UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

AVALIAÇÃO DE FATORES CLÍNICOS E BIOLÓGICOS ASSOCIADOS AO PROGNÓSTICO DA CIRURGIA BARIÁTRICA

INGRID BORBA HARTMANN
Orientadora: Profa. Dra. Marcia Kauer-Sant'Anna
Coorientadora: Profa. Dra. Lisia von Diemen

Porto Alegre
2016

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Tese de Doutorado a ser apresentada ao Programa de Pós-graduação em Psiquiatria e Ciências do Comportamento como requisito parcial à obtenção do título de Doutor em Psiquiatria

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"... finding a good food source,

remembering it, and finding it again.

As simple as this sounds, it is a

neurological tour de force, with just about

the entire brain participating"

Lenard et al., 2008

A meus pais e meu marido, que tornaram

possíveis tantos projetos.

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PARTE I

Resumo

Introdução: A prevalência de obesidade vem aumentando na maioria dos países, praticamente dobrando nos últimos 30 anos. A cirurgia bariátrica é o tratamento mais efetivo para a obesidade grave, levando a uma perda de peso expressiva e que usualmente se mantém em longo prazo. Apesar de sua eficácia comprovada, nem todos os pacientes apresentam perda de peso igualmente satisfatória após a cirurgia. A possibilidade de que estas diferenças nos desfechos de perda de peso possam estar relacionadas a características individuais pré-operatórias tem sido investigada. Até o momento, porém, a literatura a respeito de possíveis preditores de sucesso da cirurgia bariátrica não se mostrou conclusiva. Obesidade e dependência química parecem compartilhar alguns mecanismos neurobiológicos, sobretudo a disfunção de sistemas neurais envolvidos na modulação da resposta a estímulos recompensadores, e há evidências de que a história familiar positiva para transtorno por uso de álcool possa estar associada à obesidade. Além disso, evidências recentes sugerem que a proteína ligante de FK506 51 (FKBP51), implicada na regulação da resposta ao estresse, possa estar envolvida também na regulação da homeostase energética, influenciando o peso corporal.

Objetivos: Avaliar se a história familiar positiva de transtorno por uso de álcool e a presença do alelo T do polimorfismo de nucleotídeo simples (SNP) rs1360780 no gene *FKBP5* poderiam influenciar a perda de peso após a cirurgia bariátrica.

Método: Neste estudo prospectivo longitudinal, a presença de história familiar de transtorno por uso de álcool e do SNP rs1360780 do gene *FKBP5* foram avaliadas em pacientes com idades entre 18 e 69 anos, com índice de massa corporal (IMC) igual ou superior a 35 Kg/m2, que aguardavam a realização da cirurgia bariátrica no Hospital de Clínicas de Porto Alegre. O procedimento cirúrgico foi realizado de acordo com a indicação da equipe assistente, e em todos os casos a técnica cirúrgica empregada foi a gastroplastia em Y de Roux. No período pós-operatório, foi realizado seguimento da perda de peso pelo período de 26 meses, através de dados contidos no prontuário.

Resultados: A história familiar positiva para transtorno por uso de álcool e a presença do alelo T da SNP rs1360780 do gene *FKBP5* mostraram associação com menor perda de peso após a cirurgia bariátrica. No primeiro artigo, pacientes com história familiar positiva apresentaram perda do excesso de peso (EWL, do inglês *excess weight loss*) 18,4% menor em 2 anos de seguimento quando comparados a pacientes sem história familiar, e esta associação se deu de modo independente da presença de história pessoal de transtorno por uso de álcool ou de compulsão alimentar. No segundo artigo, pacientes portadores do alelo T da SNP rs1360780 apresentaram EWL 19,9% menor, e perda do peso total 9,0% menor em 2 anos de seguimento quando comparados a pacientes com o genótipo C/C.

Conclusões: A cirurgia bariátrica interage com características individuais, como genes envolvidos na regulação metabólica e características indicativas de uma maior fragilidade em sistemas neurais relacionados à modulação da resposta a estímulos recompensadores, levando a diferentes desfechos de perda de peso. A identificação de possíveis preditores de sucesso da cirurgia bariátrica possibilitaria o desenvolvimento de intervenções específicas, visando melhorar os desfechos da cirurgia.

Abstract

Introduction: The prevalence of obesity is increasing worldwide, nearly doubling in the last three decades. Bariatric surgery is the most effective treatment choice for severe obesity, leading to expressive weight loss that is usually sustained in the long term. Despite its proven efficacy, not all patients have equally successful weight loss after the surgery. The possibility that this difference in weight outcomes could be attributed to preoperative individual factors has been considered. However, up until now, the literature about potential predictors of success after bariatric surgery has not been conclusive. Obesity and drug addiction seem to share some neurobiological mechanisms, more specifically a disruption in neural systems which modulate the response to reward, and recent literature indicates that a positive family history of alcohol use disorder could be associated with obesity. Moreover, recent evidence indicates that the FK506-binding protein 51 (FKBP51), which is known to play an important role in the regulation of stress response, could also play a role in energy homeostasis, influencing body weight.

Objectives: To evaluate if a positive family history of alcohol use disorder and the presence of the T allele of the *FKBP5* SNP rs1360780 could influence weight loss after bariatric surgery.

Methods: In this prospective observational study, the family history of alcohol use disorder and the presence of the *FKBP5* rs1360780 polymorphism were evaluated in patients between 18 and 69 years of age, who presented a body mass index (BMI) of at least 35 kg/m2 and who were awaiting bariatric surgery at Hospital de Clínicas de Porto Alegre. The surgical procedure was carried out according to the indication of the assistant team, and in all cases the surgical technique employed was the Roux-en-Y gastric bypass. In the postoperative period, a 26-month follow-up of weight loss was performed using data from medical records.

Results: A positive family history of alcohol use disorder and the presence of the T allele of the *FKBP5* SNP rs1360780 were associated with significantly lower weight loss after bariatric surgery. In the first paper, patients with a positive family history of alcohol use disorder presented an excess weight loss (EWL) that was 18.4% lower at 2 years of follow-up when compared to patients with no family history, independent of a personal history of alcohol use disorder or binge eating. In the second paper, carriers of the T allele of the *FKBP5* SNP rs1360780 presented EWL 19.9% lower, and total weight loss 9.0% lower at 2 years of follow-up when compared to patients with the C/C genotype.

Conclusions: Bariatric surgery can interact with individual characteristics, more specifically with genes involved in metabolic regulation and with characteristics suggestive of a higher vulnerability in neural systems which modulate the response to reward, leading to different weight loss outcomes. The identification of potential predictors of success after bariatric surgery would enable the development of interventions to improve outcomes.

Abreviaturas e Siglas

BED - Transtorno de compulsão alimentar periódica (do inglês *binge eating disorder*)

BMI - Índice de Massa Corporal (do inglês *body mass index*)

CNS - Sistema Nervoso Central (do inglês *central nervous system*)

CTQ - Questionário sobre Traumas na Infância (do inglês *Childhood Trauma Questionnaire*)

DALY - *disability-adjusted life-year*

FH - história familiar de transtorno por uso de álcool (do inglês *family history of alcohol use disorder*)

FKBP51 - proteína ligante de FK506 51 (do inglês *FK506-binding protein 51*)

GABA - ácido gama-aminobutirico

GEE - Equações de Estimativas Generalizadas (do inglês *generalized estimating equations*)

GR - receptor de glicocorticoide (do inglês *glucocorticoid receptor*)

HPA - hipotálamo-pituitária-adrenal

IMC - índice de massa corporal

MC4 - receptor 4 de melanocortina

MR - receptor de mineralocorticoide (do inglês *mineralocorticoid receptor*)

PPAR-γ - receptor ativado por proliferador de peroxissoma (do inglês *peroxisome proliferator–activated receptor-γ)*

SCID-I - Entrevista Clínica Estruturada para Transtornos do Eixo I do DSM-IV (do inglês *Structured Clinical Interview for DSM-IV Axis I Disorders*)

SNC – sistema nervoso central

SNP - polimorfismo de nucleotídeo simples (do inglês *single nucleotide polymorphism)*

SPSS - *Statistical Package for the Social Sciences*

TEPT - transtorno de estresse pós-traumático

TNF-a - fator de necrose tumoral alfa (do inglês *tumor necrosis fator alpha*)

T1 - 1 a 3 meses após a cirurgia bariátrica

T2 - 6 a 8 meses após a cirurgia bariátrica

T3 - 12 a 14 meses após a cirurgia bariátrica

T4 - 18 a 20 meses após a cirurgia bariátrica

T5 - 24 a 26 meses após a cirurgia bariátrica

11ß-HSD1 - 11-beta-hidroxiesteroide-desidrogenase tipo 1 (do inglês *11-beta-hydroxysteroid dehydroxygenase type 1)*

%EWL - porcentagem de perda do excesso de peso (do inglês *percentage of excess weight loss*)

%TWL - porcentagem de perda do peso total (do inglês *percentage of total weight loss*)

Prefácio

Este material compõe a tese de doutorado apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento em julho de 2016 como requisito parcial à obtenção do título de Doutor em Psiquiatria.

Este trabalho está organizado em três partes, conforme descrito a seguir:

Parte I: Resumo, *Abstract*, Introdução, Objetivos;

Parte II: Resultados, apresentados na forma de dois artigos científicos;

Parte III: Conclusões e Considerações Finais, Referências Bibliográficas e Anexos.

A introdução discorre inicialmente sobre a obesidade, trazendo dados epidemiológicos e uma breve descrição dos mecanismos envolvidos no desenvolvimento desta patologia. A seguir, são discutidas as opções disponíveis para o tratamento da obesidade, destacando-se o papel da cirurgia bariátrica como o tratamento mais efetivo para pacientes afetados pela obesidade grave. A segunda seção da introdução descreve sucintamente alguns mecanismos regulatórios que parecem ser comuns à fisiopatologia da obesidade e da dependência química, e apresenta a história familiar de transtorno por uso de álcool como fator de risco para o desenvolvimento de ambas as patologias. A terceira e última seção da introdução apresenta a proteína FKBP51, expondo brevemente os mecanismos pelos quais poderia estar implicada na regulação do peso corporal.

Em seguida, são apresentados os objetivos da tese e os artigos produzidos. Esta tese de doutorado resultou em dois artigos: 1) *"Positive family history of alcohol use disorder is associated with lower weight loss after the Roux-en-Y gastric bypass: 26 months of follow-up"*; e 2) *"The FKBP5 polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up"*, este último aceito para publicação na revista

Surgery for Obesity and Related Diseases. Estes artigos se propõem a avaliar a influência, respectivamente, da história familiar positiva de transtorno por uso de álcool, e da presença do alelo T do polimorfismo de nucleotídeo simples rs1360780 do gene *FKBP5*, sobre a redução de peso induzida pela cirurgia bariátrica.

Por fim, são apresentadas as conclusões e considerações finais, em que os resultados dos artigos são discutidos, e as possíveis implicações clínicas destes achados, bem como questões a serem avaliadas em pesquisas futuras, são salientadas.

1. INTRODUÇÃO

1.1 Obesidade

1.1.1 Visão Geral e Epidemiologia

A obesidade é considerada um dos problemas de saúde pública mais desafiadores de nossa época (1,2). Sua prevalência vem aumentando na maioria dos países, praticamente dobrando nos últimos 30 anos (3,4). Em 2014, 11% dos homens e 15% das mulheres acima de 18 anos, ou mais de meio bilhão de adultos ao redor do mundo, eram considerados obesos (5). A prevalência desta doença costuma ser maior entre as mulheres (1), e aumentar conforme o nível de renda do país (1,5), embora estas tendências apresentem diferenças regionais. Apesar disso é importante salientar que cerca de 62% dos indivíduos afetados pela obesidade vivem em países em desenvolvimento (1).

A obesidade é definida pela Organização Mundial de Saúde como o aumento da adiposidade corporal cuja magnitude é capaz de acarretar riscos para a saúde. O índice de massa corporal (IMC), calculado como peso(kg)/[altura(m)]^2, é o critério mais comumente utilizado para o diagnóstico desta patologia em adultos, para isto utilizando como ponto de corte o valor 30 kg/m2. A obesidade pode ainda ser subdividida em categorias, de acordo com sua gravidade, em obesidade casses I, II e III (IMC igual ou superior a 30,0 Kg/m2, 35,0 Kg/m2 e 40,0 Kg/m2, respectivamente).

A associação entre obesidade, desfechos adversos em saúde e mortalidade por todas as causas está bem estabelecida (5), e estima-se que sobrepeso e obesidade tenham sido responsáveis por 3,4 milhões de mortes e por 3,8% dos anos perdidos em função de incapacidade (*disability-adjusted life-year* - DALY) em 2010 (6). Doenças clínicas crônicas

com alto impacto sobre a mortalidade, como hipertensão, diabetes tipo 2 e doença cardiovascular, dentre outras, apresentam importante associação com a obesidade (5). Esta doença está associada ainda a maior prevalência de transtornos psiquiátricos, sobretudo transtornos de humor e ansiedade (7,8), e a uma pior qualidade de vida (9,10), além de gerar elevados custos para os sistemas de saúde (11).

A obesidade é uma doença heterogênea, e de etiologia multifatorial. Acredita-se que formas comuns de obesidade resultem da interação entre fatores genéticos e ambientais atuando ao longo da vida de um indivíduo. A complexidade dos mecanismos envolvidos na regulação do peso corporal contribui para a dificuldade enfrentada na caracterização de sua fisiopatologia e no desenvolvimento de opções terapêuticas efetivas.

1.1.2 Regulação do Peso Corporal e Fisiopatologia da Obesidade

De modo simplificado, pode-se dizer que sobrepeso e obesidade são o resultado de um balanço energético cronicamente positivo. Deste modo, o aumento do aporte energético através da ingesta, a diminuição do gasto energético, que engloba gastos com metabolismo basal, termogênese e atividade muscular, ou uma associação de ambos, levariam ao armazenamento do excesso de energia no tecido adiposo, e consequentemente ao ganho de peso.

Os mecanismos envolvidos na regulação do balanço energético, porém, são complexos, e envolvem múltiplas áreas centrais e tecidos periféricos, que se comunicam através de conexões neurais, hormônios e metabólitos (12). Além de complexas, dada a importância da manutenção de estoques adequados de energia para a sobrevivência, muitas das vias envolvidas nesta regulação são também redundantes (13).

O hipotálamo, sobretudo núcleos arqueado e paraventricular e área hipotalâmica lateral, e o tronco cerebral são os principais responsáveis pela regulação central do balanço energético. Para o hipotálamo convergem sinais provenientes de órgãos sensoriais (que informarão sobre aspecto visual, odor e paladar dos alimentos), sinais advindos de tecidos periféricos, como trato gastrointestinal e tecido adiposo, dentre outros (que informarão a respeito das necessidades energéticas do organismo), e sinais provenientes de outras áreas centrais, como córtex e sistema de recompensa (que determinarão, por exemplo, o valor atribuído a alimentos específicos, e a motivação para buscá-los). Integrando todas estas informações, o hipotálamo irá determinar sinais de fome ou saciedade, além de desencadear respostas endócrinas, autonômicas e comportamentais, a fim de manter a homeostase energética (12–14).

Uma descrição mais aprofundada dos mecanismos envolvidos na regulação homeostática da ingesta e do gasto energético, ou de outros fatores implicados na fisiopatologia da obesidade, como o papel da inflamação, está além do escopo deste trabalho. Serão salientados abaixo alguns aspectos referentes ao papel de: 1) mecanismos hedônicos de regulação da ingesta; 2) tecido adiposo e cortisol; e 3) interação gene-ambiente no desenvolvimento desta patologia.

1.1.2.1 Mecanismos Hedônicos de Regulação da Ingesta

O comportamento alimentar, além de ser influenciado pelos sinais de fome e saciedade determinados por mecanismos homeostáticos de regulação conforme as necessidades de energia do organismo, é também influenciado pela expectativa de prazer e recompensa associada à ingesta de determinados alimentos (15). Os mecanismos implicados na regulação

destes aspectos da ingesta (prazer, recompensa), que neste trabalho serão denominados "mecanismos hedônicos de regulação", serão sucintamente descritos abaixo.

Na regulação hedônica da ingesta, estão envolvidas principalmente áreas corticais e límbicas, e os principais neurotransmissores implicados são dopamina, opióides, endocanabinóides, GABA e serotonina (15,16). Dentre estes, o papel da transmissão dopaminérgica é o mais bem caracterizado até o momento, e parece mediar predominantemente o "querer" (desejo e motivação por) determinados alimentos que anteriormente produziram experiência prazerosa, enquanto os sistemas opióide e canabinóide determinariam principalmente o "gostar" (palatabilidade, prazer) associado à ingestão destes alimentos (13,15,16), embora exista certa sobreposição entre estas funções.

É importante salientar a existência de importante interação entre mecanismos hedônicos e homeostáticos na regulação da ingesta. Além da interação central entre estas vias (entre hipotálamo/tronco cerebral e sistema de recompensa), sabe-se que alguns peptídeos produzidos em tecidos periféricos e envolvidos primariamente em processos de regulação homeostática, como grelina, leptina e insulina, são também capazes de modular as propriedades recompensadoras atribuídas aos alimentos (16), aumentando (grelina) ou diminuindo (leptina, insulina) o valor destes alimentos como recompensadores de acordo com as necessidades energéticas do organismo. Para exercer esta função, estes peptídeos parecem atuar diretamente no sistema de recompensa e em áreas relacionadas (15), e receptores para estes sinais periféricos foram identificados em neurônios dopaminérgicos na área tegmental ventral, e também em áreas corticais, amigdala e hipocampo (16).

O papel fundamental destes mecanismos hedônicos de regulação da ingesta, no contexto da manutenção do balanço energético e sobrevivência da espécie, seria o de direcionar a atenção e o esforço do indivíduo para a obtenção do alimento - e do prazer a ele relacionado.

Estes mecanismos permitem, também, que um alimento recompensador seja ingerido quando disponível, mesmo que as necessidades energéticas estejam supridas, comportamento vantajoso em épocas em que as fontes de alimento eram escassas e imprevisíveis (16).

Recentemente, o papel destes mecanismos hedônicos de regulação tem atraído interesse crescente, pois acredita-se que, quando disfuncionais, propiciariam o estabelecimento de um padrão de ingesta excessiva de alimentos palatáveis, deste modo favorecendo o desenvolvimento do sobrepeso e da obesidade.

1.1.2.2 Tecido Adiposo e Cortisol

1.1.2.2.1 Tecido Adiposo

O papel do tecido adiposo na regulação do metabolismo vem ganhando destaque nas últimas décadas, a partir do reconhecimento de sua função endócrina. Este tecido produz diversos hormônios e citocinas, como leptina, adiponectina, resistina, TNF-α e interleucina-1, dentre outros, que interagem com o SNC e com órgãos periféricos, participando da regulação do balanço energético (12) e da inflamação (17,18). A disfunção deste tecido, como observada na obesidade, tem sido implicada na fisiopatologia de uma variedade de doenças (17).

1.1.2.2.2 Cortisol

O cortisol influencia o desenvolvimento, o metabolismo e a função endócrina do tecido adiposo, e parece ter um importante papel em restringir sinais inflamatórios provenientes dos adipócitos (17,19). Este hormônio parece ainda ser capaz de influenciar o apetite através de sua interação com áreas centrais e tecidos periféricos (20).

Os efeitos do cortisol sobre o tecido adiposo e o apetite, e os mecanismos subjacentes a estes efeitos, ainda não foram plenamente elucidados, mas parecem depender do contexto fisiológico (ambiente hormonal e nutricional) e do tecido específico (p. ex. gordura visceral ou subcutânea) em que ocorrem (19). Deste modo, níveis cronicamente elevados de cortisol, como os observados na Síndrome de Cushing ou os decorrentes do uso crônico de glicocorticoides, quando associados a suprimentos adequados de insulina e nutrientes, resultam em aumento da adiposidade, sobretudo do tecido adiposo visceral. Por outro lado, o hipercortisolismo observado na presença de doença aguda grave, que ocorre como parte da resposta aguda ao estresse, está associado à mobilização de gordura do tecido adiposo (17).

A obesidade central e síndromes caracterizadas pela presença de excesso de glicocorticoides (como a S. de Cushing) compartilham algumas anormalidades metabólicas, como alterações no metabolismo dos lipídios e da glicose. Apesar disso, formas comuns de obesidade não se caracterizam pela presença de hipercortisolismo (17,19). Acredita-se, porém, que a obesidade possa estar associada a alterações mais sutis na dinâmica do cortisol, sugestivas de uma hiperativação crônica do eixo hipotálamo-pituitária-adrenal (HPA), e também a alterações do metabolismo local do cortisol, ou mais especificamente a uma produção de cortisol aumentada no tecido adiposo induzida pela enzima 11-beta-hidroxiesteroide-desidrogenase (11β-HSD1), que converte a cortisona (inativa) em cortisol (ativo) (19).

1.1.2.3 Interação Gene-Ambiente

O marcante aumento na prevalência de obesidade observado nas últimas décadas tem sido atribuído, em parte, à influência de fatores ambientais, e as sociedades atuais, em que prevalece uma ampla oferta de alimentos altamente palatáveis e calóricos, usualmente a

baixos custos, associada a uma menor necessidade de atividade física decorrente da motorização dos transportes e da automação de processos de trabalho (21), têm sido descritas como “obesígenas”.

Nem todos os indivíduos submetidos a estas condições ambientais, porém, desenvolverão obesidade. Fatores individuais, portanto, parecem ter também um papel fundamental no desenvolvimento desta patologia. A obesidade parece ser um traço fortemente influenciado por fatores genéticos (13,22), e estimativas de herdabilidade indicam que 40 a 70% da variação no peso corporal em humanos possa ser atribuída a estes fatores (22). Apesar disso, ainda pouco se sabe sobre o papel de genes específicos no desenvolvimento da obesidade (13).

Embora algumas mutações genéticas capazes de levar à obesidade grave tenham sido descritas, como por exemplo mutações nos genes que codificam a leptina e o receptor 4 de melanocortina (MC4) (23), estas formas monogênicas de obesidade parecem contribuir para uma parcela pequena dos casos (13). Acredita-se que, na maioria dos casos de obesidade, prevaleça a influencia de uma associação de variantes genéticas mais comuns, e que individualmente determinariam um efeito mais sutil sobre o peso corporal (obesidade poligênica) (13,22,24), conferindo sobretudo uma maior suscetibilidade ao ganho de peso. Além disso, recentemente a possibilidade de que mecanismos epigenéticos possam influenciar o peso corporal vem sendo investigada (22), e evidências sugerem que determinados tipos de dietas e o estado nutricional durante a gestação possam influenciar o peso corporal da prole (22,25). Em síntese, acredita-se que formas comuns de obesidade resultem de uma complexa interação entre fatores genéticos e ambientais.

1.1.3 Tratamento da Obesidade - Papel da Cirurgia Bariátrica

Apesar dos recentes avanços na compreensão dos mecanismos envolvidos na fisiopatologia da obesidade, o tratamento desta doença segue sendo um desafio.

As duas principais abordagens não cirúrgicas para o tratamento da obesidade são as modificações de estilo de vida (que englobam modificações na dieta e aumento da atividade física) e o tratamento farmacológico (26). Estas abordagens estão associadas a uma redução de peso geralmente modesta, e que para a maioria dos pacientes não se sustenta com facilidade em longo prazo (26). Além disso, as opções farmacológicas disponíveis são ainda hoje bastante limitadas em número, e diversas medicações foram retiradas do mercado em função de efeitos colaterais, muitos deles relacionados à ação central destes fármacos.

A cirurgia bariátrica atualmente é a opção terapêutica mais efetiva para o tratamento da obesidade grave (26), ocasionando uma perda de peso expressiva e que na maioria dos casos se mantém em longo prazo (27,28). Apresenta taxas de mortalidade cirúrgica usualmente baixas (0,08% - 0,35%) (27), e está associada a redução da mortalidade geral (28,29), melhora de comorbidades clínicas relacionadas à obesidade (27,30–33), melhora de comorbidades psiquiátricas (34) e da qualidade de vida (35).

O tratamento cirúrgico está indicado para pacientes com IMC $\geq$ 40 kg/m2 independente da presença de comorbidades, ou IMC $\geq$ 35 Kg/m2 caso pelo menos uma comorbidade ocasionada ou agravada pela obesidade esteja presente (36). Além disso, a possibilidade de indicação do tratamento cirúrgico para pacientes com IMC entre 30,0 e 34,9 kg/m2 em determinadas circunstâncias vem sendo recentemente avaliada (36).

Na realização da cirurgia bariátrica, diferentes técnicas cirúrgicas podem ser empregadas, como gastroplastia em Y de Roux, gastroplastia vertical com bandagem, banda

gástrica ajustável e derivação bileopancreática, dentre outras (26). Embora todas as técnicas atualmente utilizadas mostrem-se efetivas, pode-se observar algumas diferenças entre elas com relação às taxas de redução de peso e de melhora de comorbidades clínicas. A gastroplastia em Y de Roux (Figura 1) é uma das técnicas cirúrgicas mais frequentemente utilizadas (37), levando a uma perda média de 27,7% do peso total inicial após 6 anos de seguimento (38), e a uma redução de 40%, 56% e 92% nas taxas de mortalidade por todas as causas, por doença arterial coronariana, e por diabetes, respectivamente, após 7 anos de seguimento (39).

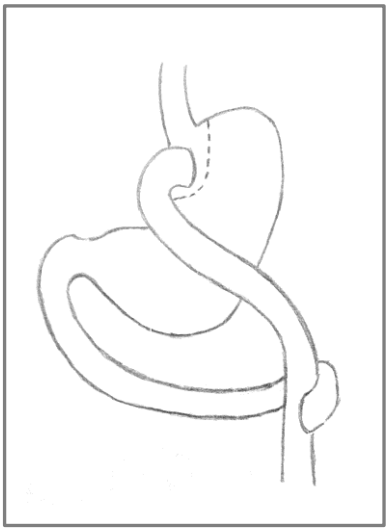


Figura 1. Desenho esquemático da Gastroplastia em Y de Roux. Adaptado de Mechanick *et al*., 2008.

As técnicas cirúrgicas descritas acima promovem a restrição da ingesta (obtida através da diminuição do volume gástrico), ou uma associação de restrição da ingesta e diminuição da absorção de nutrientes (esta última obtida através da redução da área absortiva do intestino) (37). O impacto positivo da cirurgia sobre o metabolismo e o apetite, porém, não parece se justificar simplesmente pela redução da ingesta e da absorção (40,41).

Sabe-se que a cirurgia bariátrica modifica a secreção de diversos peptídeos periféricos envolvidos na regulação do balanço energético (40), e evidências recentes sugerem que possa

também influenciar o funcionamento do eixo HPA, a atividade da enzima 11-beta-hidroxiesteroide-desidrogenase (11β-HSD1) no tecido adiposo (42), e a disponibilidade de receptores D2R e μ-opioide no sistema de recompensa cerebral (43–45).

Apesar de sua eficácia comprovada, nem todos os pacientes apresentam perda de peso igualmente satisfatória após a cirurgia. A possibilidade de que estas diferenças nos desfechos de perda de peso possam estar relacionadas a características pré-operatórias individuais tem sido investigada. Até o momento, porém, apesar de algumas características clínicas e psiquiátricas terem sido identificadas como possíveis preditores de sucesso (46–48), a literatura a este respeito permanece largamente inconclusiva (46,49).

1.2 Obesidade, Adição e Cirurgia Bariátrica

A obesidade, no que se refere ao comportamento alimentar, e a dependência química, parecem compartilhar algumas características comportamentais e biológicas, e paralelos têm sido traçados entre as duas doenças (50).

Um padrão de ingesta excessiva de alimentos muito palatáveis e calóricos, estimulada pelas propriedades prazerosas e recompensadoras destes alimentos, e dissociada das necessidades energéticas do organismo, é frequentemente observado nas formas comuns de obesidade (15). Este padrão de consumo, que contribui para o desenvolvimento da obesidade por gerar um balaço energético positivo, tem sido atribuído a um desequilíbrio entre a influência de vias hedônicas e homeostáticas na regulação da ingesta, em que o controle hedônico passaria a preponderar (15,16).

Embora os mecanismos responsáveis por estas alterações ainda necessitem de elucidação, uma possível explicação parece vir dos estudas da área da adição. As vias centrais envolvidas na regulação hedônica da ingesta apresentam grande superposição com as reconhecidamente envolvidas na fisiopatologia da dependência química (51). Sabe-se que as drogas de abuso fazem uso de, e estimulam de modo suprafisiológico, sistemas neurais que evoluíram para regular a interação do individuo com recompensadores naturais fundamentais para a sobrevivência (50), como alimento e sexo. Determinados alimentos, sobretudo os ricos em gorduras e carboidratos, assim como ocorre com as drogas de abuso, são intensamente recompensadores, e capazes de desencadear respostas neurais que irão reforçar o seu consumo, respostas estas mediadas principalmente pelo aumento de dopamina no sistema de recompensa cerebral (15).

Tem sido proposto que, em indivíduos susceptíveis, a exposição repetida a alimentos muito palatáveis levaria a um padrão de neuroadaptações, no sistema de recompensa e nos sistemas modulados por ele, semelhante ao desencadeado pela exposição repetida a drogas de abuso (15,51,52). Estas neuroadaptações resultariam, dentre outras alterações, em um aumento da influência de áreas centrais envolvidas na motivação de comportamentos (envolvidas em processos relacionados a recompensa e condicionamento), e em disfunção de áreas envolvidas no controle inibitório, deste modo perpetuando padrões disfuncionais de consumo (16).

Além disso, assim como ocorre na dependência química, somente alguns dos indivíduos expostos repetidamente a esta estimulação (seja por alimentos muito palatáveis ou por drogas de abuso) irão desenvolver algum descontrole sobre o comportamento de consumo, e este descontrole, caso ocorra, se dará em um continuum de intensidade, em que o consumo compulsivo representa o extremo de gravidade (53). Deste modo, embora obesidade e dependência química difiram em aspectos fundamentais de sua fisiopatologia, sobretudo no que diz respeito ao papel dos mecanismos homeostáticos na regulação do peso corporal, estas patologias parecem também compartilhar parte de seus mecanismos fisiopatológicos, principalmente a disfunção de vias envolvidas na regulação da resposta a estímulos recompensadores e do autocontrole, e parecem compartilhar ainda a vulnerabilidade biológica para o desenvolvimento destas alterações (53).

A história familiar positiva de transtorno por uso de álcool é um conhecido fator de risco para o desenvolvimento de história pessoal de transtorno por uso de álcool, e acredita-se que fatores genéticos contribuam de modo relevante para esta associação (54). Recentemente, a história familiar positiva de transtorno por uso de álcool tem sido associada também à obesidade (55). Poderíamos supor, deste modo, que a história familiar positiva de alcoolismo,

ao conferir maior vulnerabilidade ao desenvolvimento da obesidade, poderia influenciar os desfechos de perda de peso da cirurgia bariátrica, possibilidade esta que ainda não foi investigada.

1.3 Obesidade, Proteína FKBP51 e Cirurgia Bariátrica

A proteína ligante de FK506 51 (FKBP51, do inglês *FK506-binding protein 51*) humana é uma molécula de 51-kDa, codificada pelo gene *FKBP5*, localizado no cromossomo 6 (6p21.31). A FKBP51 é expressa no SNC e em tecidos periféricos (56,57), e nestes sua maior expressão ocorre em tecidos metabolicamente ativos, como músculo e tecido adiposo. Polimorfismos de nucleotídeo simples (SNP) no gene *FKBP5* foram identificados em humanos e, dentre estes, o alelo T do SNP rs1360780 está associado a expressão aumentada da FKBP51 (*high-induction allele*) (58).

Desde sua descrição, a FKBP51 vem atraindo interesse crescente em função de seu envolvimento em diversos processos biológicos relevantes, como a regulação de fatores de transcrição, enzimas e proteínas estruturais (59,60). Uma de suas funções mais bem estabelecidas é a de atuar como co-chaperona que regula a atividade do receptor de glicocorticoide (GR), diminuindo a sensibilidade deste receptor ao cortisol. Ao mesmo tempo, o *FKBP5* também tem sua expressão induzida pela ativação do GR. Deste modo, a FKBP51 teria um importante papel na regulação da resposta ao estresse (61).

Um possível envolvimento da FKBP51 na adipogênese foi sugerido desde a descrição desta proteína por Yeh e colaboradores em 1995 (62) e, recentemente, o papel desta proteína na regulação do metabolismo e na fisiopatologia da obesidade tem sido investigado.

Evidências indicam que os níveis de expressão do *FKBP5* poderiam influenciar o peso corporal. Mais especificamente, estudos experimentais observaram que ratos que tiveram este gene inativado (*knockout*) apresentaram menor peso corporal quando em condições basais (63), e foram resistentes ao ganho de peso quando submetidos a uma dieta rica em gorduras

(64). A expressão hipotalâmica aumentada deste gene, por outro lado, parece estar associada a um maior ganho de peso (65,66).

Os mecanismos pelos quais a FKBP51 poderia influenciar o metabolismo e o peso corporal são ainda pouco compreendidos, mas tanto uma ação local no tecido adiposo quanto uma ação sistêmica parecem ser possíveis. No tecido adiposo, a FKBP51 interage com pelo menos 3 receptores nucleares com importante participação no metabolismo dos adipócitos: GR (como mencionado acima), receptor de mineralocorticoide (MR) e receptor ativado por proliferador de peroxissoma (*peroxisome proliferator–activated receptor-γ*, PPAR-γ). A partir de sua interação com o PPAR-γ, a FKBP51 ativa este receptor (19), o qual age como um dos principais reguladores da adipogênese. Sua interação com o GR e MR, modulando o funcionamento destes receptores (61,67), torna-se especialmente relevante se considerarmos que na obesidade parece haver uma produção local aumentada de cortisol no tecido adiposo (19), e que o cortisol parece ser o principal ligante do MR neste tecido (17). Além disso a FKBP51 parece modular a Akt (68), que dentre outras funções tem importante papel na captação de glicose mediada por insulina no músculo e tecido adiposo (69).

Uma ação sistêmica da FKBP51 sobre o peso corporal poderia se dar pela ação desta proteína na regulação do eixo hipotálamo-pituitária-adrenal (HPA). A obesidade tem sido associada a alterações do funcionamento do eixo HPA sugestivas de hiperativação prolongada deste eixo (19). Estes achados poderiam ser, ao menos em parte, influenciados pela ação da FKBP51, uma vez que SNPs do *FKBP5* associadas a expressão mais elevada da FKBP51, como o rs1360780, parecem influenciar o funcionamento do eixo HPA, por induzir uma menor eficiência da alça de retroalimentação negativa do eixo (58).

Considerando-se que: 1) através da redução da eficiência da alça de retroalimentação negativa do eixo HPA, os SNPs que induzem maior expressão do *FKBP5* parecem conferir

maior vulnerabilidade aos efeitos deletérios do estresse e trauma (por levar a uma ativação mais prolongada do eixo HPA em resposta ao estresse), sendo mesmo consideradas como fatores de risco para o desenvolvimento de doenças psiquiátricas relacionadas ao estresse, como o TEPT (58); 2) obesidade tem sido associada a estresse (20), trauma (70) e alterações do funcionamento do eixo HPA; e 3) algumas evidências indicam que a cirurgia bariátrica poderia influenciar positivamente o funcionamento do eixo HPA e a atividade da 11β-hidroxiesteroide desidrogenase tipo 1 (11β-HSD1) no tecido adiposo (42), a avaliação da influência do SNP rs1360780 no gene *FKBP5* sobre a redução de peso induzida pela cirurgia bariátrica seria relevante.

2. OBJETIVOS

2.1 Objetivo Geral

Investigar fatores clínicos e biológicos associados ao prognóstico da cirurgia bariátrica.

2.2 Objetivos Específicos

1. Avaliar se a história familiar de transtorno por uso de álcool influencia a perda de peso induzida pela cirurgia bariátrica.
2. Avaliar o impacto da história pessoal de transtorno por uso de álcool e da história de compulsão alimentar, investigadas no período pré-operatório, sobre a associação entre história familiar de transtorno por uso de álcool e perda de peso induzida pela cirurgia bariátrica.
3. Avaliar se o SNP rs1360780 no gene *FKBP5* influencia a perda de peso induzida pela cirurgia bariátrica.

PARTE II

3. ARTIGOS CIENTÍFICOS

3.1 Artigo 1

Positive family history of alcohol use disorder is associated with lower weight loss after the Roux-en-Y gastric bypass: 26 months of follow-up.

Ingrid Borba Hartmann, Silvia Bassani Schuch, Kelen Patrícia Bürke Bridi, Letícia Sanguinetti Czepielewski, Monise Costanzi, Daniel Prates Baldez, Marcia Kauer-Sant'Anna e Lísia von Diemen.

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Positive family history of alcohol use disorder is associated with lower weight loss after the Roux-en-Y gastric bypass: 26 months of follow-up.

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ABSTRACT

BACKGROUND: The prevalence of obesity is increasing worldwide, nearly doubling in the last three decades. Bariatric surgery is the most effective treatment choice for severe obesity. It has been suggested that obesity and drug addiction could share neurobiological substrates and recent literature indicates that a positive family history of alcohol use disorder could be associated with higher odds of obesity.

OBJECTIVE: To evaluate if a positive family history of alcohol use disorder could influence weight loss after bariatric surgery.

SETTING: Hospital de Clínicas de Porto Alegre, Brazil.

METHODS: 45 patients awaiting bariatric surgery were included, and the family history of alcohol use disorder was evaluated. In the postoperative period, a 26-month follow-up of weight loss was performed (n = 45, 38, 36, 35 and 31, from the first to fifth postoperative evaluation, respectively. Loss to follow-up: 31.11%).

RESULTS: Patients with a positive family history of alcohol use disorder presented significantly lower weight loss after the 6th-8th month follow-up period, and at 2 years of follow-up their excess weight loss was 18.4% lower when compared to patients with no family history.

CONCLUSIONS: A positive family history of alcohol use disorder was associated with weight loss after bariatric surgery. Although our results need further confirmation, we could hypothesize that bariatric surgery can interact with the vulnerability in neural systems that regulate reward and self-control, which is believed to be present in a subset of patients with obesity as well as in drug addiction, leading to different weight loss outcomes.

KEYWORDS: obesity; family history; bariatric surgery.

INTRODUCTION

The prevalence of obesity is increasing around the world. Epidemiologic studies indicate that obesity is a significant public health challenge, with 33.0% of the world's adult population (1.3 billion people) overweight or obese in 2005 (1).

Currently, in the presence of severe obesity, the only treatment that achieves substantial long-term weight loss and sustained improvements in obesity-related comorbidities is bariatric surgery. Despite its proven efficacy, not all patients have equally successful weight loss after surgery (2). The possibility that this difference in weight outcomes could be attributed to preoperative clinical, psychological and behavioral factors has been considered (3–5). However, up until now, the literature about potential predictors of success after bariatric surgery has not been conclusive (6,7).

In recent years, the mechanisms driving the intake of food and addictive drugs have been elucidated, and in many aspects overlap (8). Therefore, although the concept of food addiction remains controversial (9), the presence of a shared neurobiological vulnerability for the development of obesity and drug addiction has been hypothesized (8,10). Evidence of links between these pathologies can be found in clinical and preclinical studies, which have shown a significantly lower lifetime risk of substance use disorders in obese patients (11), an inverse relationship between alcohol consumption and body mass index (BMI) (12), and attenuated responses to drug rewards in animal models of obesity (10).

Moreover, the relationship between obesity and family history of alcohol use disorder (FH), a known risk factor for the development of personal alcohol use disorder with a strong influence of genetic factors (13), has also been investigated. Individuals with a positive FH were shown to present higher odds of obesity (14), and it was observed that biological

children of alcoholic parents have a greater risk of having a strong sweet preference, which may manifest in some as an eating disorder (15,16). Besides that, the influence of a positive FH on the frequency of personal alcohol consumption seems to be moderated by BMI, such that family history effects on the frequency of personal alcohol consumption were shown to be present only among non-obese individuals (12).

It is not known, however, if a positive family history of alcohol use disorder, which seems to lead to increased vulnerability to the development of obesity, could also influence weight loss after bariatric surgery. The purpose of this study is to, therefore, verify this association.

MATERIAL AND METHODS

Participants

In this prospective observational study, patients between 18 and 69 years of age, who presented a BMI of at least 35 kg/m2 and who were awaiting bariatric surgery at Hospital de Clínicas de Porto Alegre were recruited from June 2011 to March 2013. All enrolled participants had already undergone a routine preoperative evaluation carried out by the assistant care team, and had already concluded their surgery approval process. Exclusion criteria were the presence of current suicide risk, indication of psychiatric hospitalization, and the diagnosis of intellectual disability or dementia. Of the 56 patients initially included, 45 underwent the surgical procedure by the deadline established by the study. Data regarding these 45 participants will be presented throughout this paper (Figure 1).

Procedures

In the preoperative period, patients were evaluated using a research protocol. The surgical procedure was then carried out according to the recommendations of the assistant team. In all cases, the surgical technique employed was the Roux-en-Y gastric bypass.

In the postoperative period, a follow-up of weight loss was performed using data from medical records. The postoperative period was divided as follows: T1: 1-3 months after surgery; T2:6-8 months after surgery; T3:12-14 months after surgery; T4:18-20 months after surgery; and T5: 24-26 months after surgery.

Psychiatric assessment

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for the diagnosis of Axis I psychiatric disorders.

Anthropometric assessment

Measurements of weight and height were obtained from medical records. All other calculations were performed using the Statistical Package for the Social Sciences (SPSS), version 20.0.

The preoperative measurements of weight and height included in the study were those previously recorded at hospital admission for the surgical procedure. In the postoperative period, when more than one measure of weight was available within the specified periods of the study (T1 to T5), the most recent was selected.

Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. The percentage of excess weight loss (%EWL) was calculated as [(weight loss/excess weight) X100], and excess weight was taken as the weight in kilograms above the weight corresponding to the BMI of 24.9 kg/m2.

Ethics

The study followed the conditions established in Resolution 196/96 of the National Health Council and was submitted to the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre. All patients signed a Written Informed Consent.

Statistical analysis

Continuous data were expressed as means and standard deviation, and were analyzed using the Student t-test. Categorical variables were expressed as number of subjects and percentages and compared using the χ^2 test. Some psychiatric disorders were grouped into broad categories (e.g. any anxiety disorder). %EWL, BMI, and percentage of total weight loss (%TWL) after bariatric surgery were examined by means of generalized estimating equations model (GEE) using all available observations. Loss to follow-up is described in figure 1. The factors used in the models were: 1: time, family history of alcohol use disorder, and interaction time by family history of alcohol use disorder, adjusted for sex, age, personal history of alcohol use disorder, binge eating (bulimia plus BED), and lifetime diagnosis of major depressive disorder; 2: time, lifetime diagnosis of major depressive disorder, and interaction time by lifetime diagnosis of major depressive disorder; and 3: time, lifetime diagnosis of binge eating (bulimia plus binge eating disorder), and interaction time by binge eating. The Bonferroni test was utilized for all post hoc comparisons. In all experiments, $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 20.0.

RESULTS

BASELINE CHARACTERISTICS OF THE SAMPLE

Most of the sample consisted of female (86.7%), Caucasian (53.3%) patients. There was no significant difference between the BMI of male and female patients at baseline (P = 0.508).

Socio-demographic and anthropometric characteristics, as well as psychiatric diagnoses of the sample in the preoperative period according to family history of alcohol use disorder, are described in Table 1.

LONGITUDINAL ASSESSMENT

Using GEE, the interaction between time and family history of alcohol use disorder (FH) was found to be statistically significant when %EWL and %TWL were considered (Wald chi-square P = 0.037 and 0.042, respectively). This interaction was not significant when BMI was considered (Wald chi-square P = 0.112). As the association between FH and the lifetime diagnosis of major depressive disorder was found to be statistically significant at baseline, the analysis above (GEE) was adjusted for the diagnosis of major depressive disorder, as well as for sex, age, personal history of alcohol use disorder, and binge eating.

The interaction between time and lifetime diagnosis of major depressive disorder, and between time and binge eating were also analyzed by means of the GEE and were found to be not significant, regardless of the weight loss parameter considered (EWL, TWL or BMI). The small sample size precluded the evaluation of the interaction between time and personal history of alcohol use disorder by the GEE.

Comparison of weight loss between family history groups

In the post-hoc analysis, comparing the weight loss between FH groups, we have found that patients with a positive FH presented EWL 11.1%, 15.4%, 13.7% and 18.4% lower at T2, T3, T4 and T5, respectively (P = 0.016, 0.013, 0.034 and 0.027, respectively); and TWL 5.9% lower at T3 (P = 0.028). These data are presented in Table 2.

Comparison of weight loss between follow-up times

Patients with a negative FH significantly lost weight from T0 to T3 regardless of the weight loss parameter considered (%EWL or %TWL; P <0.001 for all comparisons between times). From T3 to T5, however, their weight loss was not significant.

Patients with a positive FH presented a significant weight loss from T0 to T2 (%EWL or %TWL; P <0.001 for all comparisons between times), but in the comparison between T2 and T5 their weight change was not significant (Figure 2).

DISCUSSION

We have found that a positive family history of alcohol use disorder was associated with significantly lower weight loss at 2 years of follow-up after the Roux-en-Y gastric bypass.

More specifically, patients with a positive family history presented an earlier cessation of weight loss, and at 2 years of follow-up, their EWL was 18.4% lower when compared to patients with a negative family history, independent of a personal history of alcohol use disorder or binge eating.

Obesity and drug addiction appear to share some behavioral characteristics, and it has been found that neurobiological pathways classically involved in the pathophysiology of drug addiction have also played an important role in the regulation of eating behavior (17). Therefore, it has been proposed that similar disruptions of these pathways, especially on the brain reward system, could contribute to the development of obesity and drug addiction, through dysfunctional responses to food and drug reinforcers (10,17,18).

In common forms of obesity, the overconsumption of palatable food is a characteristic usually present, however not necessarily characterizing a binge eating disorder. Similarly to addictive drugs, certain foods, particularly those rich in sugar and fat, have powerful rewarding effects, and the ability to induce learned associations, mediated mostly by dopamine increases in the reward system (10). For vulnerable individuals, the repeated exposure to highly palatable food or addictive drugs is believed to lead to similar neuroadaptive responses in the reward system and in the neuronal systems modulated by it (18,19), resulting in imbalances between circuits that motivate behavior and the ones responsible for inhibiting pre-potent responses (prefrontal regulatory circuits), ultimately perpetuating dysfunctional patterns of intake (19). Furthermore, impairments on circuits

involved in stress reactivity and interoceptive awareness have also been described in both disorders (19). Taken together, these processes provide a possible explanation concerning how, for some individuals, hedonic aspects of feeding come to prevail over homeostatic mechanisms of satiety, and sometimes even over the voluntary control, contributing to the development of obesity and imposing great obstacles to adherence to nutritional recommendations. Therefore, we might presume that these same processes could influence weight loss after bariatric surgery.

Moreover, a complex interaction between hedonic and homeostatic mechanisms in the regulation of eating behavior has been demonstrated, which could also influence weight outcomes after surgery. In addition to the central pathways connecting the hypothalamus, which is the main structure responsible for the regulation of energy homeostasis, with the reward system, it has been found that some peripheral hormones and peptides involved in the homeostatic regulation, such as ghrelin, leptin and insulin, can also influence feeding behavior by modulating the rewarding properties of food (20), and it has been shown that neurons in ventral tegmental area express receptors for many of these peripheral signals (20,21).

In recent years, the impact of bariatric surgery on this interaction between homeostatic and reward systems has begun to be elucidated. The surgery has been associated with a reduced preference and motivation for sugar and fat (palatable food) consumption (22,23), but at the same time a higher susceptibility to alcohol abuse has been observed at the postoperative period (24–27), findings somehow paradoxical, since they seem to account for a differential response to food and drug reinforcers. Besides that, the surgery seems to influence the availability of μ-opioid and D2R receptors in the reward system (28–30), and can modify the secretion of a number of gastrointestinal and adipose related peptides, some of which have been found to interact with the reward system. Recent evidence has indicated that some of the

peripheral signals influenced by bariatric surgery, such as ghrelin, besides influencing eating behavior through homeostatic pathways and modulating the rewarding properties of food, can also modulate the rewarding effects of addictive drugs (10), findings that could contribute to the understanding of the relationship between obesity, drug addiction and bariatric surgery.

Interestingly, our results show that a positive family history of alcohol use disorder seems to specifically influence surgery-induced weight loss, and not weight at baseline in our population. Although the mechanisms that could explain this differential influence are yet to be elucidated, it seems to account for a complex interaction between surgery-induced modifications in the regulation of energy homeostasis and individual neurobiological vulnerabilities, most probably in the brain reward system.

Furthermore, it has been found at the preoperative evaluation, a significant association between family history of alcohol use disorder and the lifetime diagnosis of major depressive disorder, which is in accordance with previous studies that have shown increased levels of depression in adult children of alcoholic parents (31). The relation between both obesity and alcoholism with major depressive disorder is, however, complex and multifactorial, and a more comprehensive approach of these interrelations is beyond the scope of this work.

These are, however, preliminary findings, that require replication in larger and independent cohorts. The prospective design of the study favors our results, although limitations such as the small sample size, the possibility of confounding due to unmeasured variables, the lack of replication of data, the lack of evaluation of patterns of food and alcohol intake at the postoperative period, and the rates of loss to follow-up preclude a more definite conclusion. Additionally, a longer follow-up period would be relevant to evaluate the impact of a positive family history of alcohol use disorder on the long-term outcomes of the surgery.

CONCLUSIONS

We might hypothesize, thus, that bariatric surgery can interact with individual characteristics, more specifically with a neurobiological vulnerability in neural systems that regulate reward and self-control, and which is believed to be present in a subset of patients with obesity as well as in drug addiction, leading to different weight loss outcomes. Moreover, our findings, if confirmed by additional research, indicate that bariatric surgery candidates possessing a first degree relative with alcohol use disorder might benefit from a more individualized approach in the pre and postoperative periods in order to ensure satisfactory weight loss after surgery, even in the absence of a diagnosis of binge eating disorder.

It would be interesting, in future studies, to evaluate the impact of dysfunction in systems related to reward and self-control on the variability of weight loss after bariatric surgery utilizing more direct neurobiological markers. The identification of potential predictors of success after surgery would enable the development of interventions to improve outcomes.

DISCLOSURE:

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Table 1. Baseline characteristics of the sample according to Family History of Alcohol Use Disorder

Parameters	Family History - (n = 28)	Family History + (n = 17)	*P* value
Age (years)			
Mean ± SD	40.36 ± 10.05	45.18 ± 9.64	0.121
Sex, n (%)			
Female	25 (89.3%)	14 (82.4%)	0.658
Male	3 (10.7%)	3 (17.6%)	
Ethnicity, n (%)			
White	17 (60.7%)	7 (41.2%)	0.334
Non-white	11 (39.3%)	10 (58.8%)	
Marital Status, n (%)			
Unmarried, widowed or divorced	12 (42.9%)	6 (35.3%)	0.851
Married	16 (57.1%)	11 (64.7%)	
Occupational Status, n (%)			
Without paid employment	14 (50.0%)	10 (58.8%)	0.789
With paid employment	14 (50.0%)	7 (41.2%)	
Education (completed years of study)			
Mean ± SD	10.36 ± 3.82	8.00 ± 4.11	0.058
BMI (Kg/m2)			
Mean ± SD	47.13 ± 5.75	49.15 ± 7.98	0.373
Excess Body Weight [a] (Kg)			
Mean ± SD	59.32 ± 13.72	62.74 ± 24.23	0.599
Major Depressive Disorder			
No	22 (78.6%)	6 (35.3%)	0.010
Yes	6 (21.4%)	11 (64.7%)	
Anxiety Disorders			
No	19 (67.9%)	7 (41.2%)	0.148
Yes	9 (32.1%)	10 (58.8%)	
Substance Use Disorders			
No	27 (96.4%)	14 (82.4%)	0.144
Yes	1 (3.6%)	3 (17.6%)	
Bulimia + Binge Eating Disorder			
No	24 (85.7%)	11 (64.7%)	0.143
Yes	4 (14.3%)	6 (35.3%)	

a. Excess weight was taken as the weight in kilograms above the weight at BMI of 24.9 kg/m2; n, number of subjects; SD, standard deviation; BMI, body mass index. Psychiatric disorders are described as lifetime prevalence.

Table 2. Postoperative weight loss according to family history of alcohol use disorder

Time	%EWL			%TWL		
	Mean (SE)	95% CI	*P*value†	Mean (SE)	95% CI	*P*value†
T1						
FH -	33.5 (6.3)	21.2 - 45.8	0.777	12.8 (2.4)	8.1 - 17.5	0.420
FH +	32.6 (5.5)	21.9 - 43.3		14.0 (2.2)	9.6 - 18.4	
T2						
FH -	63.5 (6.6)	50.6 - 76.4	0.016	26.3 (2.5)	21.3 - 31.3	0.299
FH +	52.4 (6.7)	39.3 - 65.6		24.0 (2.9)	18.2 - 29.7	
T3						
FH -	79.1 (6.9)	65.6 - 92.5	0.013	34.2 (2.7)	28.9 - 39.5	0,028
FH +	63.7 (9.0)	46.1 - 81.2		28.3 (3.4)	21.6 - 34.9	
T4						
FH -	81.6 (6.9)	68.1 - 95.1	0.034	35.3 (2.8)	29.7 - 40.9	0.099
FH +	67.9 (9.0)	50.3 - 85.5		30.3 (3.5)	23.5 - 37.1	
T5						
FH -	82.5 (6.8)	69.2 - 95.9	0.027	35.2 (2.8)	29.6 - 40.7	0.160
FH +	64.1 (9.2)	46.1 - 82.1		29.0 (4.0)	21.1 - 37.0	

Pairwise comparison of estimated marginal means of %EWL and %TWL between family history groups. Post hoc test: Bonferroni. †Bonferroni-adjusted p-values. Statistical significance was set at $P \leq 0.05$. FH -, negative family history of alcohol use disorder; FH +, positive family history of alcohol use disorder. T0: preoperative evaluation (n = 45); T1: 1-3 months after surgery (n = 45); T2: 6-8 months after surgery (n = 38); T3: 12-14 months after surgery (n = 36); T4: 18-20 months after surgery (n = 35); T5: 24-26 months after surgery (n = 31). %EWL, percentage of excess weight loss; %TWL, percentage of total weight loss; SE, standard error.

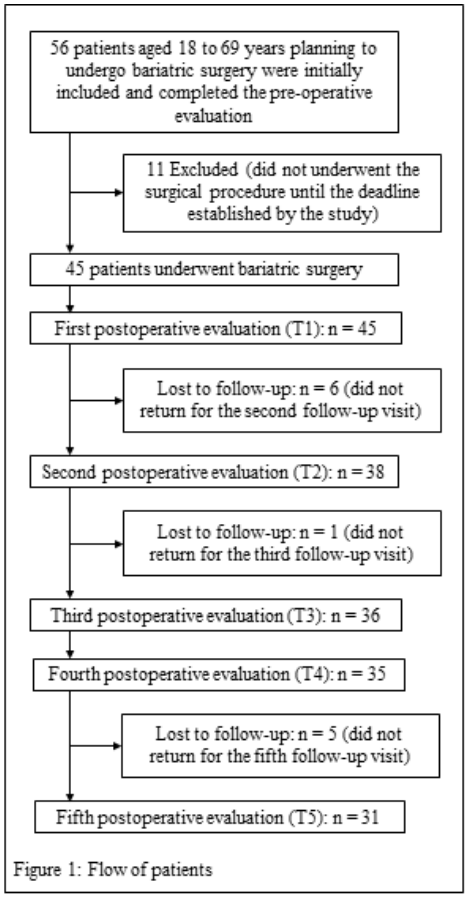


Figure 1: Flow of patients

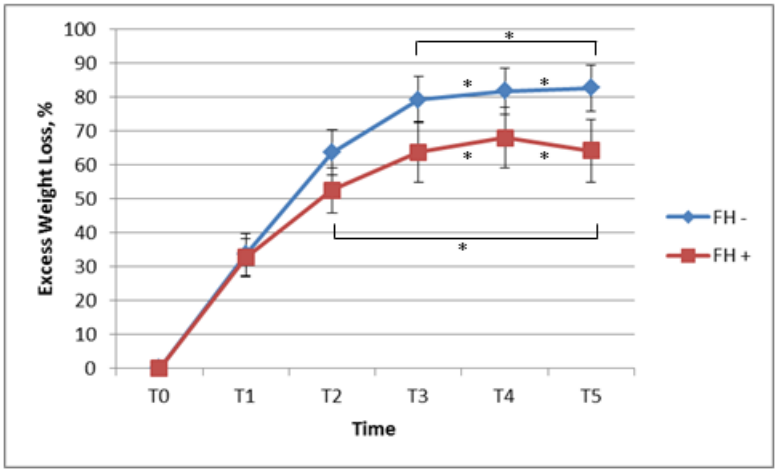


Figure 2A

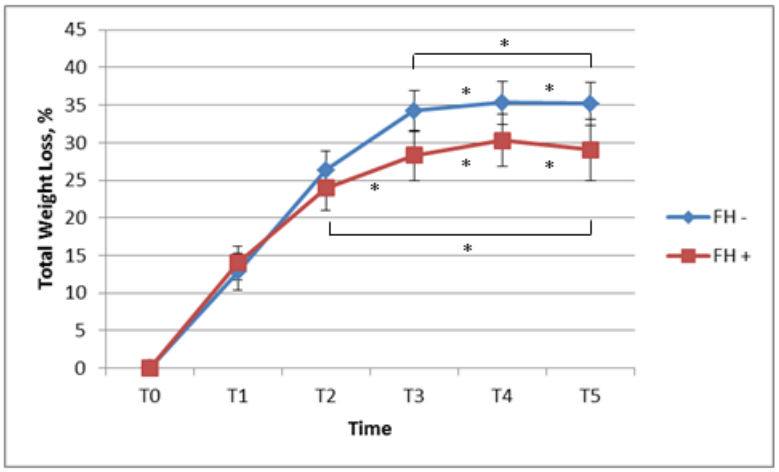


Figure 2B

Figure 2 (A and B): Pairwise comparison of estimated marginal means of excess weight loss and total weight loss between follow-up times. Post-hoc test: Bonferroni. Statistical significance was set at $p \leq 0.05$. T0: preoperative evaluation (n = 45). T1: 1-3 months after surgery (n = 45); T2: 6-8 months after surgery (n = 38); T3: 12-14 months after surgery (n = 36); T4: 18-20 months after surgery (n = 35); T5: 24-26 months after surgery (n = 31). FH -, negative family history of alcohol use disorder; FH +, positive family history of alcohol use disorder. * Non-significant weight loss between times of follow-up. P<0.05 for all other comparisons between times.

3.2 Artigo 2

The FKBP5 polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up.

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The *FKBP5* polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up.

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ABSTRACT:

BACKGROUND: Bariatric surgery is the most effective treatment choice for severe obesity. Recent literature indicates that FK506-binding protein 51 (FKBP51) could play a role in energy homeostasis, influencing adipogenesis and body weight.

OBJECTIVE: To evaluate if the presence of the T allele of the *FKBP5* SNP rs1360780, associated with increased FKBP51 expression, could influence weight loss after bariatric surgery.

SETTING: Hospital de Clínicas de Porto Alegre, Brazil.

METHODS: 42 patients awaiting bariatric surgery were included, and the presence of the *FKBP5* rs1360780 polymorphism was evaluated. During the postoperative period, a 26-month follow-up of weight loss was performed (n = 42, 36, 35, 35 and 30, from the first to fifth postoperative evaluation, respectively. Loss to follow-up: 28.6%).

RESULTS: Carriers of the T allele presented significantly lower weight loss when compared to patients with the C/C genotype after the 12^{th}-14^{th} month follow-up period. Differences in weight loss between genotypes ranged from 14.2% to 19.9% of excess weight loss (P = 0.045 and 0.004, respectively), and from 7.6% to 9.0% of total weight loss (P = 0.002 for both comparisons). Besides that, carriers of the T allele also presented an earlier cessation of weight loss after surgery.

CONCLUSIONS: The presence of the T allele of the *FKBP5* SNP rs1360780 was associated with weight loss after bariatric surgery. Bariatric surgery can interact with genes involved in metabolic regulation, leading to different weight loss outcomes.

KEYWORDS: obesity; *FKBP5* SNP rs1360780; bariatric surgery.

INTRODUCTION

Obesity is one of the most challenging public health problems of our times. Its prevalence is increasing worldwide, and has nearly doubled since 1980 (1).

Obesity is a heterogeneous condition (2) resulting from a complex interaction between genes and environmental factors acting throughout an individual's lifetime. The complexity of regulatory mechanisms involved in energy balance contributes to the difficulty faced in characterizing its physiopathology and in developing effective therapeutic choices.

Bariatric surgery is the most effective treatment choice for severe obesity, leading to expressive weight loss that is usually sustained in the long term (3–6). In addition, it is associated to the improvement of obesity-related comorbidities (4,5), and to a long-term reduction in overall mortality (6,7).

Despite its proven efficacy and generally low mortality rates (0,08% - 0,35%) (4), not all patients have similar weight loss following surgery. The possibility that this difference in weight outcomes could be attributed to pre-operative clinical, psychological and behavioral factors has been considered. However, up until now, the existing literature about potential predictors of success after bariatric surgery is not conclusive, and few studies have evaluated the influence of genetic characteristics on its outcome.

In this context, recent literature indicate that FK506-binding protein 51 (FKBP51), encoded by the *FKBP5* gene, could play a role in energy homeostasis (8), and even be considered a potential new drug target in the treatment of obesity and related disorders (9). FKBP51 is expressed both centrally and at peripheral tissues (10,11), and its highest expression has been observed in metabolically active tissues, such as muscle and the adipose tissue (10). The mechanisms by which FKBP51 can interfere in body weight and adipogenesis, and whether this action is predominantly central or peripheral, however, are

questions yet to be answered. FKBP51 seems to be an important regulator of cellular adipogenesis, necessary for the complete transformation of preadipocytes into mature adipocytes, and *FKBP5* knockout has been shown to be associated with reduced expression of lipogenic genes (9).

Evidence from experimental studies has indicated that expression levels of *FKBP5* gene could be associated with body weight. Specifically, *Fkbp5* knockout mice seem to have lower body weight compared to wild-type animals under basal conditions (12) and to be resistant to weight gain when subjected to a high fat diet (13), while a higher hypothalamic expression of FKBP5 has been associated with increased body weight gain (8,14).

Common single nucleotide polymorphisms (SNPs) at the *FKBP5*gene have been identified in humans. Specifically, the T allele of the SNP rs1360780 is known to be associated with increased FKBP51 expression (high-induction allele) (15). However, it is not known whether the SNP-induced increased expression of FKBP51 could interfere in body weight in humans, and particularly in weight loss after bariatric surgery. Therefore, the objective of this study is to evaluate if this SNP, known to increase the expression levels of FKBP5, could influence the outcome of bariatric surgery.

MATERIALS AND METHODS

Participants:

In this prospective observational study, patients between 18 and 69 years of age, who presented a body mass index (BMI) of at least 35 kg/m2 and who were awaiting bariatric surgery at Hospital de Clínicas de Porto Alegre were recruited from June 2011 to March 2013. All enrolled participants had already undergone the routine preoperative evaluation carried out by an assistant care team, having their surgery approval process concluded. Exclusion criteria were the presence of current suicide risk, indication of psychiatric hospitalization and diagnosis of intellectual disability or dementia. Of the 56 patients initially included, 42 underwent the surgical procedure by the deadline established for the study. Data regarding these 42 participants will be presented (Figure 1).

Procedures:

In the preoperative period, patients were evaluated through the application of a research protocol. The surgical procedure was then carried out according to the indication of the assistant team. In all cases the surgical technique employed was the Roux-en-Y gastric bypass.

At the postoperative period, a follow-up of weight loss was performed using data from medical records. The postoperative period was divided as follows: T1: 1st-3rd month after surgery; T2: 6th-8th month after surgery; T3: 12th-14th month after surgery; T4: 18th-20th month after surgery; and T5: 24th-26th month after surgery.

Psychiatric and socio-demographic assessments:

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for the diagnosis of Axis I psychiatric disorders.

Anthropometric assessment:

Measurements of weight and height were obtained from medical records. All other calculations were performed using the Statistical Package for the Social Sciences (SPSS), version 20.0.

The preoperative measurements of weight and height included were the ones recorded at hospital admission for the surgical procedure. In the postoperative period, when more than one measurement of weight was available within the specified periods of the study (T1 to T5), the most recent one was selected.

Body mass index (BMI) was calculated according to the formula: weight (kg)/[height (m)]^2. The percentage of excess weight loss (%EWL) was calculated as: [(weight loss/excess weight) X100], and excess weight was taken as the weight in kilograms above the weight corresponding to the BMI of 24.9 kg/m2.

Laboratory analysis:

Genomic DNA was extracted using the illustra blood genomicPrep Mini Spin Kit (GE Healthcare). Genotyping of the *FKBP5* rs1360780 polymorphism was performed using a 5'nuclease TaqMan® allelic discrimination assay (C_8852038_10) on the Applied Biosystems 7500 Real-Time PCR System (Applied Biosystems).

Ethics:

The study followed the conditions established in Resolution 196/96 of the National Health Council and was submitted to the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre. All patients signed a Written Informed Consent.

Statistical analysis:

Continuous data were expressed as means and standard deviation, and were analyzed using the Student t-test. Categorical variables were expressed as number of subjects and percentages and compared using the χ^2 test. Some psychiatric disorders were grouped in broad categories (e.g. any anxiety disorder). %EWL, BMI and percentage of total weight loss (%TWL) after bariatric surgery were examined by means of generalized estimating equations model (GEE) using all available observations. Loss to follow-up is described in figure 1. The factors used in the model were: time, genotype, and interaction time*genotype, adjusted for sex, ethnicity and age. The Bonferroni test was utilized for all post hoc comparisons. In all experiments, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 20.0.

RESULTS

BASELINE CHARACTERISTICS OF THE SAMPLE

Most of the sample consisted of female patients (88.1%), caucasian (52.4%). There was no significant difference between the BMI of men and women at baseline (P = 0.344).

Socio-demographic and anthropometric characteristics, as well as psychiatric diagnoses of the sample in the preoperative period according to the *FKBP5* genotype are described in Table 1. There was no significant difference between groups at baseline regarding the parameters evaluated.

LONGITUDINAL ASSESSMENT

Using GEE, the interaction between time and *FKBP5* genotype was found to be statistically significant (Wald chi-square P = 0.001; 0.004 and 0.008 for %EWL, %TWL and BMI, respectively).

Comparison of weight loss between genotypes

In the post-hoc analysis, comparing the weight loss between genotypes, we found that carriers of the T allele presented EWL 14.2%, 19.8% and 19.9% lower at T3, T4 and T5, respectively (P = 0.045, 0.001 and 0.004, respectively); TWL 7.6% and 9.0% lower at T4 and T5, respectively (P = 0.002 for both comparisons); and BMI 4.1 Kg/m2 higher at T4 (P = 0.013). These data are presented in Table 2.

Comparison of weight loss between follow-up times

Patients with the C/C genotype significantly lost weight from T0 to T3 regardless of the weight loss parameter considered (%EWL, %TWL or BMI; P <0.001 for all comparisons between times). From T3 to T5, however, their weight loss was no longer significant.

Carriers of the T allele presented a significant weight loss from T0 to T2 (P <0.001 for all comparisons), and no significant differences from T2 to T5 when %EWL and BMI were considered. Regarding %TWL, they presented a significant weight loss from T0 to T3 (P < 0.05 for all comparisons between times) and no significant differences from T3 to T5. Their %TWL at T5, however, was not significantly different from T2 (Figure 2).

DISCUSSION

We have shown that the presence of the T allele of the FKBP5 SNP rs1360780, known to be related to an increased expression of this gene, was associated with weight loss after bariatric surgery.

Carriers of the T allele presented significantly lower weight loss when compared to patients with the C/C genotype after the 12th-14th month follow-up period, as well as an earlier cessation of weight loss after bariatric surgery. These differences in weight loss between genotypes, which ranged from 14.2% to 19.9% of EWL, and from 7.6% to 9.0% of TWL, might be relevant to the evaluation of therapeutic success after surgery. These are, however, preliminary findings, and require replication in larger and independent cohorts.

It is important to note that no differences were observed in the BMI of these patients at baseline, which is in accordance with the findings of Pereira et al, who observed that individuals with higher endogenous *FKBP5* gene expression in adipose tissue did not differ in obesity measures from individuals with lower *FKBP5* gene expression (10).

In the last few decades, adipose tissue has been recognized as an endocrine organ which acts as an important regulator of energy homeostasis, interacting through many different pathways with peripheral tissues and the central nervous system (CNS) (16–18), and whose dysfunction, as seen in obesity, has been implicated in the physiopathology of a variety of diseases. A possible role of *FKBP5* in adipogenesis has been considered since the description of this gene by Yeh and colleagues (19). In fact, it is known that FKBP51 can interact with at least three different nuclear receptors known to be involved in the metabolism of adipocytes: glucocorticoid receptor (GR), mineralocorticoid receptor (MR), and the peroxisome proliferator–activated receptor-γ (PPAR-γ).

Specifically, by interacting with the PPARγ-Hps90 heterocomplex, FKBP51 fully activates the receptor and leads to the modulation of Akt, which plays a central role in insulin-

stimulated glucose uptake in both muscle and adipose tissue (20). Moreover, FKBP51 is a negative regulator of GR (21), and cortisol induces the expression of FKBP51 by acting through GR (15). This interaction seems to be relevant, since it has been suggested that obesity could be associated with subtle alterations in cortisol dynamics, suggestive of long-term over-activation of the hypothalamus-pituitary-adrenal (HPA) axis (22), and with an increased local production of cortisol in the adipose tissue induced by the 11-beta-hydroxysteroid dehydroxygenase type 1 (11β-HSD1) enzyme (22).

Furthermore, *FKBP5* SNPs associated with higher FKBP51 levels, as rs1360780, are supposed to influence HPA axis functioning, since they lead to GR resistance and consequently, to impaired negative feedback of the HPA axis (15). Thus, we could hypothesize that the HPA axis alterations observed in obesity could somehow be linked to FKBP5 expression levels and genotype, however this has yet to be investigated.

Besides FKBP5's possible actions in HPA axis regulation and its direct effects in the adipose tissue regulation, the interaction of this gene with bariatric surgery and related metabolic alterations must also be considered. The procedures currently employed in bariatric surgeries promote the restriction of food intake or restriction plus malabsorption of nutrients. The metabolic changes associated to the surgery, however, are far more complex than those which could be attributed to food restriction and malabsorption alone (3). The mechanisms underlying these metabolic changes are yet to be fully explored, but alterations in gut peptides secretion and their interactions with CNS and peripheral tissues, among others, are some of the already described mechanisms attributed to the surgery (23). Recent evidence also indicates that bariatric surgery could influence HPA axis functioning, reducing its activity, and also may influence the activity of 11β-HSD1 (24).

Interestingly, our results show that the *FKBP5* genotype seems to specifically influence surgery-induced weight loss, and not body weight at baseline in our population. This seems to

account for an interesting gene *vs*. environment interaction, in which the effect of the gene only becomes apparent after a specific trigger.

Limitations of our study include the small sample size, the possibility of confounding due to unmeasured variables, the lack of replication of data, and the relatively high rates of loss to follow-up, in addition to the lack of measurement of FKBP5 levels in the same sample and the limited genetic approach. A larger sample size would allow a genome-wide association of these measures, likely identifying other relevant polymorphisms that may interact with surgery outcomes, as well. Additionally, a longer follow-up period would be relevant to evaluate the impact of this polymorphism on the long-term outcomes of the surgery.

CONCLUSIONS

We might hypothesize, though, that bariatric surgery can interact with individual genetic characteristics, especially with genes involved in metabolic regulation, leading to different metabolic and weight loss outcomes. Our results point in this direction, although they still need to be confirmed. The prospective design of the study, the use of standardized instruments, and the assessment of a relevant stress- and metabolism-related genetic marker favor our results, even though the small size of the sample precludes a more definite conclusion.

It would be interesting in the future to better elucidate the mechanisms underlying *FKBP5* influence on body weight and metabolism, and also to investigate the impact of the interaction between expression levels of FKBP5 and chronic stress exposure on body weight and on the outcomes of bariatric surgery, since chronic stress exposure seems to be related to weight gain and alterations of HPA axis functioning(25), and since *FKBP5* is known for its capacity to interact with environmental stimuli such as psychological trauma and stress(15). The identification of potential predictors of success after bariatric surgery would enable the development of interventions to improve outcomes.

CONFLICTS OF INTEREST: Dr. Kauer-Sant'Anna is on speaker/advisory boards for, or has received research grants from NARSAD, Stanley Medical Research Institute, CNPq-Universal, CNPq/INCT-TM, FIPE-HCPA and Novartis. Dr. von Diemen has received research grants from CNPq-Universal and FIPE-HCPA. The other authors declare no conflict of interest.

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Table 1. Baseline characteristics of the sample according to *FKBP5* genotype

Parameters	C/C (n = 18)	C/T or T/T (n = 24)	*P* value
Age (years)			
Mean ± SD	41.1 ± 10.6	43.4 ± 10.1	0.475
Sex, n (%)			
Male	0 (0.0%)	5 (20.8%)	0.060
Female	18 (100.0%)	19 (79.2%)	
Ethnicity, n (%)			
White	9 (50.0%)	13 (54.2%)	> 0.999
Non-white	9 (50.0%)	11 (45.8%)	
Marital Status, n (%)			
Unmarried, widowed or divorced	7 (38.9%)	10 (41.7%)	> 0.999
Married	11 (61.1%)	14 (58.3%)	
Occupational Status, n (%)			
Without paid employment	10 (55.6%)	13 (54.2%)	> 0.999
With paid employment	8 (44.4%)	11 (45.8%)	
Education (completed years of study)			
Mean ± SD	9.06 ± 4.30	9.92 ± 4.09	0.513
BMI (Kg/m2)			
Mean ± SD	48.2 ± 8.4	47.7 ± 5.6	0.833
Excess Body Weight [a] (Kg)			
Mean ± SD	59.1 ± 19.6	61.7 ± 18.7	0.664
Major Depressive Disorder			
No	11 (61.1%)	15 (62.5%)	> 0.999
Yes	7 (38.9%)	9 (37.5%)	
Anxiety Disorders			
No	11 (61.1%)	13 (54.2%)	0.893
Yes	7 (38.9%)	11 (45.8%)	
Substance Use Disorders			
No	17 (94.4%)	21 (87.5%)	0.623
Yes	1 (5.6%)	3 (12.5%)	
Bulimia + Binge Eating Disorder			
No	13 (72.2%)	19 (79.2%)	0.720
Yes	5 (27.8%)	5 (20.8%)	

a. Excess weight was taken as the weight in kilograms above the weight at BMI of 24.9 kg/m2; n, number of subjects; SD, standard deviation; BMI, body mass index. Psychiatric disorders are described as lifetime prevalence.

Table 2. Postoperative weight loss according to *FKBP5* genotype

Time	%EWL			%TWL			BMI		
	Mean (SD)	95% CI	*P* value†	Mean (SD)	95% CI	*P* value†	Mean (SD)	95% CI	*P* value†
T1									
C/C	29.2 (4.5)	20.5 - 38.0	0.627	12.9 (1.7)	9.5 - 16.3	0.974	42.5 (2.4)	37.7 - 47.2	0.925
C/T or T/T	27.1 (1.7)	23.7 - 30.5		12.8 (0.9)	11.0 - 14.6		42.3 (1.3)	39.8 - 44.7	
T2									
C/C	55.5 (5.5)	44.7 - 66.2	0.818	25.0 (2.1)	20.9 - 29.0	0.913	36.9 (2.4)	32.1 - 41.7	0.777
C/T or T/T	54.0 (3.4)	47.4 - 60.7		25.2 (1.5)	22.2 - 28.2		36.2 (1.3)	33.8 - 38.7	
T3									
C/C	74.9 (5.9)	63.3 - 86.5	0.045	33.8 (2.2)	29.5 - 38.1	0.080	32.5 (2.2)	28.1 - 36.9	0.291
C/T or T/T	60.7 (4.5)	52.0 - 69.5		29.1 (2.1)	25.0 - 33.2		34.9 (1.3)	32.3 - 37.5	
T4									
C/C	82.8 (4.4)	74.1 - 91.4	0.001	37.4 (1.9)	33.7 - 41.1	0.002	30.1 (1.7)	26.8 - 33.5	0.013
C/T or T/T	62.9 (4.3)	54.4 - 71.4		29.9 (2.1)	25.8 - 33.9		34.2 (1.3)	31.7 - 36.7	
T5									
C/C	82.3 (4.5)	73.5 - 91.1	0.004	37.7 (2.1)	33.6 - 41.7	0.002	30.3 (1.8)	26.9 - 33.8	0.059
C/T or T/T	62.4 (5.1)	52.5 - 72.3		28.7 (2,3)	24.2 - 33.1		33.8 (1.4)	31.1 - 36.5	

Pairwise comparison of estimated marginal means of %EWL, %TWL and BMI between genotypes. Post hoc test: Bonferroni. †Bonferroni-adjusted *p*-values. Statistical significance was set at $p \leq 0.05$. C/C, C/T and T/T: *FKBP5* genotypes. T0: preoperative evaluation (n = 42); T1: 1st -3rd month after surgery (n = 42); T2: 6th-8th month after surgery (n = 36); T3: 12th-14th month after surgery (n = 35); T4: 18th-20th month after surgery (n = 35); T5: 24th-26th month after surgery (n = 30). %EWL, percentage of excess weight loss; %TWL, percentage of total weight loss; BMI, body mass index; SD, standard deviation.

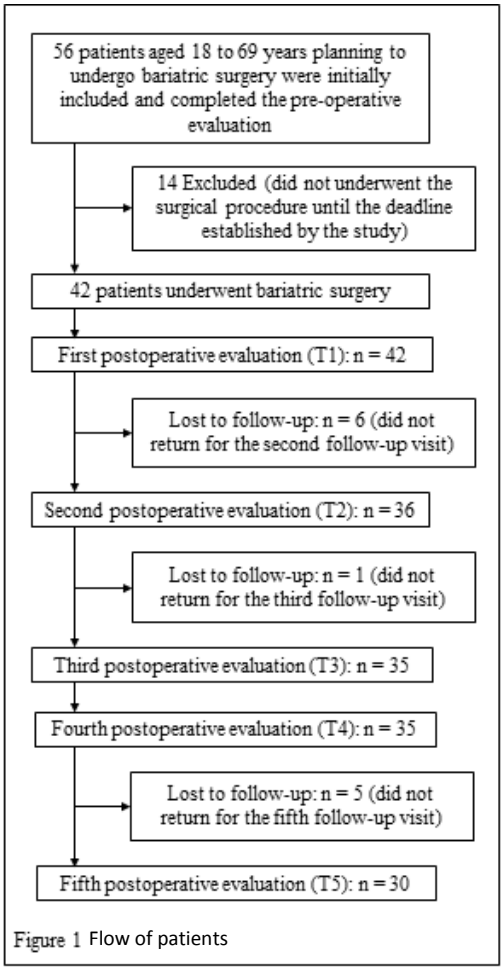


Figure 1 Flow of patients

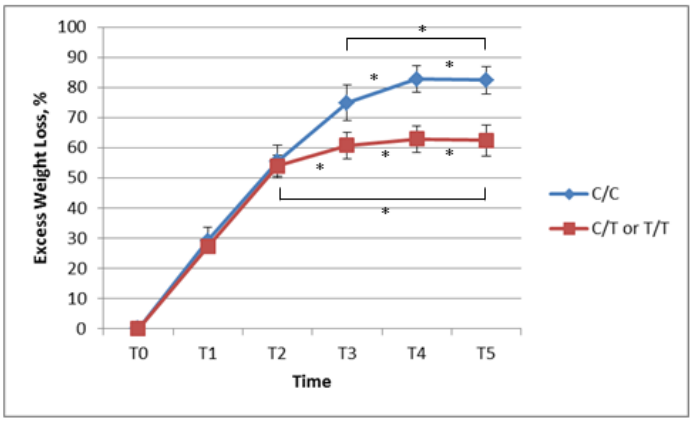


Figure 2A

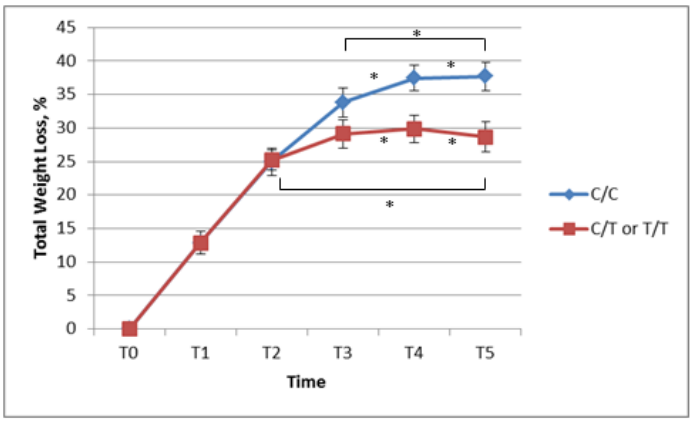


Figure 2B

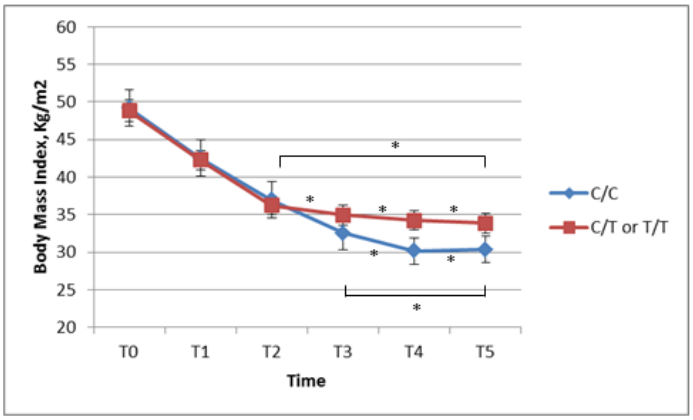


Figure 2C

Figure 2 (A, B and C): Pairwise comparison of estimated marginal means of excess weight loss, total weight loss and body mass index between times of follow-up. Post-hoc test: Bonferroni. T0: preoperative evaluation (n = 42). T1: 1st-3rd month after surgery (n = 42); T2: 6th-8th month after surgery (n = 36); T3: 12th-14th month after surgery (n = 35); T4: 18th-20th month after surgery (n = 35); T5: 24th-26th month after surgery (n = 30). C/C, C/T and T/T: *FKBP5* genotypes. * Non-significant weight loss between times of follow-up. P<0.05 for all other comparisons between times

PARTE III

4. CONCLUSÕES E CONSIDERAÇÕES FINAIS

O conhecimento acumulado até o momento a respeito da fisiopatologia da obesidade sugere que o rápido aumento do número de casos observado nas últimas décadas se deva, em parte, a um descompasso entre os mecanismos neurobiológicos que determinam a ingesta em nossa espécie, e a riqueza e diversidade da oferta de alimentos presente nas sociedades atuais.

O reconhecimento de que vias centrais classicamente envolvidas na fisiopatologia da adição exercem importante papel na regulação da ingesta, e a recente observação de um padrão semelhante de neuroadaptações nestas vias em pacientes obesos e dependentes químicos, fornecem uma possível explicação para a grande dificuldade enfrentada por alguns indivíduos em abster-se do consumo de determinados alimentos, mesmo depois de supridas suas necessidades energéticas, e mesmo quando cientes dos prejuízos que o consumo excessivo poderá acarretar.

Os resultados do primeiro artigo desta tese mostram que a história familiar positiva para transtorno por uso de álcool em familiares de primeiro grau está associada a menor perda de peso após a cirurgia bariátrica, independente da presença de história pessoal de compulsão alimentar ou de transtorno por uso de álcool. Estes achados reforçam a hipótese de que obesidade e dependência química compartilham alguns aspectos de sua fisiopatologia, sobretudo uma possível disfunção de vias centrais implicadas na interação do indivíduo com estímulos recompensadores, e corroboram ainda a existência de uma vulnerabilidade biológica comum para o desenvolvimento de ambas as patologias. Os achados deste estudo sugerem ainda, caso venham a ser confirmados por pesquisas adicionais, que candidatos ao procedimento cirúrgico que apresentem história familiar positiva de transtornos por uso de

álcool poderiam se beneficiar de uma abordagem terapêutica individualizada nos períodos pré e pós-operatório, visando melhores resultados de perda de peso.

Outro aspecto relevante na compreensão da fisiopatologia da obesidade é a influência de fatores genéticos, e sua interação com fatores ambientais. Sabe-se que fatores genéticos são capazes de influenciar, de modo mais ou menos sutil, aspectos tão diversos da regulação do balanço energético quanto a preferência por determinados tipos de alimentos, a saciedade, e o gasto energético (22,23). Além disso, influenciam outros processos potencialmente relevantes para o desenvolvimento da obesidade, como a regulação da resposta ao estresse.

Os achados do segundo artigo desta tese mostram que a presença do alelo T do SNP rs1360780 do gene *FKBP5* está associada a menor perda de peso após a cirurgia bariátrica. Sabe-se que a presença deste alelo está associada à expressão aumentada da FKBP51, uma proteína com conhecido envolvimento na regulação da resposta ao estresse, e que recentemente vem tendo seu papel na regulação do balanço energético investigado. Embora os mecanismos envolvidos na interação entre este polimorfismo do *FKBP5* e a cirurgia bariátrica ainda necessitem de elucidação, estes achados corroboram a importância da interação gene-ambiente na regulação do peso corporal, se consideradas as diversas alterações no ambiente hormonal e nutricional induzidas pelo procedimento cirúrgico. Embora em nossa amostra a presença de trauma precoce, avaliada através da escala *Childhood Trauma Questionnaire* (CTQ), não tenha influenciado a perda de peso após a cirurgia bariátrica, e não tenha sido possível, em função do pequeno tamanho amostral, avaliar o impacto da interação entre trauma e o SNP rs1360780 do gene *FKBP5* sobre a perda de peso induzida pela cirurgia, seria relevante, no futuro, a avaliação desta interação.

Além do exposto, não podemos deixar de considerar que os mecanismos responsáveis pela regulação do balanço energético, disfuncionais ou não, estão em constante interação, e

que estes sistemas de controle são imensamente complexos e muitas vezes redundantes. Consequentemente, qualquer estratégia terapêutica empregada - modificações na dieta, no nível de atividade física, intervenções farmacológicas ou cirúrgicas - desencadeará, invariavelmente, em maior ou menor grau, respostas compensatórias que influenciarão todo o resto do sistema regulatório. Estas respostas compensatórias serão mais ou menos favoráveis, no sentido de facilitar ou dificultar a redução de peso, de acordo com o tipo de intervenção utilizada, e com o emprego de uma intervenção isolada ou de uma associação de estratégias.

Deste modo, o aspecto mais relevante no estudo da obesidade talvez seja compreender que se trata de uma patologia amplamente heterogênea, e com uma enorme variedade de possíveis determinantes. Neste sentido, o fato de a cirurgia bariátrica se mostrar efetiva no tratamento da maioria dos indivíduos afetados pela obesidade grave, independente, em grande parte, destes determinantes, a torna uma ferramenta de extrema importância no tratamento desta patologia. A busca pela identificação dos fatores que influenciam o prognóstico cirúrgico contribuirá para uma melhor compreensão dos mecanismos implicados no desenvolvimento da obesidade e, talvez, para o desenvolvimento de novas estratégias terapêuticas no futuro.

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ANEXOS

Anexo 1: E-mail encaminhado pela revista *Surgery for Obesity and Related Diseases,* aceitando o artigo "*The FKBP5 polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up"* para publicação.

From: SOARD <Obesity@Stellarmed.com>
Date: April 17, 2016 at 12:03:19 GMT-3
To: marciaks.lab@gmail.com, marciaks@terra.com.br
Subject: SOARD-15-543R3 - Final Decision

Ms. No.: SOARD-15-543R3
Title: The FKBP5 polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up.
Corresponding Author: Prof. Marcia Kauer-Sant'Anna
Authors: Ingrid B Hartmann, M.D.; Gabriel R Fries, PhD; Joana Bücker, PhD; Ellen Scotton; Lísia von Diemen, PhD;

Dear Prof. Kauer-Sant'Anna,

We are pleased to inform you that your manuscript referenced above has been accepted for publication in Surgery for Obesity and Related Diseases.

Before your paper is sent to production and you receive your page proofs for reviewing we ask that you and all of your co-authors read and sign the below authorship letter and fax to the editorial office at 508-732-6766 or scan and email it toObesity@Stellarmed.com. Not returning the letter signed by each author will significantly delay your paper's publication in the next available issue.

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Many thanks for submitting your fine paper to Surgery for Obesity and Related Diseases. We look forward to receiving additional papers from you in the future.

With kind regards,

Harvey Sugerman, MD
Editor-in-Chief
Surgery for Obesity and Related Diseases

Anexo 2: E-mail encaminhado pela revista *Obesity Surgery* comprovando a submissão do artigo *"Positive family history of alcohol use disorder is associated with lower weight loss after the Roux-en-Y gastric bypass: 26 months of follow-up".*

Jun 16, 2016

Dear Professor Kauer-Sant'Anna:

We have received your manuscript entitled, "Positive family history of alcohol use disorder is associated with lower weight loss after the Roux-en-Y gastric bypass: 26 months of follow-up".

The submission id is: OBSU-D-16-00466
Please refer to this number in any future correspondence.

All co-authors have received a copy of this letter. If you have received this letter and you are not a co-author of the above manuscript, please promptly notify the Editorial Office.

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Thank you for your interest in Obesity Surgery.

Sincerely,

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