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Seguimento de polineuropatia periférica em obesos graus II e III sem diabetes (homens e mulheres na pré- e pós-menopausa): efeito da cirurgia bariátrica

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Orientadora: Profa. Dra. Helena Schmid

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“O que não me mata me torna mais forte.”

(Friedrich Wilhelm Nietzsche)

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SUMÁRIO

LISTA DE ABREVIATURAS

%PEP: percentual de perda de excesso de peso (do inglês, %EWL, *percentual excess weight loss*)

2-h 75-g OGTT: *two-hour 75-gram oral glucose tolerance test*

ABCA1: *ATP-binding cassette transporter A1*

ABCG1: *ATP-binding cassette transporter GI*

ACSM: *American College of Sports Medicine*

ADAPT: *Activity for Diabetic Polyneuropathy*

AF: Atividade física (do inglês, PA, *physical activity*)

Apo: Apolipoproteína

ASBS: *American Society for Bariatric Surgery*

CAD: *Coronary artery disease*

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CB: Cirurgia bariátrica (do inglês, BS, *bariatric surgery*)

CEC: *Cholesterol efflux capacity*)

CETP: Proteína de transferência de éster de colesterol

CVD: *Cardiovascular disease*

CVR: *Cardiovascular risk*

DBP: *Diasolic blood pressure*

DCCT*: Diabetes Control and Complications Trial*

DHGNA: Doença hepática gordurosa não alcoólica (do inglês, NAFLD, *non-alcoholic fatty liver disease*)

DM1: Diabetes mellitus tipo 1

DM2: Diabetes mellitus tipo 2 (do inglês, T2DM, *type 2 diabetes mellitus*)

DN4: *Douleur Neuropathique en 4 Questions*

ECR: Ensaio clínico randomizado (do inglês, RCT, *randomized controlled trial*)

EW: *Excess weight*

GLP-1: Peptídeo semelhante a glucagon 1

HBA1c: Hemoglobina glicada (do inglês, *glycosylated hemoglobin*)

HDL-C: Lipoproteína de alta densidade (do inglês, *high-density lipoprotein*)

HIV: Vírus da Imunodeficiência Humana (do inglês, *Human Immunodeficiency Virus*)

HR: Hazard Ratio

Hz: Hertz

IC: Intervalo de confiância (do inglês, CI, *confidencial interval*)

ICAM-1: *Intercellular adhesion molecule-1*

IMC: Índice de massa corporal (do inglês, BMI, *body mass index*)

IPAQ: Questionário Internacional de Atividade Física (do inglês, *International Physical Activity Questionnaire*)

FSH: *Follicle-stimulating hormone*

LABS-2: *Longitudinal Assessment of Bariatric Surgery-2*

LCAT: Lecitina colesterol acil-transferase

LDL-C: Lipoproteína de baixa densidade (do inglês, *low-density lipoprotein*)

LILACS: Literatura Latino-americana e do Caribe em Ciências da Saúde

LPL: Lipase lipoprotéica

MET: *Metabolic equivalent of task*

MNSI: Instrumento para Rastreamento de Neuropatia de Michigan (do inglês, *Michigan Neuropathy Screening Instrument*)

MONICA/KORA: *Monitoring Trends and Determinants on Cardiovascular Diseases/ Cooperative Research in the Region of Augsburg*

MrOS: *Osteoporotic Fractures in Men Study*

ND: Neuropatia diabética

NDS: *Neuropathy Deficit Score*

NHANES: *National Health and Nutrition Examination Survey*

NP: Neuropatia periférica

NSS: *Neuropathy Symptom Score*

OMS: Organização Mundial da Saúde (do inglês, WHO, *World Health Organization*)

OR: Odds Ratio

PASE: *Physical Activity Scale for the Elderly*

PLTP: Proteína de transferência de fosfolipídios

PNP: Polineuropatia periférica (do inglês, PPN, *peripheral polyneuropathy*)

PYY: Polipeptídio Y

RCT: Transferência reversa de colesterol

RP: Razão de prevalência (do inglês, PR, *prevalence ratio*)

RR: *Risk ratio*

RYGB: Bypass gástrico em Y de Roux (do inglês, *Roux-en-Y gastric by-pass*)

SAOS: Síndrome da apneia obstrutiva do sono (do inglês, OSAS, *obstructive sleep apnea syndrome*)

SBP: *Systolic blood pressure*

SG: Sleeve gástrico (do inglês, *sleeve gastrectomy*)

SM: Síndrome metabólica

SOS: *Swedish Obese Subjects*

SR-B1: *Scavenger-receptor B1*

STOP-BANG: *Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender*

TC: *Total cholesterol*

TG: *Triglycerides*

TNF: Fator de necrose tumoral

TSH: *Thyroid-stimulating hormone*

VCAM-1: *Vascular cell adhesion molecule-1*

VIGITEL: Vigilância de Doenças Crônicas por Inquérito Telefônico

VLDL: Lipoproteína de muita baixa densidade

WC: *Waist circumference*

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RESUMO

Introdução: A polineuropatia periférica (PNP) têm sido a complicação neurológica mais comum descrita após a cirurgia bariátrica (CB). No entanto, há pouca evidência sobre o impacto da CB na incidência e progressão da PNP.

Objetivos: Avaliar a incidência e a progressão da PNP em indivíduos obesos graves sem diabetes após CB por laparoscopia e identificar fatores de risco.

Métodos: Neste estudo de coorte prospectivo, 322 indivíduos submetidos a CB por laparoscopia, 133 ao bypass gástrico em Y de Roux (RYGB) e 189 ao sleeve gástrico (SG), foram avaliados para PNP pelo Instrumento para Rastreamento de Neuropatia de Michigan (MNSI) antes e após 6 meses da CB e divididos de acordo com a presença (+) ou ausência (–) de PNP no início do estudo. Causas conhecidas da PNP foram excluídas. Secundariamente, uma amostra menor desta coorte foi avaliada para atividade física (AF), através da versão curta do Questionário Internacional de Atividade Física (IPAQ), e para os níveis de HDL-colesterol (HDL-C) antes e após 6 e 15 meses da CB.

Resultados: A prevalência de PNP pré-CB foi de 21,4% e diminuiu para 8,7% pós-CB. Quando olhamos para o grupo PNP (+) (n = 69) no início do estudo, a persistência de PNP pós-CB foi de 20,3% (n = 14) após 6 meses. No grupo PNP (–) (n = 253) pré-operatório, a incidência de PNP pós-CB foi de 5,5% (n = 14) e mostrou-se independentemente associada com menor nível sérico de HDL-C (p = 0,001). O risco de PNP aumentou de 7,4 a 8,6% a cada redução de 1 mg/dL no HDL-C. A AF aumentou após 6 e 15 meses de CB comparado ao período pré-operatório (p < 0,001) e, ser ativo antes da CB foi associado com maior aumento de HDL-C após 15 meses da CB comparado a não ser ativo no pré-operatório (18,2% versus 10,9%; p = 0,035). Como o aumento de HDL-C ocorreu somente após 15 meses da CB e se associou com

o percentual de perda de excesso de peso (%PEP) (p = 0,030), talvez essa incidência de PNP após a CB diminua com maior tempo de acompanhamento.

Conclusão: A prevalência de PNP diminuiu após 6 meses de CB, mas novos casos de PNP pós-CB foram independentemente associados com menores níveis séricos de HDL-C. A AF talvez seja uma importante recomendação para evitar a incidência e progressão da PNP após a CB, uma vez que a prática de AF aumenta os níveis de HDL-C.

Palavras-chave: Polineuropatia periférica; Obesidade; Cirurgia bariátrica; HDL-colesterol; Atividade física; Perda de peso.

ABSTRACT

Introduction: The most common neurological complication described after bariatric surgery (BS) is peripheral polyneuropathy (PPN). However, there is poor evidence about the impact of BS on the incidence and progression of PPN.

Objectives: To evaluate the incidence and progression of PPN in non-diabetic severe obese subjects after laparoscopic BS and to identify risk factors.

Methods: In this prospective cohort study, 322 subjects undergoing laparoscopic BS, 133 by Roux-en-Y gastric bypass (RYGB) and 189 by sleeve gastrectomy (SG), were evaluated for PPN by the Michigan Neuropathy Screening Instrument (MNSI) before and after 6 months of BS and divided according to presence (+) or absence (–) of PPN at baseline. Known causes of PPN were excluded. Secondary, a minor sample of this cohort was evaluated for physical activity (PA), through the short version of the International Physical Activity Questionnaire (IPAQ), and for high-density lipoprotein cholesterol (HDL-C) levels before and after 6 and 15 months of BS.

Results: The prevalence of pre-BS PPN was 21.4% and decreased to 8.7% post-BS. When we look to the PPN (+) group (n = 69) at baseline, the persistence of post-BS PPN was 20.3% (n = 14) after 6 months. In the PPN (–) group (n = 253) at baseline, the incidence of post-BS PPN was 5.5% (n = 14) and it showed independently associated with low HDL-C levels (p = 0.001). The PPN risk increased from 7.4 to 8.6% at each 1 mg/dL decrease in HDL-C. PA increased significantly after 6 and 15 months of BS compared to preoperative (p < 0.001) and, being active before BS was associated with higher increase of HDL-C after 15 months of BS compared to being non-active at baseline (18.2% versus 10.9%; p = 0.035). As the increase in HDL-C occurred only 15 months after BS and was associated with the % excess weight loss

(%EWL) (p = 0.030), maybe this incidence of post-BS PPN decreases with longer follow-up time.

Conclusion: The prevalence of PPN decreased after 6 months of BS, but new cases of post-BS PPN appeared and they were independently associated with low HDL-C. PA could be an important recommendation to avoid the incidence and progression of post-BS PPN, since the practice of PA increases HDL-C levels.

Keywords: Peripheral polyneuropathy; obesity; bariatric surgery; HDL cholesterol; physical activity; weight loss.

1. INTRODUÇÃO

A polineuropatia periférica (PNP) representa um importante problema de saúde, por estar associada a dor neuropática, perda da sensibilidade protetora, aumento da morbidade resultante de ulceração e amputações, aumento do risco de queda e diminuição da qualidade de vida (1-4). A PNP pode estar relacionada a vários fatores causais e de risco associados a disfunções do metabolismo. A etiologia mais comum é o diabetes, representando 32 a 53% dos casos (5-7).

Em estudo prévio encontramos uma prevalência de 11% de PNP em indivíduos obesos graves (obesidade grau II e III) com síndrome metabólica (SM) sem diabetes, e houve associação independente com baixos níveis de HDL-colesterol (HDL-C) (8). Já em mulheres obesas graves sem diabetes encontramos prevalência similar (11,6%), mas uma associação independente com idade e/ou com o estado pós-menopáusico (9).

Outros estudos vêm associando a presença e/ou gravidade da PNP com as dislipidemias, em particular elevados níveis de colesterol total (10), LDL-colesterol (LDL-C) (10) e triglicerídeos (2,10-14) e baixo HDL-C (2,15). Além disso, elevados níveis de triglicerídeos podem ser um fator de risco para amputação de membros inferiores (16-18), enquanto que níveis elevados de HDL-C conferem efeito protetor (18).

Papel atero-protetor também tem sido reconhecido pela transferência reversa de colesterol do HDL (19-21) e, estudos *in vitro,* tem mostrado que partículas de HDL-C podem ser captadas por axônios distais lesados, sendo o colesterol utilizado para a regeneração destas fibras (22). Um baixo HDL-C, além de ser um marcador para uma doença cardiovascular futura ou concomitante, associa-se em inúmeras situações clínicas, a baixos níveis de atividade física

(AF) (23) e a principal recomendação feita para aumentar os níveis de HDL-C é a prática de AF (23-25).

A obesidade e suas complicações, incluindo as dislipidemias (26), vêm sendo associadas com o risco de neuropatia e/ou dor neuropática em pacientes com (3) e sem diabetes (26) e no pré-diabetes (14) e, tal risco aumenta quando a obesidade está associada à baixa AF (27). Tal hipótese vem sendo sustentada por estudos experimentais em animais obesos que sugerem uma redução da condução nervosa e alterações na função sensitiva quando estes apresentam hipertrigliceridemia (28).

A cirurgia bariátrica (CB) é considerada o tratamento mais eficaz para obesidade mórbida em comparação ao tratamento clínico convencional, causando rápida, substancial e sustentada perda de peso, com baixa mortalidade e melhora das comorbidades relacionadas à obesidade, como diabetes mellitus tipo 2 (DM2), doença hepática gordurosa não alcoólica (DHGNA) e síndrome da apneia obstrutiva do sono (SAOS) (29).

A PNP tem sido descrita como a complicação neurológica mais comumente relatada após a CB e aparentemente atribuída às deficiências nutricionais causadas pela restrição da ingestão alimentar e/ou limitação da absorção intestinal (30). Mas, quando verificamos a literatura, as evidências sobre o impacto da CB na PNP bem como fatores de risco relacionados com a incidência e progressão da PNP pós-CB não são claras.

Assim, no presente estudo, buscou-se estabelecer a incidência e progressão da PNP em indivíduos obesos graves (obesidade grau II e III) sem diabetes submetidos à CB por laparoscopia e identificar fatores de risco, tais como maior peso corporal, maior circunferência da cintura, menor percentual de perda de excesso de peso (%PEP), hipertensão arterial, hiperglicemia, hipertrigliceridemia, hipercolesterolemia, HDL-C baixo, baixos níveis séricos de vitamina B_{12}, sexo masculino, pós-menopausa e sedentarismo relacionados à CB.

2. REFERENCIAL TEÓRICO

2.1. Estratégia de busca

Inicialmente, definiu-se as palavras-chave e realizou-se a busca nas bases de dados. A busca de referências bibliográficas envolveu as seguintes palavras-chave: 1) *Peripheral Polyneuropathy*, 2) *Obesity*, 3) *Bariatric Surgery*, 4) *Menopause* 5) *Cholesterol, HDL* e 6) *Physical Activity*, nas bases de dados PubMed, Embase e LILACS (Tabela 1).

Tabela 1. Busca de palavras-chave nas bases de dados PubMed, Embase e LILACS.

Palavras-chave	PubMed	Embase	LILACS
Peripheral Polyneuropathy	26.280	675	78
Obesity	205.192	561.991	5.681
Bariatric Surgery	23.094	42.783	998
Menopause	54.750	69.994	1.215
Cholesterol, HDL	27.193	104.049	2.016
Physical Activity	178.470	432.231	11.197

Em seguida realizou-se o cruzamento das palavras-chave nas bases de dados: 1) *Peripheral Polyneuropathy* AND *Obesity;* 2) *Peripheral Polyneuropathy* AND *Bariatric Surgery*; 3) *Peripheral Polyneuropathy* AND *Menopause*; 4) *Peripheral Polyneuropathy* AND *Menopause* AND *Bariatric Surgery;* 5) *Peripheral Polyneuropathy* AND *Cholesterol, HDL;* 6) *Peripheral Polyneuropathy* AND *Bariatric Surgery* AND *Cholesterol, HDL;* 7) *Bariatric Surgery* AND *Cholesterol, HDL;* 8) *Peripheral Polyneuropathy* AND *Physical Activity*; 9)

Peripheral Polyneuropathy AND *Physical Activity* AND *Bariatric Surgery* e; 10) *Bariatric Surgery* AND *Physical Activity* (Tabela 2).

Tabela 2. Cruzamento de palavras-chave nas bases de dados PubMed, Embase e LILACS.

Palavras-chave	PubMed	Embase	LILACS
Peripheral Polyneuropathy AND *Obesity*	78	19	7
Peripheral Polyneuropathy AND *Bariatric Surgery*	26	8	4
Peripheral Polyneuropathy AND *Menopause*	28	0	0
Peripheral Polyneuropathy AND *Menopause* AND *Bariatric Surgery*	0	0	0
Peripheral Polyneuropathy AND *Cholesterol, HDL*	104	7	1
Peripheral Polyneuropathy AND *Bariatric Surgery* AND *Cholesterol, HDL*	0	0	0
Bariatric Surgery AND *Cholesterol, HDL*	82	910	16
Peripheral Polyneuropathy AND *Physical Activity*	131	21	2
Peripheral Polyneuropathy AND *Physical Activity* AND *Bariatric Surgery*	0	0	0
Physical Activity AND *Bariatric Surgery*	411	1.929	50

Após leitura dos títulos e resumos, selecionou-se os artigos pertinentes de acordo com os critérios de inclusão e exclusão estabelecidos previamente (Tabela 3). Também se realizou busca nas referências dos artigos selecionados e removeu-se os artigos duplicados. Por fim, realizou-se a leitura crítica dos artigos.

Tabela 3. Artigos selecionados nas bases de dados PubMed, Embase e LILACS.

	PubMed	Embase	LILACS
Número total de artigos	860	2.894	80
Número de artigos selecionados	180	25	5

2.2 Polineuropatia periférica

A PNP representa um importante problema de saúde, especialmente quando na sua evolução se associa a dor neuropática, perda da sensibilidade protetora, aumento da morbidade resultante de ulceração e amputações, aumento do risco de queda e diminuição da qualidade de vida (1-4). A PNP é caracterizada por um dano que acomete o nervo periférico, podendo envolver fibras motoras, sensoriais ou autonômicas (31). Entre a sintomatologia, é relatada a presença de dormência, formigamento, fraqueza muscular e/ou dor que tipicamente se inicia nos dedos e se distribui em padrão de bota-e-luva (6), classicamente descrito no diabetes (32). Outro sintoma frequente é a dificuldade de equilíbrio, que pode resultar em quedas e fraturas (33).

A PNP pode estar relacionada a vários fatores causais e de risco relacionados a disfunções do metabolismo tais como idade avançada, peso corporal, hiperglicemia (diabetes, pré-diabetes e glicemia de jejum alterada), dislipidemias (hipertrigliceridemia e HDL-C baixo), obesidade, estresse oxidativo, etilismo, hipotireoidismo, deficiência de vitamina B_{12}, doença renal crônica, doença hepática aguda, hipoproteinemias, doenças inflamatórias, vasculares (doença arterial periférica), autoimunes (artrite reumatoide, lúpus, sarcoidose) e infecciosas

(HIV positivo, hepatite B e C, hanseníase), neoplasias, drogas neurotóxicas (quimioterápicos) e CB (1,2,5,6,10,13,34-38).

No diabetes, a PNP afeta 45 a 50% dos indivíduos (26,28,39), sendo o fator de risco mais importante e prevalente para a formação de úlceras, estando presente em 80% dos pacientes diabéticos que apresentam ulceração nos pés (3,40), as úlceras nos pés precedendo 85% das amputações que ocorrem em pacientes diabéticos (3,32). Estima-se uma incidência de PNP por ano, para todas as causas, de 77 a cada 100.000 pessoas com 18 anos ou mais (41), sendo o diabetes a causa mais comumente identificada (7,42,43). A prevalência de PNP no diabetes mellitus tipo 1 (DM1) varia de 10 a 34% e de 8 a 25% no DM2, e essa prevalência aumenta com a duração do diabetes e com o aumento da idade (44-48). Se considerarmos a PNP assintomática, a prevalência chega a 54% no DM1 e 45% no DM2 (45) e, estima-se uma incidência anual de 2.800 a cada 100.000 pessoas com DM1 e 6.100 a cada 100.000 pessoas com DM2 (49,50).

Segundo a *Diabetes Control and Complications Trial* (DCCT), o controle glicêmico intensivo reduz a incidência e progressão da neuropatia em indivíduos com DM1 mas, em pacientes com DM2, não está claro que o controle da glicemia tenha efeito tão marcante, embora outras complicações microvasculares possam ser claramente prevenidas (51-54). Os fatores etiológicos mais importantes relacionados à neuropatia diabética (ND) são o mau controle glicêmico, idade, duração do diabetes, obesidade visceral, altura, hipertensão, idade, tabagismo, hipoinsulinemia e dislipidemia (6).

Evidências de estudos populacionais indicam que há um gradiente na prevalência de neuropatia, com uma maior frequência nos diabéticos (28%), seguido pelos pré-diabéticos (11,3%), nos com hiperglicemia de jejum (13%) e, finalmente, aqueles com normoglicemia (7,4%) (55). Tem sido sugerido que a neuropatia relacionada ao pré-diabetes representa a fase

mais precoce da ND (14) e é caracterizada por ser menos grave (56,57) e por inicialmente acometer as fibras finas (56,58–61). Entre 11 e 62% dos pacientes com PNP idiopática tem pré-diabetes ou glicemia de jejum alterada (58-65) e, em indivíduos com pré-diabetes, 11 a 25% apresentam neuropatia periférica (NP) e 13 a 26% tem dor neuropática (27,60,61,66-68).

Estudo prévio encontrou uma prevalência de 11% de PNP em indivíduos obesos graves com SM sem diabetes, e houve associação independente com baixos níveis séricos de HDL-C (8). Em outro estudo transversal em mulheres obesas graves sem diabetes encontramos prevalência similar (11,6%), mas uma associação independente com idade e pós-menopausa (9).

A dor neuropática está presente em aproximadamente um terço dos pacientes com PNP e é definida como consequência direta de uma lesão que afeta o sistema somato-sensorial e autonômico (69,70). Os fatores de risco descritos para dor neuropática são idade, obesidade e baixa AF (27,68). A dor neuropática é caracterizada por dor persistente ou episódica que tipicamente piora à noite e melhora durante a caminhada, localizada predominantemente nos pés e descrita como dor em queimação (1). Exerce impacto substancial no bem-estar físico, mental, psicológico e emocional do indivíduo, causando, particularmente, interferência considerável no sono e nas atividades diárias (38,71).

Dada a alta prevalência de PNP, os testes de rastreamento para neuropatia, como o Instrumento para Rastreamento de Neuropatia de Michigan (MNSI), devem ser considerados como ferramenta útil na avaliação destes pacientes. A PNP é uma desordem complexa, no qual um diferente conjunto de fibras nervosas pode ser afetado de forma gradual e distinta entre os indivíduos acometidos (1). A percepção vibratória com diapasão de 128 Hz e sensação de pressão com um monofilamento 10.0 Semmes-Weinstein são os melhores testes para discriminar aqueles com e sem neuropatia de fibras grossas (72). No entanto, alguns pacientes

podem apresentar apenas envolvimento de fibras finas. Esses pacientes podem ser difíceis de rastrear porque geralmente apresentam alterações de sensibilidade dolorosa e térmica e podem ser assintomáticos. Além disso, os estudos de velocidade de condução nervosa e eletromiografia podem apresentar-se normais, o que pode levar ao não diagnóstico (6).

2.3 Polineuropatia periférica e obesidade

A Organização Mundial da Saúde (OMS) aponta a obesidade como um dos maiores problemas de saúde pública no mundo. A projeção é de que, em 2025, cerca de 2,3 bilhões de adultos estejam com sobrepeso e mais de 700 milhões sejam obesos (73). No Brasil, a obesidade vem crescendo cada vez mais. Alguns levantamentos apontam que mais de 50% da população está acima do peso, ou seja, encontra-se entre o sobrepeso e a obesidade (74). Segundo dados da Vigilância de Doenças Crônicas por Inquérito Telefônico (VIGITEL) de 2017, 18,9% da população brasileira estava obesa (75).

A obesidade, definida como um acúmulo anormal ou excessivo de tecido adiposo, pode ser classificada de acordo com o índice de massa corporal (IMC) – peso (em quilos) dividido pela altura ao quadrado (em metros) (76) –, em obesidade grau I (IMC $\geq$ 30 a 34,9 kg/m^2), grau II (IMC $\geq$ 35 a 39,9 kg/m^2) e grau III (IMC $\geq$ 40 kg/m^2) (77).

A obesidade está associada a resistência insulínica e a SM e contribui para o desenvolvimento da hipertensão, dislipidemias e hiperglicemia (78). Vários estudos vêm ligando a obesidade e suas complicações, incluindo a dislipidemia (26), com o risco de neuropatia e/ou dor neuropática em pacientes com (3) e sem diabetes (26) e no pré-diabetes (14) e, tal risco, aumenta quando a obesidade está associada à baixa AF (27).

Lupachyk et al. (2013), em um estudo experimental com ratos Zucker obesos (n = 10), demostraram que a hipertrigliceridemia desempenha um papel importante na redução da velocidade de condução nervosa e provoca alterações na função sensorial, causando neuropatia pré-diabética por estresse oxidativo-nitrosativo (28). Outros modelos animais de obesidade induzida por dieta demonstraram tanto alterações microvasculares como disfunção neural em animais não hiperglicêmicos (79,80). Esses estudos mostram diminuição do relaxamento vascular e diminuição na velocidade da condução nervosa, do fluxo endoneural e da nocicepção térmica. Camundongos C57BL6/J alimentados com uma dieta rica em gordura desenvolvem obesidade, hiperglicemia pós-prandial e neuropatia (80).

Anderson et al. (2014) estudaram se a condição pré-diabética ou uma dieta rica em gordura poderiam causar PNP. Para isso, grupos de camundongos C57BL6 e Swiss Webster foram alimentados com uma dieta contendo 60% de gordura por 8 meses e comparados com grupos diabéticos controlados e tratados com estreptozotocina que foram alimentados com uma dieta padrão contendo 10% de gordura. Ambos desenvolveram intolerância à glicose, indicativo da resistência à insulina, mas apenas os camundongos C57BL6 mostraram hiperglicemia. Camundongos C57BL6 alimentados com dieta rica em gordura desenvolveram disfunção nervosa, indicado pela diminuição da velocidade da condução nervosa e pela hiperalgesia térmica. Estes dados indicam que uma dieta rica em gordura pode favorecer a ocorrência de neuropatia (81).

Noutro estudo, utilizando uma dieta com alto teor de gordura em camundongos pré-diabéticos C57BL6, foi visto um déficit na velocidade de condução nervosa sensitivo-motora, hiperalgesia térmica e redução do comprimento dendrítico. Dietas com alto teor de gordura podem causar grandes danos nas fibras nervosas mielinizadas e pequenos danos nas fibras nervosas sensoriais, levando assim a neuropatia. O comprimento dendrítico pode ser um

marcador mais sensível para a detecção precoce de PNP e a diminuição do fornecimento de sangue aos nervos e o aumento do estresse oxidativo podem contribuir para o desenvolvimento e gravidade da PNP (82). Camundongos não diabéticos alimentados com uma dieta rica em gordura desenvolvem níveis elevados de LDL-C, ácidos graxos livres e triglicerídeos, bem como aumento do estresse oxidativo. Estes camundongos desenvolvem déficit sensorial e na velocidade de condução nervosa antes mesmo de desenvolverem intolerância à glicose (83).

O peso e a circunferência da cintura foram fatores de risco independentes para PNP e dor neuropática em sujeitos diabéticos que participaram do estudo MONICA/KORA (27,55,68). No *National Health and Nutrition Examination Survey* (NHANES) 2001-2004, os obesos foram mais propensos a ter PNP (OR 2,20; 95%IC: 1,43-3,39) em comparação com indivíduos não obesos. Assim, a obesidade e a presença de dois ou mais fatores de risco cardiometabólicos aumentam acentuadamente a probabilidade de ocorrência de PNP (11).

A associação da PNP com a SM parece ser atribuível principalmente à obesidade, que pode levar ao aumento dos níveis de fator de necrose tumoral (TNF) e lipídios circulantes (triglicerídeos e ácidos graxos livres), que por sua vez podem agravar a hiperglicemia, por aumentar a resistência insulínica, mas também podem atuar de forma independente na função nervosa. Elevadas concentrações de TNF e de lipídios podem levar ao aumento do estresse oxidativo, disfunção endotelial e efeitos neurotóxicos (14,84).

Em um estudo conduzido em 249 indivíduos com PNP idiopática e 709 controles, 55% dos sujeitos com PNP tinham SM enquanto que, em contrapartida, no grupo controle, haviam 34%. Foi observado que a obesidade abdominal e a hipertensão foram componentes da SM prevalentes nos pacientes com PNP (85). Vários estudos apontam associações entre a presença e/ou gravidade da PNP e dislipidemia, em particular, elevados níveis de colesterol total (10),

LDL-C (10) e triglicerídeos (10-14) e, baixo HDL-C (2,14). No entanto, há estudos que não observaram tais associações (27).

Estudos apontam também que os níveis elevados de triglicerídeos podem ser um fator de risco para amputação de membros inferiores (15-17), independentemente dos níveis de HDL-C e LDL-C (17), e se correlacionam com a perda da densidade das fibras nervosas mielinizadas (13). No entanto, níveis elevados de HDL-C conferem efeito protetor para amputação (17). Tal hipótese vem sendo sustentada por estudos experimentais que sugerem um retardamento da velocidade de condução nervosa sensorial e mudanças na função sensitiva atribuídos ao HDL-C baixo sérico (28). Os triglicerídeos séricos elevados em conjunto com baixos níveis de HDL-C estão associados a SM e a obesidade e aumentam o risco cardiovascular (86). Callaghan et al. (2011) em um estudo realizado com 28.700 diabéticos, além de demonstrar associação dos níveis aumentados de triglicerídeos com o risco de amputação de membros inferiores, ainda relacionou os níveis de hemoglobina glicada (HBA1c) e a altura com o risco de amputação (17).

2.4 Polineuropatia periférica e cirurgia bariátrica

A CB é considerada o tratamento mais eficaz para obesidade mórbida comparado ao tratamento clínico convencional, causando rápida, considerável e sustentada perda de peso, com baixas taxas de mortalidade e melhora das comorbidades relacionadas à obesidade, como o DM2, hipertensão, DHGNA e SAOS, entre outras (29).

Com o aumento das taxas de obesidade em todo mundo (87,88), se presume que o número de procedimentos de CB venha a aumentar (89). Com isso, também há um aumento da

incidência das complicações cirúrgicas. Uma dessas complicações pode ser a PNP, atribuída principalmente as deficiências nutricionais causadas pela restrição na ingestão de alimentos e/ou limitação da absorção intestinal (30). No entanto, são poucas as evidências sobre o impacto da CB na incidência e progressão da PNP pós-CB.

Os procedimentos bariátricos contribuem para deficiências nutricionais, restringindo a ingestão de alimentos e/ou limitando a absorção intestinal. As deficiências nutricionais mais comumente descritas incluem deficiências de tiamina (vitamina B_1), cobalamina (vitamina B_{12}), folato (vitamina B_9), vitamina D, vitamina E, ferro, cálcio, fosfato, magnésio e cobre. Após a CB, os pacientes devem permanecer em dietas ricas em proteínas e de baixo teor de gordura com suplementação vitamínica e monitorar frequentemente possíveis deficiências nutricionais (30).

O bypass gástrico em Y de Roux (RYGB) é o procedimento cirúrgico bariátrico mais frequentemente realizado, com baixas taxas de morbidade e mortalidade em comparação com outras técnicas, além de excelente controle das comorbidades. Além disso, provoca uma importante perda de peso, aproximadamente 70% do excesso de peso após 12 meses e 83% após 24 meses (90). No RYGB, uma pequena bolsa (15-30 mL de volume) é criada na parte superior do estômago e separada do resto do estômago. Esta é ligada à porção média do intestino delgado (jejuno) para formar um braço em "Y" (Figura 1) (91).

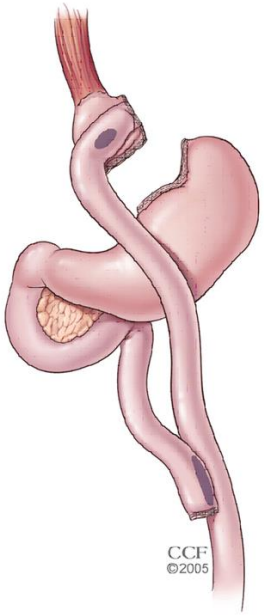

Figura 1. Procedimento de bypass gástrico em Y de Roux (RYGB) (92).

Com este procedimento, a ingestão de carboidratos pode ocasionar a chamada síndrome de dumping, caracterizada por náuseas, vômitos, rubor, dor epigástrica e sintomas de hipoglicemia. Como não há produção de ácido clorídrico e de fator intrínseco pelas células parietais do estômago, a absorção de vitamina B_{12} pode ser prejudicada (93). Também ocorre diminuição dos níveis de grelina (hormônio orexígeno e adipogênico) e uma sinalização precoce do peptídeo semelhante a glucagon 1 (GLP-1), que reduz a velocidade de esvaziamento gástrico, aumenta a secreção de insulina e promove saciedade central, e do polipeptídio Y (PYY), que diminui a motilidade intestinal e aumenta a saciedade (94).

A gastrectomia vertical, também conhecida como sleeve gástrico (SG) ou gastrectomia em manga – apresentada originalmente como o primeiro tempo do duodenal *switch* – consiste na remoção de 70 a 80% do estômago proximal ao antro, preservando o piloro e diminuindo o potencial ulcerogênico (Figura 2) (95,96). Geralmente é utilizado como primeiro tempo cirúrgico em superobesos (IMC > 50 kg/m²), objetivando significativa perda de peso, diminuindo o risco cirúrgico, e o segundo tempo do tratamento pode ser realizado com melhores

condições técnicas e melhor estado clínico do paciente. Dentre as vantagens deste procedimento tem-se a não exclusão do duodeno do trânsito alimentar, portanto, não há interferência com o sítio de absorção de ferro, cálcio, zinco e vitaminas do complexo B (97,98).

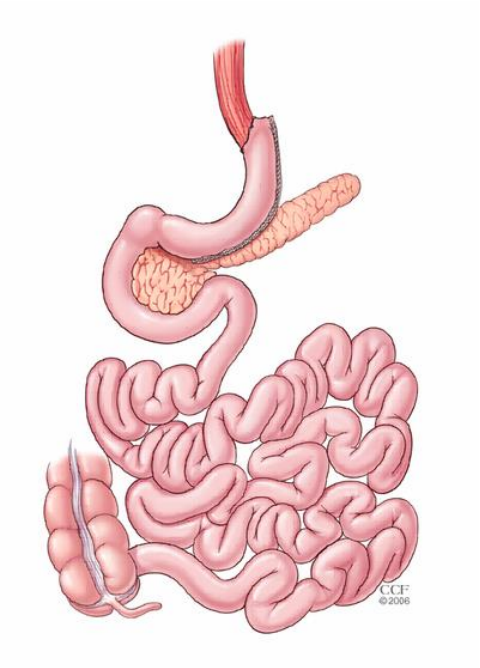

Figura 2. Procedimento de sleeve gástrico (SG) (92).

Os primeiros relatos avaliando PNP e CB surgiram a partir de séries de casos retrospectivos e relatos de caso. Chang, Adams-Huet & Provost (2004) buscaram avaliar, através de um questionário sobre NP pós-cirúrgica enviado para cirurgiões membros da *American Society for Bariatric Surgery* (ASBS), casos específicos de NP pós-CB, seu diagnóstico e tipo de CB realizada. Dos 808 questionários enviados, 257 (31,8%) retornaram. De 168.010 casos bariátricos, 109 casos de NP pós-cirúrgica foram descritos, o que equivale a 5,9 casos a cada 10.000 procedimentos cirúrgicos. Deficiências de tiamina (vitamina B_1) e/ou cobalamina (vitamina B_{12}) foram relatadas em 40% dos casos, sendo 18 casos resolvidos com suplementação vitamínica. Os diagnósticos mais comuns foram encefalopatia de Wernicke,

deficiência de tiamina e síndrome de Guillain-Barré. A procedimento cirúrgico mais comum foi o RYGB (99).

Thaisetthawatkul et al. (2004) buscaram verificar se a NP ocorria com maior frequência após a CB em comparação a uma coorte de obesos submetidos à colecistectomia, considerada uma cirurgia abdominal de grande porte similar. As coortes retrospectivas foram pareadas por idade e sexo e avaliadas para NP através de biópsia de nervo periférico. Dos 435 sujeitos submetidos à CB, 71 (16,0%) desenvolveram NP, uma frequência de NP maior do que após a colecistectomia (4/126; 3%) ($p < 0,001$). Dos casos de NP relatados, 27 foram PNP, 39 mononeuropatias e cinco radiculopatias. As biópsias de nervo mostraram dano axonal e inflamação perivascular. A desnutrição pareceu ser o fator de risco mais importante para o desenvolvimento de NP pós-bariátrica (100).

Revisão da literatura de 50 relatos de caso envolvendo 96 pacientes com sintomas neurológicos após procedimentos bariátricos, apresentou como formas mais comuns a NP (62%) e encefalopatia (31%). Dentre os 60 pacientes com NP, 40 (67%) apresentavam PNP e 18 (30%) mononeuropatias. Também foram relatadas encefalopatia de Wernicke, rabdomiólise e síndrome de Guillain-Barré. Na mesma revisão, de 18 séries cirúrgicas relatadas entre 1976 e 2004, 133 de 9996 pacientes (1,3%) apresentavam complicações neurológicas. Deficiências de micronutrientes após bypass gástrico foram avaliadas em 957 pacientes em oito relatos. Um total de 236 (25%) tinham deficiência de vitamina B_{12} e 11 (1%) tinham deficiência de vitamina B_1 (101).

Na coorte retrospectiva subsequente, Thaisetthawatkul et al. (2010) submeteram 393 sujeitos a um tratamento nutricional intensivo antes e após a CB, entre 1985 e 2002. A análise univariada apontou como fatores de risco aumento da HbA1c e triglicérides, tempo prolongado de hospitalização, presença de sintomas gastrintestinais pós-operatórios, náuseas e vômitos. A

NP mostrou-se menos frequente (7% vs. 13%, $p < 0,010$) e comumente PNP (1% vs. 7%, $p < 0,001$) em comparação a coorte anterior. Segundo os autores, uma abordagem multidisciplinar com seguimento nutricional intensivo diminuiria o risco de desenvolvimento de NP após a CB (102).

Dentre as alterações neurológicas descritas após a CB, a PNP representa em torno de 54% destas complicações, apresentando-se como um PNP sensitivo-motora, que ocorre meses a anos após a CB e é caracterizada por parestesia dolorosa nos membros inferiores, perda da sensibilidade dolorosa e térmica, fraqueza muscular e dificuldade de marcha (90,91,103-109). A dor neuropática também tem sido relatada após a CB. Uma incidência de 33% de dor neuropática pós-CB foi descrita, com melhora após reposição vitamínica (106).

A maioria dos casos de PNP pós-CB têm sido relacionados ao RYGB (91,100,101,104,110-114). Estudo retrospectivo em 592 casos de SG entre 2009 e 2014 encontrou uma prevalência de PNP de 1,18% (115). Um estudo caso-controle em 16 neuropatas e16 não-neuropatas pós-SG, associou a PNP com níveis mais baixos de vitaminas B1 e B2, cobre e maior idade (116).

Pacientes com DM2 apresentam remissão precoce da hiperglicemia após a CB entre 40 a 95% (29,117-120). Num estudo de coorte prospectivo com 20 pacientes DM2 e IMC entre 25 e 35 kg/m² submetidos a RYGB por laparoscopia, a ND foi avaliada pelo *Neuropathy Symptom Score* (NSS) e pelo *Neuropathy Deficit Score* (NDS). Houve diminuição significativa do IMC ($32,8 \pm 2,1$ kg/m² versus $25,6 \pm 2,5$ kg/m²; $p < 0,001$) e dos níveis de HbA1c ($8,5 \pm 1,2\%$ versus $7,1 \pm 1,2\%$; $p < 0,001$), e a neuropatia sintomática foi reversível em 67,0% dos pacientes após RYGB (117). Na coorte subsequente, a melhora da glicemia de jejum e da HBA1c não se correlacionaram com a melhora da neuropatia. A diminuição da nitrotirosina correlacionou-se com a melhora dos escores do NDS após 6 e 12 meses ($r = 0,9$; $p < 0,001$ e; $r = 0,68$, $p = 0,03$).

A diminuição do metilglioxal após 6 meses correlacionou-se com a diminuição dos escores do NDS após 12 meses (r = 0,897; p = 0,003). Com isso, o RYGB parece melhorar o estresse oxidativo, nitrosativo e carbonílico, envolvidos na casuística da ND (121).

Miras et al. (2015) mostraram, em um estudo prospectivo caso-controle de 70 pacientes cirúrgicos obesos com DM2 submetidos a RYGB pareados por idade, sexo e duração da diabetes com 25 obesos que seguem tratamento clínico, que a curto prazo, a CB pode melhorar a nefropatia diabética, mas não apresenta efeitos sobre a retinopatia ou neuropatia (122). Estudo de coorte retrospectivo em 17 DM2 com IMC acima de 35 kg/m² submetidos ao RYGB, encontrou um percentual menor de pacientes com neuropatia (31,3%) em comparação ao início do estudo (52,9%), mas sem significância estatística (p > 0,05). Destes, 11,8% permaneceram fazendo uso de hipoglicemiantes (p < 0,001) (123). Coleman et al. (2016) em uma coorte retrospectivo (n = 4.683) de DM2 submetidos à CB entre 2001 e 2011, mostraram que pacientes que apresentavam remissão do DM2 tinham 29% menor risco de doença microvascular incidente em comparação com pacientes que não tiveram remissão (HR 0,71; IC95%: 0,60-0,85) (124).

No estudo *Swedish Obese Subjects* (SOS), 2.010 pacientes do grupo cirúrgico (13% RYGB (n = 265), 19% banda gástrica (n = 376) e 68% SG (n = 1.369)) foram comparados com 2.037 indivíduos controles (tratamento convencional). Os indivíduos foram divididos em grupos conforme seu status glicêmico em: normal (n = 2.838), pré-diabetes (n = 591), diabetes detectada (n = 246) e diabetes estabelecida (n = 357). No estudo, a incidência de neuropatia após a CB foi baixa e mostrou-se apenas associada à CB no subgrupo com pré-diabetes (p = 0,001) (125).

As deficiências nutricionais que ocorrem após a CB, devido a ingestão restrita, sintomas gastrointestinais prolongados (como náuseas, vômitos, diarreia e síndrome de dumping), e

limitada absorção no intestino delgado, têm sido atribuídas ao desenvolvimento de PNP pós-CB (126). Dentre as deficiências vitamínicas e de micronutrientes descritas como relacionadas à PNP, têm sido citadas as deficiências de vitamina A (105,127), vitamina B_1 (30,101,108,109,115,116,126-130), vitamina B_2 (106,128), vitamina B_6 (108,127,128,131), vitamina B_9 (131), vitamina B_{12} (90,101,109,110,114,126,128,129,132), vitamina D (133,134), cobre (90,110,114,116,126,129,135-138) e selênio (134). Algumas dessas deficiências ocorrem semanas após a CB, como a deficiência de vitamina B_1, outras após meses, como a de vitamina B_{12}, ou até mesmo anos, como a de cobre (126). Em casos graves, as deficiências vitamínicas e de micronutrientes podem ser irreversíveis (129).

A deficiência de vitamina B_{12} ocorre devido à ausência ou redução da acidez do estômago, bem como do fator intrínseco. O paciente com deficiência de vitamina B_{12} apresenta parestesias, diminuição dos reflexos de estiramento muscular e fraqueza associada à espasticidade (aumento do tônus muscular, envolvendo hipertonia e hiperreflexia, no momento da contração muscular), perda da posição e da sensibilidade vibratória. Os pacientes podem ainda apresentar perda da visão, demência, psicose e alterações de humor. Raramente sintomas autonômicos podem ser observados (139).

Dentre as possíveis outras causas de PNP pós-CB relatadas na literatura, presume-se que dietas desequilibradas, rápida perda de peso e períodos prolongados de vômitos causem a desnutrição que pode levar à PNP relacionada as deficiências nutricionais (100,105,127,140). Além disso, alguns autores hipotetizam que a rápida perda de peso pode causar uma compressão no nervo (141). Um papel inflamatório e imunológico também tem sido atribuído (101,106), principalmente porque tem sido demonstrada melhora dos marcadores inflamatórios e de estresse oxidativo pós-CB e diminuição da ocorrência de PNP (107,121). Também tem sido inferido que o tipo e tempo decorrido do procedimento cirúrgico podem estar relacionados com o desenvolvimento e progressão da PNP (30,109).

Existe consenso sobre a suplementação de vitaminas e de micronutrientes após a CB, o que inclui o uso de multivitamínicos e, em casos específicos, de ferro, vitamina D, ácido fólico, citrato de cálcio, zinco, cobre, selênio e vitaminas do complexo B (74,92). É importante a adesão à suplementação após a CB para evitar o desenvolvimento de deficiências nutricionais, anemias, dificuldade de marcha e alterações de sensibilidade. Por isso, recomenda-se a suplementação vitamínica e de minerais, monitoramento dos micronutrientes, dieta adequada, seguimento nutricional pós-CB, acompanhamento da perda de peso, abordagem multidisciplinar antes e após a CB, AF e fisioterapia para prevenir atrofia e melhorar a força muscular, principalmente naqueles com deficiências nutricionais (102-105,112,126-128,131,135).

2.5 Polineuropatia periférica e menopausa

A menopausa é definida como um período de transição, caracterizado pela progressiva redução dos estrogênios, resultando em ausência da menstruação, e pela presença dos sinais e sintomas classicamente descritos, como fogachos, suores noturnos, distúrbios do sono, redução da libido, secura vaginal, ganho de peso e pele seca (Figura 3) (142). A redução dos estrogênios, por sua vez, está associada ao aumento do peso e da gordura visceral, assim como maior prevalência de hiperglicemia, hipertensão e dislipidemia. A redução do gasto energético e da AF neste período também aumenta o risco de ganho de peso das mulheres na pós-menopausa (143).

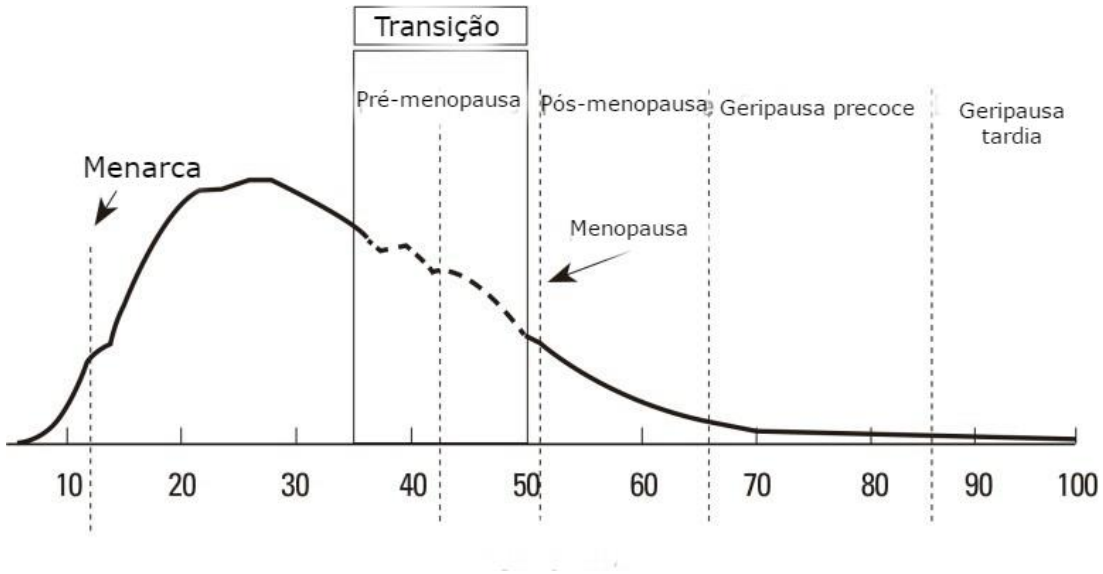

Figura 3. Menopausa e flutuação dos níveis de estrogênio.

Adaptado de Kim et al. (2015) (144).

Estudo transversal realizado pelo nosso grupo em 450 mulheres com obesidade severa pré- e pós-menopáusicas, avaliadas para PNP através do MNSI, encontrou uma prevalência de 11,6% de PNP. Na análise univariada, PNP mostrou-se associada com idade, pós-menopausa e hipertensão ($p < 0,001$, $p < 0,001$ e $p = 0,016$, respectivamente), e houve uma tendência a uma associação com o risco de apneia do sono ($p = 0,101$). Na análise multivariada, em dois modelos distintos, pós-menopausa (RP = 2,84; IC95%: 1,74-4,64; $p = 0,001$) e idade (RP = 1,05; IC95%: 1,03-1,07; $p = 0,001$) foram independentemente associadas a PNP (9). Como a idade e a pós-menopausa mostraram-se colineares, não foi possível determinar quais fatores associados com envelhecimento (por exemplo, diminuição dos níveis de estrogênio, aumento da gordura corporal) são mais importantes para causar PNP em mulheres obesas.

Um estudo caso-controle em 18 mulheres pós-menopáusicas que recebiam terapia hormonal (1 mg de estradiol + 100 mg de progesterona) e 46 mulheres pós-menopáusicas que não faziam reposição hormonal observou, após ajuste para idade e IMC, uma menor velocidade

de condução nervosa nas mulheres pós-menopáusicas que não recebiam terapia hormonal (145). No entanto, o efeito do estrogênio não foi avaliado individualmente, uma vez que a terapia hormonal consistia em estradiol e progesterona.

Singh et al. (2016) em um estudo transversal em 30 mulheres pós-menopáusicas com NP (idade: 51,4 ± 7,9) e 30 mulheres pós-menopáusicas sem NP (controle) (idade: 52,5 ± 4,9), mostraram que mulheres pós-menopáusicas com NP apresentam menor velocidade de condução nervosa (nervos mediano, ulnar e peroneal comum, bilateralmente) e menores níveis de estrogênio e progesterona do que o grupo controle. Na análise de regressão linear, o estrogênio mostrou principal efeito sobre a velocidade de condução nervosa (146). Além do pequeno tamanho amostral, o estudo não incluiu nenhum parâmetro antropométrico e laboratorial que pudessem ter interferido no desfecho do estudo.

Estes poucos estudos mostram uma possível relação entre a pós-menopausa e a PNP, o que contribui com nossa hipótese de que a PNP tem uma associação com o estado menopausal e é mais grave nas mulheres pós-menopáusicas com obesidade severa sem diabetes. Porém, estes estudos apresentam limitações quanto ao delineamento, tamanho amostral e outras variáveis não mensuradas, além de não avaliarem a incidência, progressão e fatores de risco para PNP após a CB.

2.6 Polineuropatia periférica e atividade física

Segundo a OMS, a prática de 150 minutos de AF aeróbica de intensidade moderada a vigorosa por semana (ou equivalente) reduz o risco de doença cardiovascular em 30%, o risco de diabetes em 27% e o risco de câncer de mama e cólon entre 21 e 25%. Além disso, a AF tem efeitos positivos na saúde mental, reduzindo estresse, ansiedade e depressão e, possivelmente, retardando os efeitos da doença de Alzheimer e outras formas de demência (73).

Estudos avaliando a AF em sujeitos com PNP não diabética são escassos. Quando ocorrem as complicações crônicas do diabetes, como retinopatia, nefropatia e ND, a probabilidade de os indivíduos seguirem as diretrizes de AF é menor em comparação com aqueles sem complicações (147). O dano ao nervo prejudica a função dos receptores, causando perda do equilíbrio e da propriocepção (148). No DM2, pode haver perda da força muscular dos membros inferiores (149), levando a instabilidade ao andar e aumento do risco de quedas (148). Essas limitações prejudicam a qualidade de vida, pois podem inviabilizar atividades cotidianas como caminhar (148). A perda de força muscular está relacionada com a gravidade do DM2 que, associada com o envelhecimento e a inatividade física poderia agravar a perda da força muscular, bem como a presença e gravidade da ND (149).

Atualmente, o ensaio clínico randomizado (ECR) *Activity for Diabetic Polyneuropathy* (ADAPT) busca determinar o impacto da AF na progressão da ND e na qualidade de vida destes indivíduos (150). Serão 140 indivíduos com DM2 e ND leve a moderado randomizados em grupo intervenção, o qual receberá 18 meses de treinamento físico supervisionado, aconselhamento para reduzir o comportamento sedentário e aconselhamento dietético individualizado e, em grupo controle, o qual receberá aconselhamento sobre dieta e AF no início e aos 9 meses. Os desfechos primários são a progressão da ND medida pela densidade das fibras nervosas intra-epidérmicas na biópsia da pele distal da coxa e o escore *Norfolk Quality of Life-Diabetic Neuropathy* e os desfechos secundários incluem medidas de dor, marcha, equilíbrio e mobilidade.

Um estudo transversal que avaliou a associação entre PNP e condicionamento físico a partir de dados de um estudo de coorte de base populacional de mulheres de meia-idade com e sem diabetes (n = 396), encontrou uma prevalência de PNP de 27,8% avaliada pelo MNSI e mostrou que PNP pode desempenhar um papel nas limitações do condicionamento físico e gerar

futura incapacidade. Além disso, o IMC associou-se à PNP e ao condicionamento físico. Pode ser que a obesidade seja favorecida pela PNP. Indivíduos que apresentam dormência ou dor nos membros inferiores podem ser menos ativos fisicamente e a inatividade, particularmente na meia-idade, talvez seja um fator de risco para a obesidade (148). O estudo limita-se pelo fato de serem dados secundários de uma coorte, havendo apenas uma única avaliação para PNP, inclusão de sujeitos com e sem diabetes e amostra composta exclusivamente por mulheres.

O *Osteoporotic Fractures in Men Study* (MrOS) avaliou se a função do nervo periférico sensoriomotor estava associada à AF em 328 homens mais velhos (78,8 ± 4,7 anos de idade). A função nervosa foi avaliada pelo teste de condução nervosa, monofilamento e sintomas de PNP e a AF pelo *Physical Activity Scale for the Elderly* (PASE). Houve variação na associação entre as medidas de PNP com a AF (151). Limitações do estudo incluem problemas no teste de condução nervosa (indivíduos de maior idade apresentam amplitudes muito baixas de velocidade de condução nervosa) e a amostra composta por somente homens.

Nolan et al. (2016) avaliaram o nível de AF autorreferida através do Questionário Internacional de Atividade Física (IPAQ) em 481 sujeitos com DM2, com e sem ND. Indivíduos com DM2 e ND foram fisicamente menos ativos do que aqueles sem ND (1.433 (495-3.390) MET-min/sem *versus* 2.106 (876-4.380) MET-min/sem; p = 0,04) e 49% dos diabéticos neuropatas atenderam às recomendações 150 min ou mais de AF moderada por semana, em comparação com 57% dos diabéticos sem ND (152). Esses achados demonstram que sujeitos com DM2 e ND são menos ativos do que sujeitos sem ND.

Na dor neuropática, estudo retrospectivo em 2.358 diabéticos avaliados pelo questionário *Douleur Neuropathique en 4 Questions* (DN4), encontrou uma prevalência de dor neuropática de 7,6% (n = 179). Após ajuste para possíveis confundidores, o risco de dor neuropática foi maior no grupo que não praticava AF (OR 3,38; IC95%: 1,54-9,79) (153).

Limitações do estudo incluem a utilização de ferramentas subjetivas para avaliar a dor neuropática e a avaliação da AF foi subjetiva e limitada à duração da AF e não incluiu categoria ou intensidade da AF.

Do exposto, pode-se pressupor que a AF talvez seja uma estratégia para retardar a progressão da ND. Teoricamente, a AF pode atenuar a progressão da ND por meio do papel na modulação da inflamação e regulação dos níveis glicêmicos (154). Revisão da literatura mostrou que a AF também pode ter impacto positivo na dor neuropática (155). Porém, os estudos eram de pequeno tamanho amostral, usaram diferentes instrumentos, havia alto risco de viés de cegamento e conflitos de interesse.

Dados do NHANES 2003-2004, que avaliou 339 diabéticos entre 40-85 anos de idade para ND através do monofilamento e a AF através do acelerômetro, mostrou que os diabéticos que se envolviam em níveis de AF mais elevados (moderada à vigorosa) e tinham níveis normais de HbA1c eram menos propensos a ter ND (154). Neste contexto, estudos são necessários para esclarecer os efeitos da AF na presença de PNP.

2.7 Atividade física e cirurgia bariátrica

Em indivíduos obesos graves as intervenções no estilo de vida, que incluem modificações na dieta e aumento da AF, são o primeiro passo para alcançar a perda de peso e tratar comorbidades relacionadas a obesidade, seguida por terapia farmacológica, antes de se considerar a CB (156,157). No entanto, a perda de peso significativa e sustentada por meio de mudanças no estilo de vida e da farmacoterapia não têm sido alcançadas nestes indivíduos (158).

A CB tem se mostrado eficaz na perda de peso substancial e sustentada a longo prazo e na resolução de comorbidades mas, sem a mudança de comportamentos, a manutenção do peso corporal pode ser prejudicada (158,159). A AF é um componente de programas de modificação de estilo de vida recomendado antes da CB com a finalidade de melhorar a capacidade física dos pacientes, diminuir as complicações cirúrgicas (160) e obter melhores resultados no pós-operatório (159), além de reduzir a mortalidade e o risco de doença cardiovascular, DM2 e de alguns cânceres, melhorar a saúde mental e a qualidade de vida (161,162).

A OMS e o *American College of Sports Medicine* (ACSM) recomendam a realização de um mínimo de 150 min/semana de AF de intensidade moderada a vigorosa para perda de peso e evitar o reganho de peso em adultos com excesso de peso (163,164). Apesar das recomendações para adoção da prática de AF no pré-operatório, estudos recentes mostram que a maioria dos pacientes obesos é inativa e sedentária e têm adotado pequenas mudanças de comportamento no pós-operatório (162,165). Revisão sistemática e meta-análise mostrou que a CB não influenciou o comportamento sedentário, indicando que os sujeitos pós-bariátricos precisam estar mais conscientes sobre a importância de reduzir as atividades sedentárias e aumentar o nível de AF após a CB (166).

A prática de AF no pós-operatório pode ser importante para evitar o reganho de peso e a perda de massa magra, além de melhorar a aptidão cardiorrespiratória de pacientes submetidos à CB (167). A perda e a manutenção da perda de peso variam entre os pacientes após a CB e o reganho de peso pode ser explicado pela falta de adesão às recomendações dietéticas e de AF (168). Estudos avaliando os níveis de AF pós-operatória da CB tem encontrado resultados conflitantes (168-176), incluindo ECR que utilizaram o exercício físico como intervenção (177-180) e apresentaram importantes limitações.

O *Longitudinal Assessment of Bariatric Surgery-2* (LABS-2) mostrou um aumento da AF após a CB relacionada a uma maior perda de peso após 12 meses da CB. O número de sujeitos que passaram a realizar ≥150 min/semana de AF após a CB aumentou (29,7% versus 46%, $p < 0.001$), assim como mais sujeitos deixaram de ser inativos do que se tornaram inativos após a CB ($p < 0.001$) (174). Após 3 anos da coorte, apesar dos sujeitos realizarem pequenas melhorias nos hábitos de vida e manterem a AF, os níveis de AF pós-CB não atingiram o recomendado. O número de sujeitos que realizava ≥150 min/semana de AF não se diferenciou do tempo basal (3,4% versus 6,5%, $p = 0.450$) (173). Apesar da amostra representativa e do tempo de seguimento, o estudo LABS-2 incluiu diversas técnicas cirúrgicas (RYGB, duodenal switch com derivação biliopancreática, SG, Bypass gástrico com banda e banda gástrica ajustável), não deixando claro se os resultados são generalizáveis para todos os procedimentos. Além disso, o equipamento utilizado para monitorar a AF apresentava limitações e o estudo incluiu sujeitos com obesidade grau I.

Uma coorte retrospectiva de 4.569 sujeitos submetidos ao RYGB, avaliados para AF antes e 15, 24, 36 e 48 meses após a CB, mostrou uma associação positiva da mudança de AF com o %PEP (181). No entanto, trata-se de um estudo retrospectivo e que apresentou elevada perda de seguimento, principalmente aos 36 e 48 meses pós-CB. Bergh et al. (2016), em um estudo de coorte com 230 sujeitos submetidos ao RYGB após um ano, não observaram associação entre a mudança no nível de AF e a perda de peso, mas viram que os sujeitos com maiores níveis de AF pré-operatória foram os mais ativos no pós-operatório (168). Na coorte subsequente, que avaliou 112 sujeitos submetidos ao RYGB após 18 a 24 meses, também não houve associação entre a perda de peso e a AF mensurada tanto pelo IPAQ como pelo acelerômetro (169).

Bond et al. (2009), em uma coorte de 190 sujeitos submetidos ao RYGB avaliados pelo IPAQ após um ano, categorizaram os sujeitos conforme o IPAQ pré- e pós-operatório em ativo/ativo (≥200 min/semana de AF/≥200 min/semana de AF), inativo/ativo (<200 min/sem de AF/≥200 min/semana de AF) e inativo/inativo (<200 min/semana de AF/<200 min/semana de AF). No estudo, observaram maiores reduções de peso (52,5 ± 15,4 versus 46,4 ± 12,8 kg) e de IMC (18,9 ± 4,6 versus 16,9 ± 4,2 kg/m²) nos sujeitos que ficaram ativos após a CB do que aqueles que permaneceram inativos (182). Na mesma coorte, foi visto que os participantes que passaram a ser ativos perderam 6 kg adicionais, reduziram o IMC em mais duas unidades e perderam 8% a mais do excesso de peso em comparação àqueles que permaneceram inativos, independentemente da idade, sexo, etnia, peso e IMC pré-operatórios. Também 32% dos sujeitos não alterou os seus níveis de AF no pós-operatório e, dos que se tornaram ativos (68%), passaram de 63 min/semana de AF para 846 min/semana após a CB.

ECR em 36 sujeitos pós-CB de seis meses mostrou que uma maior AF pré-operatória prediz uma maior AF pós-operatória (177), fornecendo subsídios para intervenções desde o período pré-operatório. O mesmo foi visto por Baillot et al. (2018), em 30 sujeitos randomizados em treinamento físico pré-operatório ou controle, onde a intervenção melhorou o nível de AF e a aptidão física um ano após a CB (183). Outro ECR em 96 sujeitos não diabéticos randomizados para um programa de treinamento físico de seis meses após RYGB, mostrou que sujeitos que realizam maiores mudanças de número de passos por dia têm maiores déficits de energia e perda de peso e massa gorda, independente do treinamento físico (178). Em contrapartida, um ECR em 128 sujeitos com um a três meses pós-RYGB, não mostrou maior perda de peso em comparação ao grupo controle (179). No ECR de Shah et al. (2011), 33 sujeitos submetidos ao RYGB e banda gástrica foram randomizados para doze semanas de exercício físico ou grupo controle. O grupo que sofreu a intervenção apresentou maiores níveis

de AF, melhores aptidão cardiorrespiratória e controle glicêmico, mas não perda de peso em comparação ao grupo controle (180).

Esses ECRs foram realizados durante o primeiro ano pós-operatório, quando ocorre maior perda de peso e, portanto, o efeito da CB pode ter mascarado qualquer efeito do exercício sobre a perda de peso. Além disso, o baixo déficit de energia causado pela AF pode não ser suficiente para influenciar o balanço energético, uma vez que o sujeito pós-bariátrico é caracterizado por um grande déficit de energia (167,177).

Crisp et al. (2017), em um estudo de coorte, determinaram os níveis de AF no pré- e pós-operatório de seis e doze meses em 34 mulheres submetidas ao RYGB. O tempo de AF aumentou após seis meses, no entanto esse aumento não se manteve aos doze meses de pós-operatório. A porcentagem de indivíduos que não realizou nenhum tipo de AF nos períodos pré-operatório, seis e doze meses pós-operatórios foi de 52,9%, 41,2% e 47,1%, respectivamente, e o percentual de indivíduos que atingiram ≥150 min/semana de AF foi de 5,9%, 11,8% e 14,7% (172). Já na coorte de Bergh et al. (2016), houve uma aderência de 78% ao nível recomendado de AF (600 MET-min/semana) (168).

Outro estudo de coorte em 22 sujeitos submetidos à RYGB, SG ou balão intragástrico, avaliados para AF e gasto energético antes e após 6,3 meses, mostrou que a maioria dos sujeitos eram fisicamente inativos no pré-operatório e não houveram mudanças na AF, no gasto energético e na prática de ≥150 min/semana de AF no pós-operatório (18% versus 27%) (184). Um estudo transversal que comparou um grupo pré-operatório (n = 81) com um grupo pós-operatório (n = 81) de 8,2 meses (RYGB e SG), observou que o grupo pré-operatório não diferiu do grupo pós-operatório em relação às estimativas de AF (170). Carrasco et al. (2007), mostraram um aumento de AF após a CB (171).

Wefers et al. (2016), em uma coorte com 50 sujeitos submetidos ao RYGB, observaram que 24% dos sujeitos diminuíram a AF total e 39% aumentaram o comportamento sedentário (176). Porém, trata-se de um subgrupo de participantes de um ECR, com limitações de tamanho amostral, monitor para avaliar AF e inexistência de medidas pré-operatórias. Tettero et al. (2018) mostraram que mudanças nas atividades de lazer associam-se positivamente com o %PEP enquanto que mudanças nas atividades esportivas se associam positivamente com a aptidão cardiorrespiratória após 24 meses de RYGB e SG (175).

Evans et al. (2007), compararam a perda de peso no pós-operatório de três, seis e doze meses entre pacientes com RYGB que atingiram ≥150 min/semana de AF e aqueles que não cumpriram a recomendação através do IPAQ. O número de indivíduos que relataram prática de 150 min ou mais de AF aos três, seis e doze meses após a CB foi de 50,6%, 50% e 57,4%, respectivamente. A prática de ≥150 min de AF mostrou-se associada a maior perda de peso e diminuição do IMC aos seis meses e um ano após o RYGB (161). Este estudo, no entanto, não incluiu a caminhada na avaliação da AF e, por tratar-se de um estudo transversal, consequentemente, não fornece qualquer informação sobre a AF pré-operatória.

Com o propósito de avaliar se a AF estava correlacionada com o sucesso da CB, definido como ≥ 50 %PEP, Mundi et al. (2013) conduziram uma coorte em 118 sujeitos e observaram que indivíduos que alcançaram maior %PEP realizavam maior quantidade de AF moderada e vigorosa, avaliada pelo IPAQ (185). Um estudo caso-controle com 49 sujeitos também divididos pelo %PEP, mostrou que o grupo que perdeu < 50 %PEP teve menores tempo de caminhada, de AF total e gasto energético avaliados pelo IPAQ em comparação com o grupo que perdeu ≥ 50 %PEP após um ano de RYGB. O grupo que perdeu ≥ 50 %PEP (n = 27) realizou 742,5 min/semana de caminhada, 120,0 min/semana de atividade moderada e 0,0 min/semana de atividade vigorosa (186).

Apesar de não haver nenhuma recomendação sobre a prescrição de AF (tipo, frequência, duração, intensidade) para sujeitos com obesidade severa e pós-bariátricos, Creel et al. (2016) em um ECR mostraram que o aconselhamento de exercícios aumenta a AF do período perioperatório até os 6,5 meses após a CB (187). Atualmente as recomendações de AF para sujeitos submetidos à CB são aquelas utilizadas na população em geral.

Rosenberger et al. (2011), que também mostraram aumento da AF de sujeitos submetidos ao RYGB durante os primeiros doze meses de pós-operatório, observaram que o aumento da frequência e intensidade dos níveis de AF estão associados a melhores resultados psicossociais (188). Aderir às recomendações de AF e engajar-se em ser mais ativo tem se associado a uma maior qualidade de vida, tanto no pré- como no pós-RYGB (189). Além de promover perda ponderal, aumento da AF também tem sido descrita como melhorando a qualidade de vida e depressão e, prevenindo a progressão de doença de Alzheimer (190).

2.8 Polineuropatia periférica, HDL-colesterol, atividade física e cirurgia bariátrica

As HDL são um grupo heterogêneo de partículas que diferem em tamanho, forma, densidade, teor de colesterol e fosfolipídios, bem como na composição de apolipoproteínas (Apo) (19). A HDL é rigidamente controlada por fatores genéticos que aumentam com a AF e as diferenças nas capacidades das subfrações da HDL podem explicar variações na remoção do colesterol celular (191). As principais proteínas associadas a HDL são as Apo A-I e Apo A-II, embora existam cerca de 48 outras proteínas que constituem o proteoma da HDL (23).

O ciclo de vida da HDL começa com a Apo A-I, mais abundante na HDL, sendo produzida pelo fígado. Como Apo A-I liga somente a fosfolipídios e colesterol circulantes, as

HDL muito pobres em lipídios são encontrados no plasma (19). A HDL promove a homeostase do colesterol através da transferência reversa de colesterol (RCT) ou pela transferência de colesterol centripetamente, a partir de tecidos periféricos para o fígado. Novas partículas de HDL são formadas quando o *ATP-binding cassette transporter A1* (ABCA1) transfere lipídios da periferia para lipídios pobres em Apo A-I, e a HDL aumenta de tamanho através da via *ATP-binding cassette transporter GI* (ABCG1), pois estas partículas de HDL imaturas desencadeiam o efluxo do colesterol de macrófagos e fibroblastos subendoteliais e, por interações ABCA1, armazenam o colesterol no núcleo das HDL (18,19,23).

O colesterol livre liberado por macrófagos (através da difusão, interação com ABCA1 e ABCG1 ou por *scavenger-receptor B1* (SR-B1)) é esterificado por lecitina colesterol acil-transferase (LCAT) para ésteres de colesterol, na partícula de HDL, em seguida, sendo transportado para o fígado e intestino (excreção trans-intestinal de colesterol) (18,23). Tais partículas de HDL obtêm uma forma esférica, consistindo em duas das principais partículas maduras, HDL2 e HDL3 (19).

Subsequentemente, o HDL-C entrega a sua carga diretamente para o fígado por meio do SR-B1 ou indiretamente através da transferência do colesterol para partículas de muito baixa densidade (VLDL) ou partículas de LDL, que por sua vez são captados pelo fígado após interação com o receptor de LDL. Esta mudança é efetuada pela proteína de transferência de éster de colesterol (CETP), uma proteína associada à HDL (19). Apo livres de lipídeos ou pré-β-HDL pobres em lipídios são formados em reações catalisadas por proteína de transferência de fosfolipídios (PLTP), CETP, e pela lipase hepática (20). Finalmente, o colesterol é excretado nas fezes como esteróide neutro ou ácido biliar (19).

As HDL têm sido descritas como tendo um amplo espectro de atividades biológicas, incluindo atividade de efluxo de colesterol celular, ações anti-inflamatórias e anti-oxidantes e

também contribuindo para a função das células β pancreáticas. A funcionalidade da HDL é potencialmente atero-protetora, reconhecida principalmente pela RCT do HDL (18-20), mas também aos seus efeitos antioxidante, anti-inflamatório, antitrombótico e antiapoptótico, bem como a propriedades de reparação e de estabilização do endotélio (20,22).

Aparentemente as HDLs mantém a vaso-reatividade endotelial, atenuam o estresse oxidativo, inibem a apoptose de células endoteliais, contribuem para a reparação do endotélio danificado, inibem a ativação de monócitos, e reduzem a expressão de moléculas de adesão e citocinas. A apolipoproteína Apo A-I também parece imuno-regular linfócitos e células mononucleares (192).

Além disso, a HDL e a Apo A-I parecem proteger os eritrócitos contra a geração da atividade pró-coagulante e aumentam a atividade anticoagulante da proteína S. Esta última aumenta a função da proteína C ativada, um fator crítico na regulação da coagulação do sangue através de inativação proteolítica dos fatores Va e VIIIa. HDL também afeta a agregação plaquetária e a inibição da ligação induzida por trombina do fibrinogênio. No DM2, em que a função anti-aterogênica da HDL é defeituosa, a infusão de HDL reconstituído aumenta o potencial anti-inflamatório e o efluxo de colesterol *in vitro* além de reduzir a hiper-reatividade das plaquetas através da redução do teor de colesterol nas membranas das mesmas (192). Estudos *in vitro* também demonstraram que a HDL inibe a expressão de moléculas de adesão endoteliais, tais como *vascular cell adhesion molecule-1* (VCAM-1), *intercellular adhesion molecule-1* (ICAM-1) e E-selectina (19).

Estudos epidemiológicos estão em acordo com tais efeitos benéficos acima descritos, uma vez que demonstram que o baixo HDL-C sérico está associado com risco cardiovascular, independente de outras lipoproteínas aterogênicas (19,20,22,23,193). Um baixo HDL-C, além de ser um marcador para uma doença cardiovascular futura ou concomitante, associa-se em

inúmeras situações clínicas, a baixos níveis de AF (22) e a principal recomendação feita para aumentar os níveis de HDL-C é a prática de AF (23-25).

Vários mecanismos têm sido associados com a modulação e a função da HDL com a AF. Fundamentalmente, estas vias são quase idênticas as que são responsáveis por determinar a composição da HDL e incluem alterações em proteínas transportadoras de colesterol, CETP, lipase hepática, e lipase lipoprotéica (LPL) (23).

Estima-se que cerca de 40 a 60% da variabilidade do HDL-C possa ser explicada pela heritabilidade, ou seja, por fatores genéticos (23,194). Desordens monogenéticas no metabolismo da HDL envolvendo os genes da Apo A-I, LCAT, ABCA1, SCARB1, LPL, lipase hepática (gene LIPC), CETP e alvos adicionais, tais como lipase endotelial (gene LIPG), aparentemente, modulam os aspectos funcionais do HDL-C e, em resposta à dieta e a AF (192). Mutações de perda de função em alguns genes causam condições com HDL-C sérico extremamente baixo e, em contraste, variantes de mutação de perda de função em outros genes estão associadas com HDL-C sérico extremamente alto (195,196).

Estudos sugerem que níveis elevados de HDL-C séricos conferem efeito protetor para amputação (17) e, estudos *in vitro*, tem mostrado que partículas de HDL-C podem ser captadas por axônios distais lesados e, através da RCT, o colesterol pode ser utilizado para a regeneração destas fibras (21). Estudo prévio encontrou uma prevalência de 11% de PNP em indivíduos obesos graves com SM sem diabetes, relacionada independentemente com baixos níveis séricos de HDL-C ($p = 0,047$) (8). Como estes indivíduos tinham baixos níveis séricos de HDL-C, acreditamos que a regeneração dos neurônios poderia estar prejudicada, uma vez que uma menor captação poderia ocorrer também *in vivo*, a partir da ligação de HDL plasmático pelos receptores SR-B1 descritos como presentes em axônios distais. Como consequência de HDL-

C sérico baixo, uma regeneração axonal periférica prejudicada poderia estar ocorrendo nos pacientes com HDL-C sérico baixo e daí a maior prevalência de PNP nesta população.

Cunha et al. (2016) mostraram que os níveis de HDL-C sérico podem ser um novo preditor clínico para a incidência de amputação de extremidades inferiores e morte relacionada à ferida em pacientes com úlceras do pé diabético (197). Um estudo caso-controle em indivíduos com DM2 mostrou que a Apo A-I foi positivamente associada à presença de ND. Cada aumento no desvio padrão no nível sérico de Apo A-I foi associado ao aumento da frequência de ND (OR 1,2; IC95%: 1,1-1,3, p = 0,006) (198). Em um estudo, os níveis séricos de Apo A-I foram inversamente associados à prevalência de neuropatia autonômica cardiovascular em indivíduos com DM2 (OR 0,65; IC95%: 0,43-0,97, p = 0,036) (199).

Em estudos nos quais culturas de neurônios simpáticos de ratas foram incubadas com pravastatina, na ausência de lipídeos fornecidos exogenamente, a síntese de colesterol foi inibida e o crescimento axonal foi prejudicado. A adição de colesterol nos axônios ou nos corpos celulares de neurônios tratados com este inibidor restaurou o alongamento e crescimento axonal para o normal. Em contraste, as lipoproteínas não fornecem aos axônios fosfatidilcolina suficiente para o alongamento normal quando a síntese de fosfatidilcolina axonal foi inibida. Assim, se suporta a ideia de que durante a regeneração axonal, lipoproteínas podem ser retomadas pelos axônios e fornecer colesterol suficiente para a regeneração, mas não fosfatidilcolina (23,200).

Em humanos, nos quais a presença de desnervação foi avaliada através de biópsia de pele e dos nervos intradérmicos, foi observado que mudança do estilo de vida (através da prática de AF e dieta), além de determinar melhora das alterações lipídicas presentes, determinou aumento da densidade de fibras nervosas na biópsia subsequente (201,202). Um estudo que avaliou os efeitos do exercício sobre a capacidade de regeneração cutânea na SM verificou uma

redução na capacidade de regeneração cutânea comparável à observada no diabetes. O exercício induziu uma maior capacidade regenerativa cutânea, sugerindo o potencial benefício de uma modificação comportamental e no estilo de vida para melhoria metabólica e para a função do nervo periférico (202).

Um dos mecanismos propostos para a AF diminuir a mortalidade é o aumento dos níveis séricos de HDL-C relacionados ao exercício aeróbico, com aumento correspondente no efluxo de colesterol dos macrófagos para o tecido hepático (203). A AF é amplamente reconhecida e recomendada para melhorar o HDL-C, que se encontra normalmente baixo em sujeitos diabéticos e obesos (23).

Mecanismos indiretos pelos quais a AF pode modificar a função do HDL podem incluir aumento da biodisponibilidade do óxido nítrico, o que pode diminuir a condição oxidativa do HDL e, assim, melhorar a sua função. A AF tem sido relacionada com o aumento da atividade da LPL e há também descrição de uma correlação direta entre a atividade da LPL no plasma e o nível sérico de HDL: a LPL favoreceria a maturação da partícula de HDL para carregamento de colesterol e proteínas. A atividade da LPL é alostericamente regulada pela insulina e, a resistência à insulina melhorando com a AF, a melhora da atividade da LPL contribuiria com o aumento da disponibilidade e função do HDL-C (23).

Em um estudo, exercícios físicos realizados por curto prazo (seis semanas) aumentaram os níveis de HDL-C e as subclasses HDL2 e HDL3, além dos níveis de LCAT (23). Outro estudo sugeriu que cinco semanas de treinamento aeróbio de intensidade moderada, além de implicar em mudanças significativas no peso corporal, melhoraram os níveis séricos de HDL-C em mulheres jovens (24).

Em um ECR com 19 crianças, foi realizada uma intervenção de 14 semanas de exercício num grupo de intervenção e um aconselhamento geral sobre saúde no grupo controle. Após as

14 semanas, foi observado maior nível sérico de HDL-C no grupo que recebeu a intervenção (p = 0,066) (25).

O estilo de vida que leva ao baixo HDL-C é explicado, principalmente pela não prática de AF e exercício aeróbico, tabagismo, excesso de peso corporal e composição da dieta, mas também o consumo de álcool, ressaltando o fato de que as partículas de HDL de alcoólatras são disfuncionais. Isto é importante uma vez que, tem sido demonstrado que não é apenas a quantidade de HDL e o nível de HDL-C plasmático que importa para a prevenção de doença aterosclerótica, mas também a sua qualidade e funcionalidade. A HDL de obesos e diabéticos também perde algumas de suas propriedades antiaterogênicas, mas uma característica comum destes indivíduos é a dislipidemia aterogênica que se caracteriza exatamente por baixo HDL-C e triglicerídeos elevados (22).

Estudos mostraram que o HDL-C aumenta apenas após um ano de CB (204-206), e o aumento é aparentemente similar entre RYGB e SG (206,207), o que pode estar relacionado à preservação do intestino delgado (particularmente o jejuno) (208). A perda de peso induzida cirurgicamente parece inverter efetivamente muitos passos no metabolismo do HDL-C que foram alterados com a obesidade, melhorando a estrutura e a funcionalidade do HDL (208,209). Além disso, os enterócitos provavelmente contribuem para os níveis de HDL através da síntese de Apo A-IV e A-I (208). No entanto, Heffron et al (2018) mostraram que seis meses após CB, SG produziu resposta superior em HDL-C e quantidade de Apo A-I, bem como capacidade de efluxo de colesterol e ABCA1 em comparação ao RYGB. Aos doze meses após a SG, a capacidade de efluxo de colesterol foi equivalente à dos indivíduos normais de controle do IMC, enquanto permaneceu prejudicada após o RYGB (210).

2.9 Mapa conceitual

A PNP tem sido associada a obesidade (3,11,26,27,55,68) e a CB (30,90,91,99-109). A obesidade leva à hábitos sedentários que diminuem os níveis séricos de HDL-C (27), que por sua vez, aumentam com a prática de AF (23-25). É divergente o efeito da CB sobre os níveis de AF (168-180) e de HDL-C (204-209). O baixo HDL-C poderia estar associado com a PNP (8). A pós-menopausa está associada com a obesidade (143). Não está claro se a prevalência de PNP aumenta com a idade e/ou com o estado pós-menopáusico (9), em que há diminuição dos níveis de estrogênio (142). O estrogênio pode apresentar um possível papel neuroprotetor.

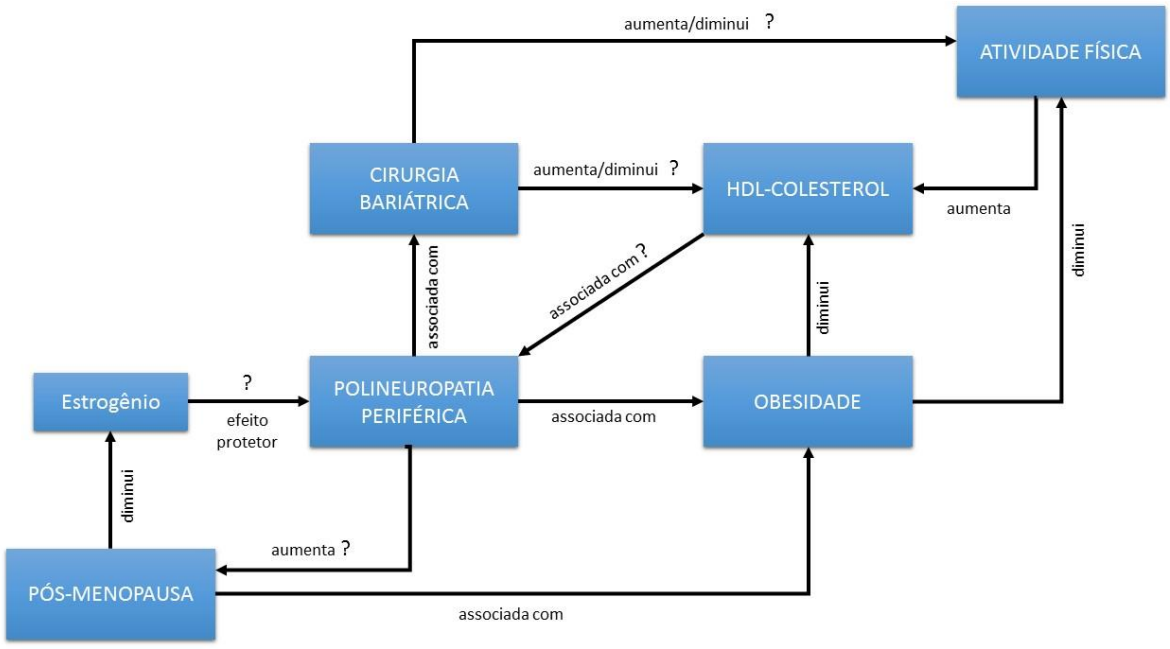

Figura 4. Mapa conceitual.

3 JUSTIFICATIVA

Estudo prévio encontrou uma prevalência de 11% de PNP em indivíduos obesos graves com SM sem diabetes que seguiam protocolo para CB, associada a baixos níveis séricos de HDL-C (8). Outro estudo em mulheres obesas graves sem diabetes, também em protocolo cirúrgico, encontrou uma prevalência de PNP similar (11,6%) associada à idade e/ou ao estado pós-menopáusico (9).

Assim, considerou-se importante estabelecer qual a incidência e progressão da PNP em pacientes obesos graus II e III sem diabetes e quais fatores poderiam ser considerados como potencialmente de risco, tais como hiperglicemia, hipertrigliceridemia, hipercolesterolemia, HDL-C baixo, peso corporal e circunferência da cintura aumentados, sexo masculino, pós-menopausa, menores níveis séricos de vitamina B_{12} e sedentarismo relacionados à CB.

Como estudos avaliando a AF pós-CB (168-180) e o efeito da CB sobre o HDL-C (204-209) tem encontrado resultados discrepantes e não claros, também procurou-se avaliar o efeito da CB sobre a prática de AF e dos níveis de HDL-C e buscar possíveis associações antropométricas e metabólicas com o aumento e/ou diminuição da AF e do HDL-C sérico após a CB.

4 PROBLEMAS DO ESTUDO

A incidência de PNP é maior em mulheres pós-menopáusicas e homens com obesidade grau II e III sem diabetes do que em mulheres pré-menopáusicas obesas sem diabetes submetidas à CB?

Mulheres pós-menopáusicas e homens com obesidade grau II e III sem diabetes têm um risco aumentado para progressão da PNP do que mulheres pré-menopáusicas obesas sem diabetes após a CB?

Há fatores de risco para PNP em sujeitos com obesidade grau II e III sem diabetes relacionados com hiperglicemia, hipertrigliceridemia, hipercolesterolemia, baixo HDL-C, peso corporal elevado, circunferência da cintura aumentada, sexo masculino, pós-menopausa, hipertensão, menores níveis séricos de vitamina B12, sedentarismo e CB?

A CB favorece a ocorrência e progressão da PNP em sujeitos com obesidade grau II e III sem diabetes?

5 HIPÓTESES

5.1 Hipóteses nulas

A incidência de PNP não difere entre mulheres pré- e pós-menopáusicas e homens com obesidade grau II e III sem diabetes submetidos à CB.

A incidência e progressão de PNP em mulheres pré- e pós-menopáusicas e homens com obesidade grau II e III sem diabetes não se associam com a hiperglicemia, hipertrigliceridemia, hipercolesterolemia, HDL-C baixo, hipertensão, sexo masculino, pós-menopausa, menores níveis séricos de vitamina B12, sedentarismo, perda de peso corporal e da circunferência da cintura relacionados à CB.

A CB não tem efeito sobre a ocorrência de PNP em sujeitos com obesidade grau II e III sem diabetes.

5.2 Hipóteses alternativas

A incidência de PNP é maior em mulheres pós-menopáusicas e homens com obesidade grau II e III sem diabetes do que em mulheres pré-menopáusicas obesas sem diabetes submetidos à CB.

A incidência e progressão de PNP em mulheres pré- e pós-menopáusicas e homens com obesidade grau II e III sem diabetes apresenta associação com a hiperglicemia, hipertriglicerídemia, hipercolesterolemia, HDL-C baixo, hipertensão, sexo masculino, pós-menopausa, menores níveis séricos de vitamina B12, sedentarismo, perda de peso corporal e da circunferência da cintura relacionados à CB.

A CB melhora/agrava e favorece/não favorece a ocorrência de PNP em sujeitos com obesidade grau II e III sem diabetes.

6 OBJETIVOS

6.1 Objetivo principal

Avaliar a incidência e progressão de PNP em mulheres pré- e pós-menopáusicas e homens com obesidade grau II e III sem diabetes e buscar pela presença ou não de fatores de risco para o desenvolvimento e progressão de PNP como hiperglicemia, hipertrigliceridemia, hipercolesterolemia, HDL-C baixo, hipertensão, sexo masculino, pós-menopausa, menores níveis séricos de vitamina B_{12}, sedentarismo, apneia do sono, perda de peso corporal e da circunferência da cintura relacionados à CB.

6.2 Objetivos secundários

Avaliar se a incidência e progressão de PNP difere entre mulheres pré- e pós-menopáusicas e homens com obesidade graus II e III sem diabetes submetidos à CB.

Avaliar se os fatores de risco para PNP diferem entre mulheres pré- e pós-menopáusicas e homens com obesidade graus II e III sem diabetes submetidos à CB.

Avaliar e relacionar os níveis de AF e gasto energético com a PNP em mulheres pré- e pós-menopáusicas e homens com obesidade graus II e III sem diabetes submetidos à CB.

Avaliar e relacionar a dor neuropática através do DN4 com a PNP em mulheres pré- e pós-menopáusicas e homens com obesidade graus II e III sem diabetes submetidos à CB.

Avaliar e relacionar o risco de apneia do sono através do STOP-BANG com a PNP em mulheres pré- e pós-menopáusicas e homens com obesidade graus II e III sem diabetes submetidos à CB.

Avaliar a adesão à medicação e à suplementação vitamínica em mulheres pré- e pós-menopáusicas e homens com obesidade graus II e III sem diabetes submetidos à CB.

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ARTIGO 1: Peripheral polyneuropathy after bariatric surgery: independent association with high-density lipoprotein (HDL) cholesterol in a cohort study

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Peripheral polyneuropathy after bariatric surgery: independent association with high-density lipoprotein (HDL) cholesterol in a cohort study

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Abstract

Background: The most common neurological complication described after bariatric surgery (BS) is peripheral polyneuropathy (PPN). However, there is poor evidence about the impact of BS on the incidence and progression PPN.

Aim: To evaluate the incidence and progression of PPN in non-diabetic severe obese subjects after laparoscopic bariatric surgery (BS) and to seek for the presence of risk factors.

Methods: In this prospective cohort study, 322 subjects undergoing laparoscopic BS were evaluated for PPN by the Michigan Neuropathy Screening Instrument (MNSI) before and after 6 months of BS and divided according to presence (+) or absence (–) of PPN at baseline. Known causes of PPN were excluded.

Results: The prevalence of pre-BS PPN was 21.4% and decreased to 8.7% post-BS. When we looked to the two groups, from baseline to 6 months, for PPN (+) group (n = 69) the persistence of post-BS PPN was 20.3% (n = 14) and for the PPN (–) group (n = 253) it was 5.5% (n = 14). In the PPN (–) group that incidence was independently associated with low high-density lipoprotein cholesterol (HDL-C) levels (p = 0.001) and the PPN risk increased from 7.4 to 8.6% at each 1 mg/dL decrease in HDL-C.

Conclusion: The prevalence of PPN decreased after 6 months of BS, but new cases of post-BS PPN appeared and they were independently associated with low HDL-C.

Keywords: Peripheral polyneuropathy; Obesity; Bariatric surgery; HDL cholesterol.

Introduction

Bariatric surgery (BS) is considered the most effective treatment for morbid obesity compared to conventional clinical treatment, causing rapid, substantial and sustained weight loss, with low mortality and improvement of obesity-related comorbidities, such as type 2 diabetes mellitus (T2DM), arterial hypertension, non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnea syndrome (OSAS) (1).

Peripheral polyneuropathy (PPN) is described as the most common neurological complication reported after BS and it is mainly attributed to nutritional deficiencies caused by restriction in food intake and / or limitation of intestinal absorption (2). When we look at medical literature, the evidence about BS impact on the post-BS PPN is poor. Therefore, the objectives of this study were to evaluate the incidence and progression of PPN in non-diabetic severe obese subjects after laparoscopic bariatric surgery (BS) and to seek for the presence of risk factors.

Methods

Study design and population

A prospective cohort study was conducted in 322 non-diabetic severe obese subjects undergoing laparoscopic BS by using the Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) techniques. All participants were evaluated for PPN preoperatively, then again at 6 months postoperative, and were divided according to presence (+) or absence (–) of PPN at baseline. The study was conducted from April 2016 to February 2019. The subjects were evaluated by two evaluators during routine consultations at the Hospital. Subjects of both sexes were included if they were older than 18 years of age and met the criteria for BS in our

country – grade II obesity (BMI ≥ 35-39.9 kg/m²) with at least one associated comorbidity or grade III obesity (BMI ≥ 40 kg/m²) – and if they were undergoing RYGB or SG. The exclusion criteria were T2DM, decompensated hypothyroidism, vitamin B12 deficiency, alcoholism, acute liver disease, chronic kidney disease, leprosy, systemic lupus erythematosus, positive serology for HIV, cancer, use of neurotoxic drugs, pregnancy, or previous BS.

From 434 initial subjects, 112 were excluded. Of the excluded subjects, 48 had T2DM, 33 had vitamin B12 deficiency, eight had decompensated hypothyroidism, eight were alcoholic abusers, six had pregnancy after BS, three had grade I obesity at baseline, two had use of neurotoxic drugs, one had systemic lupus erythematosus, one was positive for HIV, one had leprae. One did not participate because he did not come to the follow-up visits.

Diet and physical activity recommendations

In the pre- and postoperative periods, all subjects received a prescribed balanced diet in addition to other recommendations such as to eat 5 to 6 meals per day and to increase their physical activity (PA) by completing at least 150 min of walking per week. After BS, outpatient visits were scheduled for every 3 months. All subjects received multivitamin supplementation after BS.

Anthropometric, blood pressure, clinical and laboratory data

All data were collected before 3 months and after 6 months of BS. Body weight, height, BMI and waist circumference (WC) were measured using a BALMAK calibrated digital scale with a maximum capacity of 300 kg and a vertical stadiometer coupled and a 1.50 m measuring tape. The excess weight (EW) was calculated from the difference between pre- or postoperative weights and the ideal weight corresponding to a BMI of 25 kg/m² and % excess weight loss (%EWL) was obtained by the difference between pre- and postoperative body weight divided by EW.

Systolic (SBP) and diastolic blood pressure (DBP) data were measured using an OMRON HEM-7200 automatic blood pressure monitor cuff (22–32 cm and 32–42 cm).

Health history data was obtained from medical records. For menopausal status, women were classified according to their menstrual history or laboratory criteria (follicle-stimulating hormone (FSH) and estradiol levels) (3).

Serum levels of glucose, glycosylated haemoglobin (HbA1c), two-hour 75-gram oral glucose tolerance test (2-h 75-g OGTT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-HDL-cholesterol (non-HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), creatinine, thyroid-stimulating hormone (TSH) and B12 vitamin were also collected.

Physical activity and energy expenditure

To evaluate PA, the short version of the International Physical Activity Questionnaire (IPAQ) (4) was used: it evaluates daily activities over the last 7 days. The participants were classified according to the frequency and duration of the different types of PA. The time spent sitting on weekdays and the weekend was also recorded. In addition, patients were evaluated for whether they completed ≥150 min/week of PA (sum of PA from IPAQ), as recommended by the World Health Organization and the American College of Sports Medicine.

Using data collected in the IPAQ, energy expenditure was quantified and defined as the metabolic equivalent of task (MET) in min/week. The calculation of energy expenditure was performed using the Ainsworth formula (5): (days of walking x duration x 3.3) + (days of moderate PA x duration x 4.0) + (days of vigorous PA x duration x 8.0).

Peripheral polyneuropathy assessment

Subjects were assessed for PPN by Michigan Neuropathy Screening Instrument (MNSI) with a cut off ≥2.5 plus at least one neuropathic symptom before and after 6 months of BS. The MNSI

questionnaire (Portuguese version) was used as described by Oliveira et al. (2016) (6). This test has a specificity and sensitivity of 79% and 61%, respectively, when compared to the neurological exam plus nerve conduction studies (7,8). It has been described in detail in a previous publication by our group (9).

Statistical analysis

Quantitative data are presented as the median and interquartile range. Normality was defined by the Shapiro-Wilk test. To compare the PPN (+) and PPN (–) groups at baseline and before 6 months Mann-Whitney U test was used. For comparing pre- and postoperative periods in each group, Wilcoxon's test was used. Categorical data are presented as absolute values and frequencies. The Yates's continuity correction test or Pearson's chi-squared test or Fisher's exact test were used to compare the PPN (+) and PPN (–) groups at baseline and before 6 months as appropriate. The McNemar test was used to compare pre- and postoperative periods in each group. At the end, we looked for independent associations between individual variables and the progression of post-BS PPN by using multiple logistic regression analysis (Poisson). Variables that showed $p < 0.2$ in univariate analysis were included to the regression model. The association of measures was assessed by the risk ratio (RR) for a 95% confidence interval (CI). Data were analyzed by using SPSS version 18.0, and values with $p \leq 0.05$ were considered statistically significant.

For sample calculation, we used data from a cross-sectional study of our group (9) which investigated the prevalence and associations of PPN in non-diabetic severe obese subjects with metabolic syndrome who were undergoing a BS protocol. We found a prevalence of 11% of PPN associated with low HDL-C. Considering a power of 90% and a confidence interval of 5%, 108 subjects would be needed, with 54 in each group. Assuming an additional loss of 20%, there would be 130 subjects. The Sealed Envelope website was used for the sample calculation (10).

Ethical aspects

The study was approved by the Ethical Committee of the Hospital (Approval number 51843515.1.0000.5335). Written informed consent was obtained for each participant in the study.

Results

From the total sample, we found a prevalence of PPN before BS of 21.4% (n = 69) and it decreased to 8.7% (n = 28) after 6 months of BS. There was no difference between RYGB and SG in PPN prevalence's before and after 6 months of BS (p = 0.783 and p = 0.669, respectively). No difference was also found between the two surgical techniques in the other preoperative variables evaluated (data not shown). Therefore, the two surgical techniques were included together in the analysis.

Table 1 presents the demographic, anthropometric, blood pressure, clinical, laboratory and PA data of the 322 non-diabetic obese subjects at baseline. When we compared PPN (+) and PPN (–) groups, in univariate analysis, we saw an association with postmenopausal status (p = 0.004) and a trend of association with highest age (p = 0.077), height (p = 0.174), WC (p = 0.092), hypertension (p = 0.139) and HbA1c (p = 0.121), lower energy expenditure (p = 0.154), and IPAQ classification (p = 0.052). As a collinearity was observed between postmenopausal status and age, two different models (Poisson regression analyses), one with postmenopausal status and other with age, were tested including all the others cited variables (data not shown). Only postmenopausal status (PR 2.49, 95% CI 1.15–5.42, p = 0.021) and age (PR 1.03, 95% CI 1.00–1.05, p = 0.022) were independently associated with the presence of

preoperative PPN in non-diabetic severe obese subjects in the two models (p = 0.020 and p = 0.034, respectively).

In order to evaluate the incidence of PPN, we looked to the PPN (+) and PPN (-) groups separately (respectively, Tables 2 and 3).

The PPN (+) group was composed by 69 subjects (Table 2). From baseline to 6 months after BS, PPN persistence was 20.3% (n = 14) and there was a trend of association of this result with SG (p = 0.068), highest height (p = 0.199), WC (p = 0.097), glycaemia (p = 0.163) and prediabetes (p = 0.053), and IPAQ classification (p = 0.103). In the multivariate analysis, none model showed statistical significance to determine which factors could be independently related with the progression of PPN in these subjects (data not shown).

The PPN (–) group on baseline was composed by 253 subjects (Table 3). In this group, the incidence of post-BS PPN was 5.5% (n=14) and it showed an association, in univariate analysis, with highest body weights (p = 0.012), height (p = 0.021), EW (p = 0.028), TG (p = 0.020), and low %EWL (p = 0.044) and low HDL-C (p = 0.002) post BS. There was also a trend of association with a high BMI (p = 0.053), grade of obesity (p = 0.185) and WC (p = 0.066).

To determinate which risk factors could be independently associated with the incidence and progression of post-BS PPN in PPN (–) group, a multivariate analysis (Poisson regression analyses) was performed (Table 4). In four different models, only HDL-C was independently associated with the incidence and progression of post-BS PPN in non-diabetic severe obese subjects (p = 0.001). The PPN risk increases from 7.4 to 8.6% at each 1 mg/dL decrease in HDL-C.

When we looked at the 133 subjects undergoing RYGB, 20.3% (n = 27) were PPN (+) at baseline and from baseline to 6 months after BS the observed incidence was 7.4% (n = 2).

Of the 106 RYGB preoperative PPN (–) subjects, incidence of PPN from baseline to 6 months post-surgery was 7.5% (n = 8) (data not shown).

In subjects undergoing SG (n = 189), 22.2% (n = 42) were PPN (+) on baseline and from baseline to 6 months after BS the incidence was 28.6% (n = 12). A total of 147 subjects submitted to SG were PPN (–) at baseline and the postoperative incidence of PPN in this group was 4.1% (n = 6) (data not shown).

Discussion

The objective of the present study was to evaluate the incidence and progression of PPN in non-diabetic severe obese subjects and to seek for possible risk factors. We found a prevalence of PPN of 21.4% at baseline and it decreased to 8.7% after 6 months of BS. Prevalence of PPN at baseline was independently associated with postmenopausal status and age. In subjects with preoperative PPN (+), the persistence of PPN was 20.3% after 6 months of BS and no associations were found. However, in PPN (–) subjects at baseline, PPN's incidence was 5.5% after 6 months of BS and it was independently associated with lower HDL-C.

In a previously study, we showed that PPN prevalence in non-diabetic severe obese women was associated with menopause and age (11). Although this current study included male subjects, we also found a collinearity and independent association of PPN with postmenopausal status ($p = 0.021$) and age ($p = 0.022$). Aging is well established as a risk factor for PPN related to different ethiologies (12) and some studies have shown a possible relation between estrogen levels and the presence of PPN (13,14). Singh et al. (2016) in a cross-sectional study demonstrated that postmenopausal women with PPN had lower nerve conduction velocity and

estrogen levels (14). We think that estrogen could have a role on inducing neuroprotection and neuroregeneration, but future studies are necessary for evaluation of this hypothesis.

Case reports, cross-sectional and retrospective cohort studies have shown that PPN is the most frequent neurological complication and were related to vitamin deficiencies, as vitamins B1, B6 and B12, due to inadequate intake of food and its malabsorption after BS (2,15-20). In our study, subjects with B12 vitamin deficiency were excluded at baseline and during follow-up. All subjects received multivitamin supplementation after BS, which contains B complex vitamins and other micronutrients, and if there were pre- or postoperative vitamin B12 deficiency, they received B12 supplementation. In addition, participants received nutritional counseling.

Diabetic neuropathy is common in T2DM but tight glycemic control does not improve the symptoms (21). In non-severe obese diabetic subjects undergoing RYGB, nitrosative stress but not glycemic parameters appear to be correlated with improved neuropathy (22). Patients with T2DM showed remission of hyperglycemia after obesity surgery (1), with significantly decrease of BMI and HbA1c levels and reversible symptomatic neuropathy in 67% of the patients after RYGB (23). We excluded T2DM subjects in our study, but when we looked at preoperative PPN (+) group, in univariate analysis, we see a trend of association with presence of prediabetes ($p = 0.053$), and the persistence of PPN was 20.3% after BS. Studies suggest that peripheral neuropathy in prediabetes precedes diabetic neuropathy (24). As there is an improvement in blood glucose and HbA1c levels after BS, this could be a way to explain why PPN did not showed progression. We think that more PPN (+) subjects should be evaluated to clarify possible associations.

We found a trend of association of higher incidence of post-BS PPN in SG compared to RYGB (85.7% versus 14.3%, $p = 0.068$) in preoperative PPN (+) group. An experimental study

on diabetic polyneuropathy in streptozotocin-induced diabetic rats indicated that RYGB ameliorates the severity of DPN, which may be associated with increased GLP-1 and improved insulin sensitivity/action (25). Study in RYGB candidates without clinical evidence of PPN suggested an improvement in peripheral nerve regenerative capacity related to surgical weight loss with improvement of measures of peripheral nerve function, epidermal innervation and MNSI score after 1 year (26). We did not find any study associating the improvement or not of PPN with SG, which makes us think that PPN resolution maybe no differs between subjects submitted to RYGB or SG.

Callaghan et al. (2016) found a PPN prevalence of 40.5% in diabetic bariatric subjects and WC (OR 1.36, 95%CI 1.07–1.73), TG (OR 1.44, 95% CI 1.01–2.05), and SBP (OR 2.18, 95%CI 1.12–4.27) were associated (27). We also found a trend of association of post-BS PPN with higher WC compared to resolved PPN subjects (93.5 cm versus 88.0 cm, $p = 0.097$) in preoperative PPN (+) group, however we could not confirm it in the multivariate analysis.

In our study, the incidence of post-BS PPN in subjects without PPN at baseline was 5.5% and, although there was association with higher weight, height, BMI, degree of obesity, WC, EW, TG and lower %EWL in the univariate analysis, only lower HDL-C was independently associated with PPN ($p = 0.001$) in multivariate analysis. This post-BS PPN could be related to obesity or have been underdiagnosed at baseline and aggravated by HDL-C decrease that usually is described on the first months after BS (28). A previous cross-sectional study of our group evaluating the prevalence of PPN and associated factors in non-diabetic severe obese subjects with metabolic syndrome who undergone a BS protocol found an independently association of PPN prevalence with low HDL-C levels ($p = 0.047$) (9).

HDL is a heterogeneous population of particles, tightly controlled by genetic factors that increases with PA and differences in the capacities of HDL subfractions may explain

variations in removing cellular cholesterol (29). Based on scientific evidence, we had assumed previously that HDL-C particles could be captured by scavenger-receptor B-1 (SR-B1) present in injured distal axons, the cholesterol being used for the regeneration of these nerve fibers and, as these subjects had low HDL-C levels, consequently the regeneration of neurons was impaired (9). We think that the same is occurring in this cohort of subjects who developed PPN after BS and decreased their serum HDL-C levels.

Ikura et al. (2016) showed that HDL-C levels might be a novel clinical predictor for the incidence of lower-extremity amputation and wound-related death in patients with diabetic foot ulcers (30). A case-control study in T2DM subjects showed that serum apolipoprotein (Apo) A-I was positively associated with the presence of diabetic neuropathy. Each standard deviation increment in serum Apo A-I was associated with increased frequency of diabetic neuropathy (OR 1.2, 95% CI 1.1–1.3, p = 0.006) (31). In one study serum Apo A-I levels were inversely associated with the prevalence of cardiovascular autonomic neuropathy in individuals with T2DM (OR 0.65, 95% CI 0.43–0.97, p = 0.036) (32). In our study, PPN risk increased from 7.4 to 8.6% at each 1 mg/dL decrease in HDL-C.

Studies showed that HDL-C increases only after 1 year of BS (33,34,35), and the increase is apparently similar between RYGB and SG (28,35) what could be related to preservation of the small intestine (particularly the jejunum) (36). Surgically induced weight loss effectively reverses many steps in HDL-C metabolism that have been altered with obesity, improving HDL structure and functionality (36,37). Furthermore, enterocytes contribute to HDL levels through the synthesis of Apo A-IV and A-I (36). However, Heffron et al (2018) showed that 6 months after BS, SG produced superior response in HDL-C and Apo A-I quantity, as well as global and non-ABCA1 (ATP-binding cassette transporter A1)-mediated cholesterol efflux capacity (CEC) versus RYGB. At 12 months after SG, CEC was equivalent to that of normal body mass index control subjects, whereas it remained impaired after RYGB

(38). Possibly, with increasing of HDL-C levels after 1 year of BS, PPN improves. It would be necessary longer follow-up time of our subjects with post-BS PPN to verify if the increase of serum HDL-C levels would reduce PPN incidence and if it differ between RYGB and SG.

Data from the National Health and Nutrition Examination Survey (NHANES) showed that diabetic subjects who were involved in higher PA levels (moderate to vigorous intensity) and had normal HbA1c levels were less likely to have diabetic neuropathy (39). In our study, no relation was found between PA levels and the incidence of post-BS PPN. However, if we think that PA increases HDL-C levels and may prevent the development of PPN, the practice of PA after BS is an important recommendation to avoid the development of PPN after surgery.

The strengths of our study include the prospective study design, large sample size and evaluation of SG candidates. Limitations of the study were: a) low number of PPN (+) subjects, b) short follow-up time and c) absence of complementary neurological evaluation, which could contribute to better evaluation of the progression of post-BS PPN and to confirm our hypotheses.

Conclusion

In summary, the prevalence of PPN decreased after 6 months of BS. However, new cases of post-BS PPN showed independent association with lower HDL-C. More studies will be needed to support our findings.

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Table 1. Comparison of presence (+) and absence (-) groups of peripheral polyneuropathy (PPN) evaluated 3 months before laparoscopic bariatric surgery (BS) to determinate which factors could be associated with pre-BS PPN in 322 severely obese subjects without diabetes. Numbers are presented as median and interquartile amplitude (percentiles 25–75) for quantitative variables and total number and percentage for qualitative variables. The measurement units and number of patients are presented with the corresponding variables.

	Total sample (n=322)	PPN (+) (n=69)	PPN (-) (n=253)	P-value
Female sex (n, %)	254 (78.9)	51 (73.9)	203 (80.2)	0.330 (a)
Postmenopausal status (n, %)	42 (16.5)	16 (23.2)	26 (10.3)	0.004* (c)
Age (years)	36.0 (30.0–42.0)	38.0 (31.0–46.0)	35.0 (30.0–41.0)	0.077 (b)
Body weight (kg)	110.8 (99.7–126.0)	108.5 (98.1–136.9)	111.0 (100.5–125.2)	0.637 (b)
Height (cm)	164 (159–169)	164 (160–172)	164 (159–169)	0.174 (b)
BMI (kg/m²)	41.3 (38.8–44.7)	40.6 (38.6–44.4)	41.6 (39.0–44.7)	0.512 (b)
Obesity (n, %)				0.383 (a)
Grade II	114 (35.4)	28 (40.6)	86 (34.0)	
Grade III	208 (64.6)	41 (59.4)	167 (66.0)	
EW (kg)	43.7 (36.0–55.4)	42.2 (35.3– 56.6)	44.0 (36.1–54.2)	0.996 (b)
WC (cm)	110.0 (103.5–119.5)	112.0 (105.0– 120.5)	110.0 (102.5–119.0)	0.092 (b)
SBP (mmHg) (69/252)	128.0 (119.0–136.0)	129.0 (121.0– 140.0)	128.0 (119.0–136.0)	0.376 (b)
DBP (mmHg) (69/252)	86.0 (80.0–92.0)	86.0 (81.0– 91.0)	86.0 (80.0–92.5)	0.908 (b)
Hypertension (n, %)	268 (83.2)	62 (89.9)	206 (81.4)	0.139 (a)
Glycemia (mg/dL) (68/253)	91.0 (86.0–99.0)	94.0 (86.0–99.5)	91.0 (85.0–99.0)	0.821 (b)

2-h 75-g OGTT (mg/dL) (57/202)	114.0 (93.0–132.0)	112.0 (90.0–131.0)	114.0 (95.0–132.0)	0.637 (b)
HbA1c (%) (63/231)	5.4 (5.1–5.6)	5.4 (5.2–5.7)	5.3 (5.1–5.6)	0.121 (b)
Prediabetes (n, %)	68 (21.1)	18 (26.1)	50 (19.8)	0.330 (a)
TC (mg/dL) (68/250)	190.0 (172.0–213.0)	190.0 (173.0–208.5)	190.5 (171.0–214.0)	0.740 (b)
TG (mg/dL) (68/249)	127.0 (88.0–164.0)	124.0 (100.5–148.5)	128.0 (86.0–169.0)	0.550 (b)
HDL-C (mg/dL) (68/248)	47.0 (41.0–56.0)	46.5 (40.0–54.0)	47.0 (41.0–57.0)	0.357 (b)
Non-HDL-C (mg/dL) (68/248)	139.5 (120.6–162.5)	143.0 (119.5–163.5)	139.0 (121.5–162.5)	0.760 (b)
LDL-C (mg/dL) (68/247)	113.2 (95.7–135.1)	113.6 (96.2–139.5)	112.8 (95.5–124.8)	0.704 (b)
MS (n, %)	191 (59.3)	37 (53.6)	154 (60.9)	0.343 (a)
B12 vitamin (pg/mL) (69/248)	390.0 (314.0–511.5)	418.0 (320.5–535.0)	386.2 (311.0–506.5)	0.369 (b)
Total sitting time (min/day) (68/250)	600.0 (360.0–840.0)	540.0 (360.0–840.0)	600.0 (360.0–840.0)	0.311 (b)
Energy expenditure (MET - min/week) (69/252)	388.5 (360.0–840.0)	346.5 (49.5–792.0)	396.0 (148.5–1026.0)	0.154 (b)
IPAQ classification (n, %)				0.052 (c)
Sedentary	43 (13.4)	14 (20.3)	29 (11.5)	
Insufficiently active B	102 (31.7)	24 (34.8)	78 (31.0)	
Insufficiently active A	61 (18.9)	7 (10.1)	54 (21.4)	
Active	105 (32.6)	20 (29.0)	85 (33.7)	
Very active	10 (3.1)	4 (5.8)	6 (2.4)	
PA ≥150 min per week (n, %)	128 (39.8)	26 (37.7)	102 (40.5)	0.778 (a)

PPN, peripheral polyneuropathy; BMI, body mass index; EW, excess body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; OGTT, oral glucose tolerance test; HbA1c, glycosylated haemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C,

high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; MET, metabolic equivalent of task; IPAQ, International Physical Activity Questionnaire; PA, physical activity; n = absolute number.

*Statistical significance was considered at $p \leq 0.05$; (a) Yates's continuity correction test, (b) Mann-Whitney U test, (c) Pearson's chi-squared test.

Table 2. Evaluation of 69 subjects with peripheral polyneuropathy (PPN (+) on baseline) before and 6 months after the laparoscopic bariatric surgery (BS) with factors that could be associated with presence or absence of post-surgery PPN. Numbers are presented as median and interquartile amplitude (percentiles 25–75) for quantitative variables and total number and percentage for qualitative variables. The measurement units and number of patients are presented with the corresponding variables.

	PPN (+) → PPN (-) (n=55)			PPN (+) → PPN (+) (n=14)			P-value
	Pre-BS	Post-BS	P-value	Pre-BS	Post-BS	P-value	
Female sex (n, %)	42 (76.4)	NA	NA	9 (64.3)	NA	NA	0.563 (c)
Postmenopausal status (n, %)	12 (21.8)	NA	NA	4 (28.6)	NA	NA	0.418 (d)
Age (years)	38.0 (31.0–46.0)	NA	NA	40.0 (34.0–52.0)	NA	NA	0.244 (e)
BS (n, %)							
RYGB	NA	25 (45.5)	NA	NA	2 (14.3)	NA	0.068 (c)
SG	NA	30 (54.5)		NA	12 (85.7)		
Body weight (kg)	108.1 (97.6–125.8)	78.0 (72.8–95.4)	<0.001* (a)	129.9 (99.7–144.0)	88.3 (75.3–111.2)	0.001* (a)	0.230 (e)
Height (cm)	164 (160–169)	NA	NA	167 (160–181)	NA	NA	0.199 (e)
BMI (kg/m²)	40.6 (38.3–44.7)	29.8 (27.9–32.9)	<0.001* (a)	40.9 (39.7–42.3)	29.1 (27.5–34.9)	0.001* (a)	0.846 (e)
Obesity (n, %)							
Normal	0 (0.0)	5 (9.1)		0 (0.0)	1 (7.1)		
Overweight	0 (0.0)	23 (42.8)		0 (0.0)	7 (50.0)		
Grade I	0 (0.0)	19 (34.5)	<0.001* (b)	0 (0.0)	3 (21.4)	<0.001* (b)	0.478 (d)
Grade II	23 (41.8)	4 (7.3)		5 (35.7)	0 (0.0)		
Grade III	32 (58.2)	4 (7.3)		9 (64.3)	3 (21.4)		
EW (kg)	40.9 (34.8–55.2)	12.2 (7.6–22.3)	<0.001* (a)	55.2 (36.9–58.0)	11.8 (7.4–34.0)	0.001* (a)	0.777 (e)
EWL (%)	NA	68.4 (58.0–81.7)	NA	NA	72.4 (47.8–85.7)	NA	0.777 (e)
WC (cm)	112.0 (105.0–119.0)	88.0 (84.0–97.5)	<0.001* (a)	120.0 (107.0–133.0)	93.5 (89.0–112.0)	0.001* (a)	0.097 (e)

SBP (mmHg)	129.0 (121.0–136.0)	118.0 (108.0–128.0)	<0.001* (a)	134.0 (122.0–151.0)	117.5 (108.0–126.0)	0.001* (a)	0.899 (e)
DBP (mmHg)	86.0 (81.5–90.5)	74.0 (66.0–82.0)	<0.001* (a)	89.5 (81.0–95.0)	74.5 (70.0–84.0)	0.001* (a)	0.535 (e)
Hypertension (n, %)	50 (90.9)	19 (34.5)	<0.001* (b)	12 (85.7)	6 (42.9)	0.031* (b)	0.790 (c)
Glycaemia (mg/dL) (54/52) (14/13)	94.0 (87.0–99.0)	84.4 (80.0–89.5)	<0.001* (a)	93.5 (85.0–09.0)	88.0 (84.0–93.0)	0.220 (a)	0.163 (e)
HbA1c (%) (49/43) (14/12)	5.4 (5.2–5.7)	5.1 (5.0–5.3)	<0.001* (a)	5.5 (5.0–6.0)	5.1 (4.9–5.4)	0.090 (a)	0.894 (e)
Prediabetes (n, %)	14 (25.5)	2 (3.6)	0.003* (b)	4 (28.6)	3 (21.4)	0.625 (b)	0.053 (d)
TC (mg/dL) (55/45) (13/13)	191.0 (173.0–213.5)	159.0 (135.0–188.0)	<0.001* (a)	182.0 (178.0–200.0)	153.0 (136.0–192.0)	0.028* (a)	0.963 (e)
TG (mg/dL) (55/44) (13/13)	125.0 (107.0–150.0)	80.5 (71.5–95.5)	<0.001* (a)	123.0 (73.0–134.0)	78.0 (60.0–101.0)	0.033* (a)	0.739 (e)
HDL-C (mg/dL) (55/44) (13/13)	48.0 (41.0–54.0)	47.5 (37.5–55.8)	0.421 (a)	41.0 (40.0–53.0)	42.0 (36.0–54.0)	0.271 (a)	0.568 (e)
Non-HDL-C (mg/dL) (55/44) (13/13)	147.0 (122.0–165.5)	111.0 (93.4–138.5)	<0.001* (a)	137.0 (115.0–149.0)	102.0 (88.0–146.0)	0.034* (a)	0.887 (e)
LDL-C (mg/dL) (55/43) (13/13)	114.0 (96.3–141.7)	95.0 (76.7–117.8)	<0.001* (a)	111.2 (96.4–123.8)	88.0 (76.0–126.2)	0.050* (a)	0.869(e)
MS (n, %)	32 (58.2)	9 (16.4)	<0.001* (b)	5 (35.7)	4 (28.6)	1.000 (b)	0.509 (c)
B12 vitamin (pg/mL) (55/52) (14/13)	418.0 (324.0–585.5)	462.5 (365.7–831.0)	0.026* (a)	406.5 (317.0–489.0)	451.0 (361.7–556.0)	0.221 (a)	0.731 (e)
Energy expenditure (MET - min/week)	360.0 (57.8–912.3)	1154.0 (522.8–1827.0)	0.003* (a)	203.8 (0.0–540.0)	695.0 (428.5–2526.0)	0.008* (a)	0.447 (e)

IPAQ (n, %)							
Sedentary	10 (18.2)	1 (1.8)		4 (28.6)	2 (14.3)		
Insufficiently active B	18 (32.7)	9 (16.4)	0.031* (b)	6 (42.9)	2 (14.3)	0.238 (b)	0.103 (d)
Insufficiently active A	6 (10.9)	6 (10.9)		1 (7.1)	4 (28.6)		
Active	17 (30.9)	30 (54.5)		3 (21.4)	5 (35.7)		
Very active	4 (7.3)	9 (16.4)		0 (0.0)	1 (7.1)		
PA ≥150 min per week (n, %)	23 (41.8)	41 (74.5)	0.001* (b)	3 (21.4)	8 (57.1)	0.031* (b)	0.341 (c)

PPN, peripheral polyneuropathy; BS, bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BMI, body mass index; EW, excess body weight; EWL, excess weight loss; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; MET, metabolic equivalent of task; IPAQ, International Physical Activity Questionnaire; PA, physical activity; n = absolute number.

*Statistical significance was considered at $p \leq 0.05$; (a) Wilcoxon test, (b) McNemar test, (c) Yates's continuity correction test, (d) Fisher's exact test, (e) Mann-Whitney U test.

Table 3. Evaluation of 253 subjects without peripheral polyneuropathy (PPN (–) on baseline) before and 6 months after the laparoscopic bariatric surgery (BS) with factors that could be associated with presence or absence of post-surgery PPN. Numbers are presented as median and interquartile amplitude (percentiles 25–75) for quantitative variables and total number and percentage for qualitative variables. The measurement units and number of patients are presented with the corresponding variables.

	PNP (-) → PNP (-) (n=239)			PNP (-) → PNP (+) (n=14)			P-value
	Pre-BS	Post-BS	P-value	Pre-BS	Post-BS	P-value	
Female sex (n, %)	193 (80.8)	NA	NA	10 (71.4)	NA	NA	0.613 (c)
Postmenopausal status (n, %)	24 (10.0)	NA	NA	2 (14.3)	NA	NA	0.409 (d)
Age (years)	35.0 (30.0–41.0)	NA	NA	35.5 (33.0–42.0)	NA	NA	0.764 (e)
BS (n, %)							
RYGB	NA	98 (41.0)	NA	NA	8 (57.1)	NA	0.362 (c)
SG	NA	141 (59.0)		NA	6 (42.9)		
Body weight (kg)	110.7 (100.1–124.5)	79.4 (71.9–92.0)	<0.001* (a)	115.9 (110.8–138.7)	89.8 (83.0–102.0)	0.001* (a)	0.012* (e)
Height (cm)	163 (159–168.5)	NA	NA	168.5 (165–171)	NA	NA	0.021* (e)
BMI (kg/m²)	41.6 (38.8–44.6)	30.4 (27.6–33.0)	<0.001* (a)	42.6 (39.2–46.6)	32.0 (30.1–35.0)	0.001* (a)	0.053 (e)
Obesity (n, %)							
Normal	0 (0.0)	22 (9.2)	<0.001* (b)	0 (0.0)	0 (0.0)	0.011* (b)	0.185 (d)
Overweight	0 (0.0)	93 (38.9)		0 (0.0)	3 (21.4)		
Grade I	0 (0.0)	89 (37.2)		0 (0.0)	8 (57.1)		
Grade II	81 (33.9)	31 (13.0)		5 (35.7)	2 (14.3)		
Grade III	158 (66.1)	4 (1.7)		9 (64.3)	1 (7.1)		
EW (kg)	44.0 (36.0–53.5)	13.7 (6.9–22.0)	<0.001* (a)	48.6 (39.9–62.6)	19.7 (14.1–20.6)	0.001* (a)	0.028* (e)
EWL (%)	NA	67.9 (56.7–80.8)	NA	NA	58.4 (53.2–67.8)	NA	0.044* (e)

WC (cm)	110.0 (102.8–119.0)	88.0 (82.0–96.0)	<0.001* (a)	110.0 (102.8–119.5)	94.0 (86.0–102.0)	0.008* (a)	0. 066 (e)
SBP (mmHg) (238/237) (14/14)	128.0 (119.0–136.0)	118.0 (111.0–127.0)	<0.001* (a)	128.5 (125.0–137.0)	121.0 (110.0–128.0)	0.018* (a)	0.929 (e)
DBP (mmHg) (238/237) (14/14)	86.0 (80.0–93.0)	74.0 (69.0–81.0)	<0.001* (a)	87.0 (80.0–92.0)	76.5 (72.0–88.0)	0.003* (a)	0.509 (e)
Hypertension (n, %)	195 (81.6)	81 (33.9)	<0.001* (b)	11 (78.6)	5 (35.7)	0.031* (b)	1.000 (c)
Glycemia (mg/dL) (239/224) (14/13)	91.0 (86.0–99.0)	82.0 (78.0–87.0)	<0.001* (a)	92.5 (84.0–101.0)	83.0 (78.0–86.0)	0.023* (a)	0.733 (e)
HbA1c (%) (218/181) (13/7)	5.3 (5.1–5.6)	5.1 (4.9–5.3)	<0.001* (a)	5.6 (5.2–5.6)	5.2 (5.0–5.5)	0.089 (a)	0.355 (e)
Pre-diabetes (n, %)	47 (19.7)	12 (5.0)	<0.001* (b)	3 (21.4)	0 (0.0)	<0.001* (b)	0.832 (c)
TC (mg/dL) (236/198) (14/10)	191.0 (172.0–214.5)	161.0 (140.0–189.0)	<0.001* (a)	186.5 (163.0–211.0)	164.5 (148.0–171.0)	0.005* (a)	0.834 (e)
TG (mg/dL) (235/201) (14/11)	129.0 (87.0–172.0)	80.0 (66.0–98.0)	<0.001* (a)	123.0 (84.0–144.0)	102.0 (85.5–113.0)	0.182 (a)	0.020* (e)
HDL-C (mg/dL) (234/197) (14/9)	47.0 (41.3–57.0)	47.0 (40.0–54.0)	0.040* (a)	46.5 (37.0–62.0)	37.7 (35.0–39.0)	0.024* (a)	0.002* (e)
Non-HDL-C (mg/dL) (234/197) (14/8)	140.0 (122.0–162.0)	113.0 (93.0–141.0)	<0.001* (a)	128.0 (120.0–165.0)	126.5 (102.7–134.5)	0.123 (a)	0.815(e)
LDL-C (mg/dL) (233/197) (14/9)	113.2 (95.4–134.2)	96.6 (78.6–121.8)	<0.001* (a)	106.1 (98.6–143.2)	96.8 (79.4–111.8)	0.110 (a)	0.611 (e)
MS (n, %)	149 (62.3)	29 (12.1)	<0.001* (b)	5 (35.7)	3 (21.4)	0.688 (b)	0.546 (c)
B12 vitamin (pg/mL) (234/220) (14/14)	385.0 (312.0–505.0)	468.0 (340.5–676.5)	<0.001* (a)	432.0 (310.0–602.0)	432.0 (349.0–555.0)	0.875 (a)	0.601 (e)

Energy expenditure (MET - min/week) (238/239) (14/14)	396.0 (146.0–1026.0)	918.0 (492.5–1685.5)	<0.001* (a)	471.0 (351.0–1596.0)	1362.3 (560.0–1948.5)	0.510 (a)	0.322 (e)
IPAQ (n, %) (238/239) (14/14)							
Sedentary	29 (12.2)	12 (5.0)		0 (0.0)	1 (7.1)		
Insufficiently active B	73 (30.7)	30 (12.6)	<0.001* (b)	5 (35.7)	1 (7.1)	0.502 (b)	0.920 (d)
Insufficiently active A	51 (21.4)	43 (18.0)		3 (21.4)	2 (14.3)		
Active	80 (33.6)	125 (52.3)		5 (35.7)	8 (57.1)		
Very active	5 (2.1)	29 (12.1)		1 (7.1)	2 (14.3)		
PA ≥150 min per week (n, %) (238/239) (14/14)	96 (40.3)	170 (71.1)	<0.001* (b)	6 (42.9)	10 (71.4)	0.289 (b)	1.000 (e)

PPN, peripheral polyneuropathy; BS, bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BMI, body mass index; EW, excess body weight; EWL, excess weight loss; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; MET, metabolic equivalent of task; IPAQ, International Physical Activity Questionnaire; PA, physical activity; n = absolute number.

*Statistical significance was considered at $p \leq 0.05$; (a) Wilcoxon test, (b) McNemar test, (c) Yates's continuity correction test, (d) Fisher's exact test, (e) Mann-Whitney U test.

Table 4. Poisson regression analyses of variables apparently related to the dependent variable post-BS peripheral polyneuropathy (PPN) in severely obese subjects without diabetes without PPN (PPN (-)) at baseline.

	PPN post-BS (n=204)							
	Model 1 (p = 0.040*)		Model 2 (p = 0.047*)		Model 3 (p = 0.041*)		Model 4 (p = 0.031*)	
	RR (CI 95%)	P-value	RR (CI 95%)	P-value	RR (CI 95%)	P-value	RR (CI 95%)	P-value
Body weight (kg)	1.031 (0.949–1.120)	0.467	NA	NA	NA	NA	NA	NA
Height (cm)	1.031 (0.956–1.112)	0.430	NA	NA	NA	NA	NA	NA
BMI (kg/m²)	NA	NA	1.022 (0.843–1.240)	0.825	NA	NA	NA	NA
EW (kg)	NA	NA	NA	NA	1.028 (0.957–1.104)	0.447	NA	NA
EWL (%)	NA	NA	NA	NA	NA	NA	0.972 (0.926–1.020)	0.254
WC (cm)	0.944 (0.833–1.071)	0.370	0.990 (0.893–1.099)	0.855	0.970 (0.874–1.076)	0.563	0.965 (0.873–1.067)	0.492
TG (mg/dL)	1.009 (0.997–1.022)	0.126	1.011 (0.999–1.023)	0.074	1.012 (0.999–1.024)	0.064	1.011 (0.999–1.023)	0.071
HDL-C (mg/dL)	0.926 (0.884–0.969)	0.001*	0.917 (0.872–0.965)	0.001*	0.918 (0.873–0.965)	0.001*	0.914 (0.867–0.964)	0.001*

PPN, peripheral polyneuropathy; BS, bariatric surgery; BMI, body mass index; EW, excess body weight; EWL, excess weight loss; WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; RR, risk ratio; CI, confidence interval; NA, not applicable.

*Statistical significance was considered at $p \leq 0.05$.

ARTIGO 2: Metabolic effects of physical activity prior to and following bariatric surgery in severely obese subjects without diabetes: a cohort study

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Metabolic effects of physical activity prior to and following bariatric surgery in severely obese subjects without diabetes: a cohort study

Physical activity prior to and following bariatric surgery

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Abstract

Background: Even in individuals with severe obesity, physical activity (PA) reduces the risk of cardiometabolic diseases. Increasing PA is recommended prior to bariatric surgery (BS) but it is performed with poor success.

Objectives: To evaluate the PA of severely obese subjects without diabetes and to elucidate the benefits of PA practice prior to and following laparoscopic bariatric surgery (BS).

Subjects and Methods: A prospective cohort study was conducted in 91 obese (grade II and III) subjects without diabetes who were submitted to laparoscopic BS, Roux-en-Y gastric bypass (RYGB), or sleeve gastrectomy (SG) using a short version of the International Physical Activity Questionnaire prior to and 6 and 15 months post-BS. According to the performance or not of ≥ 150 min/week of PA, the patients were classified into active and inactive prior to and 15 months post-BS.

Results: PA increased significantly 6 and 15 months post-BS as compared with that preoperatively ($p < 0.001$); however, there was no difference between the two evaluated postoperative times ($p = 0.856$). Being active prior to BS was associated with a greater loss of waist circumference after 15 months as compared with being inactive (27.0% versus 24.2%; $p = 0.027$), with a greater loss in subjects submitted to RYGB than to SG (26.8% versus 24.1%; $p = 0.024$). There was also an association between being active prior to surgery and a higher high-density lipoprotein cholesterol (HDL-C) level post 15 months of BS (18.2% versus 10.9%; $p = 0.035$), but there was no difference between RYGB and SG (15.8% versus 12.4%; $p = 0.277$). Being active 15 months post-BS was not associated with any of the evaluated parameters.

Conclusion: PA increased after BS. The practice of ≥ 150 min/week of PA prior to BS resulted in a greater loss of waist circumference and a greater increase in HDL-C levels, with probable metabolic and cardiovascular repercussions.

Keywords: Severe obesity; Bariatric surgery; Physical activity; Waist circumference; HDL cholesterol

Introduction

Individuals with severe obesity are at a high risk for developing numerous cardiometabolic complications including hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, and cardiovascular disease, in addition to conditions such as osteoarthritis, obstructive sleep apnea, hepatobiliary diseases, and certain types of cancer (1). Before considering bariatric surgery (BS) in these individuals, lifestyle interventions, including changes in diet and physical activity (PA), in addition to pharmacological therapy, are the first steps in achieving weight loss and treating obesity-related comorbidities (1,2). Since weight loss is often not achieved with these noninvasive measures (3), BS has become a widely used option as it has been shown to be effective in promoting substantial and sustained weight loss in the long-term and in the resolution of comorbidities (3,4).

PA is one of the components of lifestyle modification programs recommended prior and following BS that aims to improve patients' physical capacity, reduce surgical complications and cardiovascular risk (5), and potentiate post-surgery results (4). Despite the recommendations for adopting PA practice, recent studies have shown that most obese patients are inactive and rarely perform behavioral changes, even postoperatively (6,7). Studies evaluating PA following BS have found divergent outcomes (8−22), including randomized

controlled trials (RCT) that used PA as an intervention (23−26). Therefore, the objective of the present study was to evaluate PA and the energy expenditure in severe obese individuals without diabetes who were submitted to laparoscopic BS and to elucidate the benefits of PA practice prior to and 15 months post-BS.

Subjects and Methods

Study design and population

A prospective cohort study was conducted in 91 severe obese subjects without diabetes who were submitted to laparoscopic BS, RYGB or SG, evaluating PA and energy expenditure prior to surgery (T0) and 6 (T1) and 15 months (T2) post-surgery. Subjects were divided into two distinct groups, active (≥ 150 min/week of PA) and inactive (< 150 min/week of PA), to evaluate the benefits of being active prior to and 15 months post-BS. The present study was conducted from April 2016 to December 2018. The data are part of a cohort that seeks to evaluate the incidence and progression of peripheral polyneuropathy in obese subjects following BS. Participants who had a follow up of 15 months after BS were chosen to participate. The subjects were evaluated by two evaluators during routine consultations at the Hospital. Subjects older than 18 years of age of both sexes, with criteria to perform BS in our country – grade II obesity (BMI ≥ 35–39.9 kg/m²) with at least one associated comorbidity or grade III (BMI ≥ 40 kg/m²) – and undergoing RYGB or SG were included. Exclusion criteria were: T2DM, cancer, decompensated hypothyroidism, pregnancy, alcoholic behavior, or patients who had undergone open bariatric surgery.

Of 100 initial subjects, nine were excluded: five with T2DM, three with decompensated hypothyroidism, and one who had undergone open bariatric surgery.

Diet and physical activity recommendations

During the pre- and postoperative periods, all subjects received a balanced diet prescription, in addition to other recommendations such as eating 5−6 meals a day and increasing PA by walking for at least 150 min/week. Following BS, outpatient visits were scheduled for every 3 months.

Anthropometric, blood pressure, clinical, and laboratory data

All data were collected prior to and 6 and 15 months post-BS. Body weight, height, BMI, and waist circumference (WC) were measured using a BALMAK calibrated digital scale with a maximum capacity of 300 kg, a vertical stadiometer, and a 1.50-m measuring tape. The excess weight (EW) was calculated by the difference between pre- or postoperative weights and the ideal weight, corresponding to a BMI of 25 kg/m², and % excess weight loss (%EWL) was obtained by the difference between pre- and postoperative body weight divided by EW.

Systolic (SBP) and diastolic blood pressure (DBP) data were measured using an OMRON HEM-7200 automatic blood pressure monitor cuff (22−32 cm and 32−42 cm). To evaluate the PA variables, subjects who used antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics, were excluded. Health history data were obtained from medical records.

Serum levels of glucose, glycosylated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (non-HDL-C), and triglycerides were also measured. Smokers, alcoholics, users of antilipidemics, such as statins and fibrates, steroids, and other drugs that interfere with serum lipid levels, such as beta-blockers, were excluded from the evaluation of lipid profile variables.

Physical activity and energy expenditure

A short version of the International Physical Activity Questionnaire (IPAQ) was used to evaluate PA according to daily activities over the last 7 days (27). The participants were classified according to the frequency and duration of different types of PA: sedentary, insufficiently active B and A, active, or very active. The time spent sitting on weekdays and weekends was also questioned. In addition, patients were evaluated with respect to ≥150 min/week of PA (sum of PA from IPAQ), as recommended by the World Health Organization (WHO) and the American College of Sports Medicine.

Moreover, energy expenditure was quantitated by IPAQ and defined as the metabolic equivalent of task (MET) in min/week. Calculation of the energy expenditure was obtained using the Ainsworth formula (28): (days of walking x duration x 3.3) + (days of moderate PA x duration x 4.0) + (days of vigorous PA x duration x 8.0).

Statistical analysis

Quantitative data are presented as the median (interquartile range). Normality was defined by the Shapiro−Wilk test. For comparison of the pre- (T0) and postoperative (T1 and T2) periods, Wilcoxon's test was used. The Mann−Whitney U-test was used to compare active and inactive subjects prior to and 15 months post-BS. Categorical data are presented as absolute numbers (frequency). The McNemar test was used to compare pre- (T0) and postoperative (T1 and T2) periods. For comparison of active and inactive subjects prior to and 15 months psot-BS, Yates' Continuity Correction or Fisher Exact tests were used, as appropriate. Data were analyzed using SPSS version 18.0, with a confidence interval of 95%, and $p \leq 0.05$ is considered significant.

Sample calculation was performed according to the study by Bond et al., (2009) (8), in which PA was evaluated by IPAQ prior to and 1 year post-RYGB. It was found that PA

increased from 35.8% to 79.5% following BS, with active being considered as ≥ 200 min/week of PA. Considering a power of 95% and a confidence interval of 5%, 54 subjects would be needed, 27 in each group (active and inactive). Assuming a loss of 20%, 65 subjects would be needed. The Sealed Envelope website was used for sample calculation (29).

Ethical aspects

The present study was approved by the Ethical Committee of the Hospital (Approval number 51843515.1.0000.5335). Written informed consent was obtained for each participant.

Results

Of the 91 subjects included in the present study, 85.7% (n = 78) were female aged 38.0 (33.0–44.5) years old and 56.0% (n = 51) underwent RYGB. Preoperative IPAQ classification regarding the practice of ≥ 150 min/week of PA and energy expenditure were not different between RYGB and SG ($p = 0.143$, $p = 0.528$, and $p = 0.433$, respectively), and there was also no difference 15 months post-surgery between RYGB and SG ($p = 0.802$, $p = 0.372$, and $p = 0.578$, respectively). Therefore, the two surgical techniques were taken together for the analysis.

There was an improvement in all anthropometric, blood pressure, and laboratory parameters following BS (Table 1). Moreover, there was an increase in PA and energy expenditure 6 and 15 months post-BS ($p < 0.001$); however, there was no difference between the values obtained at these times ($p = 0.856$). Of the 57 (62.6%) subjects who did not perform ≥ 150 min/week of preoperative PA, 32 (56.1%) began during the 15 months post-BS, and of the 34 (37.4%) who fulfilled preoperative PA, 27 (79.4%) continued to perform until T2. Regarding the IPAQ classification, 12.1% of subjects were considered sedentary at T0, i.e., they performed less than 10 min/week of PA. After 15 months, 1.1% remained sedentary. Of

those who were considered active or very active during the preoperative period (33.0%, n = 30), the majority remained active or very active at T2 (23.2%, n = 21). The energy expenditure increased from 367.5 MET-min/week at T0 to 906.5 MET-min/week at T2 ($p < 0.001$).

According to the practice, or not, of ≥ 150 min/week of PA prior to and 15 months post-BS, the subjects were divided into two groups, active and inactive. Neither T0 nor T2 groups differed in preoperative demographic, anthropometric, blood pressure, or laboratory variables (Table 2).

To search for benefits between being active prior to and 15 months post-BS, we evaluated the changes in anthropometric, blood pressure, and laboratory parameters from T0 to T2 (Table 3). Being active in T0 and T2 was not associated with a greater loss of %EWL or a higher percentage decrease in BMI, SBP, DBP, fasting glycaemia, HbA1c, non-HDL-C, and triglycerides. We found an association between being active at T0 and a higher percentage loss of WC at 15 months post-BS as compared with being inactive (27.0% versus 24.2%, $p = 0.027$), which was not seen in individuals who were active only at T2 (25.7% versus inactive 24.4%, $p = 0.196$). Being active during the preoperative period was also associated with a higher percentage increase in HDL-C 15 months post-BS as compared with being inactive (18.2% versus 10.9%, $p = 0.035$), which was not seen postoperatively (15.1% versus 15.7%, $p = 0.895$).

We also sought to identify whether the greater WC loss and higher increase in HDL-C associated with being active at T0 occurred regardless of the type of BS (RYGB and SG). Comparison of the pre- (T0) and postoperative WC measurements (T1 and T2) between RYGB and SG showed that subjects submitted to SG had a higher preoperative WC as compared with those submitted to RYGB (115.3 cm versus 108.0 cm, respectively, $p = 0.043$), which was already expected, since SG was indicated for subjects with a higher WC. After 6 and 15 months, the SG group maintained a higher WC (88.0 cm versus 92.8 cm, $p = 0.044$ and 81.0 cm versus

86.5 cm, $p < 0.001$, respectively) (Figure 1A). The percentage WC (%WC) loss differed between RYGB and SG ($p = 0.024$), and there was a greater %WC loss in subjects submitted to RYGB (26.8%) as compared those submitted to SG (24.1%) (Figure 2A). HDL-C levels were not different between RYGB and SG at T0, T1, or T2 ($p = 0.666$, $p = 0.884$, and $p = 0.115$, respectively) (Figure 1B), and the percentage increase in HDL-C at 15 months did not differ between the two surgical procedures (15.8% versus 12.4%, $p = 0.277$) (Figure 2B).

Discussion

The objective of the present study was to evaluate the PA in obese individuals without diabetes and elucidate possible benefits of PA practice prior to and following BS. Being active prior to BS was associated with: a) a greater WC loss 15 months post-surgery, with a higher loss in subjects submitted to RYGB as compared with those submitted to SG and; b) a greater increase in HDL-C. During the postoperative period, there was an increase in PA (IPAQ classification and achievement of ≥ 150 min/week of PA) and energy expenditure, with no difference between the evaluated postoperative periods (6 and 15 months).

In the present study, it was also observed that some subjects who were active at 6 months post-BS became insufficiently active at 15 months. We found no association between post-BS PA change and %EWL. A similar result was reported by Bergh et al., (2016) in a cohort study with 230 subjects submitted to RYGB with a follow up of 1 year (11), as well as in the subsequent cohort evaluating 112 of these subjects after 18−24 months (12). This may have occurred due to the low energy deficit induced by the PA practice not being sufficient to influence the energy balance, since the post-bariatric subject is characterized by a great deficit in energy (15,23).

In a meta-analysis, it was seen that for each increase in 1-MET in cardiorespiratory fitness, there is a 13% reduction in mortality due to cardiovascular disease (30). One of the proposed mechanisms for this decrease in mortality is the increase in serum levels of HDL-C related to aerobic exercise with a corresponding increase in cholesterol efflux from macrophages into hepatic tissue (31). In view of these data, seeking augmentation of PA should always be a goal in sedentary or underactive individuals; however, due to the limitations imposed by comorbidities and a well-established unhealthy lifestyle, this goal is generally not achieved in severely obese individuals (32). On the other hand, an RCT performed in 36 subjects 6 months post-BS showed that a higher preoperative PA predicts a higher post-BS PA (23), providing subsidies for interventions from the preoperative period. Another RCT in 96 non-diabetic subjects, randomized to a physical training program 6 months after RYGB, showed that subjects who make the greatest changes in the number of steps taken per day have greater energy deficits and a greater loss of body weight and fat mass, irrespective of previous physical training (24). However, in another RCT, in which 128 subjects 1−3 months post-RYGB were randomized to increase PA, there was no greater weight loss in the group that underwent the intervention (25). In an RCT conducted by Shah et al., (2011), 33 subjects submitted to RYGB and gastric banding were randomized to 12 weeks of exercise or a control group. The individuals in the group that increased PA showed better cardiorespiratory fitness and glycemic control but did not lose more body weight than those in the control group (26). All the findings cited are in agreement with ours, since we also observed no association between postoperative PA and greater weight loss.

The RCTs cited above were performed during the first post-BS year, when greater weight loss occurred, and therefore, the effect of BS and the respective decrease in dietary intake could have masked any effect of PA increase on weight loss and consequent benefits. Our study, on the other hand, evaluated PA for up to 15 postoperative months, when the weight

loss was lower; nevertheless, no effect of PA was observed on the body weight reached. A double-blind randomized study in 130 obese, non-diabetic patients, whose lifestyle intervention consisted of diet and intensive PA for 12 months in the experimental group and diet and PA after 6 months of beginning the dietary intervention in the control group, showed that both groups had a significant reduction in WC at 6 and 12 months ($p < 0.001$ in both). The group submitted to higher PA from the beginning, however, had significantly a greater reduction in WC at 6 months as compared with the late PA group ($p = 0.010$), but there was no difference in the subsequent 6 months ($p = 0.270$), during which both groups were engaged in PA (33). According to the WHO, WC, regardless of weight or BMI, predicts cardiovascular risk (34). A study in non-diabetic, obese patients showed that WC reduction, through dietary guidance and PA, reduced blood pressure, blood glucose, triglycerides, and Framingham risk over 10 years (35).

In our study, being active (as compared with being inactive) during the preoperative period showed an association with a greater WC loss and a higher HDL-C increase 15 months post-BS, with WC loss being higher in the RYGB group as compared with that in the SG group. Such effects were not seen when the subjects only became active during the postoperative period. Our results suggest that even for individuals who cannot prevent weight gain throughout life, it is important to stop being sedentary because cardiovascular risk reduction benefits should occur for those who do not undergo BS, with an additional effect for those who choose BS.

The main strengths of the present study are the prospective cohort, follow-up time, and sample size. In addition, it is one of the few studies evaluating PA and its effects in subjects submitted to BS. As a limitation of our study, we highlight the subjective manner in which PA and energy expenditure were assessed. IPAQ is a validated instrument, but some studies have found divergences between self-reported PA and that measured objectively, such as using an

accelerometer or a pedometer (12,36,37). Bergh et al., (2017) observed that, while only 17.9% of the subjects reached the recommended level of moderate to vigorous PA of ≥ 150 min/week evaluated by an accelerometer, 80.2% reached the same level according to IPAQ (12). For the use of objective methods, on the other hand, the low adherence to using the proposed devices, especially by women, is very frequent; thus, IPAQ remains in use even in recent studies (37).

Increased PA and energy expenditure occurred 6 and 15 months post-BS, but greater benefits from being active occurred when individuals were already active preoperatively. These benefits were a greater WC loss, mainly in subjects submitted to RYGB, and a higher HDL-C increase. These results suggest that, although BS is the most effective treatment for long-term weight loss and maintenance in severely obese individuals, a non-sedentary lifestyle should be sought permanently, even in those obese individuals who apparently benefit less because they do not present significant weight loss. Active behavior prior to BS is the best predictor for the practice of postoperative PA, since it is difficult to establish new habits following BS.

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Competing Interests

The authors declare no competing financial interests.

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Figures

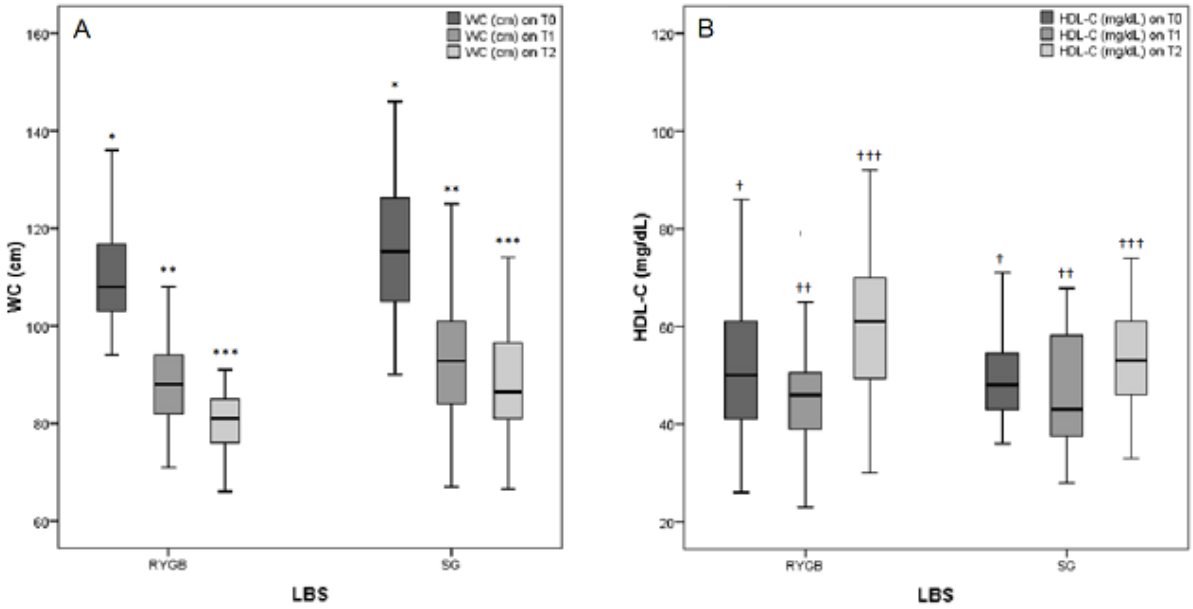

Figure 1. Comparison of T0, T1, and T2 waist circumference (cm) (A) and levels of high-density lipoprotein cholesterol (HDL-C) (mg/dL) (B) between patients undergoing Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). Median and interquartile amplitude (percentiles 25–75) are presented. WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; BS, laparoscopic bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy. *p = 0.044; **p = 0.043; ***p < 0.001; †p = 0.666; ††p = 0.884; †††p = 0.115; Mann−Whitney U−test.

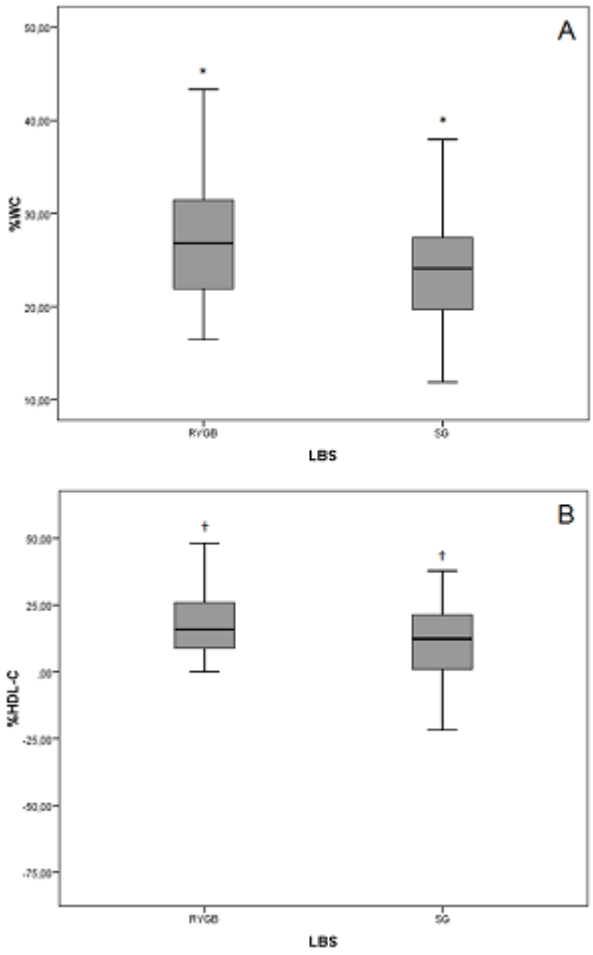

Figure 2. Comparison of the percentage decrease in waist circumference (A) and percentage increase in high-density lipoprotein cholesterol (HDL-C) (B) between patients undergoing Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). Median and interquartile amplitude (percentiles 25–75) are presented. WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; BS, laparoscopic bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy. *p = 0.024; †p = 0.277; Mann−Whitney U−test.

Table 1. Anthropometric, blood pressure, laboratory, and physical activity data of 91 pre- (T0) and postoperative obese subjects without diabetes, evaluated 6 (T1) and 15 months (T2) following laparoscopic bariatric surgery. Numbers are presented as the median and interquartile amplitude (percentiles 25–75) for quantitative variables and total numbers and percentages for qualitative variables. The measurement units and number of patients are presented with the corresponding variables

				T0 vs. T1	T0 vs. T2	T1 vs. T2
	T0 (n = 91)	T1 (n = 91)	T2 (n = 91)	*p*-value	*p*-value	*p*-value
Body weight (kg)	111.2 (100.0–125.6)	81.5 (71.9–92.6)	71.8 (64.0–79.8)	<0.001* (a)	<0.001* (a)	<0.001* (a)
BMI (kg/m²)	41.7 (39.4–45.1)	30.6 (28.2–33.1)	26.9 (25.1–28.9)	<0.001* (a)	<0.001* (a)	<0.001* (a)
%EWL	NA	67.0 (53.7–76.9)	87.7 (79.8–99.5)	NA	NA	<0.001* (a)
EW (kg)	44.3 (36.8–55.9)	14.7 (8.1–22.2)	4.9 (0.3–11.4)	<0.001* (a)	<0.001* (a)	<0.001* (a)
WC (cm)	112.0 (104.0–119.5)	89.0 (82.5–97.0)	83.0 (77.0–88.5)	<0.001* (a)	<0.001* (a)	<0.001* (a)
SBP (mmHg) (67/67/67)	125.0 (119.0–132.0)	112.0 (107.5–120.0)	116.0 (106.0–122.0)	<0.001* (a)	<0.001* (a)	0.251 (a)
DBP (mmHg) (67/67/67)	87.0 (81.0–92.0)	72.0 (67.0–76.5)	71.0 (64.5–77.0)	<0.001* (a)	<0.001* (a)	0.214 (a)
Fasting glycaemia (mg/dL) (90/88/75)	91.5 (86.0–97.0)	82.0 (78.0–87.0)	81.0 (78.0–86.5)	<0.001* (a)	<0.001* (a)	0.788 (a)
HbA1c (%) (85/67/45)	5.3 (5.1–5.6)	5.1 (4.9–5.3)	5.1 (4.9–5.2)	<0.001* (a)	<0.001* (a)	0.449 (a)
HDL-C (mg/dL) (78/63/60)	49.0 (42.0–59.0)	45.0 (38.0–56.0)	58.0 (48.5–68.0)	0.045* (a)	<0.001* (a)	<0.001* (a)
Non-HDL-C (mg/dL) (78/62/60)	150.0 (128.0–175.0)	111.0 (92.0–137.0)	95.5 (77.2–115.5)	<0.001* (a)	<0.001* (a)	<0.001* (a)
Triglycerides (mg/dL) (79/64/60)	144.0 (95.0–183.0)	81.5 (66.0–104.5)	65.5 (49.5–89.5)	<0.001* (a)	<0.001* (a)	0.001* (a)
MS (%)	63 (69.2)	15 (16.5)	4 (4.4)	<0.001* (b)	<0.001* (b)	0.013* (b)

Walking (min/week)	30.0 (0.0–75.0)	60.0 (30.0–120.0)	70.0 (30.0–165.0)	<0.001* (a)	<0.001* (a)	0.259 (a)
Total PA (min/week)	105.0 (30.0–235.0)	230.0 (80.0–382.5)	270.0(95.0–477.5)	0.001* (a)	0.001* (a)	0.537 (a)
Total sitting time (min/day)	480.0 (270.0–720.0)	480.0 (360.0–740.0)	540.0 (360.0–780.0)	0.636 (a)	0.139 (a)	0.208 (a)
Energy expenditure (MET-min/week)	367.5 (99.0–954.5)	819.0 (282.0–1773.0)	906.5 (321.8–1909.5)	0.001* (a)	0.001* (a)	0.979 (a)
IPAQ Classification (n, %)				0.012* (b)	0.013* (b)	0.530 (b)
Sedentary	11 (12.1)	6 (6.6)	6 (6.6)			
Insufficiently active B	30 (33.0)	14 (15.4)	18 (19.8)			
Insufficiently active A	20 (22.0)	17 (18.7)	13 (14.3)			
Active	27 (29.7)	39 (42.9)	44 (48.4)			
Very active	3 (3.3)	15 (16.5)	10 (11.0)			
PA ≥ 150 min per week (n, %)	34 (37.4)	61 (67.0)	59 (64.8)	<0.001* (b)	<0.001* (b)	0.856 (b)

%EWL, % excess weight loss; EW, excess body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; MS, metabolic syndrome; PA, physical activity; MET, metabolic equivalent of task; IPAQ, International Physical Activity Questionnaire; NA, not applicable; n = absolute number; vs = versus

*Statistical significance is considered at $p \leq 0.05$; (a) Wilcoxon test, (b) McNemar test

Table 2. Demographic, anthropometric, blood pressure, and laboratory data of 91 active and inactive obese subjects without diabetes evaluated prior to (T0) and 15 months (T2) post-laparoscopic bariatric surgery. Numbers are presented as the median and interquartile amplitude (percentiles 25–75) for quantitative variables and total numbers and percentages for qualitative variables. The measurement units and number of patients are presented with the corresponding variables

	Active at T0 (n = 34)	Inactive at T0 (n = 57)	*p*-value	Active at T2 (n = 59)	Inactive at T2 (n = 32)	*p*-value
Female gender (n, %)	29 (85.3)	49 (86.0)	1.000 (a)	49 (83.1)	29 (90.6)	0.501 (a)
BS (n, %)						
SG	NA	NA	NA	27 (45.8)	13 (40.6)	0.802 (a)
RYGB				32 (54.2)	19 (59.4)	
Age (years)	39.0 (35.0–47.0)	36.0 (35.0–42.0)	0.066 (b)	38.0 (33.0–46.0)	37.0 (32.5–42.0)	0.845 (b)
Body weight (kg)	111.2 (103.4–119.1)	114.3 (97.5–127.9)	0.971 (b)	72.5 (64.0–79.8)	69.5 (63.2–79.9)	0.752 (b)
BMI (kg/m²)	41.1 (39.2–44.0)	42.8 (39.5–45.2)	0.292 (b)	27.1 (25.2–28.4)	26.5 (24.7–29.8)	0.580 (b)
%EWL	NA	NA	NA	86.5 (81.3–98.7)	90.5 (71.3–102.4)	0.733 (b)
EW (kg)	43.4 (38.6–49.5)	46.4 (34.8–57.9)	0.552 (b)	5.4 (0.6–9.6)	3.9 (-0.9–12.1)	0.660 (b)
WC (cm)	112.8 (107.0–121.5)	111.0 (102.0–119.0)	0.078 (b)	82.0 (77.0–87.5)	83.5 (77.5–90.5)	0.391 (b)
SBP (mmHg) (25/42) (45/22)	124.0 (120.0–131.0)	127.0 (118.0–133.0)	0.337 (b)	116.0 (105.0–121.0)	118.0 (109.0–123.0)	0.430 (b)
DBP (mmHg) (25/42) (45/22)	86.0 (80.0–92.0)	88.0 (82.0–92.0)	0.964 (b)	88.0 (80.0–93.0)	87.0 (82.0–90.0)	0.570 (b)

Fasting glycemia (mg/dL) (33/57) (48/27)	92.0 (87.0–97.0)	91.0 (86.0–98.0)	0.831 (b)	81.5 (78.0–86.5)	81.0 (78.5–86.5)	0.947 (b)
HbA1c (%) (30/55) (30/15)	5.5 (5.0–5.7)	5.3 (5.1–5.6)	0.539 (b)	5.1 (4.9–5.2)	5.1 (4.8–5.3)	0.875 (b)
HDL-C (mg/dL) (28/50) (37/23)	50.0 (41.5–54.0)	49.0 (43.0–63.0)	0.591 (b)	55.0 (49.0–65.0)	61.0 (47.5–71.1)	0.456 (b)
Non-HDL-C (mg/dL) (28/50) (37/23)	146.5 (128.5–182.0)	152.5 (127.0–168.0)	0.447 (b)	99.0 (81.0–115.0)	87.0 (70.5–113.5)	0.528 (b)
Triglycerides (mg/dL) (28/51) (38/22)	140.5 (108.0–172.0)	147.0 (92.0–187.0)	0.667 (b)	65.0 (48.0–91.0)	69.5 (56.0–83.0)	0.412 (b)
MS (n, %)	22 (64.7)	41 (71.9)	0.626 (a)	3 (5.1)	1 (3.1)	1.000 (c)

BS, bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; %EWL, % excess weight loss; EW, excess body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; MS, metabolic syndrome; NA, not applicable; n = absolute number.

*Statistical significance is considered at $p \leq 0.05$; (a) Yates's Correction for Continuity, (b) Mann−Whitney U−test, (c) Fisher's exact test

Table 3. Evaluation of anthropometric, blood pressure, and laboratory changes (T0 to T2) in active and inactive obese subjects without diabetes evaluated prior to (T0) and 15 months (T2) post-laparoscopic bariatric surgery. Numbers are presented as the median and interquartile amplitude (percentiles 25–75) for quantitative variables and total numbers and percentages for qualitative variables

	Active at T0 (n = 34)	Inactive at T0 (n = 57)	*p*-value	Active at T2 (n = 59)	Inactive at T2 (n = 32)	*p*-value
% EWL	90.2 (83.0–104.9)	85.2 (78.7–97.3)	0.311 (a)	86.5 (81.3–98.7)	90.5 (71.3–102.4)	0.733 (a)
% decreased BMI	36.7 (31.8–40.0)	35.2 (30.9–40.1)	0.688 (a)	36.0 (31.0–40.2)	35.1 (31.7–39.5)	0.648 (a)
% decreased WC	27.0 (21.4–33.3)	24.2 (20.8–27.8)	0.027* (a)	25.7 (21.3–31.4)	24.4 (20.0–29.2)	0.196 (a)
% decreased SBP (25/42) (45/22)	8.0 (4.8–12.2)	8.9 (3.3–14.0)	0.969 (a)	9.2 (4.7–14.0)	6.5 (2.5–11.3)	0.157 (a)
% decreased DBP (25/42) (45/22)	18.6 (14.0–27.2)	19.2 (9.3–23.0)	0.315 (a)	19.8 (14.1–27.2)	15.9 (9.0–21.8)	0.087 (a)
% decreased fasting glycemia (27/47) (47/27)	10.6 (6.5–15.2)	11.4 (4.9–17.0)	0.871 (a)	11.4 (5.6–15.2)	9.1 (5.8–17.9)	0.835 (a)
% decreased HbA1c (19/25) (29/15)	5.3 (2.0–8.9)	5.9 (-2.0–9.6)	0.915 (a)	3.6 (-1.9–9.1)	7.1 (2.9–11.2)	0.225 (a)
% increased HDL-C (20/38) (36/22)	18.2 (14.1–26.7)	10.9 (-1.2–22.7)	0.035* (a)	15.1 (5.8–27.4)	15.7 (5.5–21.9)	0.895 (a)
% decreased non-HDL-C (20/38) (36/22)	39.8 (21.5–48.3)	34.6 (18.0–49.0)	0.665 (a)	31.9 (17.3–49.0)	40.9 (25.0–49.1)	0.410 (a)
% decreased triglycerides (21/37) (37/21)	45.2 (37.0–51.7)	51.7 (36.3–60.8)	0.365 (a)	49.8 (35.8–58.5)	45.5 (37.9–54.3)	0.645 (a)
ΔPA total (min/week)	-20.0 (-420.0–180.0)	160.0 (40.0–390.0)	0.001* (a)	265.0 (75.0–470.0)	5.0 (-92.5–55.0)	<0.001* (a)

%EWL, % excess weight loss; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; PA, physical activity; n, absolute number. Change (Δ) was calculated as the difference between T0 and T2 and compared between active and inactive groups.

*Statistical significance is considered at $p \leq 0.05$; (a) Mann−Whitney U−test, (b) Fisher's exact test.

ARTIGO 3: Effect of bariatric surgery on high-density lipoprotein (HDL) cholesterol in non-diabetic patients with severe obesity

O presente artigo encontra-se nas normas da *Obesity Surgery*, ao qual foi submetido. O periódico é Qualis A2 na área Medicina III e tem fator de impacto de 3.895 (2017).

Complete title: Effect of bariatric surgery on high-density lipoprotein (HDL) cholesterol in non-diabetic patients with severe obesity

Short tittle: HDL cholesterol after BS for obesity

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Abstract

Background: This study evaluated changes in serum high-density lipoprotein cholesterol (HDL-C) induced by laparoscopic bariatric surgery (BS) in non-diabetic obese subjects with low (L-HDL-C) or normal (N-HDL-C) levels of HDL-C. We assessed whether increased HDL-C is associated with weight loss, serum non-HDL cholesterol (non-HDL-C), serum triglycerides (TG) and physical activity (PA) before BS and 6 and 15 months after BS.

Methods: In this prospective cohort study, 76 subjects undergoing laparoscopic BS (45 by Roux-en-Y gastric bypass and 31 by sleeve gastrectomy) were evaluated for the % Excess Weight Loss (%EWL), serum levels of HDL-C, non-HDL-C, glucose, glycosylated haemoglobin and TG, and the degree, time and energy expenditure related to PA. The short version of the International Physical Activity Questionnaire was used to assess PA.

Results: Levels of HDL-C significantly increased 15 months after BS ($p < 0.001$) in subjects with low ($p < 0.001$) or normal ($p = 0.027$) values at baseline. A similar %EWL, decrease in non-HDL-C, glucose and TG levels and increase in energy expenditure related to PA were observed in both groups (L-HDL-C and N-HDL-C) at 6 and 15 months after BS. In subjects with increased HDL-C 15 months after BS, there was an association between this increase and the %EWL ($p = 0.019$), but there was no association with the change in PA.

Conclusion: Irrespective of PA after BS, subjects with low and normal HDL-C levels at baseline showed an increase in HDL-C after BS, and this increase was associated with %EWL induced by BS.

Keywords: HDL cholesterol; Obesity; Bariatric surgery; Weight loss.

Introduction

One of the key risk factors used by clinicians to assess cardiovascular risk (CVR) is the serum

level of high-density lipoprotein cholesterol (HDL-C) [1]. According to large-scale studies, a low concentration of serum HDL-C increases CVR [2], and for each 1 mg/dL increase in HDL-C there is a 2–3% decrease in the risk of coronary artery disease (CAD) [3]. There are several well-known risk factors for low HDL-C, including a high body mass index (BMI), alcoholism, smoking, type 2 diabetes mellitus (T2DM), the use of certain drugs like beta blockers and anabolic steroids, a sedentary lifestyle [3,4] and a genetic predisposition [5].

There is a positive correlation between BMI and non-HDL cholesterol (non-HDL-C) and triglyceride (TG) levels [6], and it has also been reported that a higher BMI increases the risk for hypertriglyceridemia, high LDL cholesterol (LDL-C) and low HDL-C [7]. Physical activity (PA), as well as certain drugs and interventions, is known to decrease non-HDL-C, which could lead to an increase in serum HDL-C [8].

It has been estimated that about 40–60% of the variability in HDL-C can be explained by heritability [5]. Loss-of-function mutations in some genes cause conditions with extremely low HDL-C and, in contrast, loss-of-function mutation variants in other genes are associated with extremely high HDL-C [9,10]. Because of this, the response of HDL-C levels to dietary changes, exercise and medications are not homogeneous, and the extent of the response varies with different baseline levels of serum HDL-C.

In subjects with severe obesity, bariatric surgery (BS) results in significant and sustained weight loss, in addition to reductions in all-cause mortality and cause-specific mortality associated with CAD [11]. Furthermore, BS is considered safe and effective for treating these patients. In our country, it is currently recommended for patients with a BMI $\geq$40 kg/m^2 or for those with a BMI between 35 and 39.9 kg/m^2 who have at least one comorbidity [12]. In addition, BS has been shown to decrease LDL-C, TG and non-HDL-C levels and increase HDL-C [13,14].

An increase in HDL-C could be one of the factors related to the decrease in mortality associated with BS. In subjects with low HDL-C, efforts to use statins, niacin and cholesteryl ester transfer protein inhibitors to raise HDL-C levels and to protect against cardiovascular disease (CVD) have been disappointing [15]. Thus, it seems of great importance to determine the magnitude of the effect of the HDL-C serum response to the weight reduction induced by BS. As exercise-induced weight loss has been shown to affect HDL-C concentrations in men to a different extent depending on their baseline level [16], we decided to evaluate the response to BS in subjects with low HDL-C serum levels prior to BS.

In patients undergoing laparoscopic BS, an increased level of PA is always precociously prescribed as an auxiliary measure to lose weight and then maintain weight loss. It is also expected that patients who lose a higher percentage of weight will have greater mobility, thus an increase in PA will probably occur irrespective of counseling, which could also influence HDL-C levels.

There were three main aims of the present study: (1) to determine whether serum HDL-C is increased 15 months after BS; (2) to assess whether the changes in HDL-C levels after BS are related to weight loss, increased PA or decreased serum non-HDL-C and TG levels; and (3) if the increase in HDL-C induced by BS differs between subjects whose HDL-C levels prior to BS were normal or low.

Materials and Methods

Study design and population

A prospective cohort study was conducted in 76 obese subjects undergoing laparoscopic BS, performed using the Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) techniques. All participants were evaluated for PA and energy expenditure preoperatively (T0), then again

at 6 (T1) and 15 (T2) months postoperative. The study was conducted from April 2016 to December 2018. This study used data from a cohort of patients that looked to evaluate the incidence and progression of peripheral polyneuropathy after BS. Participants with a follow up of 15 months after BS were chosen to participate. The subjects were evaluated by two evaluators during routine consultations at the hospital. Subjects of both sexes were included if they were older than 18 years of age and met the criteria for BS. The exclusion criteria were T2DM, cancer, decompensated hypothyroidism, pregnancy, infants, alcoholism, smoking or the use of statins, fibrates, beta blockers or steroids.

From 102 initial subjects, 26 were excluded. Of the excluded subjects, five had T2DM, three had decompensated hypothyroidism, three were smokers, one was an alcoholic, four used beta blockers, seven used statins, and three had no serum HDL-C measurements prior to BS.

Diet and physical activity recommendations

In the pre- and postoperative periods, all subjects received a prescribed balanced diet in addition to other recommendations such as to eat 5 to 6 meals per day and to increase their PA by completing at least 150 min of walking per week. After BS, outpatient visits were scheduled for every 3 months.

Anthropometric, clinical and laboratory data

Body weight, height, BMI and waist circumference (WC) were measured and health history data were obtained from medical records in the basal and postoperative periods. Serum levels of glucose, glycosylated haemoglobin (HbA1c), HDL-C, LDL-C, non-HDL-C and TG were also collected. The excess weight (EW) was calculated from the difference between pre- or postoperative body weights, with the ideal weight corresponding to a BMI of 25 kg/m², and the % Excess Weight Loss (%EWL) was obtained by the difference between the subject's pre- and postoperative body weight divided by EW.

Physical activity and energy expenditure

To evaluate PA, the short version of the International Physical Activity Questionnaire (IPAQ) [17] was used, which evaluates daily activities over the last 7 days. The participants were classified according to the frequency and duration of the different types of PA. The time spent sitting on weekdays and the weekend was also recorded. In addition, patients were evaluated for whether they completed ≥150 min/week of PA (sum of PA from IPAQ), as recommended by the World Health Organization and the American College of Sports Medicine.

Using data collected in the IPAQ, energy expenditure was quantified and defined as the metabolic equivalent of task (MET) in min/week. The calculation of energy expenditure was performed using the Ainsworth formula [18].

HDL cholesterol group definition

Subjects were divided into two groups according to their serum HDL-C levels before BS: those who had low HDL-C (L-HDL-C group, <40 mg/dL for men and <50 mg/dL for women), and those who had normal HDL-C (N-HDL-C group, ≥40 mg/dL for men and ≥50 mg/dL for women). An increase in HDL-C 15 months after BS was defined as a percentage equal to or greater than the median obtained for each group.

Statistical analysis

Quantitative data are presented as the median and interquartile range. Normality was defined by the Shapiro-Wilk test. To compare the L-HDL-C and N-HDL-C groups and groups with no change or increased HDL-C at T2, we used the Mann-Whitney U test. For comparing T0 and T2 in each group, Wilcoxon's test was used. Categorical data are presented as absolute values and frequencies. The Yates' continuity correction test was used to compare L-HDL-C and N-HDL-C groups and groups with no change or increased HDL-C at T2. The McNemar test was used to compare T0 and T2 in each group. Data were analyzed using SPSS version 18.0, and values with $p \leq 0.05$ were considered statistically significant.

For sample calculation, we used data from the 2017 study by Praveen Raj et al. [19], which investigated changes in the lipid profile 1 year after RYGB and SG. They found an increase in serum HDL-C levels from 41.40 ± 9.98 mg/dL to 52.06 ± 16.16 mg/dL after 1 year. Considering a power of 80% and a confidence interval of 5%, 74 subjects would be needed, with 37 in each group. Assuming a loss of 10%, there would be 82 subjects. The Sealed Envelope website was used for the sample calculation [20].

Results

Table 1 presents the demographic, anthropometric and PA data of the 76 non-diabetic obese subjects at baseline. Before BS, when the L-HDL-C group was compared with the N-HDL-C group, the number of females, subject age, BMI, EW, serum glucose and TG levels and PA measures were similar. The WC and non-HDL-C level were higher in the L-HDL-C group compared to the N-HDL-C group, and, as expected, differences between groups were observed for HDL-C levels.

Fifteen months after BS, patients had a mean %EWL of 88.4 ± 20.4%, correspondingly to a mean reduction in BMI of 15.6 ± 4.9 kg/m², and there was a significant reduction in CVR indicated by a change in the total cholesterol:HDL-C ratio from 4.2 to 2.6 ($p < 0.001$; data not shown).

Changes in anthropometric and laboratory measures and PA at 6 (T1) and 15 (T2) months post-BS for the L-HDL-C and N-HDL-C groups are shown in Table 2. BS was associated with a similar decrease in the L-HDL-C and N-HDL-C groups at 15 months and for serum TG (52.3% versus 45.1%, $p = 0.074$), LDL-C (24.0% versus 30.9%, $p = 0.623$) and non-HDL-C (31.7% versus 39.8%, $p = 0.415$), along with an increase in HDL-C (20.5% versus 14.2%, $p = 0.085$). Six months after BS, neither group showed an increase in HDL-C from

baseline, but a significant increase appeared 15 months after BS. Walking time, PA, energy expenditure and the number of subjects completing ≥150 min/week of PA increased from T0 to T2 in both groups, with no differences observed between the two groups for these parameters.

Table 3 presents data looking for association between increased HDL-C with %EWL, WC, glucose, HbA1c, TG, non-HDL-C, LDL-C, energy expenditure and PA ≥150 min/week. Only %EWL was associated with an increase in HDL-C ($p = 0.019$), but only in subjects who presented an increase in HDL-C 15 months after BS.

Discussion

The observation that there was a correlation between low serum levels of HDL-C with increased mortality from CVD led researchers to seek strategies to increase the levels of HDL-C in people with low HDL-C [21]. In the search for these treatments, it was seen that subjects' responses could vary depending on their baseline HDL-C levels, where individuals with low HDL-C levels presented greater resistance to response to different therapeutic proposals [22].

Among the treatments proposed to increase the HDL-C levels of individuals at increased risk for atherosclerotic disease, the most noteworthy include a diet low in saturated fat, physical exercise, and the use of drugs such as statins and nicotinic acid [15]. As a consequence of this change in diet, it is common to observe weight loss and even an increase in PA; however, it is not clear whether the effect on HDL-C is due to the low-calorie diet, restriction of fats (with a consequent decrease in the influx of lipoproteins from the intestine to circulation), increased PA or weight loss.

In the present study, we sought to clarify the effect of BS on HDL-C levels in individuals with low or normal serum HDL-C levels before BS. We observed a mean increase

in HDL-C level post-BS of 7.1 mg/dL. The increase in HDL-C occurred when the baseline values were low or normal, and both groups simultaneously showed decreases in non-HDL-C, TG, LDL-C and fasting plasma glucose, along with an increase in PA. In the subjects who showed increased HDL-C after BS, there was an association between this increase and the %EWL.

The typical dyslipidaemia described in obese patients consists of elevated fasting and postprandial TGs, reduced HDL-C and normal or slightly elevated LDL-C [23]. However, for each patient, the serum HDL-C level depends on their genetic predisposition, degree of obesity, diet, non-HDL-C levels, daily PA and the presence of other co-morbidities that could decrease HDL-C, such as T2DM, hypothyroidism, smoking and alcoholism [21].

In patients submitted to BS, both a decrease in the influx of lipoproteins from the diet and an increase in fatty acid turnover (due to a loss of fat mass associated with greater PA and/or use of reserves due to caloric restriction) are predicted, and these effects could be related to an increase in HDL-C levels. In fact, studies that assessed the effect of BS have shown no change or increase in HDL-C after 1 year of follow up [19]. In an attempt to elucidate this discrepancy, the present study is the first longitudinal evaluation with 15 months of follow up and the first to look into the effect of BS on patients with low HDL-C levels at baseline.

In order to decrease the impact of co-morbidities that could influence HDL-C levels on the metabolic results observed after the surgery, patients with these conditions were excluded from our sample. Taking into account these exclusions, we believe that the results for lipid measurements and glycaemic control can be predominantly attributed to the effects of the surgery and the subsequent change in behavior, as well as the genetic predisposition.

In our study, the mean HDL-C increased to 9.1 mg/dL in the L-HDL-C group and 5.5 mg/dL in the N-HDL group at 15 months after BS. Given that for every 1 mg/dL increase in

HDL-C there is a 2–3% decrease in the risk of CAD [2], the percentage decrease in the risk of CVD in our subjects was 11.0–27.3%.

The strengths of our study include the evaluation of subjects with low HDL-C levels at baseline and the subsequent follow up at 15 months. A limitation of the study was that the subjects evaluated did not have a very high risk for CVD according to the Framingham score [24].

Conclusion

Subjects with low and normal HDL-C levels before BS showed an increase in serum HDL-C levels after 15 months, and this increase was associated with the %EWL. In addition, it was possible to show that BS decreased the CVR of subjects, even when they had low HDL-C. In order to evaluate the benefits of the observed HDL-C increase, it will be important to include subjects with a higher CVR in future studies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the Ethical Committee of the Hospital (Approval number 51843515.1.0000.5335).

Informed Consent Written informed consent was obtained for each participant in the study.

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Table 1. Demographic, anthropometric, laboratory and physical activity data of 76 non-diabetic subjects with low (L-HDL-C) or normal (N-HDL-C) levels of high-density lipoprotein cholesterol (HDL-C) before laparoscopic bariatric surgery (T0). Numbers are presented as median and interquartile amplitude (percentiles 25–75) for quantitative variables and total number and percentage for qualitative variables. The measurement units and number of patients are presented with the corresponding variables.

	Total sample (n = 76)	L-HDL-C (n = 36)	N-HDL-C (n = 40)	p-value
BS (n, %)				
RYGB	45 (59.2)	23 (63.9)	22 (55.0)	0.580 (a)
SG	31 (40.8)	13 (36.1)	18 (45.0)	
Female sex (n, %)	64 (84.2)	31 (86.1)	33 (82.5)	0.908 (a)
Age (years)	37.0 (32.5–42.0)	35.0 (32.0–39.5)	38.5 (33.5–47.0)	0.091 (b)
BMI (kg/m²)	42.0 (39.4–45.2)	42.4 (39.3–45.2)	41.8 (39.6–45.1)	0.930 (b)
WC (cm)	112.0 (103.5–120.0)	115.8 (106.0–125.3)	108.5 (102.5–117.0)	0.044* (b)
EW (kg)	44.9 (38.0–57.4)	46.6 (37.0–57.4)	43.8 (39.2–56.0)	0.655 (b)
Fasting plasma glucose (mg/dL) (75) (36) (39)	91.0 (86.0–95.5)	92.0 (88.0–96.5)	90.0 (84.0–95.0)	0.306 (b)
HbA1c (%) (73) (34) (39)	5.3 (5.1–5.6)	5.3 (5.0–5.5)	5.4 (5.2–5.7)	0.302 (b)
TG (mg/dL)	146.5 (1.2.0–185.0)	147.5 (112.5–191.5)	144.5 (87.0–176.0)	0.210 (b)
HDL-C (mg/dL)	49.0 (42.0–58.5)	41.5 (38.0–45.5)	57.5 (51.0–67.0)	<0.001* (b)
Non-HDL-C (mg/dL)	152.5 (128.5–175.0)	161.5 (141.5–181.0)	139.0 (120.8–165.0)	0.019* (b)
LDL-C (mg/dL)	120.1 (102.2–141.7)	125.7 (112.8–150.4)	113.7 (95.3–140.0)	0.052 (b)
Walking time (min/week)	30.0 (0.0–77.5)	42.5 (17.5–77.5)	20.0 (0.0–77.5)	0.093 (b)

Total sitting time (min/day) (75) (35) (40)	480.0 (300.0–780.0)	480.0 (330.0–787.5)	540.0 (285.0–750.0)	0.975 (b)
PA ≥150 min per week (n, %)	27 (35.5)	12 (33.3)	15 (37.5)	0.889 (a)
Energy expenditure (MET - min/week)	346.5 (99.0–1007.3)	382.8 (112.5–954.5)	313.5 (99.0–1013.3)	0.946 (b)

BS, bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BMI, body mass index; WC, waist circumference; EW, excess body weight; HbA1c, glycosylated haemoglobin; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; MET, metabolic equivalent of task; n, absolute number.
*Statistical significance was considered at $p \leq 0.05$; (a) Yates's correction for continuity, (b) Mann-Whitney U test.

Table 2. Anthropometric, laboratory and physical activity evaluation in 76 non-diabetic subjects with low (L-HDL-C) or normal (N-HDL-C) levels of high-density lipoprotein cholesterol, assessed at baseline (T0) and 6 (T1) and 15 months (T2) after laparoscopic bariatric surgery. Numbers are presented as median and interquartile amplitude (percentiles 25–75) for quantitative variables and total number and percentage for qualitative variables. The measurement units and number of patients are presented with the corresponding variables.

	L-HDL-C (n = 36)				N-HDL-C (n = 40)				Δ (T0 - T2) between groups
	T0	T1	T2	T_0 vs. T_2	T0	T1	T2	T0 vs. T2	
				p-value				p-value	p-value
%EWL (%)	NA	70.3 (62.2–76.9)	92.9 (83.0–100.2)	NA	NA	62.4 (52.7–74.7)	85.0 (74.2–100.1)	NA	0.140 (c)
HDL-C (mg/dL) (36/31/25) (40/27/32)	41.5 (38.0–45.5)	42.0 (35.0–47.0)	49.3 (44.0–54.0)	<0.001* (a)	57.5 (51.0–67.0)	53.0 (43.0–60.5)	63.5 (56.5–72.0)	0.027* (a)	0.624 (c)
Glucose (mg/dL) (36/36/30) (39/38/34)	92.0 (88.0–96.5)	81.0 (77.0–87.0)	80.0 (78.0–83.0)	<0.001* (a)	90.0 (84.0–95.0)	81.0 (78.0–87.0)	81.0 (78.0–86.0)	<0.001* (a)	0.979 (c)
HbA1c (%) (34/25/18) (39/30/20)	5.3 (5.0–5.5)	5.0 (4.9–5.3)	5.2 (4.9–5.3)	0.075 (a)	5.4 (5.2–5.7)	5.1 (4.9–5.2)	5.1 (4.9–5.2)	0.020* (a)	0.426 (c)
TG (mg/dL) (36/31/25) (40/28/32)	147.5 (112.5–191.5)	77.0 (72.5–103.0)	62.0 (50.0–88.0)	<0.001* (a)	144.5 (87.0–176.0)	87.5 (63.5–107.5)	69.0 (50.5–87.5)	<0.001* (a)	0.247 (c)
Non-HDL-C (mg/dL) (36/30/25) (40/27/32)	161.5 (141.5–181.0)	128.5 (99.0–143.0)	103.0 (8.0–115.0)	<0.001* (a)	139.0 (120.8–165.0)	99.0 (86.7–125.6)	93.5 (71.9–113.5)	<0.001* (a)	0.705 (c)
LDL-C (mg/dL) (36/31/26) (40/27/32)	125.7 (112.8–150.4)	106.4 (81.1–124.8)	92.6 (76.0–99.2)	<0.001* (a)	113.7 (95.3–140.0)	84.4 (69.9–110.1)	80.0 (61.6–98.7)	<0.001* (a)	0.784 (c)

Walking time (min/week)	42.5 (17.5–77.5)	90.0 (25.0–150.0)	75.0 (35.0–145.0)	0.031* (a)	20.0 (0.0–77.5)	55.0 (30.0–135.0)	55.0 (20.0–195.0)	0.001* (a)	0.237 (c)
Total sitting time (min/week)	480.0 (330.0–787.5)	540.0 (390.0–770.0)	510.0 (420.0–720.0)	0.138 (a)	540.0 (285.0–750.0)	480.0 (255.0–810.0)	600.0 (330.0–840.0)	0.752 (a)	0.566 (c)
Total PA (min/week)	107.5 (32.5–255.0)	245.0 (90.0–435.0)	312.5 (100.0–505.0)	0.028* (a)	95.0 (30.0–262.5)	200.0 (105.0–370.0)	280.0 (90.0–500.0)	0.037* (a)	0.550 (c)
Energy expenditure (MET - min/week)	382.8 (112.5–954.5)	939.0 (307.5–1773.0)	1220.3 (361.5–1971.0)	0.024* (a)	313.5 (99.0–1013.3)	765.5 (396.8–2184.8)	925.5 (312.3–2130.0)	0.056 (a)	0.052 (c)
PA ≥150 min/week (n, %)	12 (33.3)	25 (69.4)	24 (66.7)	0.008* (b)	15 (37.5)	27 (67.5)	26 (65.0)	0.003* (b)	1.000 (d)

%EWL, % Excess Weight Loss; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated haemoglobin; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; MET, metabolic equivalent of task; n, absolute number. The change (Δ) was calculated as the difference between T0 and T2 and compared between L-HDL-C and N-HDL-C groups.

*Statistical significance was considered at $p \leq 0.05$; (a) Wilcoxon test, (b) McNemar test, (c) Mann-Whitney U test, (d) Yates's correction for continuity.

Table 3. Associations between increased high-density lipoprotein cholesterol levels 15 months after laparoscopic bariatric surgery (T2) and anthropometric, laboratory and physical activity data in subjects without diabetes. Numbers are presented as median and interquartile amplitude (percentiles 25–75) for quantitative variables and total number and percentage for qualitative variables.

	Increased HDL-C at T2 (n = 28)	No increase in HDL-C at T2 (n = 29)	p-value
%EWL (%)	89.6 (83.7–102.3)	82.9 (65.1–93.7)	0.019* (a)
Δ WC (cm)	27.3 (22.5–34.3)	28.0 (24.0–34.0)	0.917 (a)
Δ Glucose (mg/dL) (28/28)	10.0 (6.0–15.2)	8.5 (3.0–15.5)	0.412 (a)
Δ HbA1c (%) (16/16)	0.3 (0.1–0.5)	0.2 (-0.3–0.6)	0.642 (a)
Δ TG (mg/dL) (27/29)	73.0 (43.0–102.0)	57.0 (35.0–90.0)	0.231 (a)
Δ Non-HDL-C (mg/dL)	65.5 (48.0–75.0)	40.0 (20.0–69.0)	0.069 (a)
Δ LDL-C (mg/dL)	45.8 (26.5–62.6)	29.8 (7.6–50.0)	0.059 (a)
Δ Energy expenditure (MET - min/week)	0.8 (-74.6–710.6)	223.2 (-59.8–755.0)	0.416 (a)
PA ≥150 min/week (n, %)	19 (67.9)	17 (58.6)	0.654 (b)

HDL-C, high-density lipoprotein cholesterol; %EWL, % Excess Weight Loss; WC, waist circumference; HbA1c, glycosylated haemoglobin; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; PA, physical activity; n, absolute number. Change (Δ) was calculated as the difference between T0 and T2 and compared between groups with and without increased serum HDL-C levels.
*Statistical significance was considered at $p \leq 0.05$; (a) Mann-Whitney U test, (b) Yates's correction for continuity.

CONSIDERAÇÕES FINAIS

A prevalência de PNP diminuiu após 6 meses de CB. No entanto, novos casos de PNP pós-LB mostraram associação independente com menor HDL-C. O risco de PNP aumentou de 7,4 a 8,6% a cada redução de 1 mg/dL no HDL-C. Em nosso estudo, não foi encontrada relação entre os níveis de AF e a incidência de PNP pós-CB. No entanto, se pensarmos que a AF aumenta os níveis de HDL-C e pode impedir o desenvolvimento de PNP, a prática de AF após a CB é uma recomendação importante para evitar o desenvolvimento de PNP após a cirurgia da obesidade. Mais estudos serão necessários para apoiar nossas descobertas.

O aumento do gasto energético e da AF ocorreu aos 6 e 15 meses após a CB, mas os maiores benefícios ocorreram quando os indivíduos já eram ativos no pré-operatório. Ser ativo antes da CB mostrou maior perda de circunferência da cintura, principalmente em indivíduos submetidos a RYGB, e maior aumento dos níveis de HDL-C. Os resultados sugerem que, embora a CB seja o tratamento mais eficaz para perda e manutenção de peso a longo prazo, o estilo de vida não sedentário deve ser adotado permanentemente, mesmo naqueles indivíduos obesos que aparentemente se beneficiam menos porque não apresentam perda significativa de peso após a CB. O comportamento ativo antes da CB provavelmente é o melhor preditor para a prática de AF pós-operatória, uma vez que é difícil estabelecer mudanças de hábitos somente após a CB.

Indivíduos com níveis baixos e normais de HDL-C antes da CB mostraram um aumento nos níveis séricos de HDL-C após 15 meses, e esse aumento foi associado com o %PEP. Além disso, foi possível mostrar que a CB diminuiu o risco cardiovascular, mesmo quando apresentavam baixo HDL-C no pré-operatório.

PERSPECTIVAS

Com base nos resultados encontrados, acredita-se que mais estudos relacionados a incidência e progressão de PNP, bem como a busca por fatores de risco, em indivíduos obesos graves sem diabetes submetidos à CB devem continuar sendo realizados. Uma das formas seria dar prosseguimento ao atual estudo, incluindo maior número de participantes, de ambos os sexos, e com maior tempo de seguimento. Aumentando o número de sujeitos, poder-se-ia avaliar a progressão e incidência de PNP pós-CB distinguindo os tipos cirúrgicos e, com maior tempo de seguimento, poderíamos confirmar melhor a relação entre PNP e lipídeos séricos, uma vez que tem sido observada queda do HDL-C sérico após seis meses de CB, mas aumento após um ano da cirurgia. Tal ideia se reforça ao vermos que nossos resultados mostram fatores que se associam a PNP, que se comprovados poderiam ser modificados em intervenções terapêuticas, farmacológicas ou não.

Com relação as minhas expectativas profissionais e acadêmicas, pretendo aplicar e desenvolver meus conhecimentos na docência e na pesquisa. Também almejo realizar pós-doutorado na área de obesidade, CB e PNP.