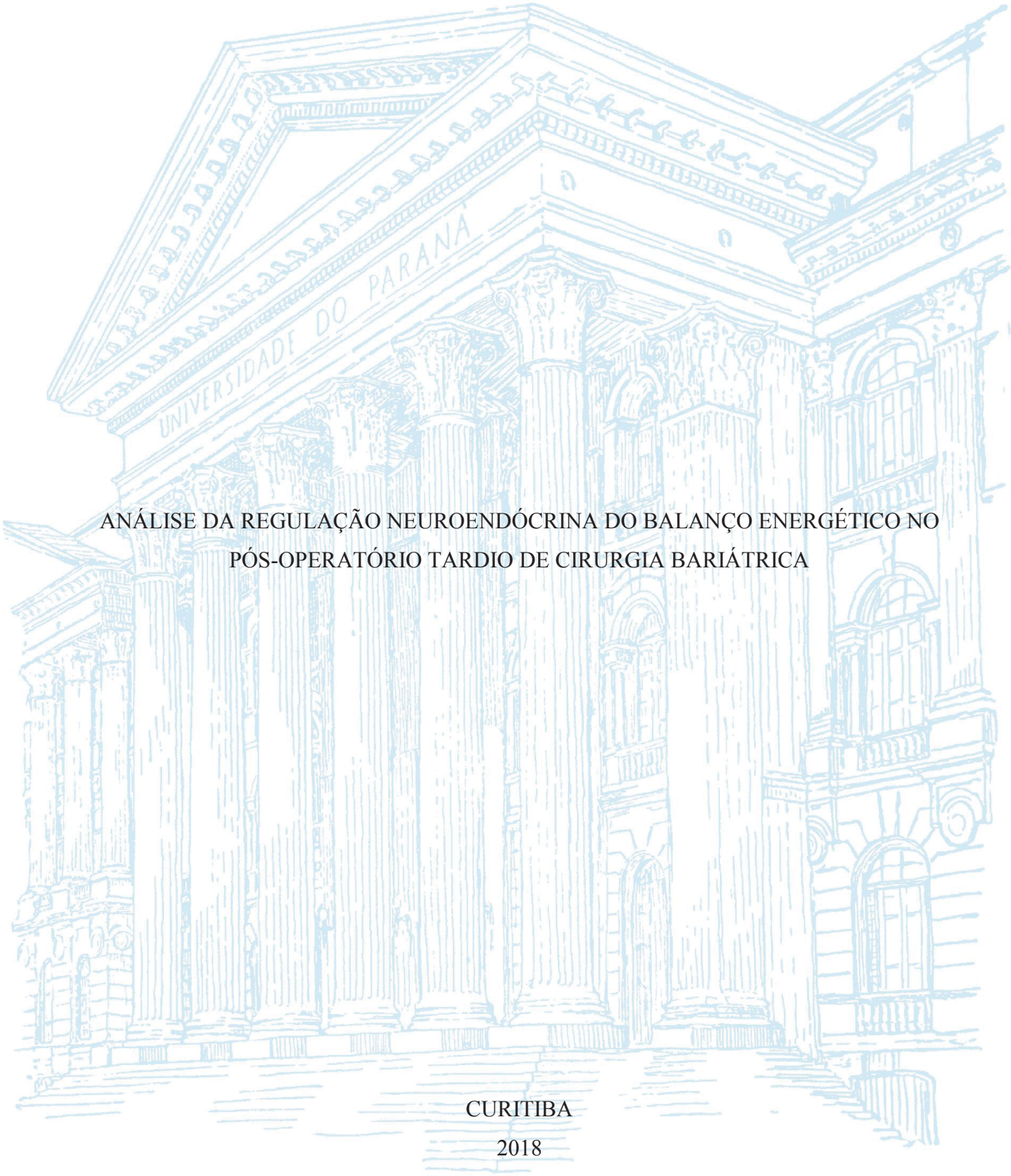
UNIVERSIDADE FEDERAL DO PARANÁ

GISELE FARIAS



ANÁLISE DA REGULAÇÃO NEUROENDÓCRINA DO BALANÇO ENERGÉTICO NO PÓS-OPERATÓRIO TARDIO DE CIRURGIA BARIÁTRICA

CURITIBA

2018

GISELE FARIAS

ANÁLISE DA REGULAÇÃO NEUROENDÓCRINA DO BALANÇO ENERGÉTICO NO PÓS-OPERATÓRIO TARDIO DE CIRURGIA BARIÁTRICA

Tese apresentada como requisito parcial à obtenção do grau de Doutora em Clínica Cirúrgica, no Curso de Pós-Graduação em Clínica Cirúrgica, Setor de Ciências da Saúde, da Universidade Federal do Paraná.

Orientador: Prof. Dr. Alexandre Coutinho Teixeira de Freitas

Coorientadora: Profa. Dra. Bárbara Dal Molin Netto

CURITIBA

2018

FICHA CATALOGRÁFICA ELABORADA PELO SISTEMA DE BIBLIOTECAS/UFPR
BIBLIOTECA DE CIÊNCIAS DA SAÚDE, BIBLIOTECÁRIA: RAQUEL PINHEIRO COSTA
JORDÃO CRB 9/991 COM OS DADOS FORNECIDOS PELA AUTORA

F224 Farias, Gisele
Análise da regulação neuroendócrina do balanço energético no pós-operatório tardio de cirurgia bariátrica / Gisele Farias. – Curitiba, 2018.
107 f. ; 30 cm.

Orientador: Prof. Dr. Alexandre Coutinho Teixeira de Freitas
Coorientadora: Prof.ª Dr.ª Bárbara Dal Molin Netto
Tese (Doutorado) – Programa de Pós-Graduação em Clínica Cirúrgica. Setor de Ciências da Saúde. Universidade Federal do Paraná.

1. Obesidade. 2. Cirurgia bariátrica. 3. Metabolismo energético. 4. Perda de peso. I. Freitas, Alexandre Coutinho Teixeira de. II. Netto, Bárbara Dal Molin. III. Programa de Pós-Graduação em Clínica Cirúrgica. Setor de Ciências da Saúde. Universidade Federal do Paraná. IV. Título.

NLMC: WD 210

MINISTÉRIO DA EDUCAÇÃO
SETOR CIÊNCIAS DA SAÚDE
UNIVERSIDADE FEDERAL DO PARANÁ
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO MEDICINA (CLÍNICA CIRÚRGICA)

TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em MEDICINA (CLÍNICA CIRÚRGICA) da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **GISELE FARIAS** intitulada: **ANÁLISE DA REGULAÇÃO NEUROENDÓCRINA DO BALANÇO ENERGÉTICO NO PÓS-OPERATÓRIO TARDIO DE CIRURGIA BARIÁTRICA**, após terem inquirido a aluna e realizado a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no ato de defesa.

A outorga do título de doutor está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 05 de Agosto de 2015.

ALEXANDRE COUTINHO TEIXEIRA DE FREITAS
Presidente da Banca Examinadora (UFPR)

ULA MASSAE OYAMA
Avaliador Externo (UNIFESP)

JORGE EDUARDO FOUTO MATIAS
Avaliador Interno (UFPR)

MARCOS FABIANO SEGUALL
Avaliador Externo (UP)

Dedico este trabalho aos indivíduos que, direta ou indiretamente, são afetados pela obesidade e aos pesquisadores deste tema, que assim como eu, estão em busca da solução para este grave problema de saúde pública.

AGRADECIMENTOS

Primeiramente agradeço à Deus por me abençoar com força, persistência e coragem para realização deste trabalho.

Aos meus pais Paulo e Mara, que muitas vezes renunciaram aos seus sonhos para investir em minha educação. Sem o apoio e amor de vocês durante esta caminhada eu não conseguiria. Obrigada por me ensinarem a lutar pelos meus sonhos, mas sempre agindo com respeito, simplicidade, dignidade, honestidade e amor ao próximo. Tenho certeza que só venci os obstáculos por me inspirar no exemplo de resiliência de vocês.

Ao meu orientador, Professor Dr. Alexandre Coutinho Teixeira de Freitas pela oportunidade, pelos ensinamentos e por contribuir para meu amadurecimento profissional.

À Dra. Solange Cravo Bettini, minha inspiração e motivação. Tenho muito orgulho de citá-la como uma das responsáveis pela minha formação profissional. Agradeço pela confiança, pela amizade, pelos conselhos e pela paciência. Você é um exemplo de simplicidade, compreensão e competência. Todos que trabalham com você admiram sua dedicação e amor ao trabalho.

À Professora Dra. Bárbara Dal Molin Netto, coorientadora e amiga, por confiar a mim a missão de continuar o seu talentoso trabalho. Obrigada pela liberdade e confiança referente ao presente trabalho, além dos indiscutíveis ensinamentos, amizade e compreensão em momentos difíceis. Obrigada por contribuir para meu crescimento pessoal e profissional e pelo apoio incondicional em todos os momentos.

À Professora Dra. Ana Dâmaso, o meu reconhecimento e a minha gratidão pela oportunidade de participar de um projeto em um grupo de pesquisa que transpira sabedoria; meu respeito e admiração pela sua seriedade e pelo seu dom no ensino da ciência e pesquisa.

Aos funcionários do departamento de Bioquímica e da Seção de Coleta da Unidade de Apoio Diagnóstico do HC-UFPR por contribuírem com dedicação e comprometimento para a coleta das amostras.

À farmacêutica Kátia Cristina Boritza, pela solicitude, prontidão e suporte para a coleta e armazenamento das amostras durante todo o estudo.

Às alunas de graduação Larissa Gabriele da Silva, Sandy Souza e Priscilla Peixoto Policarpo da Silva pelo auxílio na coleta e tabulação dos dados.

Aos Professsores participantes da banca examinadora: Dra. Lila Missae Oyama, Dr. Marcos Fabiano Sigwalt e Dr. Jorge Eduardo Fouto Matias, pela disponibilidade e pelo interesse. Suas contribuições enriqueceram este trabalho.

À Professora Dra. Maria Emília Von der Heyde pelo incentivo para minha participação neste projeto, mas sobretudo por ter "conectado" a equipe do Atendimento Multidisciplinar ao Obeso Cirúrgico (AMOC) do HC-UFPR com o Grupo de Estudos em Obesidade (GEO) da Unifesp.

À toda minha família (irmãs, cunhados, sobrinhos, minha sobrinha Sofia que em breve estará entre nós e à integrante da família de espécie canina, minha fiel companheira e doce Cacau); pelo apoio, torcida e confiança que sempre depositam em mim; pelos momentos que não estivemos juntos e souberam entender.

À equipe do AMOC do HC-UFPR, pelo acolhimento, amizade e colaboração durante a pesquisa.

Aos pacientes, que se dispuseram voluntariamente em participar deste estudo, pela paciência e participação. Devo a realização deste trabalho a vocês.

À Universidade Federal do Paraná, em especial à equipe docente e à equipe administrativa do Programa de Pós-Graduação em Clínica Cirúrgica pela atenção e qualidade que sempre fui recebida. Os conhecimentos adquiridos carregarei para toda vida.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) pela provisão da bolsa de doutorado.

À Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) pelo apoio financeiro para realização do projeto.

À minha eterna e querida amiga Fernanda Soares Possebon (*In memoriam*) que com muito otimismo me motivou a enfrentar o novo desafio que foi o ingresso neste projeto.

Aos meus amigos e amigas que inúmeras vezes cederam os seus ouvidos e seus ombros nos momentos de aflição, mas também suas companhias repletas de carinho e alegrias nos momentos de descontração.

A todos que caminharam ao meu lado nessa jornada, seja desde o início ou próximo a conclusão, ou até mesmo durante uma parte deste período, meu sincero agradecimento pela paciência, dedicação, força, estímulo, torcida, e, por, junto comigo contornarem os tantos obstáculos.

"Cada pessoa que passa em nossa vida, passa sozinha, é porque cada pessoa é única e nenhuma substitui a outra! Cada pessoa que passa em nossa vida passa sozinha e não nos deixa só porque deixa um pouco de si e leva um pouquinho de nós. Essa é a mais bela responsabilidade da vida e a prova de que as pessoas não se encontram por acaso." Charles Chaplin

“Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no mar. Mas o mar seria menor se lhe faltasse uma gota”.

(Madre Teresa de Calcuta)

RESUMO

Introdução: A manutenção do equilíbrio do mecanismo fome-saciedade ao longo do pós-operatório e suas possíveis implicações na perda de peso sustentada após a cirurgia bariátrica tem sido alvo de pesquisas. **Objetivo:** Avaliar os efeitos da perda de peso após cirurgia bariátrica sobre a regulação neuroendócrina do balanço energético por meio da investigação do papel de peptídeos anorexígenos/orexígenos (α-MSH, PYY, NPY) e sinais periféricos (adiponectina, leptina) em adultos obesos submetidos ao Bypass Gástrico em Y-de-*Roux* (BGYR). **Métodos:** Trata-se de um estudo clínico prospectivo em pacientes submetidos ao BGYR. Foram comparados os dados antropométricos e exames laboratoriais coletados no pré-operatório e seis meses e 24 meses após a cirurgia. **Resultados:** Foram avaliados 32 pacientes: 30 do sexo feminino e dois do sexo masculino. A idade média dos participantes foi 40,10±10,00 anos e o índice de massa corporal (IMC) no período pré-operatório foi de 43,85±1,12 kg/m^2. O peso corporal e o IMC diminuíram em 35,85±10,47%, em comparação com o pré-operatório. Após 24 meses de cirurgia o peso corporal foi 70,75±2,54 kg e o IMC foi 26,45±0,92 kg/m^2. O excesso de peso diminuiu de 47,75±3,10 kg no pré-operatório para 3,67±2,35 kg após dois anos de cirurgia, correspondendo a 83,80±24,50% de perda do excesso de peso. A circunferência abdominal diminuiu de 126,20±11,02 centímetros para 94,24±10,76 centímetros após dois anos de cirurgia. Os níveis de α-MSH e NPY não se alteraram nos primeiros seis meses (0,30±0,01 ng/mL e 0,69±0,03 ng/mL, respectivamente). Houve aumento significativo de 0,96 ng/mL após 24 meses de pós-operatório nos níveis séricos de α-MSH (0,30±0,01 ng/mL para 1,26±0,16 ng/mL). Os níveis de PYY aumentaram durante os 24 meses do estudo (37,6±5,8 ng/mL para 58,7±9,8 ng/mL). Os níveis de leptina diminuíram de 38,00±3,96 ng/mL para 4,87±1,48 ng/mL e os níveis séricos de adiponectina aumentaram de 6,82±0,61 μg/mL para 27,13±4,14 μg/mL. **Conclusão:** O BGYR promoveu perda de peso significativa após 24 meses de cirurgia. A possível melhora do perfil inflamatório, representado pelo aumento dos níveis séricos de adiponectina e pelo restabelecimento da sensibilidade à leptina, reflete para melhor controle do balanço energético evidenciado pela manutenção do estímulo das vias anorexígenas, conforme aumento dos níveis séricos de PYY e α-MSH.

Palavras-chave: Obesidade. Cirurgia Bariátrica. Balanço Energético.

ABSTRACT

Introduction: Maintaining the balance of the hunger-satiety mechanism throughout the postoperative period and its possible implications for sustained weight loss after bariatric surgery has been the subject of research. **Objetive:** To evaluate the effects of weight loss after bariatric surgery on the neuroendocrine regulation of energy balance through the investigation of the role of anorexigenic / orexigenic peptides (α-MSH, PYY, NPY) and peripheral signals (adiponectin, leptin) in obese adults submitted to Roux-en-Y Gastric Bypass (BGYR). **Methods:** This is a prospective clinical study in patients submitted to BGYR. We compared the anthropometric data and biochemical markers collected in the preoperative period and six months and 24 months after surgery. **Results:** Thirty-two patients were evaluated: 30 females and two males. The mean age of the participants was 40.10 ± 10.00 years and the body mass index (BMI) in the preoperative period was 43.85 ± 1.1.12 kg/m2. Body weight and BMI decreased by 35.85 ± 10.47%, compared with preoperative. After 24 months of surgery the body weight was 70.75 ± 2.54 kg and the BMI was 26.45 ± 0.92 kg/m2. The excess weight decreased from 47.75 ± 3.10 kg in the preoperative period to 3.67 ± 2.35 kg after two years of surgery, corresponding to 83.80 ± 24.50% of excess weight loss. Abdominal circumference decreased from 126.20 ± 11.02 cm to 94.24 ± 10.76 cm after two years of surgery. The levels of α-MSH and NPY did not change in the first six months (0.30 ± 0.01 ng/mL and 0.69 ± 0.03 ng/mL, respectively). There was a significant increase of 0.96 ng/mL after 24 months postoperatively in the serum levels of α-MSH (0.30 ± 0.01 ng/mL to 1.26 ± 0.16 ng/mL). PYY levels increased during the 24-month study (37.6 ± 5.8 ng/mL to 58.7 ± 9.8 ng/mL). Leptin levels decreased from 38.00 ± 3.96 ng/mL to 4.87 ± 1.48 ng/mL and serum adiponectin levels increased from 6.82 ± 0.61 μg/mL to 27.13 ± 4.14 μg/mL. **Conclusion:** BGYR promoted significant weight loss after 24 months of surgery. The possible improvement of the inflammatory profile, represented by the increase of serum levels of adiponectin and the reestablishment of leptin sensitivity, reflects for better control of the energy balance evidenced by the maintenance of the anorexigenic pathway stimulation, as the serum levels of PYY and α-MSH increased.

Key words: Obesity. Bariatric surgery. Energy balance.

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

® - Marca registrada

ºC – Graus celsius

α-MSH – Hormônio Estimulador de Melanócitos

ABESO - Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica

AgRP – Peptídeo agouti relacionado

AHL – Área Hipotalâmica Lateral

AMOC – Atendimento Multidisciplinar ao Obeso Cirúrgico

ANOVA – Análise de Variância com Medidas Repetidas

ARC – Núcleo Arqueado do Hipotálamo

BGYR – *Bypass* Gástrico em Y-de-*Roux*

CART – Transcrito Regulado pela Cocaína e Anfetamina

CEP – Comitê de Ética de Pesquisa em Seres Humanos

CFM – Conselho Federal de Medicina

cm - Centímetros

EP – Excesso de Peso

GLP-1 – Peptídeo semelhante ao Glucagon tipo 1

GLP-2 – Peptídeo semelhante ao Glucagon tipo 2

HC-UFPR – Hospital de Clínicas da Universidade Federal do Paraná

IMC – Índice de Massa Corporal

Kg – Quilograma

Kg/m^2 – Quilograma por metro ao quadrado

m - Metros

MC4R – Receptor de melanocortina 4

mL – mililitro

ng - Nanograma

NPY – Neuropeptídeo Y

p-valor – Probabilidade

PEP – Perda de Excesso de Peso

pg - picograma

POMC – Pró-opiomelanocortina

PVN – Núcleo Paraventricular do Hipotálamo

PYY – Peptídeo YY

rpm – Rotações por minuto

SBCBM – Sociedade Brasileira de Cirurgia Bariátrica e Metabólica

SNC – Sistema Nervoso Central

μg - Micrograma

VIGITEL – Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico

VMN – Núcleo Ventromedial do Hipotálamo

WHO – World Health Organization

SUMÁRIO

1 INTRODUÇÃO

A prevalência da obesidade cresceu em proporção exponencial nos últimos anos. De acordo com dados levantados em 2016 pela Organização Mundial da Saúde, existem mais de 1,9 bilhões de adultos acima do peso ideal, sendo que destes, mais de 600 milhões são considerados obesos, o que equivale a mais de 13% da população mundial. No Brasil, a Pesquisa Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (VIGITEL) de 2016 revelou que mais da metade da população adulta apresenta excesso de peso e 18,9% estão obesos (BRASIL, 2017; WHO, 2018).

Já está bem consolidado na literatura que a obesidade possui etiologia multifatorial, uma vez que fatores genéticos, dietéticos, ambientais, endócrinos, socioeconômicos, psicológicos e comportamentais se relacionam com mecanismos envolvidos no desenvolvimento desta patologia. O pivô etiológico é o desequilíbrio crônico positivo no balanço energético, ou seja, quando o consumo alimentar supera o gasto energético, induzindo alterações hormonais e favorecendo o aumento na lipogênese e adipogênese e consequentemente aumento do peso corporal (VELLOSO; ARAÚJO, 2016).

O balanço energético depende, em grande parte, do controle da fome-saciedade que ocorre pela interação do Sistema Nervoso Central (SNC) com sinais periféricos neurais, hormonais e de nutrientes provenientes do trato gastrointestinal, pâncreas e tecido adiposo, os quais geram respostas de curto prazo sobre a ingestão alimentar e de longo prazo sobre a reserva energética corporal (CHAKRAVARTTY et al., 2015; MOEHLECKE et al., 2016).

Os sinais periféricos chegam ao SNC via nervo vago ao tronco cerebral e ao núcleo do trato solitário, atravessam a barreira hematoencefálica e se ligam a receptores específicos em duas subpopulações de neurônios no Núcleo Arqueado do Hipotálamo (ARC): a pró-opiomelanocortina (POMC) e o transcrito regulado pela cocaína e anfetamina (CART), um subgrupo com função catabólica; e o peptídeo agouti relacionado (AgRP) e o neuropeptídeo Y (NPY), um subgrupo com atividade anabólica (LIMA-JÚNIOR et al., 2015; POSOVSZKY; WABITSCH, 2015; MOEHLECKE et al., 2016; UENO; NAKAZATO, 2016).

O POMC libera o hormônio estimulador de melanócitos (α-MSH), que age como um agonista do receptor de melanocortina 4 (MC4R). Por sua vez, MC4R suprime o apetite e aumenta o gasto de energia. Estudos recentes sugerem que o α-MSH atua na regulação periférica da homeostase energética, pois está envolvido no aumento do gasto energético e na manutenção da perda de peso através da mobilização de reservas de gordura e aumento do nível de ácidos graxos livres circulantes. Além disso, estudos experimentais em roedores

encontraram uma associação entre α-MSH e *browning* adipocitário (DÂMASO et al., 2011; PERINO et al., 2014; SHIPP et al., 2016).

Dos neurônios do ARC partem sinais para outros núcleos hipotalâmicos, como núcleo paraventricular do hipotálamo (PVN), área hipotalâmica lateral (AHL) e o núcleo ventromedial do hipotálamo (VMN). No PVN estão alguns hormônios anorexígenos, como por exemplo: hormônio liberador de corticotropina, nesfatina, ocitocina e o hormônio liberador de tireotropina (UENO; NAKAZATO, 2016; VELLOSO; ARAÚJO, 2016). A AHL é influenciada por sinais vagais, memória e sistema de recompensa. Os neurônios desta região expressam dois neuropeptídeos que estimulam o apetite: hormônio concentrador de melatonina e orexinas (BROWN et al., 2015; MOEHLECKE et al., 2016; UENO; NAKAZATO, 2016; VELLOSO; ARAÚJO, 2016). O VMN é conhecido como o "centro da saciedade" e expressa receptores hormonais para leptina e MC4R com atividades anorexígenas (VELLOSO; ARAÚJO, 2016).

O maior reservatório de energia do organismo é o tecido adiposo. Neste tecido são secretados dois hormônios importantes para a modulação do balanço energético: leptina e adiponectina (MOEHLECKE et al., 2016).

A leptina atua como sinalizador hormonal de adiposidade e é considerada o sinalizador periférico mais importante para o controle do balanço energético. É produzida em proporção direta à massa de gordura corporal e acessa seus alvos no hipotálamo e em outras regiões do cérebro porque pode atravessar na barreira hematoencefálica, tendo em vista a sua capacidade em se ligar a receptores no ARC inibindo a expressão de NPY/AgRP e estimulando a expressão de POMC/CART, o que, consequentemente, reduz o apetite e aumenta o gasto energético (VELLOSO; ARAÚJO, 2016).

Por outro lado, a adiponectina atua no fígado, músculo e no SNC. Aumenta a sensibilidade à insulina e reduz a produção de glicose hepática. Atua também na modulação do metabolismo lipídico, estimula a oxidação de ácidos graxos e possui importante função antiinflamatória, uma vez que suprime as citocinas pró-inflamatórias e aumenta outros marcadores antiinflamatórios. Além disso, aumenta a sensibilidade à leptina através da supressão dos neurônios NPY/AgRP (SUN et al., 2016).

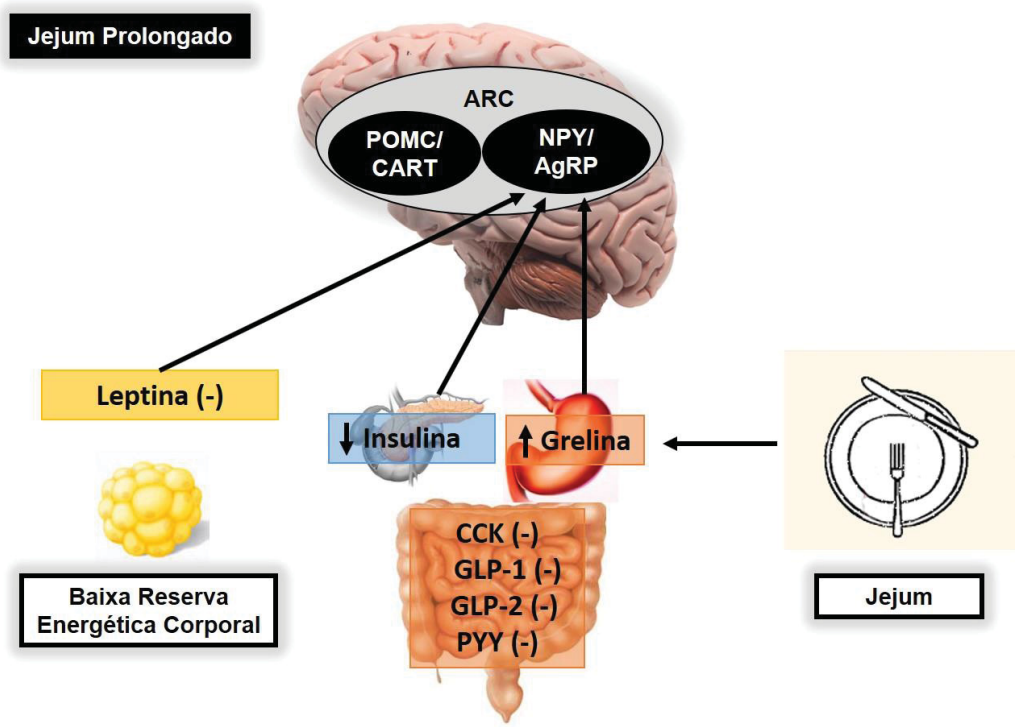
Outro sinalizador hormonal de adiposidade e classificado como o segundo sinalizador periférico mais importante é a insulina. Este hormônio possui uma função intermediária entre o controle dos estoques de energia e sinais de saciedade, uma vez que seus níveis sanguíneos variam de acordo com a ingestão alimentar e também da massa de gordura corporal (MOEHLECKE et al., 2016).

O tamanho de uma refeição e o conteúdo calórico estimulam quimiorreceptores e mecanorreceptores a informar sobre a quantidade de nutrientes armazenados no trato gastrointestinal por meio da secreção de peptídeos intestinais. Os nutrientes se integram aos sinais hormonais de curto prazo (sinais de saciedade ou de controle imediato da fome) que informam a situação atual de nutrientes. Estes sinais hormonais são detectados por neurônios do ARC, os quais conforme já descrito acima, enviam sinais neurais para outras regiões do hipotálamo, gerando respostas de fome ou saciedade (POSOVSZKY; WABITSCH, 2015; BAUER et al., 2016; MOEHLECKE et al., 2016).

Em estado de jejum prolongado, a redução da disponibilidade de nutrientes e baixos níveis de leptina e insulina enviam ao SNC mensagem de escassez energética, e com isso, a produção do hormônio orexígeno grelina é estimulada no estômago. À medida que os níveis circulantes deste hormônio aumentam, há estímulo de efeitos orexígenos no hipotálamo. Após a ingestão alimentar, os níveis de grelina reduzem rapidamente, e também há estímulo da secreção de hormônios sacietógenos, como por exemplo: colecistocinina, peptídeo semelhante ao glucagon 1 (GLP-1), o peptídeo semelhante ao glucagon 2 (GLP-2), o peptídeo YY (PYY) e oxintomodulina. Tais hormônios associados com o sinal de disponibilidade energética da insulina promovem respostas anorexígenas (MICHALAKIS; LE ROUX, 2012; BALDASSANO et al., 2016; CAZZO et al., 2016; MISHRA et al., 2016; MOEHLECKE et al., 2016; CHURM et al., 2017; STEINERT et al., 2017).

A figura 1 retrata de forma resumida a regulação neuroendócrina do balanço energético em jejum e após consumo alimentar.

(a)



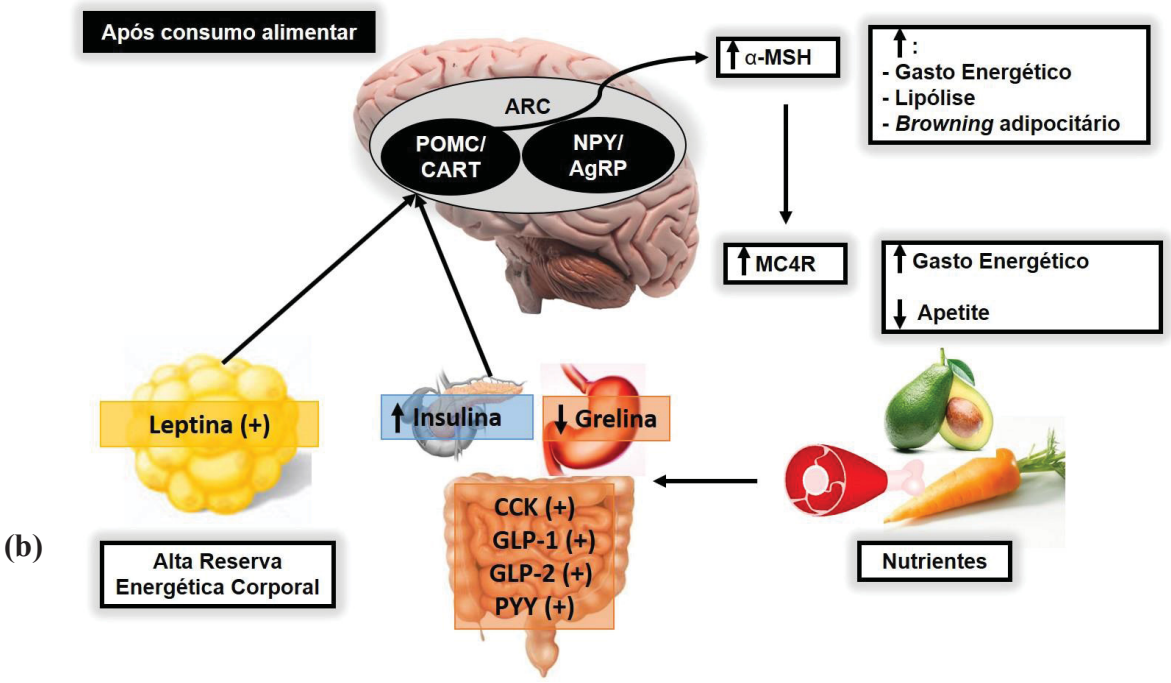


Figura 1. Regulação neuroendócrina do balanço energético: (a) em jejum; (b) após consumo alimentar. Em estado de jejum prolongado, a redução da disponibilidade de nutrientes e baixos níveis de leptina e insulina enviam ao SNC mensagem de baixa reserva energética, e com isso, a produção do hormônio orexígeno grelina é estimulada no estômago. À medida que os níveis circulantes deste hormônio aumentam, há estímulo da subpopulação de peptídeos orexígenos NPY/AgRP no hipotálamo, os quais enviam sinais neurais para outros núcleos hipotalâmicos gerando respostas de fome. Após consumo alimentar, os níveis de grelina reduzem rapidamente e o contato do bolo alimentar com quimiorreceptores e mecanorreceptores presentes no trato gastrointestinal estimula a secreção de peptídeos intestinais (CCK, GLP-1, GLP-2, PYY) que informam sobre a situação atual de nutrientes, enviando sinais de saciedade, que se integram aos sinais hormonais de curto prazo (por exemplo redução de grelina e aumento de insulina) e sinais de longo prazo sobre reserva energética corporal fornecidos pela leptina e insulina. Estes sinais periféricos chegam ao SNC via nervo vago, atravessam a barreira hematoencefálica e se ligam a receptores específicos de neurônios catabólicos POMC e CART no ARC. Consequentemente, há liberação de α-MSH, o qual está envolvido com o aumento do gasto energético e estímulo a lipólise. O α-MSH age como agonista de MC4R. Em seguida são enviados sinais neurais para outras regiões do hipotálamo e como resultado final há inibição do apetite e aumento do gasto energético.

Em indivíduos obesos esse controle do apetite pode estar alterado. O aumento da gordura corporal aumenta a secreção de leptina e insulina, tornando os indivíduos com obesidade resistentes à ação desses hormônios, o que compromete o *feedback* negativo para o NPY/AgRP gerando aumento da fome. Sugere-se que defeitos na expressão do receptor da leptina e/ou deficiência em seu sistema de transporte na barreira hematoencefálica e/ou o aumento da expressão do supressor de sinalização de citoquina-3, o qual atua como um bloqueador da sinalização hipotalâmica da leptina são os possíveis mecanismos relacionados com a ineficiência da ação deste hormônio sobre o controle do apetite via hipotálamo (CRUJEIRAS et al., 2015). Além disso, pesquisas sugerem que em obesos, os níveis de GLP-

1, GLP-2 e PYY são menores em comparação com indivíduos eutróficos, proporcionando menor sensação de saciedade (CHEN et al., 2012; GUEUGNON et al., 2012; HALUZÍKOVÁ et al., 2013; LIPS et al., 2013; SYSKO et al., 2013; TERRA et al., 2013; LEAN; MALKOVA, 2016; NAUCK; MEIER, 2018; VANAVANAN et al., 2018).

Além disso, os polimorfismos genéticos que ocorrem em genes associados ao controle da ingestão alimentar, gasto energético e adipogênese podem modificar o balanço energético e influenciar negativamente a resposta às intervenções no estilo de vida para perda de peso (JOFFE; HOUGHTON, 2016).

O fato da obesidade possuir origem multifatorial é o principal limitante no sucesso do tratamento. Portanto, o principal objetivo é proporcionar um desequilíbrio negativo no balanço energético, por meio de uma abordagem multidisciplinar inicialmente estimulando mudanças no estilo de vida, como reeducação alimentar, prática regular de atividade física e uso de medicamentos (ABESO, 2016).

Entretanto, estima-se que há recidiva do peso perdido em 90% dos obesos mórbidos submetidos a estes tratamentos clínicos e apenas 5% obtém resultados satisfatórios (BETTINI; BETTINI, 2018a).

Neste contexto, destaca-se o tratamento cirúrgico para obesidade, que é indicado para pacientes que atendam aos critérios estabelecidos pela Resolução do Conselho Federal de Medicina (CFM) nº. 2131/2015: adultos (18 anos a 65 anos) com obesidade grave instalada há mais de cinco anos, obesos grau III, que são aqueles portadores de Índice de Massa Corporal (IMC) igual ou superior a 40 kg/m^2; ou obesos grau II, que são os portadores de IMC $\geq$ 35 kg/m^2 com comorbidades associadas. A resolução também prevê a necessidade de comprovação que o indivíduo tenha sido submetido à tratamentos clínicos por no mínimo dois anos sem sucesso (CFM, 2016). Em casos de pacientes com IMC maior que 50 Kg/m^2, a intervenção cirúrgica é indicada até mesmo sem início de tratamento clínico devido ao risco elevado de morte (CFM, 2016). Vale ressaltar, que é imprescindível que os pacientes e familiares estejam conscientes dos riscos e mudanças de hábitos inerentes a uma cirurgia de grande porte sobre o tubo digestório e da necessidade de acompanhamento pós-operatório com a equipe multidisciplinar no longo prazo (CFM, 2016).

Além disso é necessário atestar ausência de drogadição e/ou alcoolismo, de transtorno de humor grave, de quadros psicóticos em atividade ou quadros demenciais (CFM, 2016).

Pacientes entre 16 e 18 anos e acima de 65 anos poderão realizar a cirurgia desde que adicionalmente aos critérios supracitados seja feita avaliação criteriosa do risco benefício (CFM, 2016).

Segundo dados da Sociedade Brasileira de Cirurgia Bariátrica e Metabólica (SBCBM) o Brasil é o segundo país que mais realiza cirurgias bariátricas no mundo. Nos últimos 15 anos o número de cirurgias no Brasil aumentou em proporções expressivas. Em 2003, realizaram-se 16.000 cirurgias e dados da SBCBM apontam que em 2016 esse número superou 100.000 procedimentos (ANGRISANI et al., 2015; SBCBM, 2017).

As duas técnicas mais realizadas são: a Gastrectomia Vertical, puramente restritiva e também conhecida como *Sleeve*; e o *bypass* gástrico em Y-de-Roux (BGYR), técnica mista que associa componente restritivo e disabsortivo. Essa última resulta em perda de excesso de peso entre 65% e 70%, em melhora ou remissão das comorbidades e em melhora da qualidade e da expectativa de vida (ANGRISANI et al., 2015; BETTINI; BETTINI, 2018b).

Pacientes submetidos ao BGYR geralmente atingem o máximo de perda ponderal entre 18 e 24 meses de pós-operatório (SJOSTROM, 2013; FARIAS et al., 2016). No entanto, dois anos após a cirurgia, alguns pacientes recuperam algum peso. Em publicação anterior do nosso grupo de pesquisa, constatou-se que no Atendimento Multidisciplinar ao Obeso Cirúrgico (AMOC) do Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR), 21,3% dos pacientes submetidos ao BGYR há cinco anos recuperaram mais de 20% do menor peso (FARIAS et al., 2016).

A perda de peso após BGYR ocorre devido à restrição mecânica, má absorção e também devido às modificações nos mecanismos envolvidos no controle do balanço energético. Existem hormônios gastrointestinais que participam do mecanismo fome-saciedade que após a alteração anatômica provocada pelo procedimento cirúrgico, caracterizada pela restrição gástrica e desvio intestinal, podem ter suas concentrações modificadas, contribuindo com o processo de emagrecimento. Acredita-se que a cirurgia bariátrica contribua para o equilíbrio da regulação neuroendócrina do balanço energético por meio da diminuição da concentração sérica de substâncias orexígenas e aumento das anorexígenas e que esse equilíbrio se mantenha ao longo do pós-operatório (WOELNERHANSSEN et al., 2011; HERDER et al., 2014; DIXON et al., 2015; MUNZBERG et al., 2015; NETTO et al., 2016; BIAGIONI et al., 2017; KALINOWSKI et al., 2017; STEFANIDIS; OLDFIELD, 2017; HANKIR et al., 2018; HOLST et al., 2018).

1.1 JUSTIFICATIVA

Os indivíduos submetidos à cirurgia bariátrica atingem a perda de peso máxima entre 18 e 24 meses após o procedimento cirúrgico. Após esse período, há aumento da prevalência

de pacientes que recuperam peso. Assim sendo, é de extrema importância estender a investigação dos marcadores envolvidos na regulação neuroendócrina a partir de 24 meses de cirurgia.

O conhecimento mais profundo sobre o comportamento desses fatores pode contribuir para o entendimento das diferentes respostas clínicas no pós-operatório em longo prazo nestes indivíduos. Isso permite que os profissionais da saúde que participam do acompanhamento desta população compreendam melhor as alterações provenientes da regulação neuroendócrina que podem dificultar o emagrecimento após o tratamento cirúrgico da obesidade.

1.2 OBJETIVOS

1.2.1 Objetivo Geral

Avaliar os efeitos da perda de peso após cirurgia bariátrica sobre a regulação neuroendócrina do balanço energético.

1.2.2 Objetivos Específicos

Os objetivos específicos do trabalho são:

a) Descrever o mecanismo da regulação neuroendócrina do balanço energético e as substâncias envolvidas neste processo, destacando as alterações no controle do balanço energético em obesos e após a cirurgia bariátrica.
b) Avaliar o papel dos seguintes marcadores: adiponectina, leptina, NPY, PYY e α-MSH em indivíduos submetidos ao BGYR e verificar possíveis relações com a manutenção da perda de peso após 2 anos de cirurgia.

O formato do texto apresentado corresponde ao formato alternativo autorizado pelo colegiado do Programa de Pós-graduação em Clínica Cirúrgica da UFPR onde parte do conteúdo serão apresentados sobre a forma de artigos científicos já submetidos e/ou aceitos para publicação em periódicos científicos.

2 SUJEITOS E MÉTODOS

2.1 DELINEAMENTO DO ESTUDO

O presente estudo é caracterizado como estudo de coorte, prospectivo e com 24 meses de seguimento de pacientes submetidos ao BGYR com uso de órtese, via laparotomia, por uma única equipe multidisciplinar no AMOC do HC-UFPR.

2.2 APROVAÇÃO COMITÊ DE ÉTICA

O projeto de pesquisa foi aprovado pelo Comitê de Ética em Pesquisas em Seres Humanos (CEP) do HC-UFPR sob o registro n°: 2625.232/2011-10 (ANEXO A), seguindo as normas nº 466/2012 do Conselho Nacional de Saúde do Ministério da Saúde e em concordância com os princípios éticos contidos no *World Medical Association – Declaration of Helsinki* (2013).

2.3 TERMO DE CONSENTIMENTO INFORMADO

Todos os indivíduos foram informados sobre o objetivo da pesquisa e confidencialidade dos dados, tendo assinado, no momento da consulta clínica, consentimento de participação avaliado pelo CEP do HC-UFPR, respeitando as normas legais e éticas vigentes (APÊNDICE A).

2.4 CRITÉRIOS DE INCLUSÃO

Indivíduos entre 18 e 65 anos, de ambos os sexos, com obesidade grave instalada há mais de cinco anos (IMC $\geq$ 40 Kg/m^2 ou $\geq$ 35 Kg/m^2 com alguma comorbidade associada) submetidos à tratamentos clínicos por no mínimo dois anos sem sucesso e conscientes dos riscos e mudanças de hábitos inerentes a uma cirurgia de grande porte sobre o tubo digestório e da necessidade de acompanhamento pós-operatório com a equipe multidisciplinar no longo prazo (CFM, 2016).

2.5 CRITÉRIOS DE NÃO INCLUSÃO

Foram excluídos os pacientes com transtorno psíquico grave, com dependência alcóolica ou droga-dependência e os que não consentiram sua partipação na pesquisa. Devido a análises de parâmetros inflamatórios referentes à outra tese de doutorado desta mesma amostra foram excluídos pacientes portadores de câncer, insuficiência renal crônica, doenças hepáticas, artrite reumatoide, doenças auto-imunes, obesidade causada por desordens endócrinas, tabagistas e os que estavam em tratamento com uso de insulina, imunossupressores, antirreumáticos e antiinflamatórios. Estes dados foram coletados durante entrevista inicial com os voluntários.

2.6 SUJEITOS DO ESTUDO

A população do estudo foi constituída de 32 pacientes (30 mulheres e dois homens), com idade média de 40,10±10,00 anos e IMC de 43,85±1,12 kg/m^2.

2.7 CAPTAÇÃO DA AMOSTRA

No período entre março de 2013 e outubro de 2013 os pacientes submetidos ao BGYR foram selecionados por conveniência de acordo com o fluxo de cirurgias realizadas durante o período do estudo. Na figura 2 está representado o modelo de composição da amostra do presente estudo.

2.8 COLETA DE DADOS

Os dados pessoais e clínicos foram coletados do prontuário do paciente e do sistema de informação hospitalar do AMOC do HC-UFPR.

As aferições das medidas antropométricas aconteceram em um ambiente ambulatorial após a realização de grupos de apoio do serviço do referido hospital. As coletas de sangue para as determinações bioquímicas foram realizadas no laboratório do referido hospital.

Todos os dados foram coletados no pré-operatório e 6 meses e 24 meses após a cirurgia.

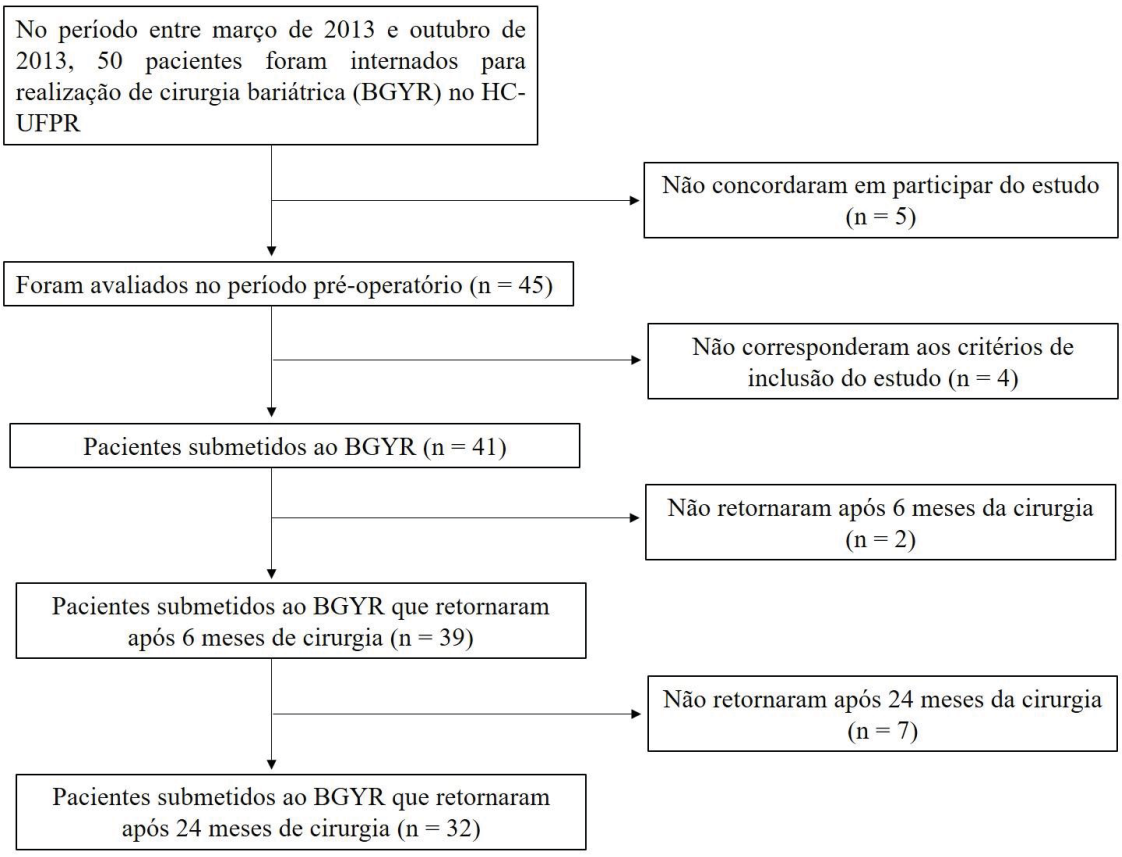


Figura 2. Representação esquemática da amostra do estudo.

2.9 DADOS ANTROPOMÉTRICOS

A avaliação antropométrica consistiu em aferição de massa corporal, altura e circunferência abdominal. Todas as medidas antropométricas foram feitas pela autora do projeto e estudantes de graduação de nutrição previamente treinadas.

Para obtenção do primeiro dado, foi utilizada uma balança mecânica da marca Filizola® (Indústrias Filizola S/A, modelo 31 São Paulo-SP, Brasil) com capacidade de 300 Kg e precisão de 100 g, instalada sobre superfície lisa, plana, firme e afastada da parede. Para medida da massa corporal, o avaliado estava sem sapatos, vestindo o mínimo de roupas possível. O mesmo posicionou-se no centro da plataforma da balança, em posição ereta, sem tocar em nada e com o peso do corpo distribuído em ambos os pés mantidos juntos, assim como os braços estendidos ao longo do corpo.

Para aferição da estatura, foi utilizado o antropômetro da balança mecânica, posicionando o paciente descalço no centro do equipamento, com a cabeça livre de adereços,

em pé, ereto, com os braços estendidos ao longo do corpo e a cabeça orientada para o plano de Frankfurt.

Utilizando uma fita métrica inelástica, foi aferida a medida da circunferência abdominal, realizada de acordo com os passos abaixo:

- Solicitou-se ao paciente que ficasse em pé, ereto, abdômen relaxado, braços estendidos ao longo do corpo e os pés separados numa distância de 25 a 30 cm.
- A roupa foi afastada, de forma que a região da cintura ficou despida.
- Com o auxílio de uma fita métrica inelástica, circundou-se o paciente no ponto médio entre a última costela e a crista ilíaca.
- A leitura foi realizada no momento da expiração.

2.9.1 Avaliação dos dados antropométricos

O parâmetro antropométrico utilizado para diagnóstico da obesidade é o IMC, que resulta da divisão do peso atual pelo quadrado da altura.

A partir do resultado da equação, obtem-se a seguinte classificação:

Quadro 1. Classificação da obesidade de acordo com o IMC

IMC (Kg/m^2)	Classificação
< 18,5	Magreza
≥ 18,5 – 24,99	Eutrofia
≥ 25,0 – 29,99	Sobrepeso
≥ 30,0 – 34,99	Obesidade grau I
≥ 35,0 – 39,99	Obesidade grau II
≥ 40,0	Obesidade grau III

FONTE: WHO (2000)

Existem ainda outras duas categorias: super-obesos (obesidade grau IV), com IMC entre 50 e 59,9 Kg/m^2 e os super super-obesos (obesidade grau V), acima de 60 Kg/m^2 (WHO, 2000; MECHANICK et al., 2008).

O percentual de perda de excesso de peso (PEP) foi obtido por meio da fórmula:

$$\% \text{ PEP} = [(\text{Peso Inicial} - \text{Peso Atual}) / \text{Excesso de Peso Inicial}] \times 100$$

Para o cálculo do Excesso de Peso Inicial (EP) utilizou-se a seguinte fórmula:

EP = Peso Inicial – Peso Ideal

Para obtenção do valor do peso ideal considerou-se como referência o IMC = 25 Kg/m^2.
Fonte: Deitel; Gawdat; Melissas, 2007

2.10 PARÂMETROS BIOQUÍMICOS

A coleta de sangue foi realizada por auxiliar/técnico de enfermagem do Laboratório de Análises Clínicas do HC-UFPR. Após oito horas de jejum, a coleta foi realizada por sistema a vácuo na região cubital e as amostras foram centrifugadas a 2.500 rpm, por dez minutos para a obtenção do plasma. Em seguida, as amostras foram transferidas para *eppendorfs*, devidamente identificadas e congeladas sob uma temperatura de -80ºC.

Posteriormente as amostras foram transferidas para o Instituto Gênese de Análises Científicas e foram feitas as determinações bioquímicas em concordância com os métodos descritos a seguir.

A Leptina e o PYY foram avaliados pelo *kit Milliplex MAP Human Metabolic Hormone Magnetic Bead 2 Plex Panel* (Millipore, Billerica, Massachusetts, EUA). Os resultados de leptina foram expressos em ng/mL e os do PYY em pg/mL.

As concentrações plasmáticas de α-MSH e NPY foram dosadas com *kits* comercialmente disponíveis da *USCN life style* (Uscn Life Science, Wuhan, People's Republic of China). Os resultados foram expressos em ng/mL.

A adiponectina foi analisada com kit *Milliplex MAP Human Adipokine Magnetic Bead Panel 1* (Millipore, Billerica, Massachusetts, USA). Os resultados foram expressos em μg/mL.

2.11 ANÁLISE ESTATÍSTICA

Os dados foram analisados nos programas Excel e IBM SPSS Statistics v. 20.0 (SPSS Inc, Chicago, IL, USA).

A estatística descritiva foi apresentada pela média e desvio padrão quando a variável apresentou distribuição normal. Para as variáveis que não apresentaram distribuição simétrica utilizou-se a mediana, erro padrão da média e valores mínimo e máximo.

Foi verificada a distribuição gaussiana pelo teste Shapiro-Wilk.

Para as variáveis que atenderam a condição de normalidade nos três momentos de avaliação foi utilizado o modelo de análise de variância com medidas repetidas (ANOVA) para comparar as diferenças na avaliação basal e após seis meses e 24 meses da cirurgia. No caso de rejeição da hipótese nula, o *post-hoc* do teste de Bonferroni foi aplicado para múltiplas comparações.

Os dados que apresentaram distribuição não-gaussiana foram analisados pelo teste não paramétrico de Friedman. No caso de rejeição da hipótese nula, o *post-hoc* do teste de Friedman foi aplicado para múltiplas comparações.

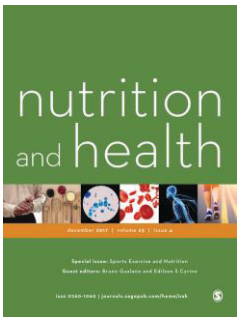
Para avaliar os efeitos da intervenção cirúrgica, o delta dos valores foi calculado (Δ = valor pós-operatório – valor pré-operatório).

As possíveis relações entre as variáveis foram examinadas pela Correlação de Pearson. Para esta análise, as variáveis que não apresentaram a distribuição simétrica corrigiu-se a distribuição pela padronização em escore-Z e então aplicou-se o teste paramétrico de Correlação de Pearson.

A análise de regressão linear simples foi realizada a fim de identificar a influência dos níveis de α-MSH sobre sobre as variações da massa corporal após a cirurgia.

Como critério de significância, utilizou-se $p<0,05$.

3 APRESENTAÇÃO DOS RESULTADOS



3.1 ARTIGO 1, PUBLICADO NA REVISTA NUTRITION AND HEALTH

(Formatação da Revista)

Review Article

Title: Neuroendocrine regulation of energy balance: implications on the development and surgical treatment of obesity

Authors: Gisele Farias[1], Bárbara Dal Molin Netto[2], Solange Cravo Bettini[3], Ana Raimunda Dâmaso[2], Alexandre Coutinho Teixeira de Freitas[1]

[1] Surgical Clinic Post Graduate Program – Department of Surgery – Hospital de Clínicas - Universidade Federal do Paraná, UFPR. Surgical Clinic Post Graduate Program, Curitiba-Pr, Brazil

[2] Nutrition Post Graduate Program, Universidade Federal de São Paulo – Escola Paulista de Medicina – UNIFESP-EPM. Nutrition Post Graduate Program, São Paulo-SP, Brazil

[3] Gastrointestinal Surgery Service of Hospital de Clínicas, Federal University of Paraná (UFPR), Curitiba-PR, Brazil

Corresponding authors:

Farias, G.; Msc. Surgical Clinic Post Graduate Program – Department of Surgery – Hospital de Clínicas - Universidade Federal do Paraná. Rua General Carneiro, 81 - Centro – Curitiba/ PR, Postal Code: 80060-900, Brazil. Telephone number: +55 41 3360 1800

E-mail: gisele.nutri.farias@gmail.com

Netto, BDM, PhD, Post Graduate Program of Nutrition, Escola Paulista de Medicina – Universidade Federal de São Paulo, Rua Marselhesa, 630 – Vila Clementino – São Paulo, São Paulo 04020-060, Brazil

E-mail: barbaradmnetto@gmail.com

Word Count: 3446.

Number of figures and tables: 5.

Conflict of Interest: The authors Gisele Farias, Bárbara Dal Molin Netto, Solange Cravo Bettini, Ana Raimunda Dâmaso and Alexandre Coutinho Teixeira de Freitas declare that they have no conflict interest.

Abstract

Obesity, a serious public health problem, occurs mainly when food consumption exceeds energy expenditure. Therefore, energy balance depends on the regulation of hunger-satiety mechanism, which involves interconnection of the central nervous system and peripheral signals from the adipose tissue, pancreas, and gastrointestinal tract, generating responses in short-term food intake and long-term energy balance. Increased body fat changes the gut- and adipose tissue-derived hormone signaling, which promotes modifications in appetite-regulating hormones decreasing satiety and increasing hunger senses. With the failure of conventional weight loss interventions (dietary treatment, exercise, drugs, and lifestyle modifications), bariatric surgeries are well-accepted tools for the treatment of severe obesity with long-term and sustained weight loss. Bariatric surgeries may cause weight loss due to restriction/malabsorption of nutrients from the anatomical alteration of the GI tract, which would decrease energy intake, but also by other physiological factors associated with better results of the surgical procedure. This review discusses the neuroendocrine regulation of energy balance, with description of the predominant hormones and peptides involved in the control of energy balance in obesity and after all currently available bariatric surgeries. According to the findings of our review, bariatric surgeries promote effective and sustained weight loss not only by reducing calorie intake, but also by changes in appetite control, satiation and satiety, and physiological changes in gut, neuro- and adipose tissue-derived hormone signaling.

Introduction

Obesity, currently considered one of the greatest public health problems all over the world, is mainly due to dysregulation of energy balance. In turn, energy balance is controlled by a complex process coordinated by a cross-talk between the central and peripheral signals, including the central nervous system, adipose tissue, pancreas, gut peptides, and gastric peptides, which regulate food intake mechanism (appetite and hunger-satiety) and energy expenditure (Chakravartty et al., 2015).

According to an individual's dietary intake and metabolic state, the adipose tissue and gastrointestinal tract provide information to two neuronal groups in the arcute nucleus of the hypothalamus (ARC): the first, composed of neuropeptide Y (NPY) and agouti-related protein (AgRP), has orexigenic properties and the other group has an opposite function, that is, it inhibits the appetite, by the action of the pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) neurotransmitters. For instance, adiponectin and leptin are secreted by the adipose tissue, which are important in anorexigenic pathways; cholecystokinin (CCK), glucagon like peptide 1 (GLP-1), glucagon like peptide 2 (GLP-2), peptide YY (PYY) and oxyntomodulin (OXM) are provided by the intestine and lead an individual to end their meal by a feeling of satiety; and still gastrin and ghrelin by the stomach and amylin, glucagon, insulin, and polipeptide pancreatic (PP) by the pancreas. On the other hand, note that ghrelin plays a key role in energy balance, enhancing hunger and food intake (Bauer et al., 2016; Camilleri, 2015; Larder and O'Rahilly, 2012; Moehlecke et al., 2016; Ochner et al., 2011).

Research over the last several decades demonstrated that in obesity, neural, gut- and adipose tissue-derived hormone signaling are altered. They promote changes in appetite-regulating hormones decreasing satiety and increasing hunger senses, such as leptin and

insulin resistance, and also cause a decrease in serum levels of gastrointestinal hormones: glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), peptide YY (PYY), and pancreatic polypeptide (PP) (Barazzonni et al., 2013; Buss et al., 2014; Gelisgen et al., 2012; Gueugnon et al., 2012; Terra et al., 2013). Besides that, genetic polymorphisms associated with food intake control and energy expenditure, such as MC4R, POMC, LEP, LEPR, FTO, and CPUs may also affect the response to dietary treatment and exercises (Joffe and Houghton, 2016).

In addition, studies suggest that during weight loss, there may be alteration in the action of these hormones, which could justify the difficulty of maintaining the weight lost and in some cases, induces weight regain (Fernandez et al., 2015; Steinert et al., 2017). Some studies indicate an average reduction of 3- to 6-kg body weight in individuals with obesity after 12 months of lifestyle modification and dietary treatment, and up to 11% when associated with drugs, but with poor long-term success and high prevalence of regaining almost all of their initial weight within 5 years (Attalah et al., 2014; Leblanc et al., 2011).

In this way, bariatric surgeries may cause massive weight loss due to restriction/malabsorption of nutrients from the anatomical alteration of the GI tract, which would decrease energy intake. However, in addition to mechanical factors, there are other physiological factors, including changes in some hormones, such as increase of adiponectin levels, improvement of leptin and insulin sensitivity, decrease in serum levels of ghrelin, and increase in serum levels of gut peptides, for example, CCK, GLP-1, and PYY, which are associated with sustained weight loss and prevention of weight regain (Abdeen and Le Roux, 2016; Chakravartty et al., 2015; Jonge et al., 2016; Michalakis and Le Roux, 2012; Munzberg et al., 2015).

This review focused on recent literature regarding the neuroendocrine regulation of energy balance and provided a brief summary of the predominant hormones and peptides

involved in the control of energy balance before and after all currently available bariatric surgeries, including RYGB, laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), and biliopancreatic diversion with duodenal switch (BPD/DS).

Evidence acquisitions

A narrative review of current literature was performed using online databases, such as Pubmed, Lilacs, Medline, and Science Direct. Original studies in humans, published within the previous 6 years or less, were identified by searching for the MeSH terms in the title or abstract: 'obesity', 'bariatric surgery', 'gastric bypass', 'sleeve gastrectomy', 'biliopancreatic diversion', 'gastric band'; in conjunction with 'appetite', 'satiety'; and together with: 'alpha-melanocyte-stimulating hormone', 'agouti-related protein', 'amylin', 'AgRP', 'cocaine and amphetamine-regulated transcript', 'CART', 'cholecystokinin', 'CCK', 'gastrin', 'ghrelin', 'glucagon', 'glucagon-like peptide 1', 'GLP-1', 'glucagon-like peptide 2', 'GLP-2', 'insulin', 'leptin', 'melatonin concentrating hormone', 'MCH', 'Neuropeptide Y', 'NPY', 'oxyntomodulin', 'pancreatic polypeptide', 'peptide YY', 'PYY', 'proopiomelanocortin', and 'POMC'. We selected 92 articles published from January 2011 to February 2017, involving original prospective randomized clinical trials as well as review articles in the English language.

Mechanisms of appetite control and energy balance

The regulation of metabolism is a result of the highly complex balance between food consumption and energy expenditure primarily controlled by the central nervous system (CNS). The control of food intake depends on the regulation of appetite, which is also

coordinated by the CNS. Despite this, the decision to eat or not to eat involves interconnection of the hypothalamus and afferent signals from the adipose tissue, pancreas, and gut; and efferent signals generating responses in short-term and long-term food intake (Bauer et al., 2016; Larder and O'Rahilly, 2012; Moehlecke et al., 2016; Munzberg et al., 2015; Ochner et al., 2011).

The hypothalamus acts as a protagonist on feeding and metabolism control. It comprises more than 40 distinct nuclei and areas, and each sub-region controls specific facets of energy balance, the most important are the arcuate nucleus of the hypothalamus (ARC), the paraventricular nucleus of the hypothalamus (PVH), the ventromedial nucleus of the hypothalamus (VMH), and the lateral hypothalamic (LHA) areas (Ueno and Nakazato, 2016).

The ARC, located outside the bloodbrain barrier, is permeable to peripheral factors and receives afferent signals and circulating hormones through the brainstem and nucleus tractus solitarius. Therefore, it plays an important role in controlling food intake and is considered the main regulatory system of energy balance (Posovszky and Wabitsch, 2015).

The cross-talk between peripheral signals and hypothalamic and brainstem centers is regulated by two subpopulations of neurons in the neuropeptidergic system of ARC. Pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) form a subgroup with catabolic function. On the other hand, agouti-related protein (AgRP) and neuropeptide Y (NPY) form the subpopulation with anabolic activity. POMC releases alpha-melanocyte-stimulating hormone (α-MSH), which acts as an agonist of the melanocortin 4 receptor (MCR4). In turn, MC4R suppresses appetite and enhances energy expenditure. In contrast, NPY/AgRP neurons stimulate food consumption and reduce energy expenditure acting as an antagonist at the MC4R (Lima-Júnior et al., 2015; Moehlecke et al., 2016; Posovszky and Wabitsch, 2015; Ueno and Nakazato, 2016).

In the PVH, there are neuronal inputs from the ARC and LHA and also anorexigenic neurons, such as corticotropin-releasing hormone (CRH), nesfatin, oxytocin, and thyrotropin-releasing hormone (TRH) (Ueno and Nakazato, 2016).

Since 1940, VMH has been known as the "satiety center" and expresses hormone receptors for leptin and MC4R with anorexigenic activities. In contrast, the LHA has been classically referred to as the "feeding center" of the brain. The LHA is influenced by vagal signals, memory, and reward system. Neurons in the LHA express two neuropeptides that stimulate appetite: melatonin concentrating hormone (MCH) and orexins (Brown et al., 2015; Moehlecke et al., 2016; Ueno and Nakazato, 2016).

The adipose tissue is considered a long-term reservatory of energy since it is the biggest energy storage in the body and transmits information about the amount of body fat. There are two hormones produced in the white adipose tissue that appear to play an important role in the modulation of energy balance: adiponectin and leptin (Moehlecke et al., 2016).

Adiponectin acts in the liver, muscle, and in the CNS. It increases insulin sensitivity and reduces hepatic glucose production. It also acts in the modulation of lipid metabolism, stimulates fatty acid oxidation, and has an important anti-inflammatory function since it suppresses pro-inflammatory cytokines and increases other anti-inflammatory markers. A study on adults showed that high visceral abdominal fat and low adiponectin levels associated with waist circumference, blood pressure, glucose, and lipid profile were independent predictors for metabolic syndrome (Cho et al., 2017). Another investigation with animal models found that adiponectin reduces insulin resistance and enhances leptin sensitivity through the suppression of NPY/AgRP neurons, and consequently, exerts influence in energy balance control (Sun et al., 2016).

Leptin is an anorexigenic hormone and circulating leptin levels is highly associated with body mass index. Leptin accesses its targets in the hypothalamus and other regions of the

brain because it can penetrate the bloodbrain barrier. It binds to receptors in the ARC and reduces food intake and increases energy expenditure by stimulating the expression of POMC/CART and by inhibiting the expression of NPY/AgRP. However, increased body fat results in increased leptin, but the response to that hormone is eliminated, characterized by leptin resistance, and does not prevent the development of obesity (Michalakis and Le Roux, 2012; Moehlecke et al., 2016)

Some studies have demonstrated that high protein-containing meals stimulate the pancreas to release satiety-inducing hormones, such as amylin, pancreatic polypeptide (PP), insulin, and glucagon (Meek et al., 2016; Riediger, 2012). For example, glucagon is a 29-amino acid peptide hormone that favors the increase of circulating levels of glucose and stimulates glycogenolysis (Lean and Malkova, 2016). Insulin is a 51-amino acid peptide hormone responsible for the use of glucose as an energy source after meals and their serum levels are proportional to body fat weight (especially visceral fat) and acts similarly to leptin (Meek et al., 2016; Ochner et al., 2011). Pancreatic polypeptide (PP) is a 36-amino acid peptide hormone responsible for the control of exocrine and endocrine pancreatic enzymes (Camilleri, 2015; Lean and Malkova, 2016).

The presence of food stimulates the stomach to produce hormones, such as gastrin, that reduce appetite, increase acid secretion, and stimulate gastric motility and emptying. In contrast, ghrelin, a 28-amino acid peptide secreted when the stomach is empty, is the only gastric hormone known to control the connection between the stomach and CNS by sending positive feedback to NPY/AgRP neurons. Additionally, ghrelin is responsible for stimulating hunger and food intake and also influences gastric acid secretion and gastric motility (Churm et al., 2017; Steinert et al., 2017).

Ghrelin circulates in active form, known as acyl-ghrelin, which represents less than 10% of total ghrelin and is responsible for stimulating appetite and reducing energy

expenditure. Desacyl-ghrelin, the inactive form, acts in glucose metabolism while ghrelin and leptin are hormones that exert the greatest influence on energy balance although they also have antagonistic functions (Churm et al., 2017; Simpson et al., 2012; Steinert et al., 2017).

Gut-brain axis

The gut-brain axis is a communication system of the enteric nervous and the central nervous systems through efferent and afferent neurotransmitters (Bauer et al., 2016; Chen et al., 2016).

The size of a meal, the caloric content, and the quality of food stimulate chemo- and mechano-receptors inform about the amount of nutrients stored in the gastrointestinal tract. It is done through the secretion of gut peptides and neuronal signals that act directly within different brain areas (Bauer et al., 2016; Moehlecke et al., 2016; Posovszky and Wabitsch, 2015).

Macronutrients, especially protein and fat, stimulate the small intestine to produce cholecystokinin (CCK), which sends satiety signals via the gut-brain-axis to the CNS. The same happens in the lower intestine in response to the presence of nutrients and as a reflex originating from the upper portion of the gut. Satiety hormones responsible for termination of feeding are produced, such as glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), peptide YY (PYY), and oxintomodulin (OXM) (Bauer et al., 2016). GLP-1, a 30-amino acid peptide hormone, is an incretin transcription product derived from the proglucagon gene, and its biologically active forms are GLP-1 (7-37) and GLP-1 (7-36), and they control glycemia and satiety (Mishra et al., 2016; Ochner et al., 2011). Another product from the proglucagon cleavage is GLP-2, which is a 33-amino acid gastrointestinal hormone that exerts influence on energy balance,

such as increase on the permeability of gut mucosa, and consequently, enhances nutrient absorption, besides improving insulin sensitivity, control of bone resorption, and regulation of food intake (Baldassano et al., 2016; Cazzo et al., 2016, 2017).

PYY is a 36-amino acid peptide hormone that belongs to the family of NPY and PP. It circulates in two forms: PYY 1-36 and PYY 3-36, the latter being the predominant form. Secretion begins 15 minutes after food intake, peaking between 60 and 90 minutes. Its half-life is 7 to 10 minutes but its effects can last for up to 6 hours. The secretion is proportional to the caloric content of the meal and does not suffer the influence of gastric distension. PYY participates in the regulation of insulin secretion and glycemic control; inhibits gastric, pancreatic, and intestinal secretions; and delays gastrointestinal transit time (Michalakis and Le Roux, 2012; Mishra et al., 2016; Moehlecke et al., 2016; Ochner et al., 2011). Table 1 shows a brief summary of the main hormones and neuropeptides associated with the neuroendocrine control of energy balance. Hunger-satiety mechanism is illustrated in Figure 1.

The 'Obese Brain'

It is known that the increase in body fat is a consequence of high dietary energy intake and low energy expenditure, which results in a positive energy balance. It is not known what causes increased appetite and why some people have resistance to weight loss or difficulty in maintaining weight loss (Joffe and Houghton, 2016).

Moreover, strong evidence suggests that energy homeostasis is influenced by many other factors, such as environmental, behavioral, and hormonal, changes in food processing, nutrient intake, macronutrient composition, metabolic functions, hedonic/reward brain

systems, genes, and the interactions of these factors (Amin and Mercer, 2016; Joffe and Houghton, 2016).

Recent studies identified that there are hormonal differences in individuals with obesity in relation to normal weight individuals. Increased body fat enhances secretion of leptin and insulin, making individuals with obesity resistant to the action of these hormones. They affect negative feedback to the NPY/AgRP and cause increased hunger. They also modify energy balance through changes in signaling involved in food choices, appetite, satiety, and energy expenditure. As a result, leptin determines a new set point on energy balance which makes it difficult to lose weight due to the maintenance of the 'obese brain' (Chen et al., 2012; Gelisgen et al., 2012; Gueugnon et al., 2012; Haluzíková et al., 2013; Illán-Gomez et al., 2012; Lima-Júnior et al., 2015; Lips et al., 2013; Moehlecke et al., 2016; Munzberg et al., 2015; Palikhe et al., 2014; Sysko et al., 2013; Terra et al., 2013).

Additionally, it has been suggested by researchers that in individuals with obesity, the levels of ghrelin and satiety hormones, such as GLP-1, GLP-2, PP, PYY, are lower compared to lean individuals (Barazzonni et al., 2013; Buss et al., 2014; Gelisgen et al., 2012; Gueugnon et al., 2012; Haluzíková et al., 2013; Sysko et al., 2013; Terra et al., 2013). One possible explanation to lower levels of ghrelin is in regards to leptin and insulin resistance; however, also due to a physiological adaptation to long-term state of positive energy balance, higher leptin levels may downregulate ghrelin levels (Fernandez et al., 2015; Moehlecke et al., 2016; Reinehr and Roth, 2015; Simpson et al., 2012; Steinert et al., 2017)

Moreover, genetic polymorphisms can modify energy balance and negatively influence the response to lifestyle interventions to weight loss. It occurs in genes associated with food intake control, such as MC4R, POMC, LEP, LEPR, and FTO; energy expenditure, such as ADBRs and CPUs; and adipocytokinesynthesis, such as ADIPOQ and IL6 (Joffe and Houghton, 2016).

Figure 2 illustrates the effects of obesity on the main hormones and neuropeptides associated with neuroendocrine control of energy balance.

Mechanisms of Action and Resetting Energy Balance Following Bariatric Surgery

Bariatric surgeries are well-accepted tools for the treatment of individuals with obesity, especially in comparison to conventional weight loss interventions, such as nutritional counseling, exercise, and/or pharmacological treatments. Surgery is beneficial in expressive weight loss (20% to 40% of initial weight) and long-term weight maintenance; also in the improvement or control of associated comorbidities, hormonal and inflammatory parameters, and quality of life (Farias et al., 2016; Mechanick et al., 2008).

According to the consensus of the National Institute of Health (NIH) of 1991, reformatted by the guidelines for clinical pre-operative, trans-operative, and postoperative nutritional and metabolic practice, surgical treatment of patients with obesity is indicated for those with BMI $\geq$ 40 kg/m^2 or 35 kg/m^2 with associated comorbidities, for at least 2 years, and with previous unsuccessful conventional treatments or weight recovery programs (Mechanick et al., 2008, 2013).

Surgical techniques are divided into three types according to operating mechanisms: restrictive, disabsorptive, and both. Pure disabsorptive procedures are no longer used and considered only for historical purposes. Restrictive techniques promote weight loss controlling or reducing early satiety through gastric volume reduction. Sleeve gastrectomy (SG) removes the greater gastric curvature; and adjustable gastric banding (AGB) is an inflatable silicone ring that encircles the upper portion of the stomach.

Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) are a combination of restrictive and malabsorptive procedures. In RYGB, the restrictive component

is more important. It is obtained through the division of the stomach into a small, 30-mL gastric pouch, significantly decreasing food intake. The malabsorptive component is less important and is obtained through a Roux-en-Y reconstruction that creates a 50-cm to 100-cm biliopancreatic limb excluding food transit from the remaining segment of the stomach, the duodenum, and the proximal jejunum (Amin and Mercer, 2016; Dixon et al., 2015).

In BPD, the restrictive component is less important and is obtained through a distal gastrectomy (removal of the distal 2/3 of the stomach) or a vertical gastrectomy identical to SG. In this procedure, the malabsorptive component is more important and is also obtained through a Roux-en-Y reconstruction, along with a very long biliopancreatic limb, an alimentary limb anastomosed to the 400-mL remanescent stomach, and a very short common limb of 50 cm in length. This common limb is the only portion of the small intestine where food is mixed with bile and pancreatic enzymes (Sweeney and Morton, 2014).

Sustaining body weight loss after bariatric surgery is not only limited to mechanical restriction and/or malabsorption. Modifications in gut-brain-neuro-endocrine signaling also occur, which cause changes in appetite, energy expenditure and food-choice decision, and resetting energy balance (Dixon et al., 2015; Lean and Malkova, 2016; Michalakis and Le Roux, 2012; Munzberg et al., 2015; Sweeney and Morton, 2014).

Reduction in food intake is primarily responsible for early weight loss after bariatric surgery. Weight loss during low calorie diet causes changes in hormones involved in the regulation of hunger-satiety in an attempt to maintain body energy storage and prevent starvation. In the first 2 weeks after RYGB, a decrease in serum levels of ghrelin is observed, as a rise in satiety hormones is also induced (Evans et al., 2012; Jacobsen et al., 2012).

Additionally, in response to food intake restriction or reduced body fat mass, there are changes in signaling fat-derived hormones, such as increase in adiponectin levels, leptin and insulin sensitivity, and consequently, decrease in leptin and insulin levels. Note that these

changes are observed during the early postoperative period, and are not always associated with a significant and long-term weight loss. This may be explained by the theory that leptin resistance can be caused by an unknown factor produced in the duodenum and jejunum, and the bypass created by RYGB and BDP excludes this factor and restores normal levels of leptin, favoring weight loss (Camilleri, 2015; Dixon et al., 2015; Lima-Júnior et al., 2015).

This activates the NPY system and decreases energy expenditure, facilitating weight regain. This is a long-lasting (even after 1 year) counter-regulatory effect of appetite-regulating hormones that contribute to increased food intake and weight regain (Moehlecke et al., 2016; Posovszky and Wabitsch, 2015).

Changes in the GI tract anatomy following surgical procedures may promote physiological changes on gastric emptying and delivery of nutrients to the enteroendocrine cells. This exerts influence on afferent vagal gut-brain nerve function that plays a role in neuroendocrine status following bariatric surgery, and which may modify energy balance and metabolism (Baldassano et al., 2016; Dixon et al., 2015; Munzberg et al., 2015; Ochner et al., 2011; Stefater et al., 2012).

One of the first effects after bariatric surgery is the reduction of hunger, which can be partly explained by a decrease in serum levels of ghrelin, but the exact mechanism behind it remains unclear. Majority of studies show that changes in ghrelin levels after RYGB and SG occur within the first weeks following surgery (Basso et al., 2011; Jacobsen et al., 2012).

Studies that compared gut peptides (CCK, GLP-1, GLP-2 and PYY) between pre- and postoperative periods observed higher concentrations of these hormones after surgical procedure, mainly after RYGB and BPD (Table 2).

Bariatric surgeries, with exclusion of the proximal part of the small intestine, particularly the duodenum, such as RYGB and BPD, inhibit the secretion of a putative signal with anti-incretin effect, which improves glucose tolerance. These hormones delay gut transit

time (“ileal brake” theory), reducing hunger and increasing satiety. This mechanism is known as “foregut hypothesis” or proximal hypothesis proposed by Rubino et al. (2006).

Similar results are observed after SG and can be justified by “hindgut hypothesis” or distal hypothesis, created by Cummings et al. (2007) and Patrita et al. (2007) as alternative to the “foregut hypothesis”. The idea is that quick transit of nutrients to the distal intestine stimulates secretion of GLP-1, PYY, and OXM from the enteroendocrine L-cells increasing insulin secretion and improving glucose homeostasis, which, consequently, enhances satiety, reduces food intake, and contributes to weight loss (Chakravartty et al., 2015; Sweeney and Morton, 2014).

Finally, there are some limitations in the literature included in this study. For instance, the studies’ designs are different, only a few included a control group (Alamuddin et al., 2017; Barazzonni et al., 2013; Basso et al., 2011; Chen et al., 2012; Dar et al., 2012; Dixon et al., 2011; Evans et al., 2012; Falkén et al., 2011; Gelisgen et al., 2012; Haluzíková et al., 2013; Illán-Gomez et al., 2012; Jorgensen et al., 2012; Lips et al., 2013; Palikhe et al., 2014; Malin et al., 2014; Romero et al., 2016; Tam et al., 2016; Urbanavicius et al., 2013; Yousseif et al., 2014).

In addition, most of the studies have a small sample size (<30 participants) (Alam et al., 2012; Basso et al., 2011; Bradley et al., 2012; Cazzo et al., 2016; Dirksen et al., 2013; Evans et al., 2012; Jacobsen et al., 2012; Papamargaritis et al., 2013; Peterli et al., 2012; Ramón et al., 2012; Rigamonti et al., 2017; Romero et al., 2012; Tsoli et al., 2013; Umeda et al., 2011; Usinger et al., 2011; Woelnerhanssen et al., 2011; Yousseif et al., 2014), and of the 43 studies evaluated, only five (Biagioni et al., 2017; Dar et al., 2012; Haluzíková et al., 2013; Hoffstead et al., 2017; Malin et al., 2014) included subjects that underwent bariatric surgery at least 24 months, which may impair understanding of the mechanism behind weight loss after

bariatric surgeries. In addition, the studies have a small number because biochemical measurements for incretins and hormones are expensive.

There are a few studies on central nervous system changes after bariatric surgery. In the last 5 years, some observational or randomized studies have described the characteristic of hormonal changes after the interventions: AGB, BPD, RYGB, and SG. A summary of these findings are presented in Table 2. Figure 3 shows the main hormonal changes after bariatric surgery in the two most performed techniques in the world.

Summary and Direction for Future Research

In summary, the regulation of body weight depends on the complex interplay between gut, brain, and other organs involved in energy metabolism. The mechanisms that promote effective and sustained weight loss after bariatric surgeries can be explained not only by reducing calorie intake, but also by changes in appetite control, satiation and satiety, and physiological changes in gut, neuro- and adipose tissue-derived hormone signaling. Although the number of researches has increased in recent years, understanding obesity is not yet completely clear and more studies are needed. Better understanding of the pathophysiology of obesity may help speed up the knowledge and development of new targets for more effective therapeutics of surgical and non-surgical treatments for obesity.

References

Abdeen G and Le Roux CW (2016) Mechanism Underlying the Weight Loss and Complications of Roux-en-Y Gastric Bypass. Review. *Obesity Surgery* 26(2): 410-421.

Alam I, Stephens JW, Fielding A, Lewis KE, Lewis MJ and Baxter JN (2012) Temporal changes in glucose and insulin homeostasis after biliopancreatic diversion and laparoscopic adjustable gastric banding. *Surgery for Obesity and Related Diseases* 8(6): 752-763.

Alamuddin N, Vetter ML, Ahima RS, Hesson L, Ritter S, Minnick A et al. (2017) Changes in Fasting and Prandial Gut and Adiposity Hormones Following Vertical Sleeve Gastrectomy or Roux-en-Y Gastric Bypass: an 18-Month Prospective Study. *Obesity Surgery* 27(6): 1563-1572.

Amin T and Mercer JG (2016) Hunger and Satiety Mechanisms and Their Potential Exploitation in the Regulation of Food Intake. *Current Obesity Reports* 5(1): 106–112.

Attalah R, Filion KB, Wakil SM, Genest J, Joseph L, Poirier P et al. (2014) Long-Term Effects of 4 Popular Diets on Weight Loss and Cardiovascular Risk Factors: A Systematic Review of Randomized Controlled Trials. *Circulation. Cardiovascular Quality and Outcomes* 7(6): 815-827.

Baldassano S, Amato A and Mulè F (2016) Influence of glucagon-like peptide 2 on energy homeostasis. *Peptides* 86: 1-5.

Barazzonni R, Zanetti M, Nagliati C, Cattin MR, Ferreira C, Giuricin M et al. (2013) Gastric Bypass Does Not Normalize Obesity-Related Changes in Ghrelin Profile and Leads to Higher Acylated Ghrelin Fraction. *Obesity* 21(4): 718-722.

Basso N, Capoccia D, Rizzello M, Abbatini F, Mariani P, Maglio C et al. (2011) First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. *Surgical Endoscopy* 25(11): 3540-3550.

Bauer PV, Hamr SC and Duca FA (2016) Regulation of energy balance by a gut–brain axis and involvement of the gut microbiota. *Cellular and Molecular Life Sciences* 73(4): 737–755.

Biagioni MFG, Mendes AL, Nogueira CR, Leite CV, Gollino L and Mazeto GMFS (2017) Bariatric Roux-en-Y Gastric Bypass Surgery: Adipocyte Proteins Involved in Increase Bone

Remodeling in Humans. *Obesity Surgery*. Epub ahead of print 13 January 2017. DOI: 10.1007/s11695-017-2546-4.

Bradley D, Conte C, Mittendorfer B, Eagon JC, Varela E, Fabbrini E et al. (2012) Gastric bypass and banding equally improve insulin sensitivity and cell function. The *Journal of Clinical Investigation* 122(12): 4667-4674.

Brown JA, Woodworth HL and Leinninger GM (2015) To ingest or rest? Specialized roles of lateral hypothalamic area neurons in coordinating energy balance. *Frontiers in Systems Neuroscience* 9: 1-25.

Buchwald H (2014) The Evolution of Metabolic/Bariatric Surgery. *Obesity Surgery* 24(8): 1126–1135.

Buss J, Havel PJ, Epel E, Lin J, Blackburn E and Daubenmier J (2014) Associations of ghrelin with eating behaviors, stress, metabolic factors, and telomere length among overweight and obese women: Preliminary evidence of attenuated ghrelin effects in obesity? *Appetite* 76: 84–94.

Camilleri M (2015) Peripheral Mechanisms in Appetite Regulation. *Gastroenterology* 148: 1219–1233.

Carrasco F, Basfi-fer K, Rojas P, Valencia A, Csendes A, Codoceo J et al. (2014) Changes in Bone Mineral Density After Sleeve Gastrectomy or Gastric Bypass: Relationships with Variations in Vitamin D, Ghrelin, and Adiponectin Levels. *Obesity Surgery* 24(6): 877-884.

Cazzo E, Gestic MA, Utrini MP, Chaim FDM, Genoleze B, Pareja JC et al. (2016) GLP-2: A Poorly Understood Mediator enrolled in Various Bariatric/Metabolic Surgery-Related Pathophysiologic Mechanisms. *Arquivos Brasileiros de Cirurgia Digestiva* 29(4): 272-275.

Cazzo E, Pareja JC, Geloneze B, Chaim EA, Barreto MRL and Magro DO (2017) Postprandial GLP-2 Levels Are Increased After Biliopancreatic Diversion in Diabetic Individuals with Class I Obesity: a Prospective Study. *Obesity Surgery*. Epub ahead of print 18 January 2017. DOI: 10.1007/s11695-017-2554-4.

Cazzo E, Pareja JC, Geloneze B, Chaim EA, Barreto MRL and Magro DO (2017) GLP-1 and GLP-2 Levels are Correlated with Satiety Regulation After Roux-en-Y Gastric Bypass: Results of an Exploratory Prospective Study. *Obesity Surgery* 27(3): 703-708.

Chakravartty S, Tassinari D, Salerno A, Giorgakis E and Rubino F (2015) What is the Mechanism Behind Weight Loss Maintenance with Gastric Bypass? *Current Obesity Reports* 4(2): 262–268.

Chen J, Spagnoli A and Torquati A (2012) Omental Gene Expression of Adiponectin Correlates with Degree of Insulin Sensitivity Before and After Gastric Bypass Surgery. *Obesity Surgery* 22(3): 472-477.

Chen X, Eslamfam S, Fang L, Qiao S and Ma X (2016) Maintenance of Gastrointestinal Glucose Homeostasis by the Gut-Brain Axis. *Current Protein and Peptide Science*. Epub ahead of print 26 June 2016.

Cho S, Joo HJ, Cho J, Lee SH, Park JH, Hong SJ et al (2017) Visceral Fat Area and Serum Adiponectin Level Predict the Development of Metabolic Syndrome in a Community-Based Asymptomatic Population. *Plos One* 12(1): 1-13.

Churm R, Davies JS, Stephens JW and Prior SL (2017) Ghrelin function in human obesity and type 2 diabetes: a concise review. *Obesity Reviews* 18(2): 140-148.

Cummings D, Overduin J, Foster-Schubert K and Carlson M (2007) Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery. *Surgery for Obesity and Related Diseases* 3(2): 109-115.

Dar MS, Chapman WH, Pender JR, Drake AJ, O'Brien K and Tanenberg RJ (2012) GLP-1 Response to a Mixed Meal: What Happens 10 Years after Roux-en-Y Gastric Bypass (RYGB)? *Obesity Surgery* 22(7): 1077-1083.

Dirksen C, Bojsen-Møller KN, Jorgensen NB, Jacobsen SH, Kristiansen VB, Naver LS et al. (2013) Exaggerated release and preserved insulinotropic action of glucagon-like peptide-1

underlie insulin hypersecretion in glucose-tolerant individuals after Roux-en-Y gastric bypass. *Diabetologia* 2013; 56(12): 2679-2687.

Dixon AFR, Le Roux CW, Ghatei MA, Bloom SR, McGee TL and Dixon JB (2011) Pancreatic Polypeptide Meal Response May Predict Gastric Band-Induced Weight Loss. *Obesity Surgery* 21(12): 1906-1913.

Dixon JB, Lambert EA and Lambert GW (2015) Neuroendocrine adaptations to bariatric surgery. *Molecular and Cellular Endocrinology* 418: 143e-152.

Evans S, Pamuklar Z, Rosko J, Mahaney P, Jiang N, Park C et al. (2012) Gastric Bypass Surgery Restores Meal Stimulation of the Anorexigenic Gut Hormones Glucagon-Like-Peptide-1 and Peptide YY Independently of Caloric Restriction. *Surgical Endoscopy* 26(4): 1086-1094.

Falkén Y, Hellstro¨m PM, Holst JJ and Naslund E (2011) Changes in Glucose Homeostasis after Roux-en-Y Gastric Bypass Surgery for Obesity at Day Three, Two Months, and One Year after Surgery: Role of Gut Peptides. *The Journal of Clinical Endocrinology and Metabolism* 96(7): 2227-2235.

Farias G, Thieme RD, Teixeira LM, Heyde ME, Bettini SC and Radominski RB (2016) Good weight loss responders and poor weight loss responders after Roux-en-Y gastric bypass: clinical and nutritional profiles. *Nutricion Hospitalaria* 33(5):1108–1115.

Farr OM, Li CR and Mantzoros CS (2016) Central nervous system regulation of eating: Insights from human brain imaging. *Metabolism* 65(5): 699-713.

Fernandez SB, Folgueira C, Castelao C, Leis R, Casanueva FF and Seoane LM (2015) Peripheral Signals Mediate the Beneficial Effects of Gastric Surgery in Obesity. *Gastroenterology Research and Practice* 2015: 1-12.

Garrido-Sanchéz L, Murri M, Rivas-Becerra J, Ocaña-Willhelmi L, Cohen RV, Garcia-Fuentes E et al. (2012) Bypass of the duodenum improves insulin resistance much more rapidly than sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 8(2): 145-150.

Gelisgen R, Zengin K, Kocael A, Baysal B, Kocael P, Erman H et al. (2012) Effects of Laparoscopic Gastric Band Applications on Plasma and Fundic Acylated Ghrelin Levels in Morbidly Obese Patients. *Obesity Surgery* 22(2): 299-305.

Gueugnon C, Mougin F, Nguyen NU, Bouhaddi M, Nicolet-Guenát M and Dumoulin G (2012) Ghrelin and PYY levels in adolescents with severe obesity: effects of weight loss induced by long-term exercise training and modified food habits. *European Journal of Applied Physiology* 112(5): 1797–1805.

Haluzíková D, Lacinová Z, Kaválkova P, Drápalova J, Krizová J, Bártlová M et al. (2013) Laparoscopic Sleeve Gastrectomy Differentially Affects Serum Concentrations of FGF-19 and FGF-21 in Morbidly Obese Subjects. *Obesity* 21(7): 1335-1342.

Hansen EN, Tamboli RA, Isbell JM, Saliba J, Dunn JP, Marks-Shulman PA et al. (2011) Role of the foregut in the early improvement in glucose tolerance and insulin sensitivity following Roux-en-Y gastric bypass surgery. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 300(5): G795-G802.

Hoffstead J, Andersson DP, Eriksson HD, Theorell J, Naslund E, Thorell A et al. (2017) Long-Term Protective Changes in Adipose Tissue After Gastric Bypass. *Diabetes Care* 40(1): 77-84.

Illán-Gomez F, González-Ortega M, Orea-Soler I, Alcaraz-Taffala, Aragón-Alonso A and Pascual-Diáz M (2012) Obesity and Inflammation: Change in Adiponectin, C-Reactive Protein, Tumour Necrosis Factor-Alpha and Interleukin-6 After Bariatric Surgery. *Obesity Surgery* 22(6): 950-955.

Jacobsen SH, Olesen SC, Jorgensen NB, Bojsen-Møller KN, Kielgast U, Worm D et al. (2012) Changes in Gastrointestinal Hormone Responses, Insulin Sensitivity, and Beta-Cell Function Within 2 Weeks After Gastric Bypass in Non-diabetic Subjects. *Obesity Surgery* 22(7): 1084-1096.

Joffe YT and Houghton CA (2016) A Novel Approach to the Nutrigenetics and Nutrigenomics of Obesity and Weight Management. *Current Oncology Reports* 18(7): 43.

Krieger AC, Youn H, Modersitzki F, Chiu Y, Gerber LM, Weinshel E et al. (2012) Effects of laparoscopic adjustable gastric banding on sleep and metabolism: a 12-month follow-up study. *International Journal of General Medicine* 5: 975-981.

Jonge C, Rensen SS, Verdam FJ, Vincent RP, Bloom SR, Buurman WA et al. (2016) Impact of Duodenal-Jejunal Exclusion on Satiety Hormones. *Obesity Surgery* 26(3): 672–678.

Jorgensen NB, Jacobsen SH, Dirksen C, Bojsen-Møller KN, Naver LS, Hvolris L et al. (2012) Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *American Journal of Physiology. Endocrinology and Metabolism* 303(1): E-122-E131.

Larder R and O'Rahilly S (2012) Shedding pounds after going under the knife: guts over glory-why diets fail. *Nature Medicine* 18(5): 666–667.

Lean MEJ and Malkova D (2016) Altered gut and adipose tissue hormones in overweight and obese individuals: cause or consequence? *International Journal of Obesity* 40(4): 622–632.

Leblanc ES, O'Connor E, Whitlock EP, Patnode CD and Kapka T (2011) Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the US preventive sevices task force. *Annals of Internal Medicine* 155(7): 434-447.

Lima-Júnior JC de, Velloso LA, Geloneze B (2015) The Obese Brain—Effects of Bariatric Surgery on Energy Balance Neurocircuitry. *Current Atherosclerosis Reports* 17(10): 57.

Lips MA, Pijl H, Klinken JBV, Groot GH, Janssen IM, Ramshorst BV et al. (2013) Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. *European Journal of Endocrinology* 169(3): 339-347.

Malin SK, Samat A, Wolski K, Abood B, Pothier CE, Bhatt DL et al. (2014) Improved acylated ghrelin suppression at 2 years in obese patients with type 2 diabetes: effects of bariatric surgery vs standard medical therapy. *International Journal of Obesity* 38(3): 364-370.

Mallipedhi A, Prior SL, Barry JD, Caplin S, Baxter JN and Stephens JW (2014) Temporal changes in glucose homeostasis and incretin hormone response at 1 and 6 months after laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 10(5): 860-870.

Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S, et al. (2008) American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. *Surgery for Obesity and Related Diseases* 4:S109-S184.

Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, et al. (2013) Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient - 2013 Update: Cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society. *Endocrine Practice* 19(2):e1–36.

Meek CL, Lewisa HB, Reimanna F, Gribblea FM and Parka AJ (2016) The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. *Peptides* 77: 28–37.

Melvin A, Le Roux CW and Docherty NG (2016) The Gut as an Endocrine Organ: Role in the Regulation of Food Intake and Body Weight. *Current Atherosclerosis Reports* 18(8):49.

Michalakis K and Le Roux CW (2012) Gut hormones and leptin: impact on energy control and changes after bariatric surgery. *Obesity Surgery* 22(10): 1648-1657.

Mishra AK, Dubey V and Ghosh AR (2016) Obesity: An overview of possible role(s) of gut hormones, lipid sensing and gut microbiota. *Metabolism* 65(1): 48-65.

Moehlecke M, Canani LH, Silva LOJ, Trindade MRM, Friedman R and Leitão CB (2016) Determinants of body weight regulation in humans. *Archives of Endocrinology and Metabolism* 60(2):152-162.

Münzberg H, Laque A, Yu S, Rezai-Zadeh K and Berthoud H (2015) Appetite and body weight regulation after bariatric surgery. *Obesity Reviews* 16(Suppl 1):77–90.

Nannipieri M, Baldi S, Mari A, Colligiani D, Guarino D, Camastra S et al. (2013) Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: Mechanisms of Diabetes Remission and Role of Gut Hormones. *The Journal of Clinical Endocrinology and Metabolism* 98(11): 4391-4399.

Netto BDM, Bettini SC, Clemente AP, Ferreira JP, Boritza K, Von der Heyde ME et al. (2015) Roux-en-Y gastric bypass decreases pro-inflammatory and thrombotic biomarkers in individuals with extreme obesity. *Obesity Surgery* 25(6): 1010-1018.

Netto BDM, Earthman CP, Bettini SC, Clemente APG, Masquio DCL, Farias G et al. (2016) Early effects of Roux-en-Y gastric bypass on peptides and hormones involved in the control of energy balance. *European Journal of Gastroenterology & Hepatology* 28(9): 1050-1055.

NIH (National Institutes of Health) (1991) Consensus Development Conference Statement. Gastrointestinal surgery for severe obesity. *Annals of Internal Medicine* 115: 956-961.

Ochner CN, Gibson C, Shanik M, Goel V and Geliebter A (2011) Changes in neurohormonal gut peptides following bariatric surgery. *International Journal of Obesity* 35(2): 153–166.

Palikhe G, Gupta R, Behera BN, Sachdeva N, Gangadhar P and Bhansali A (2014) Efficacy of Laparoscopic Sleeve Gastrectomy and Intensive Medical Management in Obese Patients with Type 2 Diabetes Mellitus. *Obesity* Surgery 24(4): 529-535.

Papamargaritis D, Le Roux CW, Sioka E, Koukoulis G, Tzovaras G and Zacharoulis D (2013) Changes in gut hormone profile and glucose homeostasis after laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 9(2): 192-201.

Patrita A, Aisa M, Annetti C, et al. (2007) How the hindgut can cure type 2 diabetes. Ileal transposition improves glucose metabolism and β-cell function in Goto-kakizaki rats through enhanced proglucagon gene expression and L-cell umber. *Surgery* 142:74-85.

Peterli R, Steinert RE, Woelnerhanssen B, Peters T, Christoffel-Courtin C, Gass M et al. (2012) Metabolic and Hormonal Changes After Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: a Randomized, Prospective Trial. *Obesity Surgery* 22(5): 740-748.

Posovszky C and Wabitsch M (2015) Regulation of Appetite, Satiation, and Body Weight by Enteroendocrine Cells. Part 2: Therapeutic Potential of Enteroendocrine Cells in the Treatment of Obesity. *Hormone Research in Paediatrics* 83(1):11–18.

Ramón JM, Salvans S, Crous X, Puig S, Goday A, Benaiges D et al. (2012) Effect of Roux-en-Y gastric bypass vs sleeve gastrectomy on glucose and gut hormones: a prospective randomized trial. *Journal of Gastrointestinal Surgery* 16(6):1116–1122.

Reinehr T and Roth CL (2015) The gut sensor as regulator of body weight. *Endocrine* 49(1): 35-50.

Riediger T (2012) The receptive function of hypothalamic and brainstem centres to hormonal and nutrient signals affecting energy balance. *The Proceedings of the Nutrition Society* 71(4): 463-477.

Rigamonti AE, Bini S, Rocco MC, Giardini V, Massimini D, Crippa MG C et al. (2017) Post-prandial anorexigenic gut peptide, apetite and glucometabolic responses at different eating rates in obese patients undergoing laparoscopic sleeve gastrectomy. *Endocrine* 55(1):113-123.

Romero F, Nicolau J, Flores L, Casamitjana R, Ibarzabal A, Lacy A et al. (2012) Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. *Surgical Endoscopy* 26(8): 2231-2239.

Rubino F, Forgione A, Cummings DE, Vix M, Gnuli D, Mingrone G, Castagneto M and Marescaux J (2006) The mechanism of diabetes control after gastrointestinal bypass surgery

reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. *Annals of Surgery* 244(5): 741–749.

Simpson K, Parker J, Plumer J and Bloom S (2012) CCK, PYY and PP: the control of energy balance. In: Joost H-G, editor. Appetite Control. In: Handbook of experimental pharmacology. Berlin, Heidelberg: Springer-Verlag, pp. 342; 555.

Stefater MA, Wilson-Pérez HE, Chambers AP, Sandoval DA and Seeley RJ (2012) All Bariatric Surgeries Are Not Created Equal: Insights from Mechanistic Comparisons. *Endocrine Reviews* 33(4): 595-622.

Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C and Geary N (2017) Ghrelin, CCK, GLP-1, and PYY (3-36): Secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. *Physiological Reviews* 97(1): 411-463.

Sun J, Gao Y, Yao T, Huang Y, He Z, Kong X et al. (2016) Adiponectin potentiates the acute effects of leptin in arcuate Pomc neurons. *Molecular Metabolism* 18(5): 882-891.

Sweeney TE and Morton JM (2014) Metabolic surgery: action via hormonal milieu changes, changes in bile acids or gut microbiota? A summary of the literature. *Best Practice & Research. Clinical Gastroenterology* 28(4):727–740.

Sysko R, Devlin MJ, Schebendach J, Tanofsky-Kraff M, Zimmerli E, Korner J et al. (2013) Hormonal responses and test meal intake among obese teenagers before and after laparoscopic adjustable gastric banding. *The American Journal of Clinical Nutrition* 98(5): 1151–1161.

Tam CS, Redman LM, Greenway F, LeBlanc KA, Haussmann MG and Ravussin E (2016) Energy Metabolic Adaptation and Cardiometabolic Improvements One Year After Gastric Bypass, Sleeve Gastrectomy, and Gastric Band. *The Journal of Clinical Endocrinology and Metabolism* 101(10): 3755-3764.

Terra X, Auguet T, Guiu-Jurado E, Berlanga A, Orellana-Gavaldà JM, Hernández M et al. (2013) Long-term Changes in Leptin, Chemerin and Ghrelin Levels Following Different

Bariatric Surgery Procedures: Roux-en-Y Gastric Bypass and Sleeve Gastrectomy. *Obesity Surgery* 23(11): 1790–1798.

Tsoli M, Chronaiou A, Kehagias I, Kalfarentzos F and Alexandrides TK (2013) Hormone changes and diabetes resolution after biliopancreatic diversion and laparoscopic sleeve gastrectomy: a comparative prospective study. *Surgery for Obesity and Related Diseases* 9(5): 667-678.

Ueno H and Nakazato M (2016) Mechanistic relationship between the vagal afferent pathway, central nervous system and peripheral organs in appetite regulation. *Journal of Diabetes Investigation* 7(6): 812-818.

Umeda LM, Silva EA, Carneiro G, Arasaki CH, Geloneze B and Zanella MT (2011) Early Improvement in Glycemic Control After Bariatric Surgery and Its Relationships with Insulin, GLP-1, and Glucagon Secretion in Type 2 Diabetic Patients. *Obesity Surgery* 21(7): 896-901.

Urbanavicius V, Abaliksta T, Brimas G, Abraitiené A, Gogeliené L and Strupas K (2013) Comparison of Changes in Blood Glucose, Insulin Resistance Indices, and Adipokine Levels in Diabetic and Nondiabetic Subjects with Morbid Obesity After Laparoscopic Adjustable Gastric Banding. *Medicina (Kaunas)* 49(1): 9-14.

Usinger L, Hansen KB, Kristiansen VB, Larsen S, Holst JJ and Knop FK (2011) Gastric Emptying of Orally Administered Glucose Solutions and Incretin Hormone Responses Are Unaffected by Laparoscopic Adjustable Gastric Banding. *Obesity Surgery* 21(5): 625-632.

Woelnerhanssen B, Peterli R, Steinert RE, Peters T, Borbély Y, Beglinger C (2011) Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy—a prospective randomized trial. *Surgery for Obesity and Related Diseases* 7(5): 561-568.

Yousseif A, Emmanuel J, Karra E, Millet Q, Elkalaawy M, Jenkinson AD et al. (2014) Differential Effects of Laparoscopic Sleeve Gastrectomy and Laparoscopic Gastric Bypass on Appetite, Circulating Acyl-ghrelin, Peptide YY3-36 and Active GLP-1 Levels in Non-diabetic Humans. *Obesity Surgery* 24(2): 241-252.

Table 1. Summary of the main hormones and neuropeptides associated with the neuroendocrine control of energy balance

Hormone	Production site	Stimulus for secretion	Production inhibitors	Effects on appetite	Likely actions	References
Central Nervous System						
AgRP	ARC	• Fasting • Ghrelin	• α-MSH • Leptin • PYY	↑	Opposes it the action of MC4R	Moehlecke et al., 2016
α-MSH	ARC	• Leptin	• AgRP	↓	Favors action of MC4R Energy homeostasis	Moehlecke et al., 2016
CART	ARC	• Food intake • GLP-1 • Leptin • PYY	• Fasting • Ghrelin	↓	↓ food intake	
MCH	LHA	• Food palatability • AgRP/ NPY	• MSH-producing neurons	↑	Regulation of feeding behaviour and energy homeostasis	Moehlecke et al., 2016
NPY	ARC	• Fasting • Ghrelin	• CCK • Leptin • Insulin • PYY	↑	↑ food intake and lipogenesis ↓ energy expenditure	Moehlecke et al., 2016
POMC	ARC	• Food intake • Leptin • PYY	• Fasting • Ghrelin	↓	Precursor of products that act in MC3R and MC4R, for example ∝-MSH	
Adipose Tissue						
ADIPONECTIN	White adipose tissue	• Peroxisome proliferator-activated receptor gamma (PPAR-gamma)	• Catecholamines, • TNF-alpha	↓	Energy homeostasis ↑ insulin sensitivity and fatty acid oxidation ↓ hepatic glucose production and inflammatory process	Moehlecke et al., 2016
LEPTIN	White adipose tissue	• Body fat • Insulin	• Fasting • GLP-1	↓	Reports amount of body fat ↑ lipolysis; activation of POMC/CART, CRH and the satiety effects of CCK ↓:lipogenesis and release of NPY/ AgRP	Buchwald, 2014; Farr et al., 2016; Lean and Malkova, 2016; Moehlecke et al., 2016; Ochner et al., 2011

Hormone	Production site	Stimulus for secretion	Production inhibitors	Effects on appetite	Likely actions	References
Pancreas						
AMYLIN	Pancreatic β-cells	• Hypoglycemia • Protein		↓	Delayed gastric emptying Participates in the glucose homeostasis	Reinehr and Roth, 2015; Riediger, 2012
GLUCAGON	Pancreatic alpha-cells	• Fast	• GLP-1		↑ blood sugar levels; glycogenolysis and gluconeogenesis	Reinehr and Roth, 2015
INSULIN	Pancreatic β-cells	• Food intake • Body adiposity • Hyperglycemia	• Fasting	↓	Optimize glucose use for energy after ingest of food ↑ glycogen synthesis Produces of catabolic neuropeptides	Camilleri, 2015; Moehlecke et al., 2016; Reinehr and Roth, 2015
PP	Pancreatic PP cells	• Exercise • Insulin • Gastric distension • CCK • Gastrin • Motilin • Secretin • Food Intake	• Somatostatin	↓	↓ gastric emptying rate, ↑ exocrine pancreatic secretion and gallbladder motility	Lean and Malkova, 2016; Mishra et al., 2016; Reinehr and Roth, 2015
Gut peptides						
CCK	I-cells of proximal small intestine	• Lipids • Protein • Insulin • Leptin	• Fasting	↓	↑ gallbladder contraction; pancreatic; satiety; enzyme secretion Delays gastric emptying ↓ NPY and provides feedback to reduce food intake and meal duration	Bauer et al., 2016; Lean and Malkova, 2016; Meek et al., 2016; Mishra et al., 2016; Moehlecke et al., 2016; Ochner et al., 2011; Reinehr and Roth, 2015
GIP	K-cells of the duodenum	• GLP-1	• Fasting	↓	↑ insulin secretion	Buchwald, 2014
GLP-1	L cells in distal small intestine and larger intestine	• Carbohydrate • Proteins • Lipids • Exercise • Insulin	• Fasting	↓	Activates ileal brake and reduce GI motility ↑ lipolysis; adiponectin expression; energy expenditure; insulin secretion; GIP secretion ↓ glucagon secretion; glucagon release;	Bauer et al., 2016; Buchwald, 2014; Lean and Malkova, 2016; Meek et al., 2016; Melvin et al., 2016; Mishra et al.,

		• Leptin			gastric acid secretion; gastric emptying	2016; Moehlecke et al., 2016; Ochner et al., 2011; Reinehr and Roth, 2015
Hormone	**Production site**	**Stimulus for secretion**	**Production inhibitors**	**Effects on appetite**	**Likely actions**	**References**
GLP-2	L cells in distal small intestine and larger intestine	• Proteins • Lipids	• Fasting	↓	↑ gut cell proliferation; capacity of absorption of nutrients; insulin sensitivity; satiety ↓ enterocyte and crypt cell apoptosis; acid secretion and gastric emptying; gastrointestinal motility; bone resorption; food intake	Baldassano et al., 2016; Cazzo et al., 2016, 2017; Meek et al., 2016; Reinehr and Roth, 2015
OXM	L cells in distal small intestine and large intestine	• Lipids	• Fasting	↓	↑ satiety; energy expenditure; insulin secretion Agonist of glucagon receptor and GLP-1 receptors	Meek et al., 2016; Reinehr and Roth, 2015
PYY	L cells in distal small intestine and larger intestine	• Food intake: proportional to the size and type of macronutrient (mainly lipids) • Low carb diet • Exercise • Low duodenal pH	• Fasting	↓	↑ satiety; in water and electrolyte absorption Activates ileal brake ↓ gastric emptying; gastric acid and pancreatic exocrine secretions	Bauer et al., 2016; Lean and Malkova, 2016; Meek et al., 2016; Melvin et al., 2016; Michalakis and Le Roux, 2012; Mishra et al., 2016; Ochner et al., 2011; Reinehr and Roth, 2015; Sweeney and Morton, 2014; Ueno and Nakazato, 2016
Gastric peptides						
GASTRIN	G cells in the gastric antrum and duodenum	• Food in the stomach • Gastric distension • Alcohol	• Somastatin • Secretin • GIP • Neurotensin	↓	↑ production of hydrochloric acid, pepsinogen, intrinsic factor, pancreatic	Meek et al., 2016; Reinehr and Roth, 2015

		• Caffeine • Protein	• Low pH • High fat diet		secretions and bile ↑ satiety	
Hormone	**Production site**	**Stimulus for secretion**	**Production inhibitors**	**Effects on appetite**	**Likely actions**	**References**
GHRELIN	X/A cells of the gastric fundus	• Fasting, • Hunger • Prolonged state of negative energy balance	• After feeding • During hyperglycemia • Obesity • Carboydrates and lipids	↑	↑ NPY/AgRP neurons in the ARC; gut motility and the rate of gastric emptying; gastrointestinal motility ↓insulin secretion Modulates pancreatic function and is involved in energy balance regulation and glucose homeostasis Growth hormone release	Buchwald, 2014; Meek et al., 2016; Melvin et al., 2016; Mishra et al., 2016; Moehlecke et al., 2016; Ochner et al., 2011; Reinehr and Roth, 2015

Table 2. Summary of gastrointestinal peptide changes after bariatric operations: studies from January 2011 to February 2017

Hormone	AGB/VGB					RYGB					SG					BPD				
	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Central Nervous System																				
AgRP * (fasting)								↔[1]												
α-MSH * (fasting)								↔[1]												
CART																				
MCH * (fasting)								↔[1]												
NPY * (fasting)								↔[1]												
POMC																				
Adipose Tissue																				
Adiponectin (fasting) †		↔[2]		↑[2,3]	↑[4]		↔[2,5]	↑[6]	↑[2,4,7,8,9,10,11]	↑[11,12]		↑[13] ↔[2]	↑[14]	↑[2,9,10]	↑[15]		↑[13]			
Leptin (fasting) †				↑[16] ↓[2,3,17]	↓[4]	↔[18]	↓[2,5,19]	↓[1,20]	↓[2,4,10,11,20,21]	↓[11]		↓[13]	↓[14,20]	↓[2,10,20,21]	↓[15]		↓[13]		↓[16]	
Leptin (postprandial) †						↔[18]			↓[21,22]					↓[21]						
Pancreas																				
Amylin (fasting)*						↔[18]			↓[23]					↔[23]	↓[15]					
Glucagon (fasting)*		↔[24]					↔[25]		↔[22,23]					↔[23]					↓[27]	

							↓[26]							↓[27]						
Hormone	**AGB/VGB**					**RYGB**					**SG**					**BPD**				
	T1	**T2**	**T3**	**T4**	**T5**	**T1**	**T2**	**T3**	**T4**	**T5**	**T1**	**T2**	**T3**	**T4**	**T5**	**T1**	**T2**	**T3**	**T4**	**T5**
Insulin (fasting) †		↔[24]	↓[40]	↓[16]	↓[4]	↓[18]	↓[5,26] ↔[25]		↓[4,7,8,10, 22,28,41]		↔[32]	↓[13,29]	↓[31]	↓[10,27,30]	↔[15]		↓[13]	↓[31]	↓[16,27]	
PP (fasting) †					↔[33]	↓[18]			↑[23] ↔[21,22]					↑[23] ↔[21]						
Gut peptides																				
CCK (fasting)*						↔[18]														
CCK (postprandial) †						↑[18]			↔[34]					↑[34]						
GIP (fasting)*		↔[24]				↔[18]	↔[5,35]		↓[22] ↔[28]			↔[35]			↔[15]					
GIP (postprandial)*		↔[24]					↔[26,35]		↑[22] ↓[28]			↑[35]	↔[31]					↓[31]		
GLP-1 total (fasting)*		↔[24]				↔[18,36]	↔[5,25,26, 35,37]	↔[20]	↔[20,22,28] ↓[23]		↑[32]	↔[29,35,37]	↔[20]	↔[20,23,30, ↓[27]	↔[15]				↔[27]	
GLP-1 (postprandial)†		↔[24]				↑[18,36]	↑[25,35,37]	↑[20]	↑[20,21,22, 28,34,38 ↔[23]	↑[42]		↑[35,37]	↑[20,31]	↑[30,34 ↔[23,27]				↑[31]	↑[27]	
GLP-2 total (fasting)*						↔[18]	↔[35]					↔[35]							↔[43]	

Hormone	AGB/VGB					RYGB					SG					BPD				
	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
GLP-2 (postprandial)*						↑[18]	↑[35]		↑[38]			↑[35]							↑[43]	
OXM*									↑[22]											
PYY3-36 (fasting)*					↓[33]	↓[18] ↔[36]	↔[37]	↑[1,20]	↑[23,20]		↑[32]	↔[29,37]	↔[20]	↑[23,20] ↓[27] ↔[30]	↓[15]				↑[27]	
PYY3-36 (postprandial) †						↑[18] ↔[36]	↑[37]	↑[20]	↑[20,23,34] ↔[21]			↑[37]	↑[20]	↑[20,23,30] ↓[27] ↔[21,34]					↑[27]	
Gastric Peptides																				
Gastrin (fasting)*						↔[18]														
Gastrin (postprandial)*						↓[18]														
Ghrelin active (fasting)*			↑[40]			↓[18]	↓[5] ↔[37]					↔[37]			↓[15,39]					
Ghrelin active (postprandial)*						↓[18]	↔[37]		↑[41]	↓[39]		↓[37]			↓[39]					
Ghrelin total (fasting) †				↔[17]		↓[18]	↔[5]	↑[20]	↔[41] ↓[23] ↑[20]		↓[32]	↓[29]	↓[14,20]	↓[9,20, 21,23,27					↔[27]	
Ghrelin total (postprandial) †						↓[18]			↑[21,41] ↔[34] ↓[21,23]					↔[21,34] ↓[23,27]					↑[27]	

Legend: ↑ - Postsurgical increase; ↓: Postsurgical decrease; ↔: No significant postsurgical change

T1: until 30 days follow-up T2: 3 months follow-up T3: 6 months follow-up T4: 12 months folow-up T5: ≥ 24 months follow-up

*- observational clinical studies only; † - randomized clinical trials and observational clinical studies

References

1 - Netto BDM, Earthman CP, Bettini SC, Clemente APG, Masquio DCL, Farias G et al. (2016) Early effects of Roux-en-Y gastric bypass on peptides and hormones involved in the control of energy balance. *European Journal of Gastroenterology & Hepatology* 28(9): 1050-1055.

2 - Tam CS, Redman LM, Greenway F, LeBlanc KA, Haussmann MG and Ravussin E (2016) Energy Metabolic Adaptation and Cardiometabolic Improvements One Year After Gastric Bypass, Sleeve Gastrectomy, and Gastric Band. *The Journal of Clinical Endocrinology and Metabolism* 101(10): 3755-3764.

3 - Urbanavicius V, Abaliksta T, Brimas G, Abraitiené A, Gogeliené L and Strupas K (2013) Comparison of Changes in Blood Glucose, Insulin Resistance Indices, and Adipokine Levels in Diabetic and Nondiabetic Subjects with Morbid Obesity After Laparoscopic Adjustable Gastric Banding. *Medicina (Kaunas)* 49(1): 9-14.

4 - Bradley D, Conte C, Mittendorfer B, Eagon JC, Varela E, Fabbrini E et al. (2012) Gastric bypass and banding equally improve insulin sensitivity and cell function. The *Journal of Clinical Investigation* 122(12): 4667-4674.

5 - Hansen EN, Tamboli RA, Isbell JM, Saliba J, Dunn JP, Marks-Shulman PA et al. (2011) Role of the foregut in the early improvement in glucose tolerance and insulin sensitivity following Roux-en-Y gastric bypass surgery. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 300(5): G795-G802.

6 - Netto BDM, Bettini SC, Clemente AP, Ferreira JP, Boritza K, Von der Heyde ME et al. (2015) Roux-en-Y gastric bypass decreases pro-inflammatory and thrombotic biomarkers in individuals with extreme obesity. *Obesity Surgery* 25(6): 1010-1018.

7 - Chen J, Spagnoli A and Torquati A (2012) Omental Gene Expression of Adiponectin Correlates with Degree of Insulin Sensitivity Before and After Gastric Bypass Surgery. *Obesity Surgery* 22(3): 472-477.

8 - Illán-Gomez F, González-Ortega M, Orea-Soler I, Alcaraz-Taffala, Aragón-Alonso A and Pascual-Diáz M (2012) Obesity and Inflammation: Change in Adiponectin, C-Reactive Protein, Tumour Necrosis Factor-Alpha and Interleukin-6 After Bariatric Surgery. *Obesity Surgery* 22(6): 950-955.

9 - Carrasco F, Basfi-fer K, Rojas P, Valencia A, Csendes A, Codoceo J et al. (2014) Changes in Bone Mineral Density After Sleeve Gastrectomy or Gastric Bypass: Relationships with Variations in Vitamin D, Ghrelin, and Adiponectin Levels. *Obesity Surgery* 24(6): 877-884.

10 - Woelnerhanssen B, Peterli R, Steinert RE, Peters T, Borbély Y, Beglinger C (2011) Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy—a prospective randomized trial. *Surgery for Obesity and Related Diseases* 7(5): 561-568.

11 - Biagioni MFG, Mendes AL, Nogueira CR, Leite CV, Gollino L and Mazeto GMFS (2017) Bariatric Roux-en-Y Gastric Bypass Surgery: Adipocyte Proteins Involved in Increase Bone Remodeling in Humans. *Obesity Surgery*. Epub ahead of print 13 January 2017. DOI: 10.1007/s11695-017-2546-4.

12 – Hoffstead J, Andersson DP, Eriksson HD, Theorell J, Naslund E, Thorell A et al. (2017) Long-Term Protective Changes in Adipose Tissue After Gastric Bypass. *Diabetes Care* 40(1): 77-84.

13 - Garrido-Sanchéz L, Murri M, Rivas-Becerra J, Ocaña-Willhelmi L, Cohen RV, Garcia-Fuentes E et al. (2012) Bypass of the duodenum improves insulin resistance much more rapidly than sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 8(2): 145-150.

14 - Palikhe G, Gupta R, Behera BN, Sachdeva N, Gangadhar P and Bhansali A (2014) Efficacy of Laparoscopic Sleeve Gastrectomy and Intensive Medical Management in Obese Patients with Type 2 Diabetes Mellitus. *Obesity* Surgery 24(4): 529-535.

15 - Haluzíková D, Lacinová Z, Kaválkova P, Drápalova J, Krizová J, Bártlová M et al. (2013) Laparoscopic Sleeve Gastrectomy Differentially Affects Serum Concentrations of FGF-19 and FGF-21 in Morbidly Obese Subjects. *Obesity* 21(7): 1335-1342.

16 - Alam I, Stephens JW, Fielding A, Lewis KE, Lewis MJ and Baxter JN (2012) Temporal changes in glucose and insulin homeostasis after biliopancreatic diversion and laparoscopic adjustable gastric banding. *Surgery for Obesity and Related Diseases* 8(6): 752-763.

17 - Krieger AC, Youn H, Modersitzki F, Chiu Y, Gerber LM, Weinshel E et al. (2012) Effects of laparoscopic adjustable gastric banding on sleep and metabolism: a 12-month follow-up study. *International Journal of General Medicine* 5: 975-981.

18 - Jacobsen SH, Olesen SC, Jorgensen NB, Bojsen-Møller KN, Kielgast U, Worm D et al. (2012) Changes in Gastrointestinal Hormone Responses, Insulin Sensitivity, and Beta-Cell Function Within 2 Weeks After Gastric Bypass in Non-diabetic Subjects. *Obesity Surgery* 22(7): 1084-1096.

19 - Lips MA, Pijl H, Klinken JBV, Groot GH, Janssen IM, Ramshorst BV et al. (2013) Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. *European Journal of Endocrinology* 169(3): 339-347.

20 - Alamuddin N, Vetter ML, Ahima RS, Hesson L, Ritter S, Minnick A et al. (2017) Changes in Fasting and Prandial Gut and Adiposity Hormones Following Vertical Sleeve Gastrectomy or Roux-en-Y Gastric Bypass: an 18-Month Prospective Study. *Obesity Surgery* 27(6): 1563-1572.

21 - Ramón JM, Salvans S, Crous X, Puig S, Goday A, Benaiges D et al. (2012) Effect of Roux-en-Y gastric bypass vs sleeve gastrectomy on glucose and gut hormones: a prospective randomized trial. *Journal of Gastrointestinal Surgery* 16(6):1116–1122.

22 - Falkén Y, Hellstro¨m PM, Holst JJ and Naslund E (2011) Changes in Glucose Homeostasis after Roux-en-Y Gastric Bypass Surgery for Obesity at Day Three, Two Months, and One Year after Surgery: Role of Gut Peptides. *The Journal of Clinical Endocrinology and Metabolism* 96(7): 2227-2235.

23 - Nannipieri M, Baldi S, Mari A, Colligiani D, Guarino D, Camastra S et al. (2013) Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: Mechanisms of Diabetes Remission and Role of Gut Hormones. *The Journal of Clinical Endocrinology and Metabolism* 98(11): 4391-4399.

24 - Usinger L, Hansen KB, Kristiansen VB, Larsen S, Holst JJ and Knop FK (2011) Gastric Emptying of Orally Administered Glucose Solutions and Incretin Hormone Responses Are Unaffected by Laparoscopic Adjustable Gastric Banding. *Obesity Surgery* 21(5): 625-632.

25 - Umeda LM, Silva EA, Carneiro G, Arasaki CH, Geloneze B and Zanella MT (2011) Early Improvement in Glycemic Control After Bariatric Surgery and Its Relationships with Insulin, GLP-1, and Glucagon Secretion in Type 2 Diabetic Patients. *Obesity Surgery* 21(7): 896-901.

26 - Dirksen C, Bojsen-Møller KN, Jorgensen NB, Jacobsen SH, Kristiansen VB, Naver LS et al. (2013) Exaggerated release and preserved insulinotropic action of glucagon-like peptide-1 underlie insulin hypersecretion in glucose-tolerant individuals after Roux-en-Y gastric bypass. *Diabetologia* 2013; 56(12): 2679-2687.

27 – Tsoli M, Chronaiou A, Kehagias I, Kalfarentzos F and Alexandrides TK (2013) Hormone changes and diabetes resolution after biliopancreatic diversion and laparoscopic sleeve gastrectomy: a comparative prospective study. *Surgery for Obesity and Related Diseases* 9(5): 667-678.

28 - Jorgensen NB, Jacobsen SH, Dirksen C, Bojsen-Møller KN, Naver LS, Hvolris L et al. (2012) Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *American Journal of Physiology. Endocrinology and Metabolism* 303(1): E-122-E131.

29 - Rigamonti AE, Bini S, Rocco MC, Giardini V, Massimini D, Crippa MG C et al. (2017) Post-prandial anorexigenic gut peptide, apetite and glucometabolic responses at different eating rates in obese patients undergoing laparoscopic sleeve gastrectomy. *Endocrine* 55(1):113-123.

30 - Papamargaritis D, Le Roux CW, Sioka E, Koukoulis G, Tzovaras G and Zacharoulis D (2013) Changes in gut hormone profile and glucose homeostasis after laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 9(2): 192-201.

31 - Mallipedhi A, Prior SL, Barry JD, Caplin S, Baxter JN and Stephens JW (2014) Temporal changes in glucose homeostasis and incretin hormone response at 1 and 6 months after laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases* 10(5): 860-870.

32 - Basso N, Capoccia D, Rizzello M, Abbatini F, Mariani P, Maglio C et al. (2011) First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. *Surgical Endoscopy* 25(11): 3540-3550.

33 - Dixon AFR, Le Roux CW, Ghatei MA, Bloom SR, McGee TL and Dixon JB (2011) Pancreatic Polypeptide Meal Response May Predict Gastric Band-Induced Weight Loss. *Obesity Surgery* 21(12): 1906-1913.

34 - Peterli R, Steinert RE, Woelnerhanssen B, Peters T, Christoffel-Courtin C, Gass M et al. (2012) Metabolic and Hormonal Changes After Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: a Randomized, Prospective Trial. *Obesity Surgery* 22(5): 740-748.

35 - Romero F, Nicolau J, Flores L, Casamitjana R, Ibarzabal A, Lacy A et al. (2012) Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. *Surgical Endoscopy* 26(8): 2231-2239.

36 - Evans S, Pamuklar Z, Rosko J, Mahaney P, Jiang N, Park C et al. (2012) Gastric Bypass Surgery Restores Meal Stimulation of the Anorexigenic Gut Hormones Glucagon-Like-Peptide-1 and Peptide YY Independently of Caloric Restriction. *Surgical Endoscopy* 26(4): 1086-1094.

37 – Yousseif A, Emmanuel J, Karra E, Millet Q, Elkalaawy M, Jenkinson AD et al. (2014) Differential Effects of Laparoscopic Sleeve Gastrectomy and Laparoscopic Gastric Bypass on Appetite, Circulating Acyl-ghrelin, Peptide YY3-36 and Active GLP-1 Levels in Non-diabetic Humans. *Obesity Surgery* 24(2): 241-252.

38 - Cazzo E, Pareja JC, Geloneze B, Chaim EA, Barreto MRL and Magro DO (2017) GLP-1 and GLP-2 Levels are Correlated with Satiety Regulation After Roux-en-Y Gastric Bypass: Results of an Exploratory Prospective Study. *Obesity Surgery* 27(3): 703-708.

39 - Malin SK, Samat A, Wolski K, Abood B, Pothier CE, Bhatt DL et al. (2014) Improved acylated ghrelin suppression at 2 years in obese patients with type 2 diabetes: effects of bariatric surgery vs standard medical therapy. *International Journal of Obesity* 38(3): 364-370.

40 - Gelisgen R, Zengin K, Kocael A, Baysal B, Kocael P, Erman H et al. (2012) Effects of Laparoscopic Gastric Band Applications on Plasma and Fundic Acylated Ghrelin Levels in Morbidly Obese Patients. *Obesity Surgery* 22(2): 299-305.

41 - Barazzonni R, Zanetti M, Nagliati C, Cattin MR, Ferreira C, Giuricin M et al. (2013) Gastric Bypass Does Not Normalize Obesity-Related Changes in Ghrelin Profile and Leads to Higher Acylated Ghrelin Fraction. *Obesity* 21(4): 718-722.

42 - Dar MS, Chapman WH, Pender JR, Drake AJ, O'Brien K and Tanenberg RJ (2012) GLP-1 Response to a Mixed Meal: What Happens 10 Years after Roux-en-Y Gastric Bypass (RYGB)? *Obesity Surgery* 22(7): 1077-1083.

43 - Cazzo E, Pareja JC, Geloneze B, Chaim EA, Barreto MRL and Magro DO (2017) Postprandial GLP-2 Levels Are Increased After Biliopancreatic Diversion in Diabetic Individuals with Class I Obesity: a Prospective Study. *Obesity Surgery* 27: 1809-1814.

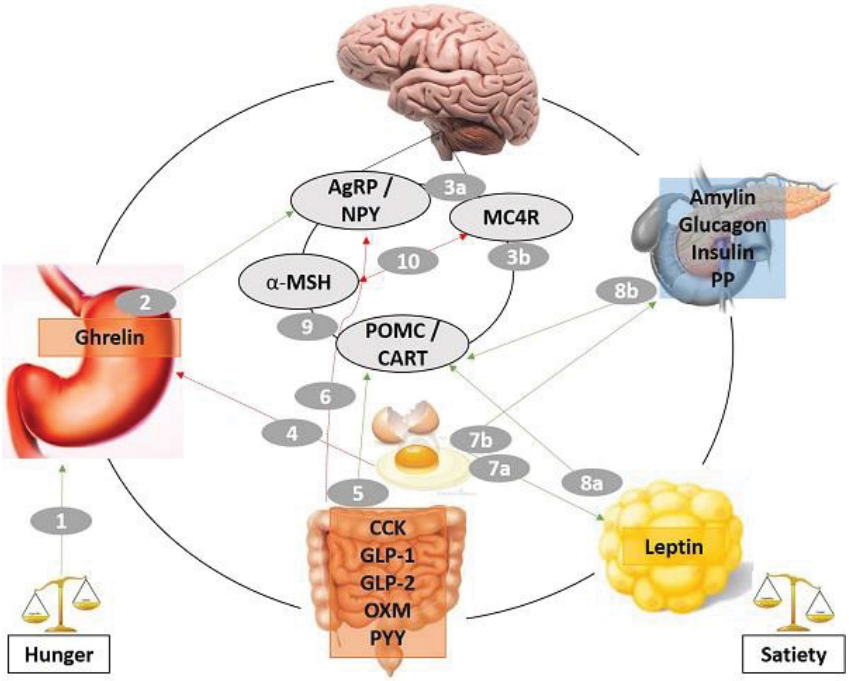


Figure 1. Hunger-satiety mechanism in 10 steps

1. In a fasted state (hunger or negative energy balance), secretion of orexigenic hormone ghrelin is stimulated in the stomach (1 – 2 h before meal).

2. Ghrelin acts on the arcuate nucleus of the hypothalamus and vagus nucleus in the brainstem to stimulate hunger: AgRP/NPY.

3. AgRP inhibits the action of MC4R, which enhances the expression of other orexigenic neurotransmitters, such as MCH and orexins A and B.

4. After food consumption, plasma levels of the ghrelin fall shortly.

5. Immediately after meal, with the distension of the stomach or in response to intraluminal food content (mainly protein or fat) in the small intestine and beginning digestion of food, there is stimulation of the vagus and spinal nerves to release CCK, GLP-1, OXM, and PYY.

6. CCK, GLP-1, GLP-2, OXM, and PYY act on the ARC, inhibiting NPY/AgRP and determining the end of the meal.

7. Meanwhile, in accordance with the increase of body fat and positive energy balance situations, other peripheral regulators, such as leptin, amylin, insulin, and pancreatic peptide (PP) are released.

8. The adipose tissue-derived and the pancreas-derived hormones stimulate the transcription of anorexigenic POMC/ CART peptides.

9. POMC neurons synthesize and release α-MSH.

10. α-MSH acts on MC4R and sends negative feedback to orexigenic peptides NPY and AGRP, leading to reduced food intake, signaling the end of the meal.

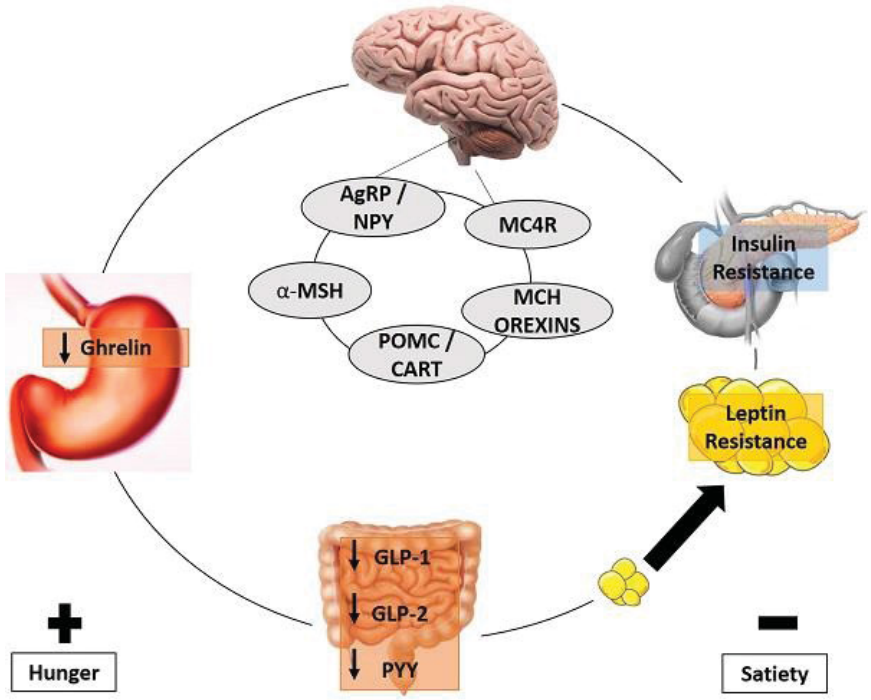


Figure 2. The 'Obese Brain'

Increased body fat enhances the secretion of leptin and insulin, and consequently, favors resistance to the action of these hormones. Additionally, in individuals with obesity, the levels of ghrelin and satiety hormones, such as GLP-1, GLP-2, and PYY, are lower compared to lean individuals. They affect the signaling network to the brain, which contributes to increased hunger and reduces satiety.

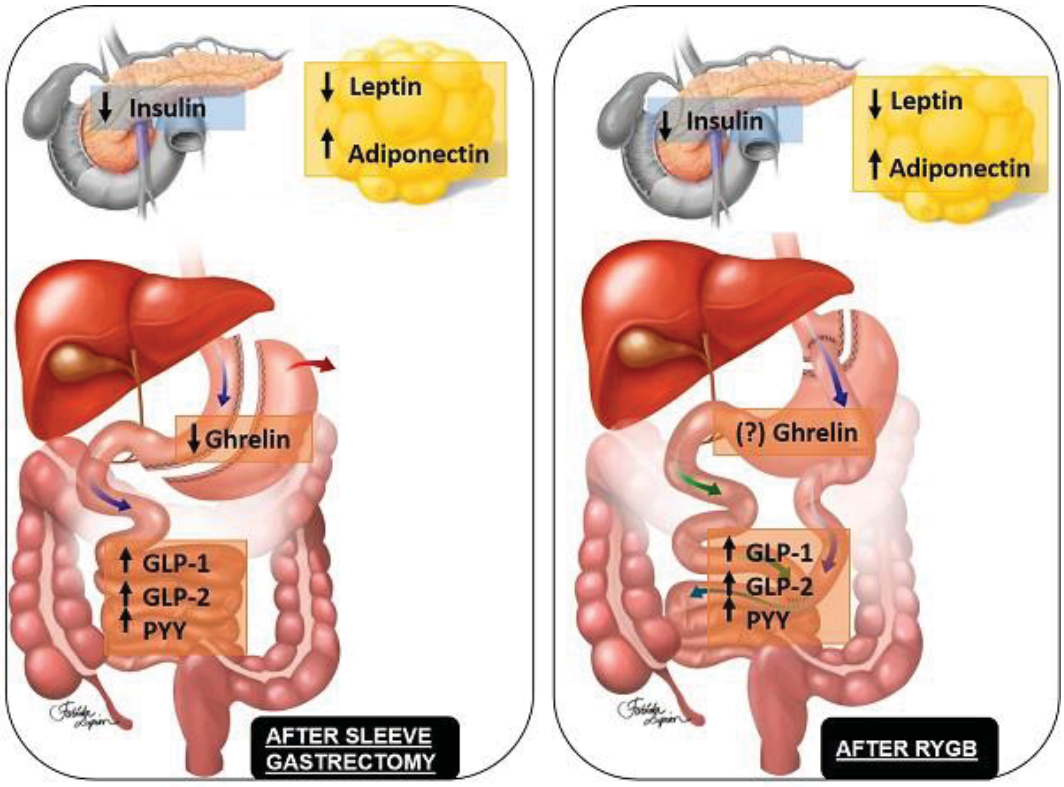


Figure 3. Energy balance changes in response to different surgeries

One of the first effects after bariatric surgery is the reduction of hunger, which can be partly explained by a decrease in serum levels of ghrelin. Majority of studies show that changes in ghrelin levels after RYGB and SG occur within the first weeks following surgery, but in the long term, it is maintained only in the SG technique. Studies that compared gut peptides (GLP-1, GLP-2, and PYY) between pre- and postoperative periods observed higher concentrations of these hormones after surgical procedure, mainly after RYGB and BPD. Adapted from Netto et al. (2016)

Credits: Fabíola Grigoletto Lupion

3.2 ARTIGO 2, PUBLICADO NA REVISTA NEUROPEPTIDES

(Formatação da Revista)

Original Contribuition

Title: ***Mechanisms of sustained long-term weight loss after RYGB: a-MSH is a key factor***

Authors: Gisele Farias (MsC; phD student)[1] Bárbara Dal Molin Netto (phD)[2], Katia Boritza (MsC)[3], Solange Cravo Bettini (MsC)[4], Ana Raimunda Dâmaso (phD)[2], Alexandre Coutinho Teixeira de Freitas (phD)[1]

[1] Surgical Clinic Post Graduate Program – Department of Surgery – Hospital de Clínicas - Universidade Federal do Paraná, UFPR. Surgical Clinic Post Graduate Program, Curitiba-Pr, Brazil

[2] Nutrition Post Graduate Program, Universidade Federal de São Paulo – Escola Paulista de Medicina – UNIFESP-EPM. Nutrition Post Graduate Program, São Paulo-SP, Brazil

[3] Biochemistry Section, Hospital de Clínicas - Universidade Federal do Paraná, UFPR, Curitiba-PR, Brazil

[4] Gastrointestinal Surgery Service of Hospital de Clínicas, Federal University of Paraná, UFPR, Curitiba-PR, Brazil

Corresponding authors:

Farias, G.; MsC, phD student. Surgical Clinic Post Graduate Program – Department of Surgery – Hospital de Clínicas - Universidade Federal do Paraná. Rua General Carneiro, 81 - Centro – Curitiba/ PR, Postal Code: 80060-900, Brazil. Telephone number: +55 41 3360 1800
E-mail: gisele.nutri.farias@gmail.com

Netto, BDM, PhD, Post Graduate Program of Nutrition, Escola Paulista de Medicina – Universidade Federal de São Paulo, Rua Marselhesa, 630 – Vila Clementino – São Paulo, São Paulo 04020-060, Brazil
E-mail: barbaradmnetto@gmail.com

Short tittle: Neuroendocrine regulation after RYGB.

Abstract

Background: Recent studies suggested that α-MSH functions in the peripheral regulation of energy homeostasis by increasing energy expenditure and sustaining weight loss. However, such observation is still to be confirmed in patients two years after RYGB.

Objective: This study aims to assess the role of anorexigenic/orexigenic peptides and peripheral signals in obese adults submitted to Roux-en-Y Gastric Bypass (RYGB) after long-term follow-up and its possible implications in sustained weight loss.

Methods: Anthropometric and biochemical markers of 32 obese adults (two men and 30 females) submitted to RYGB were collected preoperatively and 6 and 24 months post-operatively.

Results: Body weight and Body Mass Index (BMI) were noted to be decreased by 35.8±10.5% (p<0.001), corresponding to 83.8±24.5% excess weight loss at 24 months. Interestingly, α-MSH levels did not change in the first 6 months (p>0.05); however, α-MSH levels presented a significant increase of 1.0 ng/mL 24 months post-operatively (p<0.001). Additionally, PYY levels significantly increased within 24 months of the study (37.6±5.8 *vs*. 58.7±9.8, p<0.01). Furthermore, with regards to inflammatory process, plasma hyperleptinemia state was significantly controlled and reached normal values 6 months post-operatively; on the other hand, adiponectin exponentialy increased postoperatively (p<0.001).

Conclusion: Our results allow us to hypothesize that improvement of leptin sensitivity and both α-MSH and PYY have intrinsic actions in stimulating anorexigenic pathways post-RYGB, thus demonstrating their effectivity in inducing long-term weight loss. These findings pave new avenues of research to develop strategies promoting sustained weight loss and preventing weight regain after bariatric surgeries.

Keywords: Appetite regulation; obesity; bariatric surgery; weight loss; energy balance

Introduction

Obesity, a disease characterized by excessive fat accumulation, is a serious public health problem. Recent data from the World Health Organization show that obesity affects 13% of the global adult population and 17% of adult population in Brazil. In brief, obesity is mainly a result of higher food intake with respect to energy expenditure. As a consequence, obesity is also associated with a higher risk of development of cardiometabolic disorders (Ahl et al., 2015; Di Chiara et al., 2015; Ma et al., 2016; Jamar et al., 2017).

Feeding and metabolism control depends on communication between the hypothalamus and the gastrointestinal tract. It occurs through neural and humoral inputs such as leptin, insulin, glucose, and ghrelin. There are two physiologically opposing neuronal populations responsible for appetite control that are located in the hypothalamic arcuate nucleus (ARC): orexigenic neurons, which secrete neuropeptide Y (NPY) and agouti peptide (AgRP); and anorexigenic neurons, which secrete cocaine- and amphetamine-regulated transcript (CART) peptides and proopiomelanocortin (POMC) (Fernandez et al., 2015). POMC releases alpha-melanocyte-stimulating hormone (α-MSH), a 13-amino acid peptide that acts as a potent anorexigenic, thus reducing food intake and enhancing energy expenditure (Lima-Junior et al., 2015; Posovszky and Wabitsch, 2015; Farias et al., 2017).

Recents studies suggest that α-MSH functions in the peripheral regulation of energy homeostasis, as it is involved in increasing energy expenditure and sustaining weight loss through the mobilization of fat stores and increasing the level of circulating free fatty acids; moreover, experimental studies in rodents found an association between α-MSH and browning of white adipose tissue (Dâmaso et al, 2011; Rossi et al., 2011; Perino et al., 2014; Shipp et al., 2016).

Clinical protocols often fail to treat severe obesity, which is defined with body mass index (BMI) >35 kg/m^2. Hence, more effective interventions are necessary. The most effective intervention for people with extreme obesity is bariatric surgery. The two most frequently performed bariatric surgery include Sleeve Gastrectomy (SG), a purely restrictive surgical technique, and Roux-en-Y Gastric Bypass (RYGB), which is considered as the gold standard and is a combination of a small gastric pouch and a bypassed small bowel (malabsorptive component) (Angrisani et al., 2015).

Patients who underwent RYGB usually achieve significant weight loss, reaching the minimum weight between 18 and 24 months (Sjostrom, 2013; Farias et al., 2016). However, two years after the surgery, some patients regain some weight. Farias et al. (2016) found that five years after surgery, 21.3% of individuals recovered more than 20% of the lowest weight.

We believe that the mechanisms of weight loss after RYGB are still not well understood. Consistently, previous studies argued that weight loss after RYGB occurs due to mechanical restriction, malabsorption, and modifications in regulation of hunger-satiety caused by changes in gut-brain axis. Over the last decade, more researches targeting the changes in central and peripheral mechanisms involved on energy balance and appetite control regulation after bariatric surgery had been done (Dixon et al., 2015; Munzberg et al., 2015; Posovszky and Wabitsch, 2015; Lean and Malkova, 2016; Netto et al., 2016; Farias et al., 2017). Changes in signaling of fat-derived hormones can be observed thirty days postoperatively, as leptin and insulin levels are noted to be decreased and adiponectin levels are increased (Woelnerhanssen et al., 2011; Herder et al., 2014; Camilleri, 2015; Dixon et al., 2015; Lima-Júnior et al., 2015; Biagioni et al., 2017; Hoffstedt et al., 2017; Kalinowski et al., 2017).

However, only a few studies addressed the role of anorexigenic and orexigenic peptides, especially α-MSH, on energy balance control 24 months after RYGB; therefore, this

research aims to elucidate the role of these peptides and peripheral signals in obese adults who underwent RYGB after long-term follow-up and its possible implications in sustained weight loss after bariatric surgery.

Subjects and Methods

We performed a prospective, descriptive, and analytic study in obese patients who underwent RYGB at public hospital, between March 2013 and October 2013, with 24 months follow-up.

This study was approved by the ethics committee (n. 2625.232/2011-10). Furthermore, this study was designed as per guidelines of the Declaration of Helsinki and was registered on Clinical Trials Registry (NCT 02101814). All subjects were informed about the objectives and procedures of the study and data confidentiality. They were provided written informed consents as well prior to participating in the study.

Subjects

All patients were assessed by a multidisciplinary team composed of bariatric surgeon, psychiatrist, psychologist, dietitian, and endocrinologist.

RYGB was performed through laparotomy by an experienced surgeon. A 50-mL gastric pouch was created. The jejunum was divided 100 cm distal to the ligament of Treitz. The gastrojejunostomy was handsewn, and the duodenum and proximal portion of the jejunum were bypassed to create a 100-cm Roux limb. A silastic ring was inserted between the stomach pouch and the small bowel.

All patients satisfied the surgical criteria for bariatric surgery as outlined by the National Institutes of Health Consensus Development Panel report of 1991. Eligibility for participation in this study was limited to individuals older than 18 years of age with a BMI $\geq$40 kg/m^2, or a BMI $\geq$35 kg/m^2 with comorbid conditions. Exclusion criteria included the use of insulin, cigarettes, anti-inflammatory and/or immunosuppressant therapies, malignancies, chronic kidney or liver disease, obesity caused by an endocrine disorder, psychiatric disorders, alcohol dependence, rheumatoid arthritis, autoimmune diseases, major surgical complications, and incompliance to the study protocol.

Study Protocol

Individuals were assessed during the preoperative period (baseline) and 6 and 24 months after surgery. The following data were analyzed and compared over these periods of time: medical history and comorbidity; anthropometric measurements (body weight, height, and waist circumference [WC]); and fasting blood samples for biochemical measurements of leptin, peptide YY (PYY), α-MSH, NPY, and adiponectin.

Anthropometric Measurements

The BMI of patients was calculated as the ratio of weight (kg) to height squared (m2) using a Filizola scale/stadiometer (model 31; Indústrias Filizola/SA, São Paulo, Brazil) with a precision of 100 g and 0.01 m. The percentage of excess weight loss (%EWL) was calculated using the method described by Deitel et al. (2007). WC was measured at the largest circumference between the iliac crest and the rib cage at minimal respiration.

Sample Collection and Storage

After an 8-h fast, antecubital venous blood samples (10 ml at each time point, with EDTA as anticoagulant) were drawn from the patients at baseline, as well at 6 months and 24 months after surgery. Plasma was obtained by immediately centrifuging blood samples at 4°C during collection period and was stored in small aliquots at - 80°C until analysis.

Biochemical Measurements

The samples were analyzed for leptin and total PYY levels using the Milliplex MAP Human Metabolic Hormone Magnetic Bead 2 Plex Panel (Millipore, Billerica, Massachusetts, USA). For leptin, the intra-assay and interassay coefficients of variation were both < 5%. For PYY, the intra-assay coefficient was 2%, whereas the interassay coefficient was 11%.

α-MSH and NPY concentrations were determined using a commercial enzyme-linked immunosorbent assay kit (Uscn Life Science, Wuhan, People's Republic of China). The intra-assay and interassay coefficients of variation were both < 12%.

Adiponectin was measured using a commercial Milliplex MAP Human Adipokine Magnetic Bead Panel 1 (Millipore, Billerica, Massachusetts, USA). The intra-assay and interassay coefficients of variation were both < 10%.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v.20 (SPSS Inc, Chicago, IL, USA). All variables were checked for normal distribution using the Shapiro-Wilk test.

For the variables with normal distribution, a repeated-measures analysis of variance (ANOVA) model was used to evaluate the effects of surgery, time, and the interaction surgery at three time points on variables such as weight, BMI, WC, PYY, NPY, α-MSH, leptin, and adiponectin levels. A posthoc Bonferroni test was applied for multiple comparisons.

For the variables with nonnormal distribution, a nonparametric Friedman test was used. A posthoc Friedman test was applied for multiple comparisons.

In addition, a delta (Δ) value was calculated to reflect postoperative changes (Δ value = postoperative value − baseline value).

To evaluate the association among variables, Pearson's correlation coefficient analysis was employed. In cases of statistically significant correlation, linear regression models were fitted with α-MSH as the independent variable.

The level of statistical significance was established at $p < .05$.

Results

Participants

The study included 32 patients (two men and 30 females) who previously underwent RYGB. The mean age was 40.1 ± 10.0 years. In this study, all patients returned for follow-up evaluations at 6 and 24 months after surgery.

BMI, WC, and postoperative NPY levels before surgery and 6 and 24 months after RYGB are shown in Table 1.

Weight loss

Both BMI and excess weight significantly decreased at 6 months after surgery (31.7 ± 10.4 kg), with further reductions at 24 months (41.8 ± 16.2 kg). Body weight and BMI both decreased by 35.8 ± 10.5%, in comparison with baseline values (both $p < .001$). Excess weight decreased from 47.7 kg at baseline to 3.7 kg ($p < .001$) at 24 months, which corresponds to 83.8±24.5% excess weight loss. Mean WC significantly decreased as well, from 126.2 ± 11.0 cm to 94.2 ± 10.8 cm at 24 months ($p < .001$) (Table 1).

Energy balance control

PYY levels significantly increased within 24 months of the study (37.6 ± 5.8 *vs*. 58.7 ± 9.8, $p < .01$), with the greatest increase at 6 months after surgery (37.6 ± 5.8 *vs*. 61.7 ± 3.5, $p < .001$) (Fig. 1a). α-MSH and NPY levels did not change in the first 6 months ($p = .613$ and $p = .564$, respectively) but increased at 24 months postoperatively (0.3 ± 0.0 *vs*. 1.3 ± 0.2, $p < .001$ and 0.7 ± 0.0 vs. 0.9 ± 0.1, $p < .001$, respectively) (Fig. 1b and Table 1).

The leptin levels significantly decreased within the study period (38.0 ± 4.0 vs. 4.9 ± 1.5 $p < .001$) (Fig. 1c). Additionally, an increase in adiponectin levels was observed at all time periods of the follow-up (6.8 ± 0.6 *vs.* 27.1 ± 4.1 $p < .001$) (Fig. 1d).

Correlations Between Weight Loss and Anorexigenic Pathways After RYGB

The present study found a positive correlation between baseline levels of α-MSH and weight loss 6 months after bariatric surgery ($r^2 = 0.42$, $p=0.01$). In other words, it was observed that higher serum α-MSH levels prior to surgery were positively associated with

lower weight loss 6 months postoperatively. Fig. 2 presents the results of the simple regression analysis.

Discussion

In the studied population, the BMI was markedly reduced from 43.8 kg/m^2 at baseline to 26.4 kg/m^2 at 24 months ($p <$ .001) after RYGB. This study aims to further elucidate the long-term role of specific orexigenic/anorexigenic peptides after RYGB. The most significant result we obtained is the increase in α-MSH concentrations after 24 months of RYGB.

Prospective studies measuring α-MSH response post-RYGB are limited. Additionally, only a few studies evaluated the concentration of α-MSH in obese subjects undergoing clinical treatment for long-term weight loss. Oyama et al. (2010) found that α-MSH was significantly increased when leptin levels are normalized after massive weight loss in obese adolescents. Recent studies in animals demonstrated the existence of an interaction between hypothalamic leptin sensitivity and POMC neurons, which is related to defense maintenance of a lower body weight and adiposity (Chhabra et al., 2016; Manning et al., 2016). It reinforces the concept that the central melanocortin system plays a key role in sustained long-term weight loss (Oyama et al., 2010).

One of the key regulators of energy balance is leptin, which is considered as a marker of energetic reserves. It is involved in food intake regulation and energy expenditure, fat storage, and insulin signalling (Leibel et al., 2015; Caron and Richard, 2016). Furthermore, our present investigation reflected the existence of leptin resistance in this studied population before surgery and the decrease in leptin levels, reaching normal values 6 months post-operatively and in long-term RYGB. The results we obtained are also in line with that of other studies (Woelnerhanssen et al., 2011; Biagioni et al., 2017; Kalinowski et al., 2017),

corroborating to the establisment of a negative energy balance in association with an increased circulating levels of α-MSH, as illustrated in Fig. 1b and c.

Leptin appears to play a dual regulatory role in energy balance. During weight loss, decreasing leptin levels favor the restoration of leptin responsivenes. This peptide acts in CNS to stimulate POMC/CART and inhibit NPY/AgRP production, and it also improves insulin sensitivity (Leibel et al., 2015; Caron and Richard, 2016).

Interestingly, a correlation was found when comparing weight loss with baseline values of α-MSH (Fig. 2). It was suggested that individuals with higher serum α-MSH levels prior to surgery had lower weight loss after the procedure. In fact, other studies performed by our group showed that obese adolescents presented lower α-MSH levels among those with hyperleptinemia state (Dâmaso et al., 2011; Corgosinho et al., 2017). Therefore, individuals with resistance to the action of some parameters related to the inflammatory process, such as leptin and insulin, as demonstrated by excess weight, have a greater weight loss response after surgery.

Thus, the obtained results confirm that neuroendocrine homeostasis is maintained by the relationship between the central melanocortin system and multiple circulating peripheral signals, such as intestinal hormones, leptin, insulin, glucagon, and adiponectin detected by nuclei and hypothalamic circuits (Corgosinho et al., 2017; Shen et al., 2017; Rani et al., 2018). The reduction of inflammation state and improved insulin and leptin sensitivity favor the action of α-MSH and PYY on appetite control, increased satiety, and energy expenditure.

Dâmaso et al. (2011) observed that elevated α-MSH levels after weight loss contributes to the maintenance of high-energy expenditure and, consequently, sustained weight loss through the mobilization of fat stores and increase in circulating free fatty acids. Thus, α-MSH is significantly involved in the peripheral regulation of energy homeostasis.

Experimental studies in rodents reported a relationship between α-MSH and sympathetic nervous system (Shipp et al., 2016). Increase in α-MSH levels inhibits the phosphatidylinositol 3-kinase pathway and stimulates cAMP production in the intermediolateral nucleus of hypothalamus (Rossi et al., 2011; Perino et al., 2014). Consequently, it promotes the increase of norepinephrine concentrations in the adipose tissue, which in turn increases phosphorylation of hormone sensitive lipase, enhances lipolysis and leads to browning of white adipose tissue (Mottillo et al., 2011; Rossi et al., 2011; Perino et al., 2014; Shipp et al., 2016). Such mechanism could explain the role of α-MSH in increasing energy expenditure and sustaining long-term weight loss after RYGB, therefore contributing to our understanding of mechanisms to trigger weight regain in clinical practice.

Previous studies reported that α-MSH might not modulate NPY/AgRP neurons due to the different central effects of α-MSH and NPY in the CNS (Dâmaso et al., 2011; Netto et al., 2016). Corroborating the results of present study, we observed that NPY levels did not change until 6 months after RYGB; furthermore, a small increase in NPY levels was observed at 24 months post-RYGB. NPY levels may increase in response to stressful conditions (Reichmann and Holzer, 2016). It was proposed that a compensatory adaptation of appetite-regulating hormones lead to increase in food consumption and favoring weight recovery (Posovszky et al., 2015).

In the present study, the balance between anorexigenic and orexigenic mediators of the whole body metabolism provide a great interaction, thus favoring long-term maintenance of a significant weight loss after RYGB.

Some studies reported that adiponectin favors a negative energy balance by stimulating POMC neurons and supressing NPY/AgRP neurons. It also stimulates the activation of adenosine monophosphate-activated protein kinase in peripheral tissues, which

contributes to an improvement in insulin and leptin sensitivity (Chen et al., 2012; Sun et al., 2016).

Our findings of increased PYY levels 6 and 24 months post-RYGB are in line with other studies (Peterli et al., 2012; Nannipieri et al., 2013). Following RYGB, exclusion of the proximal segment of the small intestine, particularly the duodenum, delays gastric emptying and delivery of nutrients to the enteroendocrine cells; this is called the 'ileal brake theory'. Furthermore, the quick transit of nutrients to the distal intestine stimulates secretion of gut hormones from enteroendocrine cells, thus reducing appetite and increasing satiety that contributes to weight loss. Additionally, this affects melanocortin signaling through activation of POMC neurons via afferent vagal gut-brain nerve, which may inhibit food intake (Ochner et al., 2011; Stefater et al., 2012; Buchwald, 2014; Sweeney and Morton, 2014; Chakravartty et al., 2015; Dixon et al., 2015; Munzberg et al., 2015; Bauer et al., 2016; Netto et al., 2016; Farias et al., 2017).

Fig. 3 illustrates the effects of RYGB on the main hormones and neuropeptides associated with neuroendocrine control of energy balance.

Some limitations need to be taken into account in interpreting these findings. First, because of logistical considerations, only leptin, adiponectin, fasting PYY, α-MSH, and NPY levels were evaluated. We believe that other peptides, such as ghrelin and GLP-1, would have made our study more informative. Also, a larger sample size is necessary to validate the results of this study.

Conclusions

This present investigation provides clear evidence on the long-term substantial influence of the reduction of inflammation state and improved leptin sensitivity favor the

anorexigenic pathways after RYGB, as we were able to show a significant increase in α-MSH and PYY concentrations 24 months after RYGB. α-MSH and PYY may both stimulate the anorexigenic pathways in a long-term RYGB, thus promoting the effectivity of the procedure to induce weight loss. Our investigation suggests new avenues of research in weight loss after bariatric surgeries to develop strategies in promoting sustained weight loss, prevent weight regain, and determine why weight regain is prevalent from 24 months of surgery. Finally, future studies must elucidate: Could some orexigenic pathway, such as NPY, still be activated in obese adults submitted a bariatric surgery?

Conflict of Interest: The authors Gisele Farias, Bárbara Dal Molin Netto, Katia Boritza, Solange Cravo Bettini, Ana Raimunda Dâmaso, and Alexandre Coutinho Teixeira de Freitas declare that they have no conflict of interests.

Financial support

Grant# 2013/04136-4 São Paulo Research Foundation (FAPESP) and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) (1508044), supported the Hospital de Clínicas/Federal University of Paraná (UFPR).

References

Ahl S., Guenther M., Zhao S., James R., Marks J., Szabo A. et al., 2015. Adiponectin Levels Differentiate Metabolically Healthy vs Unhealthy Among Obese and Nonobese White Individuals. J. Clin. Endocrinol. Metab. 100, 4172–4180.

Angrisani L., Santonicola A., Iovino P., Formisano G., Buchwald H., Scopinaro N., 2013. Bariatric surgery worldwide. Obes. Surg. 25(10), 1822-1832.

Bauer P.V., Hamr S.C., Duca F.A., 2016. Regulation of energy balance by a gut–brain axis and involvement of the gut microbiota. Cell. Mol. Life Sci. 73(4), 737–755.

Biagioni M.F.G., Mendes A.L., Nogueira C.R., Leite C.V., Gollino L., Mazeto G.M.F.S., 2017. Bariatric Roux-en-Y Gastric Bypass Surgery: Adipocyte Proteins Involved in Increase Bone Remodeling in Humans. Obes. Surg. 27, 1789-1796.

Buchwald H., 2014. The Evolution of Metabolic/Bariatric Surgery. Obes. Surg. 24(8). 1126–1135.

Camilleri M., 2015. Peripheral Mechanisms in Appetite Regulation. Gastroenterology 148, 1219–1233.

Caron A., Richard D., 2016. Neuronal systems and circuits involved in the control of food intake and adaptive thermogenesis. Ann. N.Y. Acad. Sci. 2016, 1-19.

Chakravartty S., Tassinari D., Salerno A., Giorgakis E., Rubino F., 2015. What is the Mechanism Behind Weight Loss Maintenance with Gastric Bypass? Curr. Obes. Rep. 4(2), 262–268.

Chen J., Pamuklar Z., Spagnoli A., Torquati A., 2012. Serum leptin levels are inversely correlated with omental gene expression of adiponectin and markedly decreased after gastric bypass surgery. Surg. Endosc. 26, 1476-1480.

Chhabra K.H., Adams J.M., Jones G.L., Yamashita M., Schlapschy M., Skerra A., 2016. Reprogramming the body weight set point by a reciprocal interaction of hypothalamic leptin sensitivity and Pomc gene expression reverts extreme obesity. Mol. Metab. 5, 869-881.

Corgosinho F.C., Almeida S. S., Tock L., Pesquero J.B., Araújo R.C., Clemente A.P.G., Netto B.D.M., Campos R.M.S., Masquio D.C.L., Ferreira J.P.C., Sanches P.L., Ganen A.P., Rogero M.M., Oyama L.M., Tufik S., Mello M.T., Dâmaso A.R., 2017. LEPR polymorphism may affect energy balance during weight loss among Brazilians obese adolescents. Neuropeptides 66, 18-24.

Dâmaso A.R., Piano A., Sanches P.L. et al., 2011. Hyperleptinemia in obese adolescents deregulates neuropeptides during weight loss. Peptides 32, 1384-1391.

Deitel M., Gawdat K., Melissas J, 2007. Reporting weight loss 2007. Obes. Surg. 17, 565-568.

Di Chiara T., Argano C., Scaglione A., Corrao S., Pinto A., Scaglione R., 2015. Circulating adiponectin: a cardiometabolic marker associated with global cardiovascular risk. Acta Cardiol. 70, 33-40.

Dixon J.B., Lambert E.A., Lambert G.W., 2015. Neuroendocrine adaptations to bariatric surgery. *Mol. Cell. Endocr.* 418, 143e-152.

Farias G., Netto B.D.M., Bettini S.C., Dâmaso A.R., Freitas A.C.T., 2017. Neuroendocrine regulation of energy balance: implications on the development and surgical treatment of obesity. Nutr. Health 23, 131-146.

Farias G., Thieme R.D., Teixeira L.M., Heyde M.E., Bettini S.C., Radominski R.B., 2016 Good weight loss responders and poor weight loss responders after Roux-en-Y gastric bypass: clinical and nutritional profiles. Nutr. Hosp. 33(5), 1108–1115.

Fernandez S.B., Folgueira C., Castelao C., Leis R., Casanueva F.F., Seoane L.M., 2015. Peripheral Signals Mediate the Beneficial Effects of Gastric Surgery in Obesity. *Gastr. Res. Pract.* 2015, 1-12.

Herder C., Peltonen M., Svensson P. et al., 2014. Adiponectin and Bariatric Surgery: Associations with Diabetes and Cardiovascular Disease in the Swedish Obese Subjects Study. Diabetes Care 37, 1401-1409.

Hoffstedt J., Andersson D.P., Hogling D.E. et al., 2017. Long-term Protective Changes in Adipose Tissue After Gastric Bypass. Diabetes Care 40(1), 77-84.

Jamar G., Caranti D.A., Cesar H.C., Masquio D.C.L., Bandoni D.H., Pisani L.P, 2017. Leptin as a cardiovascular risk marker in metabolically healthy obese Hyperleptinemia in metabolically healthy obese. Appetite 108, 477-482.

Kalinowski P., Paluszkiewicz R., Wróblewski T. et al., 2017. Ghrelin, leptin, and glycemic control after sleeve gastrectomy versus Roux-en-Y gastric bypass—results of a randomized clinical trial. Surg. Obes. Relat. Dis. 13, 181-188.

Lean M.E.J., Malkova D., 2016. Altered gut and adipose tissue hormones in overweight and obese individuals: cause or consequence? Int. J. Obes. 40(4), 622–632.

Leibel R.L., Seeley R.J., Darsow T., Berg E.G., Smith S.R., Ratner R., 2015. Biologic responses to weight loss and weight regain: report from an American Diabetes Association Research Symposium. Diabetes 64, 2299-2309.

Lima-Júnior J.C., Velloso L.A., Geloneze B., 2015. The Obese Brain—Effects of Bariatric Surgery on Energy Balance Neurocircuitry. Curr. Atherosc. Rep. 17(10), 57.

Ma W., Huang T., Zheng Y., Wang M., Bray G.A., Sacks F.A., Qi L., 2016. Weight-loss diets, adiponectin, and changes in cardiometabolic risk in the 2-year POUNDS Lost Trial. J. Clin. Endocrinol. Metab. 101(6), 2415-2422.

Manning S., Pucci A., Batterham R.L., 2016. Roux-en-Y gastric bypass: effects on feeding behavior and underlying mechanisms. J. Clin. Invest. 125, 939-948.

Mottillo E.P., Granneman J.G., 2011. Intracellular fatty acids suppress b-adrenergic induction of PKA-targeted gene expression in white adipocytes. Am J Physiol Endocrinol Metab 301, E122-131.

Münzberg H., Laque A., Yu S., Rezai-Zadeh K., Berthoud H., 2015. Appetite and body weight regulation after bariatric surgery. Obes. Rev. 16(Suppl 1),77–90.

Nannipieri M., Baldi S., Mari A. et al., 2013. Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: Mechanisms of Diabetes Remission and Role of Gut Hormones. J. Clin. Endocrinol. Metab. 98, 4391-4399.

Netto B.D.M., Earthman C.P., Bettini S.C. et al., 2016. Early effects of Roux-en-Y gastric bypass on peptides and hormones involved in the control of energy balance. Eur. J. Gastro Hep. 28, 1050-1055.

Ochner C.N., Gibson C., Shanik M., Goel V., Geliebter A., 2011. Changes in neurohormonal gut peptides following bariatric surgery. Int. J. Obes. 35(2), 153–166.

Oyama L.M., Nascimento C.M.O., Carnier J. et al., 2010. The role of anorexigenic and orexigenic neuropeptides and peripheral signals on quartiles of weight loss in obese adolescents. Neuropeptides 44, 467–474.

Perino A., Beretta M., Kilic A. et al., 2014. Combined inhibition of PI3Kbeta and PI3Kgamma reduces fat mass by enhancing a-MSH-dependent sympathetic drive. Sci. Signal 7, ra110.

Peterli R., Steinert R.E., Woelnerhanssen B. et al., 2012. Metabolic and Hormonal Changes After Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: a Randomized, Prospective Trial. Obes. Surg. 22, 740-748.

Posovszky C., Wabitsch M., 2015. Regulation of Appetite, Satiation, and Body Weight by Enteroendocrine Cells. Part 2: Therapeutic Potential of Enteroendocrine Cells in the Treatment of Obesity. Horm. Res. Paediatr. 83, 11–18.

Rani M., Kumar R., Krishan P., 2018. Role of orexins in the central and peripheral regulation of glucose homeostasis: Evidences & mechanisms. Neuropeptides epub ahead print doi:10.1016/j.npep.2018.02.002.

Reichmann F., Holzer, P., 2016. Neuropeptide Y: A stressful review. Neuropeptides 55(2016), 99-109.

Rossi J., Balthasar N., Olson D. et al., 2011. Melanocortin-4 receptors expressed by cholinergic neurons regulate energy balance and glucose homeostasis. Cell. Metab. 13, 195-204.

Shen W., Yao T., Kong X., Williams K.W., Liu T., 2017. Melanocortin neurons: Multiple routes to regulation of metabolism. Mol. Basis Dis. 1863(2017), 2477-2485.

Shipp S.L., Cline M.A., Gilbert E.R., 2016. Recent advances in the understanding of how neuropeptide Y and a-melanocyte stimulating hormone function in adipose physiology. Adypocite 5(4), 333-350.

Sjöström L., 2013. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J. Int. Med. 273(3), 219–234.

Stefater M.A., Wilson-Pérez H.E., Chambers A.P., Sandoval D.A., Seeley R.J., 2012. All Bariatric Surgeries Are Not Created Equal: Insights from Mechanistic Comparisons. Endocr. Rev. 33(4), 595-622.

Sun J., Gao Y., Yao T. et al., 2016. Adiponectin potentiates the acute effects of leptin in arcuate Pomc neurons. Mol. Metab. 5, 882-891.

Sweeney T.E., Morton J.M., 2014. Metabolic surgery: action via hormonal milieu changes, changes in bile acids or gut microbiota? A summary of the literature. Best Pract. Res. Clin. Gastr. 28(4), 727–740.

Woelnerhanssen B., Peterli R., Steinert R.E., Peters T., Borbély Y., Beglinger C., 2011. Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy—a prospective randomized trial. Surg. Obes. Relat. Dis. 7, 561-568.

Table 1. Parameters examined in patients with extreme obesity before (baseline) and after (6 months and 24 months) RYGB.

Variables		Baseline		6 month follow up		Δ value		24 month follow up		Δ value
Body mass (kg)	108.2	(86.2 to 180)	**80.8**	**(54.5 to 140.5) ***	-30.9	(-52.2 to -11.5)	**70.7**	**(53.5 to 115.0) **†**	-40.4	(-81.0 to -15.8)
BMI (kg/m^2)	43.8	(35.9 to 70.3)	**31.2**	**(21.2 to 50.2) ***	-11.8	(-20.1 to -4.7)	**26.4**	**(22.1 to 40.3) **†**	-15.8	(-31.6 to -6.4)
Waist circumference (cm)	126.5	(11.0)	**102.8**	**(11.5) ***	-23.7	(10.5)	**94.2**	**(10.8) **†**	-32.3	(9.9)
Excess weight (kg)	47.7	(28.5 to 116.0)	**15.4**	**(-9.5 to 64.5) ***	-30.9	(-52.2 to -11.5)	**3.7**	**(-7.9 to 43.6) **†**	-40.4	(-81.0 to -15.8)
NPY (ng/mL)	0.7	(0.4 to 1.5)	0.7	(0.4 to 1.7)	0.0	(-0.9 to 1.2)	**0.9**	**(0.4 to 2.6) **†**	0.3	(-0.4 to 1.8)

Parametric data are expressed as mean (standard deviation). Nonparametric data are described as median and minimum and maximum values.
Bold entries represent significant results.
Mean values were significantly different according to Friedman test (nonparametric data) or ANOVA (parametric data).
*difference between baseline and 6 months ($p \leq 0.05$).
** difference between baseline and 24 months ($p \leq 0.05$).
† difference between 6 and 24 months ($p \leq 0.05$).
(BMI) body mass index; (NPY) neuropeptide Y; (RYGB) Roux-en-Y gastric bypass.

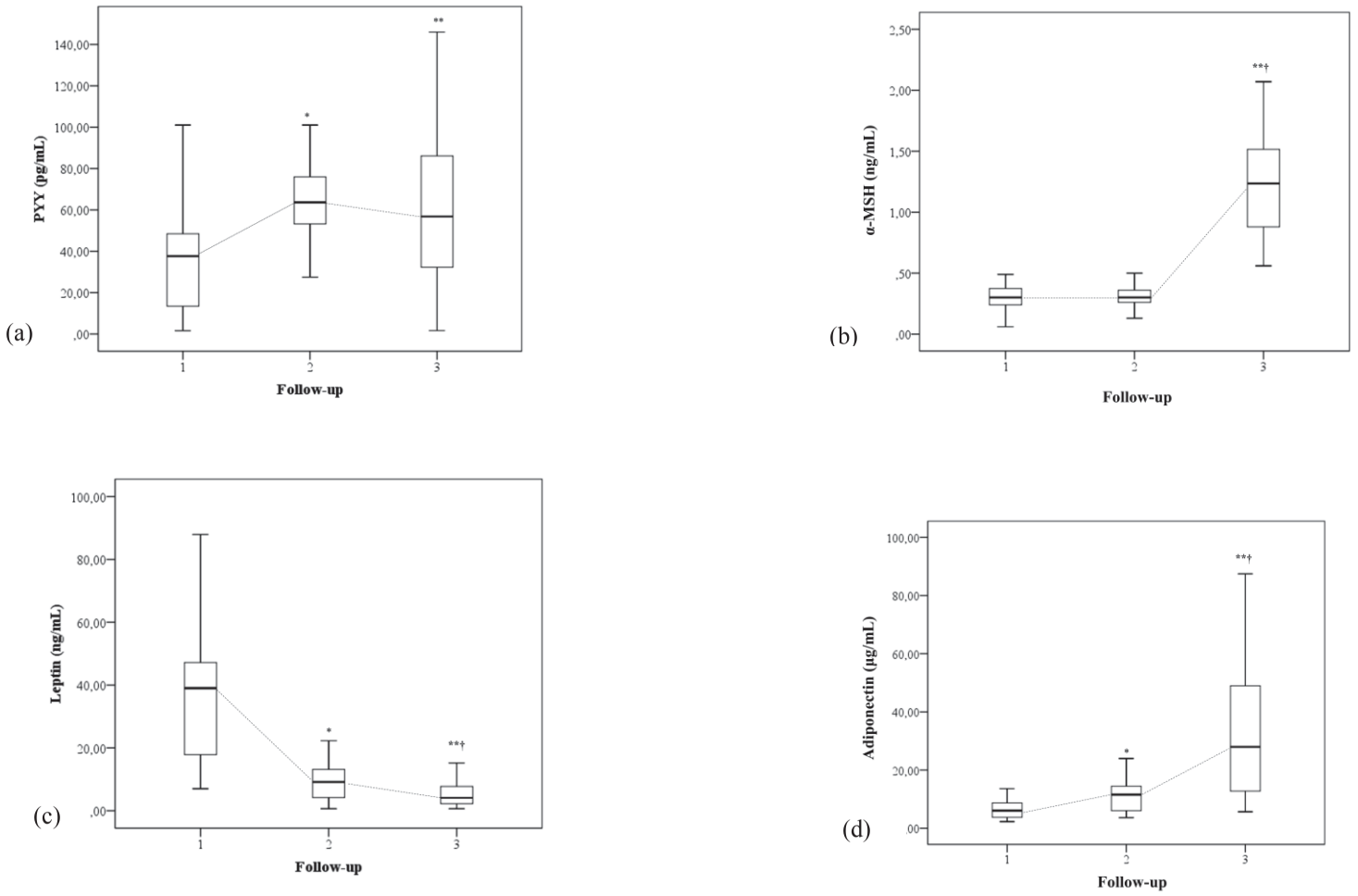


Fig. 1. Changes from baseline to 6 months and 24 months after RYGB in (a) PYY; (b) α-MSH; (c) leptin; and (d) adiponectin concentrations. (1) Baseline; (2) 6 months follow-up; (3) 24 months follow-up. (α-MSH) α-melanocyte-stimulating hormone; (EWL) excess weight loss; (PYY) peptide YY; (RYGB) Roux-en-Y gastric bypass. Box plots show the median, interquartile range, and min/max of individual variables. Parametric data are expressed as mean (standard deviation). Nonparametric data are described as median and minimum and maximum values.
* difference between baseline and 6 months according to Friedman test (nonparametric data) or ANOVA (parametric data) ($p \leq .05$).
** difference between baseline and 24 months according to Friedman test (nonparametric data) or ANOVA (parametric data) ($p \leq .05$).
† difference between 6 and 24 months according to Friedman test (nonparametric data) or ANOVA (parametric data) ($p \leq .05$).

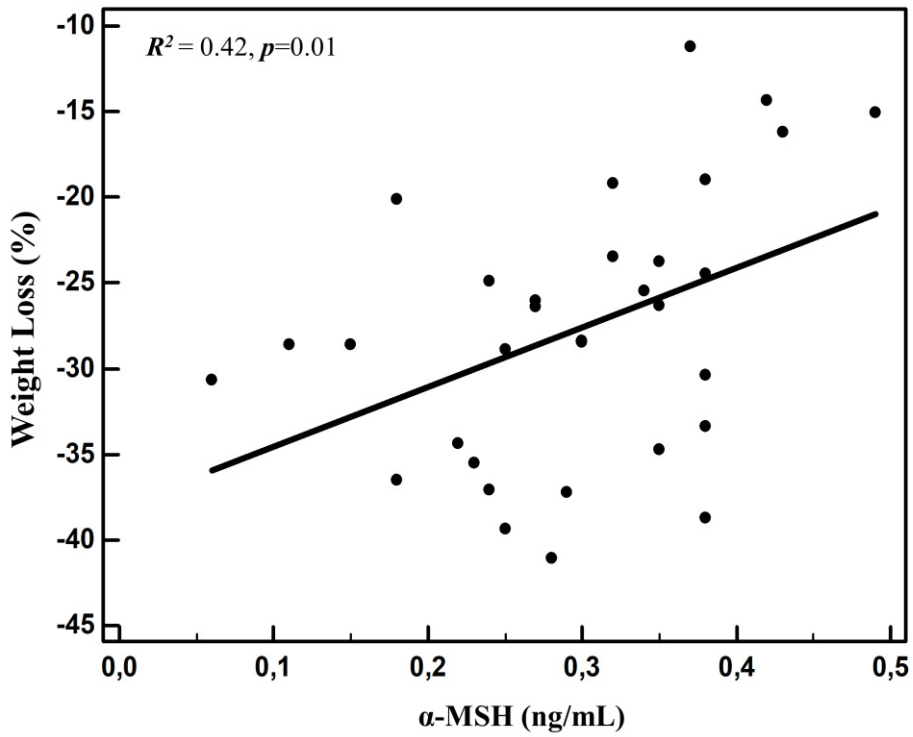


Fig. 2. Linear regression analysis and 95% confidence interval (CI) of the relationship between weight loss (%) 6 months after bariatric surgery and α-MSH (ng/mL) baseline levels. (α-MSH) α-melanocyte-stimulating hormone.

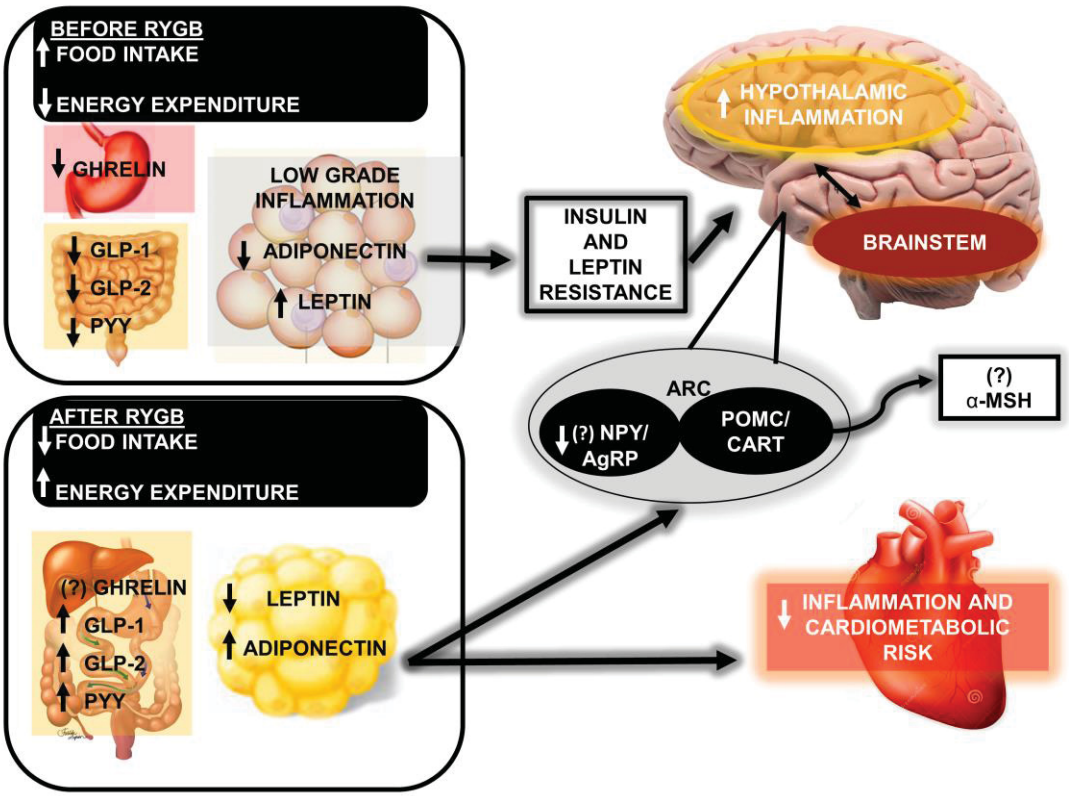


Fig. 3. Peripheral and central regulation of appetite before and after RYGB.

Before surgery, an inflammatory state and obesity status are associated with modification in the complex system of peripheral and central signals involved in the control of energy balance. Adiponectin secretion is supressed, whereas plasma leptin levels are increased. However, in individuals with obesity, there is an observed reduced ability of leptin to regulate appetite and body weight; this is known as leptin resistance. Additionally, the levels of ghrelin and satiety hormones, such as GLP-1, GLP-2, and PYY, are lower as compared to normal weight individuals

After surgery, an improvement in inflammatory profile can be observed. Adiponectin secretion increases and exerts its anti-inflammatory role through, for example, reducing cardiometabolic risk and by acting in CNS as well through the activation of POMC neurons and suppression of the melanocortin neural circuitry that may promote negative energy balance. Moreover, adiponectin intensify the effects of leptin on insulin sensitivity, energy expenditure, and weight loss.

Additionally, circulating leptin levels decreases, and adequate levels of this peptide acts on POMC and CART neurons in ARC to supress the appetite through increased secretion of peripheral blood α-MSH levels, which stimulate the anorexigenic pathway.

After RYGB, α-MSH is increased, hence leading to decreased food intake. Thus, an increase in α-MSH levels has anorexigenic effects and is considered one of the possible mechanisms that could explain sustained and long-term weight loss after bariatric procedure.

Plasma PYY, GLP-1, and GLP-2 values, which favors the anorexigenic pathways, are increased after surgery.

AgRP, agouti-related peptide; ARC, arcuate nucleus; CART cocaine and amphetamine transcript; CNS, central nervous system; GLP-1, glucagon like peptide 1; GLP-2, glucagon like peptide 2; α-MSH, α-melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass. Adapted from Netto et al.

4 CONSIDERAÇÕES FINAIS

Em conclusão, a técnica cirúrgica tipo BGYR promoveu perda de peso eficaz nos primeiros 6 meses após a cirurgia e sustentada aos 24 meses pós cirúrgico.

Foi observado que a perda de peso ocorre não só pela modificação anatômica proposta pelo procedimento cirúrgico, como também pela possível melhora no perfil inflamatório, que por sua vez, reflete para melhor controle do balanço energético.

Verificou-se que a leptina, α-MSH e PYY possuem ação sinérgica e desempenham um importante papel na perda de peso após o BGYR. Além disso, devido ao aumento das concentrações de α-MSH no 24º mês pós-operatório nota-se que o sistema central de melanocortina pode ser fundamental na perda de peso sustentada após a cirurgia bariátrica.

4.1 RECOMENDAÇÕES PARA TRABALHOS FUTUROS

Sugere-se a realização de estudos que analisem os marcadores avaliados também no período pós-prandial e que incluam análise de mais marcadores envolvidos na regulação do balanço energético, como por exemplo grelina, GLP-1 e GLP-2. Adicionalmente, sugere-se a análise dos marcadores envolvidos com o processo do *browning* adipocitário. Além disso, nota-se a importância de estudar mais o NPY e outras vias orexígenas que podem estar ativadas após a cirurgia bariátrica a fim de entender de maneira mais aprofundada todos os mecanismos envolvidos no controle do balanço energético após o procedimento cirúrgico, desenvolvendo estratégias para promover a perda de peso sustentada e prevenindo a recuperação do peso.

REFERÊNCIAS

ABDEEN, G.; LE ROUX, C. W. Mechanism Underlying the Weight Loss and Complications of Roux-en-Y Gastric Bypass. Review. **Obesity Surgery**, v. 26, n. 2, p. 410-421, 2016.

ABESO (Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. **Diretrizes Brasileiras de Obesidade 2016/ ABESO.** 4 ed., São Paulo, 2016.

AHL, S. *et al*. Adiponectin Levels Differentiate Metabolically Healthy vs Unhealthy Among Obese and Nonobese White Individuals. **The Journal of Clinical Endocrinology and Metabolism**, v. 100, p. 4172–4180, 2015.

ALAM, I. *et al*. Temporal changes in glucose and insulin homeostasis after biliopancreatic diversion and laparoscopic adjustable gastric banding. **Surgery for Obesity and Related Diseases**, v. 8, n. 6, p. 752-763, 2012.

ALAMUDDIN, N. *et al*. Changes in Fasting and Prandial Gut and Adiposity Hormones Following Vertical Sleeve Gastrectomy or Roux-en-Y Gastric Bypass: an 18-Month Prospective Study. **Obesity Surgery**, v. 27, n. 6, p. 1563-1572, 2017.

AMIN, T.; MERCER, J.G. Hunger and Satiety Mechanisms and Their Potential Exploitation in the Regulation of Food Intake. **Current Obesity Reports**, v. 5, n. 1, p. 106–112, 2016.

ANGRISANI, L. *et al*. Bariatric surgery worldwide. **Obesity Surgery**, v. 25, n. 10, p. 1822-1832, 2015.

ATTALAH, R. *et al.* Long-Term Effects of 4 Popular Diets on Weight Loss and Cardiovascular Risk Factors: A Systematic Review of Randomized Controlled Trials. **Circulation. Cardiovascular Quality and Outcomes**, v. 7, n. 6, p. 815-827, 2014.

BALDASSANO, S.; AMATO, A.; MULÈ, F. Influence of glucagon-like peptide 2 on energy homeostasis. **Peptides**, v. 86, p. 1-5, 2016.

BARAZZONNI, R. *et al.* Gastric Bypass Does Not Normalize Obesity-Related Changes in Ghrelin Profile and Leads to Higher Acylated Ghrelin Fraction. **Obesity**, v. 21, n. 4, p. 718-722, 2013.

BASSO, N. *et al.* First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: the gastric hypothesis. **Surgical Endoscopy**, v. 25, n. 11, p. 3540-3550, 2011.

BAUER, P. V.; HAMR, S. C.; DUCA, F.A. Regulation of energy balance by a gut–brain axis and involvement of the gut microbiota. **Cellular and Molecular Life Sciences**, v. 73, n. 4, p. 737–755, 2016.

BETTINI, S. C.; BETTINI, M. A. C. Tratamento Cirúrgico da Obesidade: Procedimentos Restritivos e Disabsortivos. In: NETTO, B. D. M.; DÂMASO, A; BETTINI, S. C. **Obesidade Mórbida: Manejo Clínico e Interdisciplinar**. 1 ed. São Paulo: Editora Unifesp, 2018a, p. 227-248.

BETTINI, S. C.; BETTINI, L. F. C. Cirurgia tipo Bypass Gástrico: Técnica Cirúrgica Mista. In: NETTO, B. D. M.; DÂMASO, A.; BETTINI, S. C. **Obesidade Mórbida: Manejo Clínico e Interdisciplinar**. 1 ed. São Paulo: Editora Unifesp, 2018b, p. 249-264.

BIAGIONI, M. F. G. *et al.* Bariatric Roux-en-Y Gastric Bypass Surgery: Adipocyte Proteins Involved in Increase Bone Remodeling in Humans. **Obesity Surgery**, v. 27, n. 7, p. 1789-1796, 2017.

BRADLEY, D. *et al.* Gastric bypass and banding equally improve insulin sensitivity and cell function. **The Journal of Clinical Investigation**, v. 122, n. 12, p. 4667-4674, 2012.

BRASIL. Ministério da Saúde. **Secretaria de Vigilância em Saúde, Secretaria de Gestão Estratégica e Participativa**. Vigitel Brasil 2016: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde, 2017. Disponível em: <http://portalarquivos.saude.gov.br/images/pdf/2017/abril/17/Vigitel.pdf> Acesso em: 14 abr. 2018.

BROWN, J. A.; WOODWORTH, H. L.; LEINNINGER, G. M. To ingest or rest? Specialized roles of lateral hypothalamic area neurons in coordinating energy balance. **Frontiers in Systems Neuroscience**, v. 9, p. 1-25, 2015.

BUCHWALD, H. The Evolution of Metabolic/Bariatric Surgery. **Obesity Surgery**, v. 24, n. 8, p. 1126–1135, 2014.

BUSS, J. *et al*. Associations of ghrelin with eating behaviors, stress, metabolic factors, and telomere length among overweight and obese women: Preliminary evidence of attenuated ghrelin effects in obesity? **Appetite**, v. 76, p. 84–94, 2014.

CAMILLERI, M. Peripheral Mechanisms in Appetite Regulation. **Gastroenterology**, v. 148, p. 1219–1233, 2015.

CARON, A.; RICHARD, D. Neuronal systems and circuits involved in the control of food intake and adaptive thermogenesis. **Annals of the New York Academy of Sciences**, v. 2016, p. 1-19, 2016.

CARRASCO, F. *et al.* Changes in Bone Mineral Density After Sleeve Gastrectomy or Gastric Bypass: Relationships with Variations in Vitamin D, Ghrelin, and Adiponectin Levels. **Obesity Surgery***,* v. 24, n. 6, p. 877-884, 2014.

CAZZO, E. *et al.* GLP-2: A Poorly Understood Mediator enrolled in Various Bariatric/Metabolic Surgery-Related Pathophysiologic Mechanisms. **Arquivos Brasileiros de Cirurgia Digestiva***,* v. 29, n. 4, p. 272-275, 2016.

CAZZO, E. *et al.* GLP-1 and GLP-2 Levels are Correlated with Satiety Regulation After Roux-en-Y Gastric Bypass: Results of an Exploratory Prospective Study. **Obesity Surgery**, v. 27, n. 3, p.703-708, 2017a.

CAZZO, E. *et al.* Postprandial GLP-2 Levels Are Increased After Biliopancreatic Diversion in Diabetic Individuals with Class I Obesity: a Prospective Study. **Obesity Surgery**, v. 27, n. 7, p. 1809-1814, 2017b.

CHAKRAVARTTY, S. *et al.* What is the Mechanism Behind Weight Loss Maintenance with Gastric Bypass? **Current Obesity Reports**, v. 4, n. 2, p. 262–268, 2015.

CHEN, J. *et al.* Serum leptin levels are inversely correlated with omental gene expression of adiponectin and markedly decreased after gastric bypass surgery. **Surgical Endoscopy**, v. 26, p. 1476-1480, 2012.

CHEN, J.; SPAGNOLI, A.; TORQUATI, A. Omental Gene Expression of Adiponectin Correlates with Degree of Insulin Sensitivity Before and After Gastric Bypass Surgery. **Obesity Surgery**, v. 22, n. 3, p. 472-477, 2012.

CHEN, X. et al. Maintenance of Gastrointestinal Glucose Homeostasis by the Gut-Brain Axis. **Current Protein and Peptide Science**, v. 18, n. 6, p. 541-547, 2017.

CHHABRA, K. H. *et al.* Reprogramming the body weight set point by a reciprocal interaction of hypothalamic leptin sensitivity and Pomc gene expression reverts extreme obesity. **Molecular Metabolism**, v. 5, p. 869-881, 2016.

CHO, S. *et al.* Visceral Fat Area and Serum Adiponectin Level Predict the Development of Metabolic Syndrome in a Community-Based Asymptomatic Population. **Plos One**, v. 12, n. 1, p. 1-13, 2017.

CHURM, R. *et al*. Ghrelin function in human obesity and type 2 diabetes: a concise review. **Obesity Reviews**, v. 18, n. 2, p. 140-148, 2017.

CFM (Conselho Federal de Medicina). Resolução n. 2131, de 13 de janeiro de 2016. **Diário Oficial [da] da República Federativa do Brasil,** Brasília, DF, 13 jan. 2016, Seção I, p. 66.

CORGOSINHO, F.C. *et al*. LEPR polymorphism may affect energy balance during weight loss among Brazilians obese adolescents. **Neuropeptides**, v. 66, p. 18-24, 2017.

CRUJEIRAS, A. B. *et al*. Leptin resistance in obesity: An epigenetic ladscape. **Life Sciences**, v. 140, p. 57-63, 2015.

CUMMINGS, D. *et al*. Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery. **Surgery for Obesity and Related Diseases**, v. 3, n. 2, p. 109-115, 2007.

DÂMASO, A. R. *et al*. Hyperleptinemia in obese adolescents deregulates neuropeptides during weight loss. **Peptides**, v. 32, p. 1384-1391, 2011.

DAR, M. S. *et al.* GLP-1 Response to a Mixed Meal: What Happens 10 Years after Roux-en-Y Gastric Bypass (RYGB)? **Obesity Surgery**, v. 22, n. 7, p. 1077-1083, 2012.

DEITEL, M.; GAWDAT, K.; MELISSAS, J. Reporting weight loss 2007. **Obesity Surgery**, v. 17, p. 565-568, 2007.

DI CHIARA, T. *et al.* Circulating adiponectin: a cardiometabolic marker associated with global cardiovascular risk. **Acta Cardiologica**, v. 70, p. 33-40, 2015.

DIRKSEN, C. *et al.* Exaggerated release and preserved insulinotropic action of glucagon-like peptide-1 underlie insulin hypersecretion in glucose-tolerant individuals after Roux-en-Y gastric bypass. **Diabetologia**, v. 56, n. 12, p. 2679-2687, 2013.

DIXON, A. F. R. *et al*. Pancreatic Polypeptide Meal Response May Predict Gastric Band-Induced Weight Loss. **Obesity Surgery**, v. 21, n. 12, p. 1906-1913, 2011.

DIXON, J. B.; LAMBERT, E. A.; LAMBERT, G. W. Neuroendocrine adaptations to bariatric surgery. **Molecular and Cellular Endocrinology**, v. 418, p. 143e-152, 2015.

EVANS, S. *et al.* Gastric Bypass Surgery Restores Meal Stimulation of the Anorexigenic Gut Hormones Glucagon-Like-Peptide-1 and Peptide YY Independently of Caloric Restriction. **Surgical Endoscopy**, v. 26, n. 4, p. 1086-1094, 2012.

FALKÉN, Y. *et al*. Changes in Glucose Homeostasis after Roux-en-Y Gastric Bypass Surgery for Obesity at Day Three, Two Months, and One Year after Surgery: Role of Gut Peptides. **The Journal of Clinical Endocrinology and Metabolism**, v. 96, n. 7, p. 2227-2235, 2011.

FARIAS, G. *et al*. Good weight loss responders and poor weight loss responders after Roux-en-Y gastric bypass: clinical and nutritional profiles. **Nutricion Hospitalaria**, v. 33, n. 5, p. 1108–1115, 2016.

FARIAS G. *et al.* Neuroendocrine regulation of energy balance: implications on the development and surgical treatment of obesity. **Nutrition and Health**, v. 23, p. 131-146, 2017.

FARR, O. M.; LI, C. R.; MANTZOROS, C. S. Central nervous system regulation of eating: Insights from human brain imaging. **Metabolism**, v. 65, n. 5, p. 699-713, 2016.

FERNANDEZ, S. B. *et al.* Peripheral Signals Mediate the Beneficial Effects of Gastric Surgery in Obesity. **Gastroenterology Research and Practice**, v. 2015, p. 1-12, 2015.

GARRIDO-SANCHÉZ, L. *et al.* Bypass of the duodenum improves insulin resistance much more rapidly than sleeve gastrectomy. **Surgery for Obesity and Related Diseases**, v. 8, n. 2, p. 145-150, 2012.

GELISGEN, R. *et al*. Effects of Laparoscopic Gastric Band Applications on Plasma and Fundic Acylated Ghrelin Levels in Morbidly Obese Patients. **Obesity Surgery**, v. 22, n. 2, p. 299-305, 2012.

GUEUGNON, C. *et al*. Ghrelin and PYY levels in adolescents with severe obesity: effects of weight loss induced by long-term exercise training and modified food habits. **European Journal of Applied Physiology**, v. 112, n. 5, p. 1797–1805, 2012.

HALUZÍKOVÁ, D. *et al*. Laparoscopic Sleeve Gastrectomy Differentially Affects Serum Concentrations of FGF-19 and FGF-21 in Morbidly Obese Subjects. **Obesity**, v. 21, n. 7, p. 1335-1342, 2013.

HANKIR, M. K. *et al.* Brain Feeding Circuits after Roux-en-Y Gastric Bypass. **Trends in Endocrinology & Metabolism**, v. 29, n. 4, p. 218-237, 2018.

HANSEN, E. N. *et al.* Role of the foregut in the early improvement in glucose tolerance and insulin sensitivity following Roux-en-Y gastric bypass surgery. **American Journal of Physiology. Gastrointestinal and Liver Physiology**, v. 300, n. 5, p. G795-G802, 2011.

HERDER, C. *et al.* Adiponectin and Bariatric Surgery: Associations with Diabetes and Cardiovascular Disease in the Swedish Obese Subjects Study. **Diabetes Care**, v. 37, p. 1401-1409, 2014.

HOFFSTEDT, J. *et al.* Long-Term Protective Changes in Adipose Tissue After Gastric Bypass. **Diabetes Care**, v. 40, n. 1, p. 77-84, 2017.

HOLST, J. J *et al.* Mechanisms in bariatric surgery: Gut hormones, diabetes resolution, and weight loss. **Surgery for Obesity and Related Diseases**, v. 14, n. 5, p. 708-714, 2018.

ILLÁN-GOMEZ, F. *et al*. Obesity and Inflammation: Change in Adiponectin, C-Reactive Protein, Tumour Necrosis Factor-Alpha and Interleukin-6 After Bariatric Surgery. **Obesity Surgery**, v. 22, n. 6, p. 950-955, 2012.

JAMAR, G. *et al*. Leptin as a cardiovascular risk marker in metabolically healthy obese Hyperleptinemia in metabolically healthy obese. **Appetite**, v. 108, p. 477-482, 2017.

JACOBSEN, S. H. *et al*. Changes in Gastrointestinal Hormone Responses, Insulin Sensitivity, and Beta-Cell Function Within 2 Weeks After Gastric Bypass in Non-diabetic Subjects. **Obesity Surgery**, v. 22, n. 7, p. 1084-1096, 2012.

JOFFE, Y. T.; HOUGHTON, C. A. A Novel Approach to the Nutrigenetics and Nutrigenomics of Obesity and Weight Management. **Current Oncology Reports**, v. 18, n. 7, p. 43, 2016.

JONGE, C. *et al.* Impact of Duodenal-Jejunal Exclusion on Satiety Hormones. **Obesity Surgery**, v. 26, n. 3, p. 672–678, 2016.

JORGENSEN, N. B. *et al*. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. **American Journal of Physiology. Endocrinology and Metabolism**, v. 303, n. 1, p. E-122-E131, 2012.

KALINOWSKI, P. *et al*. Ghrelin, leptin, and glycemic control after sleeve gastrectomy versus Roux-en-Y gastric bypass—results of a randomized clinical trial. **Surgery for Obesity and Related Diseases**, v. 13, p. 181-188, 2017.

KRIEGER, A. C. *et al.* Effects of laparoscopic adjustable gastric banding on sleep and metabolism: a 12-month follow-up study. **International Journal of General Medicine**, v. 5, p. 975-981, 2012.

LARDER, R.; O'RAHILLY, S. Shedding pounds after going under the knife: guts over glory-why diets fail. **Nature Medicine**, v. 18, n. 5, p. 666–667, 2012.

LEAN, M. E. J.; MALKOVA, D. Altered gut and adipose tissue hormones in overweight and obese individuals: cause or consequence? **International Journal of Obesity**, v. 40, n. 4, p. 622–632, 2016.

LEBLANC, E. S. et al. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the US preventive sevices task force. **Annals of Internal Medicine**, v. 155, n. 7, p. 434-447, 2011.

LEIBEL, R. L. *et al.* Biologic responses to weight loss and weight regain: report from an American Diabetes Association Research Symposium. **Diabetes**, v. 64, p. 2299-2309, 2015.

LIMA-JÚNIOR, J. C. de; VELLOSO, L. A.; GELONEZE, B. The Obese Brain—Effects of Bariatric Surgery on Energy Balance Neurocircuitry. **Current Atherosclerosis Reports**, v. 17, n. 10, p. 57, 2015.

LIPS, M. A. *et al*. Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. **European Journal of Endocrinology**, v. 169, n. 3, p. 339-347, 2013.

MA, W. *et al.* Weight-loss diets, adiponectin, and changes in cardiometabolic risk in the 2-year POUNDS Lost Trial. **The Journal of Clinical Endocrinology and Metabolism**, v. 101, n. 6, p. 2415-2422, 2016.

MALIN, S. K. *et al.* Improved acylated ghrelin suppression at 2 years in obese patients with type 2 diabetes: effects of bariatric surgery vs standard medical therapy. **International Journal of Obesity**, v. 38, n. 3, p. 364-370, 2014.

MALLIPEDHI, A. *et al*. Temporal changes in glucose homeostasis and incretin hormone response at 1 and 6 months after laparoscopic sleeve gastrectomy. **Surgery for Obesity and Related Diseases**, v. 10, n. 5, p. 860-870, 2014.

MANNING, S.; PUCCI, A.; BATTERHAM, R.L. Roux-en-Y gastric bypass: effects on feeding behavior and underlying mechanisms. **The Journal of Clinical Investigation**, v. 125, p. 939-948, 2016.

MECHANICK, J. I. *et al.* American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. **Surgery for Obesity and Related Diseases**, v. 4, p. S109-S184, 2008.

MECHANICK, J. I. *et al.* Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient - 2013 Update: Cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society. **Endocrine Practice**, v. 19, n. 2, p. e1–36, 2013.

MEEK, C. L. *et al*. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. **Peptides**, v. 77, p. 28–37, 2016.

MELVIN, A.; LE ROUX, C. W.; DOCHERTY, N. G. The Gut as an Endocrine Organ: Role in the Regulation of Food Intake and Body Weight. **Current Atherosclerosis Reports**, v. 18, n. 8, p. 49, 2016.

MICHALAKIS, K.; LE ROUX, C, W. Gut hormones and leptin: impact on energy control and changes after bariatric surgery. **Obesity Surgery**, v. 22, n. 10, p. 1648-1657, 2012.

MISHRA, A. K.; DUBEY, V.; GHOSH, A. R. Obesity: An overview of possible role(s) of gut hormones, lipid sensing and gut microbiota. **Metabolism**, v. 65, n. 1, p. 48-65, 2016.

MOEHLECKE, M. *et al*. Determinants of body weight regulation in humans. **Archives of Endocrinology and Metabolism**, v. 60, n. 2, p. 152-162, 2016.

MOTTILLO, E.P.; GRANNEMAN, J.G. Intracellular fatty acids suppress b-adrenergic induction of PKA-targeted gene expression in white adipocytes. **American Journal of Physiology-Endocrinology and Metabolism**, v. 301, p. E122-131, 2011.

MÜNZBERG, H. *et al*. Appetite and body weight regulation after bariatric surgery. **Obesity Reviews**, v. 16, suppl. 1, p. 77–90, 2015.

NANNIPIERI, M. *et al.* Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: Mechanisms of Diabetes Remission and Role of Gut Hormones. **The Journal of Clinical Endocrinology and Metabolism**, v. 98, n. 11, p. 4391-4399, 2013.

NAUCK, M. A; MEIER, J. J. Incretin hormones: Their role in health and disease. **Diabetes, Obesity & Metabolism**, v. 20, Supl. 1, p. 5-21, 2018.

NETTO, B. D. M. *et al.* Roux-en-Y gastric bypass decreases pro-inflammatory and thrombotic biomarkers in individuals with extreme obesity. **Obesity Surgery**, v. 25, n. 6, p. 1010-1018, 2015.

NETTO, B. D. M. *et al.* Early effects of Roux-en-Y gastric bypass on peptides and hormones involved in the control of energy balance. **European Journal of Gastroenterology & Hepatology**, v. 28, n. 9, p. 1050-1055, 2016.

NIH (National Institutes of Health). Consensus Development Conference Statement. Gastrointestinal surgery for severe obesity. **Annals of Internal Medicine***,* v. 115, p. 956-961, 1991.

OCHNER, C. N. *et al*. Changes in neurohormonal gut peptides following bariatric surgery. **International Journal of Obesity**, v. 35, n. 2, p. 153–166, 2011.

OYAMA, L. M. *et al*. The role of anorexigenic and orexigenic neuropeptides and peripheral signals on quartiles of weight loss in obese adolescents. **Neuropeptides**, v. 44, p. 467–474, 2010.

PALIKHE, G. *et al*. Efficacy of Laparoscopic Sleeve Gastrectomy and Intensive Medical Management in Obese Patients with Type 2 Diabetes Mellitus. **Obesity Surgery**, v. 24, n. 4, p. 529-535, 2014.

PAPAMARGARITIS, D. *et al*. Changes in gut hormone profile and glucose homeostasis after laparoscopic sleeve gastrectomy. **Surgery for Obesity and Related Diseases**, v. 9, n. 2, p. 192-201, 2013.

PATRITA, A. *et al*. How the hindgut can cure type 2 diabetes. Ileal transposition improves glucose metabolism and β-cell function in Goto-kakizaki rats through enhanced proglucagon gene expression and L-cell umber. **Surgery**, v. 142, p. 74-85, 2007.

PERINO, A. *et al*. Combined inhibition of PI3Kbeta and PI3Kgamma reduces fat mass by enhancing a-MSH-dependent sympathetic drive. **Science Signaling**, v. 7, p. ra110, 2014.

PETERLI, R. *et al*. Metabolic and Hormonal Changes After Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: a Randomized, Prospective Trial. **Obesity Surgery**, v. 22, n. 5, p. 740-748, 2012.

POSOVSZKY, C.; WABITSCH, M. Regulation of Appetite, Satiation, and Body Weight by Enteroendocrine Cells. Part 2: Therapeutic Potential of Enteroendocrine Cells in the Treatment of Obesity. **Hormone Research in Paediatrics**, v. 83, n. 1, p. 11–18, 2015.

RAMÓN, J. M. *et al*. Effect of Roux-en-Y gastric bypass vs sleeve gastrectomy on glucose and gut hormones: a prospective randomized trial. **Journal of Gastrointestinal Surgery**, v. 16, n. 6, p. 1116–1122, 2012.

RANI, M.; KUMAR, R.; KRISHAN P. Role of orexins in the central and peripheral regulation of glucose homeostasis: Evidences & mechanisms. **Neuropeptides**, v. 68, p. 1-6, 2018.

REICHMANN, F.; HOLZER, P. Neuropeptide Y: A stressful review. **Neuropeptides**, v. 55, p. 99-109, 2016.

REINEHR, T.; ROTH, C. L. The gut sensor as regulator of body weight. **Endocrine**, v. 49, n. 1, p. 35-50, 2015.

RIEDIGER, T. The receptive function of hypothalamic and brainstem centres to hormonal and nutrient signals affecting energy balance. **The Proceedings of the Nutrition Society**, v. 71, n. 4, p. 463-477, 2012.

RIGAMONTI, A. E. *et al*. Post-prandial anorexigenic gut peptide, apetite and glucometabolic responses at different eating rates in obese patients undergoing laparoscopic sleeve gastrectomy. **Endocrine**, v. 55, n. 1, p. 113-123, 2017.

ROMERO, F. *et al.* Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. **Surgical Endoscopy**, v. 26, n. 8, p. 2231-2239, 2012.

ROSSI, J. *et al*. Melanocortin-4 receptors expressed by cholinergic neurons regulate energy balance and glucose homeostasis. **Cell Metabolism**, v. 13, p. 195-204, 2011.

RUBINO, F. *et al*. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. **Annals of Surgery**, v. 244, n. 5, p. 741–749, 2006.

SBCBM (Sociedade Brasileira de Cirurgia Bariátrica e Metabólica). **Número de cirurgia bariátricas no Brasil cresce 7,5%, em 2016**, 2017. Disponível em: <https://www.sbcbm.org.br/numero-de-cirurgias-bariatricas-no-brasil-cresce-75-em-2016/> Acesso em: 14 abr. 2018.

SHEN, W. *et al.* Melanocortin neurons: Multiple routes to regulation of metabolism. **Molecular Basis of Disease**, v. 1863, p. 2477-2485, 2017.

SHIPP, S. L.; CLINE, M. A.; GILBERT, E. R. Recent advances in the understanding of how neuropeptide Y and a-melanocyte stimulating hormone function in adipose physiology. **Adypocite**, v. 5, n. 4, p. 333-350, 2016.

SIMPSON, K. *et al*. CCK, PYY and PP: the control of energy balance. In: Joost H-G, editor. Appetite Control. In: **Handbook of experimental pharmacology**. Berlin, Heidelberg: Springer-Verlag, pp. 342; 555, 2012.

SJÖSTRÖM, L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. **Journal of Internal Medicine**, v. 273, n. 3, p. 219–234, 2013.

STEFANIDIS, A.; OLDFIELD, B. J. Neuroendocrine mechanisms underlying bariatric surgery: Insights from human studies and animals models. **Journal of Neuroendocrinology**, v. 29, p. e12534–e12541, 2017.

STEFATER, M. A. *et al*. All Bariatric Surgeries Are Not Created Equal: Insights from Mechanistic Comparisons. **Endocrine Reviews**, v. 33, n. 4, p. 595-622, 2012.

STEINERT, R. E. *et al*. Ghrelin, CCK, GLP-1, and PYY (3-36): Secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. **Physiological Reviews**, v. 97, n. 1, p. 411-463, 2017.

SUN, J. *et al*. Adiponectin potentiates the acute effects of leptin in arcuate Pomc neurons. **Molecular Metabolism**, v. 18, n. 5, p. 882-891, 2016.

SWEENEY, T. E.; MORTON, J. M. Metabolic surgery: action via hormonal milieu changes, changes in bile acids or gut microbiota? A summary of the literature. **Best Practice & Research. Clinical Gastroenterology**, v. 28, n. 4, p. 727–740, 2014.

SYSKO, R. *et al.* Hormonal responses and test meal intake among obese teenagers before and after laparoscopic adjustable gastric banding. **The American Journal of Clinical Nutrition**, v. 98, n. 5, p. 1151–1161, 2013.

TAM, C. S. *et al*. Energy Metabolic Adaptation and Cardiometabolic Improvements One Year After Gastric Bypass, Sleeve Gastrectomy, and Gastric Band. **The Journal of Clinical Endocrinology and Metabolism**, v. 101, n. 10, p. 3755-3764, 2016.

TERRA, X. *et al*. Long-term Changes in Leptin, Chemerin and Ghrelin Levels Following Different Bariatric Surgery Procedures: Roux-en-Y Gastric Bypass and Sleeve Gastrectomy. **Obesity Surgery**, v. 23, n. 11, p. 1790–1798, 2013.

TSOLI, M. *et al*. Hormone changes and diabetes resolution after biliopancreatic diversion and laparoscopic sleeve gastrectomy: a comparative prospective study. **Surgery for Obesity and Related Diseases**, v. 9, n. 5, p. 667-678, 2013.

UENO, H.; NAKAZATO, M. Mechanistic relationship between the vagal afferent pathway, central nervous system and peripheral organs in appetite regulation. **Journal of Diabetes Investigation**, v. 7, n. 6, p. 812-818, 2016.

UMEDA, L. M. *et al*. Early Improvement in Glycemic Control After Bariatric Surgery and Its Relationships with Insulin, GLP-1, and Glucagon Secretion in Type 2 Diabetic Patients. **Obesity Surgery**, v. 21, n. 7, p. 896-901, 2011.

URBANAVICIUS, V. *et al*. Comparison of Changes in Blood Glucose, Insulin Resistance Indices, and Adipokine Levels in Diabetic and Nondiabetic Subjects with Morbid Obesity After Laparoscopic Adjustable Gastric Banding. **Medicina (Kaunas)**, v. 49, n. 1, p. 9-14, 2013.

USINGER, L. *et al*. Gastric Emptying of Orally Administered Glucose Solutions and Incretin Hormone Responses Are Unaffected by Laparoscopic Adjustable Gastric Banding. **Obesity Surgery**, v. 21, n. 5, p. 625-632, 2011.

VANAVANAN, S. *et al*. Performance of body mass index and percentage of body fat in predicting cardiometabolic risk factors in Thai adults. **Diabetes, Metabolic Syndrome and Obesity: targets and therapies**, v. 11, p. 241-253, 2018.

VELLOSO, Lício; ARAÚJO, Eliana P. Regulação Central do Balanço Energético. In: MANCINI, Márcio C. **Tratado de Obesidade**. 2 ed. Rio de Janeiro: Guanabara Koogan, 2016.

WHO (World Health Organization). **Obesity: Preventing and Managing the Global Epidemic; Report of a WHO Consultation.** Technical Report Series n. 894. Geneva, Switzerland: World Health Organization, 2000.

WHO (World Health Organization). **Obesity and overweight. Key facts.** Fact sheet no. 311; February, 2018. Disponível em: <http://www.who.int/mediacentre/factsheets/fs311/en/index.html> Acesso em: 14 abr. 2018.

WOELNERHANSSEN, B. *et al*. Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy—a prospective randomized trial. **Surgery for Obesity and Related Diseases,** v. 7, n. 5, p. 561-568, 2011.

YOUSSEIF, A. *et al*. Differential Effects of Laparoscopic Sleeve Gastrectomy and Laparoscopic Gastric Bypass on Appetite, Circulating Acyl-ghrelin, Peptide YY3-36 and Active GLP-1 Levels in Non-diabetic Humans. **Obesity Surgery**, v. 24, n. 2, p. 241-252, 2014.

APÊNDICE A – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSETIMENTO LIVRE E ESCLARECIDO

As informações contidas neste documento têm o objetivo de firmar por escrito, mediante o qual, o voluntário da pesquisa autoriza sua participação, com pleno conhecimento da natureza dos procedimentos a que se submeterá, com capacidade de livre arbítrio e sem qualquer coação.

Título do trabalho: "Análise da Regulação Neuroendócrina do Balanço Energético e Fatores Inflamatórios em Obesos Adultos Submetidos à Cirurgia Bariátrica".

Objetivo: Avaliar o efeito da perda de peso sobre a síndrome metabólica, parâmetros inflamatórios e qualidade de vida após cirurgia bariátrica.

Justificativa: Escolheu-se esta população, devido à inexistência de programas preventivos e de assistência direcionados a ela. Espera-se que o presente estudo possa contribuir com a obtenção de informações relativas quanto ao estado nutricional dos participantes, além de contribuir para a formulação apropriada de políticas públicas e desenvolvimento de ações de assistência para a coletividade.

Procedimentos realizados no estudo: O estudo será desenvolvido através de dados obtidos com a realização dos seguintes procedimentos: questionário de freqüência alimentar que irá avaliar a sua ingestão alimentar; questionário de intolerância alimentar para avaliar sua satisfação com alimentação e aceitação dos alimentos dos diferentes grupos; medidas corporais como peso, altura e circunferências corporais; coleta de sangue para a determinação de marcadores que controlam a sua fome e saciedade e um questionário que objetiva conhecer a sua percepção sobre qualidade de vida.

Desconforto ou risco: A sua participação envolve coleta de dois tubos pequenos de sangue (8 mL), o qual será colhido de uma de suas veias da dobra do cotovelo por profissional competente. A quantidade de sangue coletada será destinada à separação das células de defesa para serem usados nos ensaios do projeto. Durante a coleta do sangue você poderá sentir algum desconforto, porém passageiro, no local da coleta. Adicionalmente, após a mesma, manchas roxas poderão eventualmente aparecer, mas serão indolores e desaparecerão naturalmente após alguns dias.

Benefícios do estudo: Através do presente estudo o participante será beneficiado com informações sobre a condição nutricional, além de ser informado sobre como evitar eventuais problemas futuros relacionados à nutrição e sua qualidade de vida. Contribuir com a

comunidade científica que, atualmente, dispõe de poucos estudos de coletividade referentes à correlação do estado nutricional com consumo alimentar, especialmente em relação a esta população bariátrica. Além disso, poderá contribuir na formulação apropriada de políticas públicas e desenvolvimento de ações de assistência para os mesmos.

Informações: Os pesquisadores assumem o compromisso de fornecer informações atualizadas obtidas durante o estudo, ainda que estas possam afetar a vontade do indivíduo em continuar participando. Os resultados obtidos na pesquisa serão utilizados somente para fins de publicações científicas e/ ou cursos, palestras e aulas.

Aspecto legal: Este projeto foi elaborado de acordo com as diretrizes e normas que regulamentam as pesquisas envolvendo seres humanos, atendendo à Resolução CNS 466/2012, e suas complementares, do Conselho Nacional de Saúde / Ministério da Saúde – Brasília – DF.

Garantia de sigilo: A participação do voluntário neste estudo é confidencial e nenhum nome será divulgado em qualquer tipo de publicação. Todas as informações coletadas só serão utilizadas para fins científicos.

Retirada do consentimento: A participação neste estudo é voluntária, podendo o participante retirar-se a qualquer momento e por qualquer razão, sem alguma penalidade. No entanto, pedimos que caso deseje retirar-se do estudo entre em contato com os pesquisadores pessoalmente ou por telefone:

- (41) 9956 8420 à Bárbara (Nutricionista);
- (41) 3360-1800 (Comitê de Ética em Pesquisa em Seres Humanos)

Consentimento pós- informação:

Eu,_____, certifico que tendo lido as informações acima e estando suficientemente esclarecido (a) de todos os itens propostos, estou de pleno acordo com os dados a serem coletados, podendo os mesmos serem utilizados para a realização da pesquisa.

Curitiba,_____de_____de 2013.

RG:_____Assinatura:_____

ANEXO A – CARTA DE APROVAÇÃO COMITÊ DE ÉTICA HC-UFPR

HOSPITAL DE CLÍNICAS
UNIVERSIDADE FEDERAL DO PARANÁ

CEP/HC/UFPR

Curitiba, 28 de novembro de 2011.

Ilmo (a) Sr. (a)
Bárbara Dal Molin Netto
Hospital de Clínicas da UFPR
Curitiba - PR

Prezada Pesquisadora:

Comunicamos que o Projeto de Pesquisa intitulado: **"PERFIL METABÓLICO, INFLAMATÓRIO E QUALIDADE DE VIDA DE PACIENTES SUBMETIDOS AO BYPASS GÁSTRICO EM Y DE ROUX"**, foi analisado com pendência pelo Comitê de Ética em Pesquisa em Seres Humanos, em reunião realizada no dia 25 outubro de 2011. Após, analisadas as respostas das pendências encaminhadas pela pesquisadora principal, este CEP/HC considera o projeto aprovado em 23 de novembro de 2011.

O referido projeto atende aos aspectos das Resoluções CNS 196/96, e suas complementares, sobre Diretrizes e Normas Regulamentadoras de Pesquisa Envolvendo Seres Humanos do Ministério da Saúde.

CAAE: 0247.0.208.174-11
Registro CEP: 2625.232/2011-10

Conforme a Resolução 196/96, solicitamos que sejam apresentados a este CEP, relatórios sobre o andamento da pesquisa, bem como informações relativas às modificações do protocolo, cancelamento, encerramento e destino dos conhecimentos obtidos.

Data para entrega do primeiro relatório: maio de 2012.

Atenciosamente,

Renato Tambara Filho
Coordenador do Comitê de Ética em Pesquisa
em Seres Humanos do Hospital de Clínicas/UFPR