**UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL**
**PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE: GINECOLOGIA E OBSTETRÍCIA**

**FERNANDA DAPPER MACHADO**

# OBESIDADE E CIRURGIA BARIÁTRICA:

## I. PREVALÊNCIA DE POLINEUROPATIA PERIFÉRICA E ASSOCIAÇÕES

## II. NÍVEIS SÉRICOS DE VITAMINA D E ASSOCIAÇÕES

Porto Alegre

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia da Universidade Federal do Rio Grande do Sul como requisito para a obtenção do título de Doutor.

Orientadora: Prof. Dr. Helena Schmid

Porto Alegre
2021

CIP - Catalogação na Publicação

Dapper Machado, Fernanda
OBESIDADE E CIRURGIA BARIÁTRICA: I. PREVALÊNCIA DE POLINEUROPATIA PERIFÉRICA E ASSOCIAÇÕES II. NÍVEIS SÉRICOS DE VITAMINA D E ASSOCIAÇÕES / Fernanda Dapper Machado. -- 2021.
129 f.
Orientador: Helena Schmid.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia, Porto Alegre, BR-RS, 2021.

1. Obesidade. 2. Cirurgia bariátrica. 3. Polineuropatias. 4. Vitamina D. I. Schmid, Helena, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

## AGRADECIMENTOS

Agradeço à minha orientadora, Prof. Dra. Helena Schmid, pela oportunidade de trabalhar sob sua orientação e por me permitir desenvolver minhas habilidades como pesquisadora; aos meus colegas do Grupo de Pesquisa Neurometabólico, em especial ao colega Dr. Otto Henrique Nienov por todo companheirismo e amizade e compartilhamento de conhecimentos ao longo desses anos.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) por dispor da bolsa de doutorado; aos professores do Programa de Pós-Graduação em Ciências da Saúde: Ginecologia e Obstetrícia por todas as oportunidades e ensinamentos.

À equipe do Centro de Tratamento da Obesidade da Santa Casa de Misericórdia de Porto Alegre, que possibilitou a execução deste trabalho.

Agradeço também minha família, meus pais, irmã e noivo por todo apoio e incentivo.

## LISTA DE ABREVIATURAS

25OHD – 25-hidroxivitamina D

ARIC – do inglês, *Atherosclerosis Risk in Communities*

BS – do inglês, *Bariatric Surgery*

CAGE – do inglês, *Cut-down, Annoyed, Guilty and Eye Opener*

CB – Cirurgia Bariátrica

CI – do inglês, *Confidence Interval*

CRR – do inglês, *Cardiac Risk Ratio*

CVR – do inglês, *Cardiovascular Risk*

CVR-C – do inglês, *Classical - Cardiovascular Risk*

CVR-NC – do inglês, *Non-Classical Cardiovascular Risk*

DM – Diabetes Mellitus

DM1 – Diabetes Mellitus tipo 1

GFR – do inglês, *Glomerular Filtration Rate*

HAS – Hipertensão Arterial Sistêmica

HbA1c – Hemoglobina Glicada

HDL-Cholesterol – do inglês, *High-Density Lipoprotein Cholesterol*

IMC - Índice de Massa Corporal

IPAQ – do inglês, *International Physical Activity Questionnaire*

JCR – do inglês, *Journal Citation Report*

LDL-Cholesterol – do inglês, *Low-Density Lipoprotein Cholesterol*

MET – do inglês, *Metabolic Equivalent of Task*

MNSI – do inglês, *Michigan Neuropathy Screening Instrument*

NDS – do inglês, *Neuropathy Disability Score*

NHANES – do inglês, *National Health Nutrition Examination Survey*

NO – do inglês, *Nitric Oxide*

Non-HDL-Cholesterol – do inglês, *Non-High-Density Lipoprotein Cholesterol*

NSS – do inglês, *Neuropathy Symptom Score*

OR – do inglês, *Odds Ratio*

PMS – do inglês, *Postmenopausal Status*

PNP – Polineuropatia Periférica

PostBS-PPN – do inglês, *Post-Bariatric Surgery Peripheral Polyneuropathy*

PPN – do inglês, *Peripheral Polyneuropathy*

PreBS-PPN – do inglês, *Pre-Bariatric Surgery Peripheral Polyneuropathy*

PreDM – Pré-Diabetes

PTH – Hormônio Paratireoidiano

RYGB – do inglês, *Roux en-Y Gastric Bypass*

SET – do inglês, *Solar Exposition Time*

SET-Total – do inglês, *Total Solar Exposition Time*

SET-Wend – do inglês, *Solar Exposition Time on Weekends*

SG – do inglês, *Sleeve Gastrectomy*

SM – Síndrome Metabólica

SOS – do inglês, *Swedish Obese Subjects*

STROBE – do inglês, *Strengthening the Reporting of Observational Studies in Epidemiology*

TWL – do inglês, *Total Weight Loss*

UVB – Ultravioleta do Tipo B

UVR – do inglês, *Ultraviolet Radiation*

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

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**SUMÁRIO**

## RESUMO

Objetivos: Antes e após a cirurgia bariátrica (CB) em mulheres pré e pós-menopáusicas e homens, avaliar: I. a prevalência e associações da polineuropatia periférica (PNP) e II. avaliar os níveis séricos de 25-hidroxivitamina D (25OHD) e associações.

Métodos: Estudo transversal em participantes obesos graus II e III antes e após CB, do tipo derivação gástrica em Y de Roux ou gastrectomia vertical. O Instrumento de Rastreamento de Michigan e o Questionário Internacional de Atividade Física (versão curta) foram utilizados para avaliar a presença de PNP e os Equivalentes Metabólicos gastos por semana. Participantes com Diabetes Mellitus e outras causas conhecidas de PNP foram excluídos. Para a avaliação de PNP foram incluídos 1467 participantes; para avaliação dos níveis séricos de vitamina D versus tempo de exposição solar e atividade física, foram avaliados 821 participantes antes e após CB e, na análise de vitamina D e fatores de risco cardiovascular (CVR), foram incluídos 511 participantes com obesidade grau II e III.

Resultados: I. A prevalência de PNP foi maior na obesidade comparada com o grupo pós-CB e, nos dois grupos a PNP se associou à pós-menopausa. II. Níveis séricos de 25OHD mais baixos se associaram com maior peso corporal e IMC e com baixa exposição solar no pré e pós-CB. Na avaliação de 25OHD e CVR, IMC e glicemia mais elevados se associaram com os menores quartis de 25OHD.

## ABSTRACT

Aims: I. Evaluate peripheral polyneuropathy (PPN) prevalence and its associations and II. Evaluate 25-hydroxivitamin D serum levels (25OHD) before and after bariatric surgery (BS) on pre and post-menopausal women and men.

Methods: Cross-sectional study in grade II and III obese subjects before and after BS, Roux en-Y Gastric Bypass or Sleeve Gastrectomy. The Michigan Neuropathy Screening Instrument (MNSI) and the International Physical Activity Questionnaire (IPAQ) (short-version) were used to evaluate PPN presence and the Metabolic Equivalent of Task (MET) spent per week. Participants with Diabetes Mellitus or other known causes of PPN were excluded. To evaluate PPN 1467 were included; to evaluate 25OHD and solar exposure time and physical activity, 821 participants before and after-BS were included and, on the 25OHD and cardiovascular risk factors (CVR) analysis, 511 participants with grade II and III obesity were included.

Results: I. PPN prevalence was higher on obesity than post-BS, and in both groups, PPN prevalence was associate with post-menopause. II. Lower 25OHD serum levels were associated with higher body weight and BMI and with lower solar exposition time before and after-BS. On 25OHD evaluation with CVR, higher BMI and glycemia were associated with lower 25OHD quartiles.

## INTRODUÇÃO

Os índices de obesidade vêm aumentando no Brasil e no mundo. De acordo com os dados do VIGITEL (Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico), a obesidade atinge cerca de 20% dos brasileiros e, Porto Alegre, cidade em que foi realizado este trabalho, está entre as capitais com maiores taxas de obesidade no país (1).

Apesar da alta ingestão de calorias, a dieta das pessoas com obesidade é, em geral, pobre em micronutrientes (2). A obesidade parece estar associada à polineuropatia periférica (PNP) (3), tendo mostrado, em estudo anterior do nosso grupo, associação independente da PNP com idade e estado pós-menopausal em mulheres obesas em avaliação para cirurgia bariátrica (CB) (4). Nos nossos trabalhos, a prevalência de PNP em obesos graves ficou em torno de 11% (4,5). Outros estudos também sugerem a associação de PNP e obesidade (6,7).

A ocorrência da PNP após a CB foi inicialmente descrita na literatura por relatos de casos. Os poucos estudos com base populacional disponíveis, todos retrospectivos, encontraram prevalências que variam entre 4,6 a 16% (8–10).

Estudo retrospectivo mais recente identificou uma incidência de 0,7% de manifestações neurológicas secundárias às deficiências de vitaminas do complexo B após a CB, sendo 15% dessas manifestações, polineuropatias. Dos participantes acometidos por complicações neurológicas, 77% haviam realizado RYGB (do inglês *Roux en Y Gastric* Bypass) e 19% SG (do inglês *Sleeve Gastrectomy*). Essas complicações ocorreram de dois meses a seis anos após a cirurgia. Essa incidência, no entanto, pode ter sido subestimada pelo fato de a avaliação ter sido realizada somente

nos pacientes com queixas relacionadas às complicações neurológicas durante consultas de acompanhamento somadas a níveis inadequados de vitaminas do complexo B (11).

Em estudos epidemiológicos, a PNP tem sido rastreada através do *Michigan Screening Neuropathy Instrument* (MNSI) utilizando-se o ponto de corte ≥2,5, com especificidade de 79% e sensibilidade de 61%. O MNSI tem a vantagem de ser um instrumento de rastreio simples, não-invasivo e de rápida aplicação (12).

Embora existam estudos relacionando a presença de PNP com deficiências vitamínicas após a CB, não está definido se há associação do tipo de cirurgia com a presença de PNP. Também não está esclarecido se mulheres têm menor predisposição para a ocorrência de PNP, como ocorre no Diabetes Mellitus (DM) tipo 2.

A obesidade e sedentarismo se associam com PNP, mas também com níveis séricos baixos de 25-hidroxivitamina D (25OHD) (13,14). Em parte, a diminuição dos níveis de 25OHD na obesidade pode ser explicada pela diluição ou sequestro da vitamina D na gordura corporal (13,15). Avaliações do nível de exposição solar e atividade física em obesos e após a CB são escassas na literatura e há indícios de que a exposição solar e atividade física são capazes de melhorar os níveis de 25OHD em indivíduos magros, embora isso ainda seja controverso quando se trata de obesos (13).

Por questões didáticas, este trabalho foi dividido em dois capítulos, um para avaliar a prevalência e fatores associados à PNP; e outro, para avaliar os níveis séricos de 25OHD e fatores associados, ambos em mulheres pré e pós-menopausa e homens com obesidade e após a CB.

# CAPÍTULO I - OBESIDADE E CIRURGIA BARIÁTRICA: PREVALÊNCIA DE POLINEUROPATIA E ASSOCIAÇÕES

## I - 1 REFERENCIAL TEÓRICO

### I - 1.1 ESTRATÉGIA DE BUSCA E SELEÇÃO DE REFERÊNCIAS BIBLIOGRÁFICAS

A estratégia utilizada para a busca de referências bibliográficas iniciou com a definição dos descritores a serem utilizados, que foram: *polyneuropathies, bariatric surgery, Roux en-Y gastric by-pass, sleeve gastrectomy, obesity* e equivalentes. Em seguida, os MeSH ou *Entry Terms* foram traduzidos pelos seus equivalentes conforme a base de dados utilizada. Os resultados das buscas estão expostos no Quadro 1. As bases de dados pesquisadas incluíram Pubmed, Scielo e Embase.

| **Termos** | **Pubmed** | **Scielo** | **Embase** |
|---|---|---|---|
| Polyneuropathies AND Bariatric Surgery | 56 | 3 | 125 |
| Polyneuropathies AND Sleeve Gastrectomy | 28 | 0 | 29 |
| Polyneuropathies AND Roux em Y Gastric Bypass | 4 | 0 | 29 |
| Polyneuropathies AND Obesity | 287 | 2 | 433 |

Quadro 1 Resultado da busca de referências bibliográficas nas bases de dados.

A estratégia de busca foi montada durante o projeto de pesquisa e atualizada semanalmente através de ferramentas de alerta disponibilizadas pelas bases de dados. Outros trabalhos de interesse encontrados nas referências bibliográficas dos trabalhos lidos também foram incluídos.

## I - 1.2 MAPA CONCEITUAL

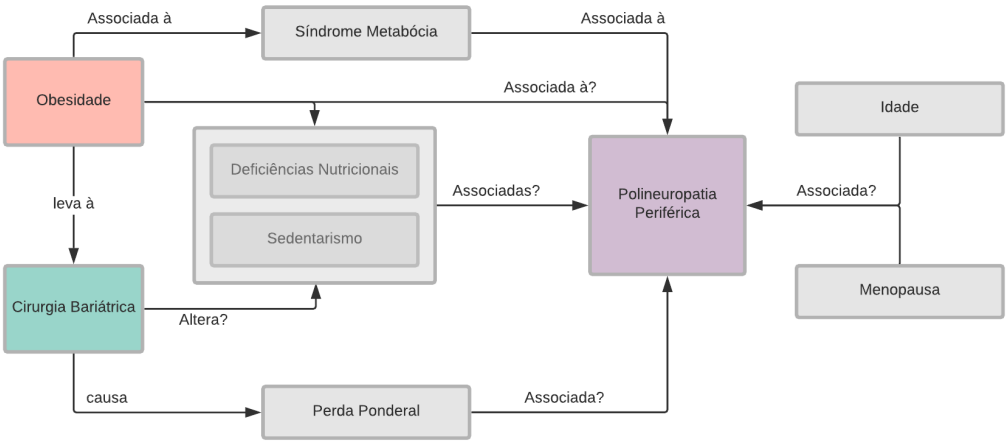


Figura 1 Mapa Conceitual do Capítulo 1.

A obesidade é um dos componentes da síndrome metabólica (SM) (16), alguns estudos sugerem que a SM e a obesidade estariam associadas com a PNP (3,4,17). Um número cada vez maior de obesos se submete à CB, e como consequência, acaba mudando hábitos de vida, o que poderia aumentar o nível de atividade física (18). A CB poderia interferir na prevalência de PNP por acentuar as deficiências nutricionais prévias, ou atenuá-las através da reposição, uma vez que sedentarismo e deficiências nutricionais poderiam estar associados à PNP (2). Por outro lado, o envelhecimento e o estado de pós-menopausa já foram descritos em associação com a PNP em obesos (5), o que poderia também ocorrer após a CB.

## I - 1.3 CIRURGIA BARIÁTRICA

O tratamento para obesidade pode ser clínico, com associação de mudança de hábitos alimentares, uso de medicamentos e prática de atividade física, ou cirúrgico, através da CB. Conforme o Conselho Federal de Medicina, o tratamento cirúrgico é

indicado para os pacientes com índice de massa corporal (IMC) acima de 40 kg/m² ou IMC acima de 35 kg/m² associado a comorbidades (19). A CB, em comparação ao tratamento clínico, apresenta melhores resultados em relação à perda e manutenção do peso, além de reduzir o risco de desfechos graves (20).

A CB é o tratamento mais eficiente para perda de peso em pacientes com obesidade grave e comorbidades e tem grande impacto na melhora da qualidade de vida e na diminuição da morbimortalidade destes pacientes. Auxilia também no controle de doenças como hipertensão (HAS), apneia do sono, DM, dislipidemias e doenças osteoarticulares (21). Estudos do nosso grupo, bem como os de outros autores, demonstraram diminuição da necessidade de uso de medicamentos para o controle do DM tipo 2, HAS e dislipidemias em pacientes obesos e diabéticos após um ano da CB do tipo RYGB e SG (22–26).

A CB pode ser recomendada para pacientes com o IMC ≥40 kg/m², ou ≥35 kg/m² associado a comorbidades, sendo a forma mais eficaz de perda de peso nestes casos (19,20).

Devido à alimentação industrializada, pobre em micronutrientes, bem como às comorbidades associadas à obesidade; indivíduos obesos comumente apresentam deficiências nutricionais. Entre essas deficiências, as principais são as seguintes: ferro, vitamina B12 e vitamina D (2,27). Após a cirurgia pode ocorrer uma piora nestas deficiências nutricionais por fatores como vômitos, perda de superfície de absorção, diminuição da produção de suco gástrico, alterações na dieta, entre outros (21). Em geral, os procedimentos são realizados por via laparoscópica, com baixa morbidade e mortalidade (28).

I - 1.3.1 Gastroplastia com Derivação Gástrica em Y de Roux - RYGB

O procedimento cirúrgico do tipo RYGB é o procedimento bariátrico mais utilizado no mundo. A perda de peso decorrente deste procedimento é maior se comparado àqueles que atingem restritivamente o estômago. Neste procedimento, a porção superior do estômago é seccionada e uma nova bolsa é criada. Esta é anastomosada para no segmento proximal do jejuno (Figura 2). Como resultado, a ingestão de alimentos fica limitada e ocorre má-absorção de alguns nutrientes (28).

Como complicações desta cirurgia, comumente, são relatados problemas pós-cirúrgicos, como intolerância persistente a alimentos ricos em proteína e a síndrome de dumping precoce ou tardia. Esta última também é vista como um efeito colateral benéfico, uma vez que contribui para a não ingestão de alimentos ricos em açúcares e gorduras (27). Por outro lado, a síndrome de dumping e a ocorrência de vômitos e diarreia parecem estar associados à ocorrência de PNP após CB (9).

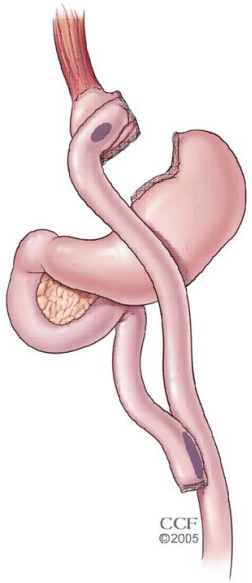


Figura 2 Ilustração do by-pass gástrico em Y de Roux (RYGB). Fonte: ASMBS, 2020.

Pacientes submetidos a cirurgia tipo RYGB apresentam alto risco de desenvolvimento de deficiências de ferro, vitaminas B12 e D (27). Apesar da suplementação vitamínica após CB, estes pacientes apresentam frequentemente níveis mais baixos de vitamina B12, mesmo não diagnósticos de deficiências. Talvez pela longa meia-vida da vitamina B12, aproximadamente 400 dias, os sintomas relacionados à sua deficiência serão percebidos meses ou anos após a cirurgia (29).

A diminuição dos níveis de vitamina B12 pode ocorrer pela ingestão insuficiente de alimentos-fonte, hidrólise inadequada da vitamina proveniente da dieta ou defeitos na quantidade e na interação do fator intrínseco com a vitamina B12 no estômago modificado pela cirurgia. A absorção da vitamina B12 requer fator intrínseco, produzido pelas células parietais gástricas, pH gástrico ácido e absorção no íleo, fatores estes que sofrem alteração na CB, em especial, a RYGB (7).

Em teoria, o RYGB levaria a uma diminuição dos níveis de vitaminas lipossolúveis circulantes, como a vitamina D, pela pequena interação das gorduras da dieta com os ácidos biliares. Porém, a perda de peso, e consequente perda de gordura corporal, parece contribuir de maneira mais importante para o aumento dos níveis séricos de 25OHD após esse tipo de procedimento (30).

I - 1.3.2 Gastrectomia Vertical - SG

A gastrectomia em manga (*sleeve gastrectomy*) está associada com a perda de 33 a 45% do excesso de peso corporal após o período de um ano. Neste procedimento uma porção (cerca de 80%) do estômago é retirada, sem desvios no caminho percorrido pelo bolo alimentar. A popularidade deste tipo de procedimento vem crescendo e recebeu acreditação pela Sociedade Americana de Cirurgia Metabólica e Bariátrica em 2011 tanto como procedimento único, quanto como um estágio de outro tipo de

procedimento, como o *duodenal switch*. Neste último caso, seu uso pode ajudar a diminuir o IMC do paciente antes da realização de procedimento disabsortivo, minimizando o risco cirúrgico (28).

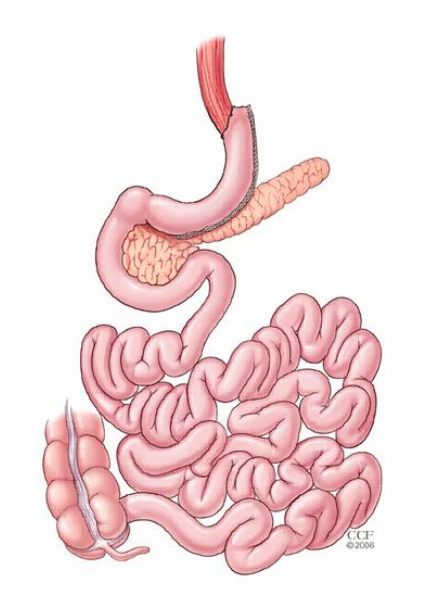

Figura 3 Ilustração da gastrectomia em manga (SG). Fonte: ASMBS, 2020.

Apesar de não muito comuns, já existem alguns relatos de casos de deficiências nutricionais após o SG, algumas com consequências neurológicas (31–33). Entre as complicações neurológicas relatadas está a PNP (34).

I - 1.3.3 Atividade Física, Obesidade, Cirurgia Bariátrica

Um estudo desenvolvido pela Clínica Mayo em Rochester correlacionou o tempo de atividade física moderada e perda de peso após um ano de CB. Para que se obtenha a perda de peso desejada após a CB são recomendados 150 minutos de atividade moderada por semana, o que corresponde às recomendações da Organização Mundial de Saúde para a manutenção da capacidade cardiorrespiratória (35). Por outro

lado, outros estudos estimaram uma necessidade maior de exercícios físicos semanais para evitar o reganho de peso nos pacientes pós-CB (36).

O estudo SOS (do inglês, *Swedish Obese Subjects*) comparou a atividade física de obesos submetidos à CB com obesos submetidos a tratamento clínico para obesidade. Neste estudo os pacientes foram classificados como sedentários ou ativos. O número de indivíduos ativos no período de lazer foi maior no grupo cirúrgico após 10 anos, apesar do grupo de tratamento clínico ser inicialmente mais ativo. Seis meses após a cirurgia até o final do estudo, o grupo CB passou a ser mais ativo e manteve-se ativo (37).

A atividade física moderada também está relacionada à melhora da qualidade de vida e a menor progressão da PNP em pacientes com DM tipo 2 (38), bem como a restes musculares melhores em pacientes com PNP crônica (39).

## I - 1.4 POLINEUROPATIA PERIFÉRICA

PNP é um termo que indica uma desordem no sistema nervoso periférico. Apresenta-se inicialmente com formigamento, queimação e parestesia nos dedos e pés (40), podendo evoluir para calosidades, deformidade de Charcot, úlceras e amputações em casos mais graves (41,42).

Os sinais e sintomas da PNP variam dependendo do tipo de fibra envolvida. Quando as fibras grossas estão envolvidas, a propriocepção e o toque ficam debilitados; quando são as fibras finas, ocorre diminuição da sensibilidade térmica, além de dor e parestesias. A diminuição ou ausência do reflexo Aquileu frequentemente se associa com neuropatia assintomática, os casos mais avançados podem apresentar ulceração ou deformidade de Charcot (43).

Uma das causas mais comuns de PNP é o DM; outras causas conhecidas incluem a hanseníase (40), o alcoolismo (43), desordens metabólicas (40), tabagismo (43) e doenças infecciosas, como HIV, hepatite B e Lyme (44) (Quadro 2). Além dos pacientes diabéticos, a neuropatia crônica pode ser encontrada em indivíduos com intolerância à glicose, glicemia de jejum aumentada e até naqueles com tolerância normal à glicose (45).

Quadro 2 Causas de polineuropatia. Adaptado de Pop-Busui, et al., 2017.

| **PRIMÁRIAS** | |
|---|---|
| Idiopática (criptogênica) | HEREDITÁRIAS/GENÉTICAS |
| | Na 1.7 –mutação<br>Na 1.8 – mutação<br>PN Familiar Amilóide<br>Doença de Fabry<br>Doença de Tangier |
| **SECUNDÁRIAS** | |
| METABÓLICAS | IMUNOLÓGICAS |
| Pré-diabetes<br>Diabetes Mellitus<br>Def de Vit B12<br>Dislipidemia<br>Hipotireoidismo<br>Doença Renal Crônica<br>Perda ponderal | Doença Celíaca<br>Sarcoidose<br>Sjögren<br>Artrite reumatoide<br>Lúpus<br>Vasculite<br>Doença Inflamatória Intestinal<br>Síndrome Paraneoplásica<br>Gamopatia monoclonal |
| TOXINAS/MEDICAMENTOS | INFECCIOSAS |
| Antirretrovirais<br>Antibióticos (metronidazol, nitrofurantoína, linezolida)<br>Quimioterapia (bortezomibe)<br>Flecainida<br>Estatinas<br>Álcool<br>Intoxicação por vit B6 | HIV<br>Hepatite C<br>Influenza |

Entre os pacientes diabéticos, as PNP são mais prevalentes entre os homens, bem como as amputações. Os motivos pelos quais as mulheres diabéticas são menos frequentemente comprometidas não são conhecidos (46). Em estudo realizado pelo nosso grupo observamos associação de PNP com HDL-colesterol baixo (4), e o HDL-colesterol de homens é, em geral, menor que o de mulheres. Níveis séricos maiores de HDL-colesterol nas mulheres, poderia ter um efeito protetor, o qual poderia ser menos efetivo quando concomitante com sedentarismo, pós-menopausa e/ou envelhecimento.

Revisão sistemática com meta-análise, que incluiu 39 estudos, identificou na análise de subgrupo que os pacientes neuropatas com DM tipo 1 têm níveis elevados de triglicerídeos. O mesmo estudo concluiu que os indivíduos com níveis séricos elevados de triglicerídeos e LDL-colesterol têm maior risco de PNP diabética (47).

Conforme já citado, descrição de alterações sugestivas de PNP existem em obesos graves que não se submeteram à CB bem como seguindo-se à CB (6,7,48).

Segundo alguns autores, a rápida perda de peso decorrente do procedimento bariátrico pode aumentar a susceptibilidade dos nervos à compressão através da perda de tecido subcutâneo, perda de proteção do tecido adiposo e outras mudanças estruturais (21). Além disso, as deficiências nutricionais poderiam induzir atividade inflamatória aumentada e alterações de imunidade que talvez favoreçam a PNP. Segundo Landais, no entanto, o mecanismo mais importante implicado na patogênese das complicações neurológicas após CB seria o efeito de deficiências nutricionais decorrentes da má-absorção ou restrição alimentar (21).

No estudo SOS, a CB diminuiu a incidência de complicações microvasculares do DM em pacientes diabéticos, pré-diabéticos e normoglicêmicos. Porém, entre as complicações microvasculares, a PNP foi rara, talvez em parte porque o estudo não foi

desenhado para esta finalidade, e a CB somente se associou com a redução da sua incidência no subgrupo pré-diabético (49).

Estudo retrospectivo de 2004 comparou a frequência de PNP após CB e após colecistectomia: a prevalência de PNP foi de 16% pós-CB e 3% pós-colecistectomia (9). Em 2010 o mesmo grupo observou prevalência de PNP pós-CB de 7%, e essa menor prevalência foi associada à mudança no acompanhamento e tratamento dos distúrbios nutricionais relacionados à cirurgia (10).

Estudo de Callaghan e cols (2016), que avaliou a prevalência de PPN de acordo com o status glicêmico de 102 participantes obesos e 53 não obesos, mostrou prevalência de PPN de 29.0% em grupo obeso pré-diabético e de 34.6% em grupo obeso diabético, sendo sugerido que a diminuição do IMC e do estado de pré-DM deva ser considerado no gerenciamento da PPN (50).

Em pacientes com DM tipo 2, estudo retrospectivo que avaliou 4.683 participantes submetidos à CB, concluiu que a remissão do DM pós-cirúrgica, mesmo que temporária, diminui o risco de desenvolvimento das complicações microvasculares, entre elas a PNP (51).

### I - 1.4.1 Avaliação de Polineuropatia Periférica

A presença da PNP pode ser avaliada de diferentes maneiras. Para o diagnóstico clínico utiliza-se exame físico e sintomas, sendo útil às vezes determinar também a velocidade de condução nervosa. Já para a avaliação epidemiológica, os testes de rastreamento para PNP têm sido bem aceitos e têm as vantagens de serem de fácil aplicação, baixo custo e minimamente invasivos (52). Dentre estes testes destacam-se o

MNSI, NSS (do inglês, *Neuropathy Symptom* Score) e NDS (do inglês, *Neuropathy Disability Score*), utilizados neste trabalho.

O MNSI é um instrumento composto por duas partes: um questionário com 15 questões autoadministráveis e o exame físico dos membros inferiores (12,52). O questionário apresenta questões sobre sintomas sensoriais positivos (dor, sensibilidade térmica, formigamento) e negativos (torpor), cólicas e fraqueza muscular, úlceras nos pés, calos e amputações (52). Uma resposta positiva para as questões 1-3, 5-6, 8-9, 11-12 e 14-15 e negativa nas questões 7 e 13 somam um ponto ao escore total. As questões 4 e 10 não avaliam PNP e, por isso, não acrescentam pontos ao escore (12).

Quando um ponto de corte ≥7 é adotado para o questionário, a sensibilidade e especificidade do teste são de 13 e 99% respectivamente. Ao diminuir o ponto de corte para ≥4, o teste se torna 40% sensível e 92% específico. O ponto de corte ≥2,5 para o exame físico, que será adotado neste trabalho e o foi em muitos outros da literatura, apresenta sensibilidade de 61% e especificidade de 79%, testado em pacientes com DM tipo 1 (12).

No exame físico, o profissional da saúde avalia a aparência dos dois pés, a presença de úlceras, o reflexo Aquileu e a sensibilidade vibratória. Cada etapa do exame corresponde a uma pontuação; um ponto é acrescido ao escore caso os pés apresentem calosidades, pele seca, deformações, infecções ou fissuras. Caso algum dos pés apresente úlcera, mais um ponto é adicionado (12,52).

No teste de sensibilidade vibratória, realizado com diapasão 128 Hz, é normal que o examinador consiga perceber a vibração por 5 segundos além do paciente quando o diapasão estiver posicionado no paciente, no primeiro dedo do pé, não apoiado, na segunda falange. O teste é repetido em uma das mãos do examinador para comparação

com o normal, na segunda falange distal do primeiro dedo. Quando o examinador puder perceber a vibração por um tempo superior a 10 segundos o teste é considerado anormal e um ponto é acrescido ao escore (12,53).

A sensibilidade à pressão é testada através do exame com monofilamento de Semmes-Weinstein 5.07, aplicado no mesmo local que o diapasão. Este teste é capaz de mensurar em parte a função sensorial do paciente e a perda da sensibilidade à pressão. O monofilamento exerce uma pressão de 10g na pele quando dobrado (53).

O teste do reflexo Aquileu é realizado nos dois tendões com o paciente sentado e os pés pendentes, não apoiados. O examinador localiza o tendão e golpeia-o com o martelo neurológico. Na ausência do reflexo o teste é repetido com reforço: solicita-se ao paciente para que realize um movimento de puxar as mãos simultaneamente ao teste. O resultado do teste é um na ausência total de reflexo mesmo com reforço; 0,5, quando presente com reforço ou zero quando presente sem reforço (53). Um escore total para o MNSI igual ou acima de 2,5 é considerado positivo para PNP, sendo 8 pontos a pontuação máxima (12).

O NSS é um questionário em que os pacientes são perguntados sobre dor ou desconforto nas pernas e pés. Se o paciente descrever queimação, letargia ou formigamento, um escore de 2 pontos é atribuído. Cansaço, câimbras ou dor acrescentam um ponto ao escore. À presença de sintomas nos pés são atribuídos dois pontos, para sintomas na panturrilha, um. Caso os sintomas sejam exacerbados à noite, dois pontos são acrescidos; se não, um ponto é atribuído. Os pacientes são questionados a respeito de alguma manobra que possa reduzir os sintomas. O escore máximo atingido é nove. Um escore de 3-4 é considerado sintomas leves, 5-6 corresponde a escore moderado e 7-9, grave (48).

O NDS é utilizado para avaliar os sinais de PNP e inclui o exame do reflexo Aquileu, sensibilidade vibratória, dolorosa e térmica nos dois pés. Como resultado dos testes o score máximo que pode ser atingido é 10 pontos, a partir de 6 pontos é considerado como resultado anormal, ou seja, positivo para PNP (12). Um escore de 3 a 5 pontos é considerado PNP leve, de 6 a 8 pontos, moderada e 9 ou 10 pontos, grave (48). A sensibilidade vibratória é testada com o diapasão de 128 HZ no ápice do primeiro pododáctilo; a sensibilidade dolorosa com uma agulha de ponta romba no mesmo ponto e a sensibilidade térmica com o cabo do diapasão resfriado. Os testes de sensibilidade recebem um ponto quando a sensibilidade está reduzida ou ausente. O reflexo Aquileu é marcado com um ponto quando presente com reforço ou dois pontos quando ausente (48). Para se diagnosticar a PNP os critérios são: sinais moderados com ou sem sintomas ou sinais e sintomas moderados, pelo menos. Sinais leves sozinhos ou com sintomas leves não são considerados adequados para diagnosticar a PNP (48).

I - 1.4.2 Polineuropatia, Obesidade e Cirurgia Bariátrica

PNP pode ocorrer por muitas causas, as mais frequentemente citadas são DM, hipotireoidismo, lúpus, deficiência de vitamina B12, HIV, hepatite e drogas neurotóxicas, entre as outras causas citadas anteriormente no Quadro 2 (44).

No caso da neuropatia diabética, os fatores de risco incluem: idade avançada (54), peso corporal aumentado (54), hiperglicemia (55–62), dislipidemias (57,60), aumento do estresse oxidativo (55–58), etilismo (61), hipotireoidismo (61), deficiência de vitamina B12 (61), síndrome metabólica e seus componentes (3,17,63) entre outros.

Estudo de Shangai, com 2035 participantes avaliados pelo NDS encontrou prevalência de 4% de PNP associado com SM, com um crescimento linear da prevalência de PNP de acordo com o número de componentes de SM. Além disso,

hemoglobina glicada (HbA1c), tratamento para DM e HAS também se associaram com PNP (64). Para Callaghan e colaboradores, utilizando o MNSI para avaliação dos participantes, a obesidade e o DM foram os principais condutores metabólicos para a PNP (3), de modo que sugerem ainda o gerenciamento da obesidade e da pré-DM, bem como outros fatores metabólicos como hiperlipidemia e HAS para o manejo clínico da PNP (50).

Estudos do nosso grupo avaliando obesos graves, sem DM, encontraram prevalência de PNP em torno de 11%. Quando as mulheres foram avaliadas, houve uma associação independente com idade e menopausa (4,5).

Inicialmente, em relatos de casos, a PNP foi descrita como uma complicação neurológica da CB (21), após Thaisetthawatkul e colaboradores, em estudos retrospectivos, demonstraram diminuição da prevalência de PNP em pacientes submetidos à CB através da adoção de um melhor controle nutricional (9,10).

Nos pacientes com DM tipo 2, os estudos têm indicado um papel protetor da CB em relação à prevalência de PNP, melhorando o peso, níveis de HbA1c, lipídios, além de sintomas neuropáticos e déficits e regeneração de fibras finas (65). Há indicação ainda de que a remissão do DM decorrente da CB diminui o risco de PNP mesmo entre aqueles que voltam a ter DM. Conforme Coleman e cols., para cada ano de remissão do DM, o risco de complicações microvasculares diminuem em 19% (51).

## I - 2 JUSTIFICATIVA

A obesidade e a síndrome metabólica se associam com a PNP em indivíduos com e sem DM em alguns estudos com base populacional. Apesar de algumas divergências entre os estudos, a prevalência de PNP nessas populações tem se mostrado alta (3,63,64).

A PNP já foi considerada uma complicação da CB, inicialmente descrita em relatos de casos (21). Posteriormente, a prevalência de PNP e outras complicações neurológicas foram avaliadas através de estudos retrospectivos (9,10). Mais recentemente, um estudo retrospectivo avaliou a prevalência de PNP apenas em participantes pós-CB que apresentaram deficiência de vitaminas do complexo B (11). São escassos na literatura estudos de rastreio de PNP em participantes submetidos à CB sem DM.

Considerando o crescimento dos índices de obesidade, a ausência de dados na literatura sobre a prevalência de PNP após a CB e os custos financeiros e de saúde associados à PNP, nos parece de grande importância a comparação da prevalência de PNP antes e após a CB, bem como os fatores associados à PNP nas duas situações.

Avaliar estes aspectos nos parece de interesse, uma vez que pacientes com PNP estão predispostos a úlceras e amputações e o conhecimento de fatores que se associam e que possivelmente sejam de risco poderá mudar a ênfase que se dá às condutas e recomendações no pós-operatório tardio da CB.

## I - 3 PROBLEMAS

Há diferença na prevalência de PPN entre mulheres na pré e pós-menopausa e homens com obesidade graus II e III, sem DM, em comparação com as mulheres na pré e pós-menopausa e homens que se submeteram à CB?

Há associação da prevalência de PNP com obesidade, síndrome metabólica, CB, nível de atividade física e estado pós-menopausal em mulheres e homens com obesidade graus II e III, sem DM, antes e após CB?

## I - 4 HIPÓTESES

### I - 4.1 HIPÓTESES NULAS

A prevalência de PPN é igual em mulheres na pré e pós-menopausa e homens com obesidade graus II e III, sem DM, em comparação com as mulheres na pré e pós-menopausa e homens que se submeteram à CB.

A prevalência de PNP não se associa com obesidade, síndrome metabólica e seus componentes, CB, nível de atividade física e estado pós-menopausal em mulheres e homens com obesidade graus II e III, sem DM, antes e após CB.

### I - 4.2 HIPÓTESES ALTERNATIVAS

A prevalência de PPN é maior em mulheres na pré e pós-menopausa e homens com obesidade graus II e III, sem DM, em comparação com mulheres na pré e pós-menopausa e homens que se submeteram à CB.

A prevalência de PNP se associa com obesidade, síndrome metabólica e seus componentes, CB, nível de atividade física e estado pós-menopausal em mulheres e homens com obesidade graus II e III, sem DM, antes e após CB.

## I - 5. OBJETIVOS

### I - 5.1 OBJETIVO GERAL

Avaliar e comparar a prevalência de PNP em mulheres na pré- e pós-menopausa e homens com obesidade graus II e III, sem DM, em pré- e pós-CB.

### I - 5.2 OBJETIVOS ESPECÍFICOS

Avaliar a associação de PNP com obesidade, síndrome metabólica e seus componentes, CB, nível de atividade física, idade e estado pós-menopausal em mulheres e homens com obesidade graus II e III, sem DM, tanto em pré, como em pós-operatório de CB.

# CAPÍTULO II – OBESIDADE E CIRURGIA BARIÁTRICA: NÍVEIS SÉRICOS DE VITAMINA D E ASSOCIAÇÕES

## II - 1 REFERENCIAL TEÓRICO

### II – 1.1 ESTRATÉGIA DE BUSCA E SELEÇÃO DE REFERÊNCIAS BIBLIOGRÁFICAS

A estratégia utilizada para a busca de referências bibliográficas iniciou com a definição dos descritores a serem utilizados, que foram: e *vitamin D/vitamin D deficiency, obesity, bariatric surgery, exercise* e equivalentes. Em seguida, os MeSH Terms foram traduzidos pelos seus equivalentes conforme a base de dados utilizada. Os resultados das buscas estão expostos na Figura 1. As bases de dados pesquisadas incluíram Pubmed, Scielo e Embase.

| **Termos** | **Pubmed** | **Scielo** | **Embase** |
|---|---|---|---|
| Vitamin D/Vitamin D deficiency AND Bariatric Surgery | 566 | 23 | 1605 |
| Vitamin D/Vitamin D deficiency AND Obesity | 3883 | 115 | 10099 |
| Vitamin D/Vitamin D deficiency AND Exercise | 2744 | 30 | 5369 |

Quadro 3 Resultado das buscas nas bases de dados.

A estratégia de busca foi montada durante a fase de projeto de pesquisa e atualizada semanalmente através de ferramentas de alerta disponibilizadas pelas bases de dados. Outros trabalhos de interesse encontrados nas referências bibliográficas dos trabalhos lidos também foram incluídos.

## II – 1.2 MAPA CONCEITUAL

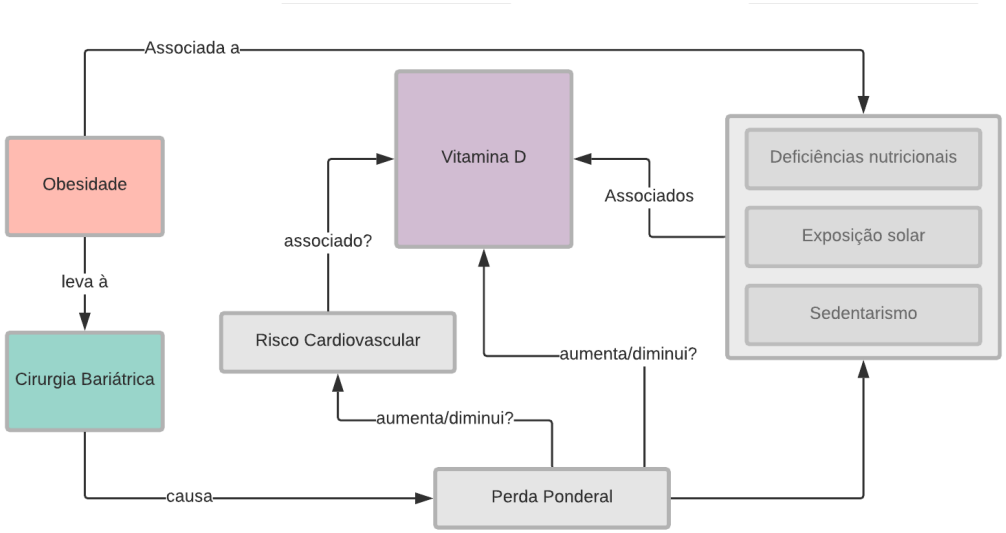


Figura 4 Mapa Conceitual do Capítulo II.

A obesidade está frequentemente associada a baixos níveis séricos de 25OHD (13), bem como a deficiências nutricionais, pouca exposição solar e hábitos sedentários (2,14). A CB, pela perda ponderal, em especial pela diminuição da gordura corporal que acarreta, poderia contribuir aumentando os níveis de 25OHD disponíveis. Deste modo, a CB contribuiria diminuindo o sedentarismo e aumentando a exposição solar, diminuiria o risco cardiovascular, que poderia estar associado aos níveis séricos de 25OHD.

## II – 1.3 VITAMINA D

No corpo humano, a vitamina D é sintetizada sob exposição à radiação UVB (ultravioleta B) e, em condições ideais, a exposição solar cobriria 95% das necessidades diárias desta vitamina. Como a exposição humana à luz solar tem diminuído, as fontes alimentares da vitamina D, o colecalciferol (vitamina D3) e o ergocalciferol (vitamina

D2) passaram a também ter contribuição importante para os estoques de vitamina D do organismo. A absorção de vitamina D proveniente da dieta acontece na porção distal do jejuno e íleo juntamente com a gordura alimentar misturada com os sais biliares (66).

As principais funções da vitamina D incluem a regulação da absorção intestinal do cálcio e fosfato e manutenção dos seus níveis séricos. O hormônio paratireoidiano (PTH) interage com a vitamina D com a finalidade de manter estas funções, essenciais para a manutenção da atividade neuromuscular. A produção de PTH também é regulada pelo calcitriol em mecanismo de feedback. A deficiência de vitamina D aumenta os níveis de PTH e diminui a absorção intestinal de cálcio (66).

Além disto, a vitamina D pode estar envolvida na regulação da liberação de insulina pelas células beta-pancreáticas. Por outro lado, seu receptor está presente em células do sistema imunológico, e parece estar associada à longevidade (66).

Em mulheres, a deficiência/insuficiência de vitamina D a longo prazo é fator de risco para ocorrência de osteoporose (67–69). A reposição de vitamina D diminui a velocidade de perda da massa óssea, sendo por isso indicada para pacientes com níveis séricos diminuídos, hiperparatireoidismo secundário e com fatores de risco para osteoporose, pacientes com osteopenia ou com osteoporose relacionada à senilidade e uso de corticosteroides (69,70).

Do mesmo modo, um papel fisiológico importante da vitamina D tem sido descrito para a manutenção da massa e força muscular (71,72). Estes efeitos são demonstrados em estudos in vitro e in vivo e sugerem que a vitamina D mantém a força muscular de atletas e indivíduos ativos além de proteger contra lesões musculares (71). A suplementação com vitamina D parece favorecer um aumento da massa magra e ganho de massa óssea (71).

Dados do estudo NHANES (do inglês, *National Health Nutrition Examination Survey*) (2005-2006) mostram associação da concentração sérica de vitaminas, entre elas a 25OHD, e alta contagem de passos diária, sugerindo que a prática de atividades físicas melhore os níveis séricos da vitamina (73).

II – 1.3.1 Vitamina D, Obesidade e Cirurgia bariátrica

A obesidade está frequentemente associada à deficiência de vitamina D (66). Explicações para esta associação vem sendo buscadas pela comunidade científica, as propostas sendo: (a) baixa exposição solar dos pacientes obesos devido aos estigmas sociais relacionados com a obesidade; (b) sequestro da vitamina D circulante pelo tecido adiposo (1); (c) diluição simples da vitamina D pelo excesso de gordura visceral (2).

Wortsman e colaboradores (2000) avaliaram, em estudo do tipo caso-controle, os níveis de 25OHD em pacientes obesos e não obesos após exposição à luz ultravioleta ou dose oral de vitamina D2. Os pacientes obesos tinham níveis de 25OHD basais mais baixos e, após a exposição à radiação, os níveis séricos ficaram 57% mais baixos que os níveis dos pacientes não obesos; apesar dos níveis do precursor 7-dehydrocholesterol na pele e sua conversão serem similares nos testes in-vitro. Além disso, o IMC estava inversamente correlacionado com as concentrações séricas pós irradiação e com o pico de concentração de vitamina após a administração oral (13). Este estudo foi o primeiro a propor a hipótese de sequestro de vitamina D pelo tecido adiposo.

Drincic e colaboradores, 2012, em estudo que comparou dados de tamanho e composição corporal e vitamina D, demonstraram que um modelo de diluição volumétrica explicaria toda a variabilidade nas concentrações séricas de 25OHD atribuídas à obesidade (15).

Carrelli e col. (2016) avaliaram as concentrações de vitamina D na gordura subcutânea e visceral em mulheres obesas comparadas com mulheres não obesas, mostraram que as pacientes obesas têm mais depósitos de vitamina D. Estes dados suportam a hipótese de que a maior massa adiposa dos pacientes obesos serve como depósito de vitamina D e, por isso, esses pacientes requerem maior ingestão de vitamina para atingir os níveis séricos considerados normais (74). Outra possibilidade para aumentar os níveis séricos de 25OHD, seria aumentar a exposição solar entre os obesos (75).

Em estudo longitudinal que comparou a suplementação de vitamina D em mulheres obesas e magras, as mulheres magras desenvolveram níveis séricos de 25OHD maiores que as obesas, o que indicou que as mulheres obesas necessitam de doses maiores para atingir os mesmos níveis (76). Tem sido apontado o fato de que após alguns tipos de CB, pela criação de desvio intestinal ocorreria má-absorção das vitaminas lipossolúveis por diminuição da interação das gorduras da dieta com os sais biliares (77).

A prevalência de deficiência de vitamina D após o RYGB chega a 51% (78). A frequência de deficiências vitamínicas foi semelhante no SG e no RYGB em ensaio clínico randomizado; neste estudo, a deficiência mais comum foi a de vitamina D (79).

Em ensaio clínico randomizado, que avaliou a perda de peso em mulheres pós-menopáusicas que receberam acompanhamento nutricional e de atividade física, divididas em grupos que receberam suplementação de vitamina D ou placebo, as doses de 2000 UI de vitamina D não aumentaram a perda de peso (80).

Em revisão sistemática de ensaios clínicos, não foi possível estabelecer claramente o benefício da reposição de vitamina D nos marcadores glicêmicos e

inflamatórios. Apesar disso, parece haver uma influência do nível de 25OHD basal nos marcadores inflamatórios (81). Ensaio clínico em chineses também não encontrou melhora nos marcadores metabólicos de pacientes com síndrome metabólica que receberam suplementação de vitamina D (82).

Analisando três diferentes cortes prospectivas europeias, Larsen e col. (2016) não encontraram relação entre vitamina D e diferença de peso corporal ou circunferência da cintura. No entanto, em análise individual, um dos estudos avaliados mostrou associação entre maiores níveis séricos de 25OHD e menor ganho de peso (83). A contribuição da exposição solar não foi avaliada nestes estudos.

II – 1.3.2 Vitamina D, Obesidade, Exposição Solar e Etnia

Considerando que o suprimento de vitamina D pode ser obtido a partir de várias fontes, incluindo síntese cutânea, alimentos fontes de vitamina D e mobilização dos estoques corporais de vitamina D, o impacto de diferentes fontes nos níveis séricos de 25OHD deve ser influenciado por fatores individuais e ambientais (84,85). Conforme refletido pela variação sazonal dos níveis de 25OHD, a síntese cutânea de vitamina D induzida por UVB parece ser a principal fonte para a maioria dos indivíduos (86). Do mesmo modo, variações na latitude também devem ser importantes (84).

Como as concentrações de vitamina D3 no sangue 24 horas após a irradiação de corpo inteiro são menores em indivíduos com obesidade quando comparados a indivíduos sem obesidade, menor ação da radiação ultravioleta após a exposição da pele, bem como diminuição do tempo de exposição ao sol, ambos descritos de obesos (13,75,87) devem ser mecanismos pelos quais níveis séricos de 25OHD diminuem. As recomendações para uso de altas doses de vitamina D em indivíduos obesos estão

relacionadas às informações acima, bem como a observações clínicas e ensaios clínicos randomizados (88).

A exposição ao sol e as atividades físicas aumentam os níveis de 25OHD em indivíduos magros (13), enquanto permanece a controvérsia sobre seu efeito em indivíduos com obesidade (14).

A exposição da pele aos raios ultravioleta desencadeia a liberação de vitamina D, mas também de óxido nítrico de locais de armazenamento dérmico para a corrente sanguínea (89,90).

A exposição ao sol é gratuita e, além de seus efeitos bem conhecidos no aumento da biodisponibilidade da vitamina D com efeitos positivos no metabolismo ósseo e mineral, a exposição ao sol também poderia desempenhar outros papéis importantes nos processos extra esqueléticos. Vários outros efeitos, além da síntese de vitamina D, são induzidos pela exposição à radicação ultravioleta (89,90). A pele humana é o maior depósito de óxido nítrico e seus derivados e a irradiação com doses relevantes de UVA induz a translocação de óxido nítrico para a circulação, levando à vasodilatação, redução da resistência vascular e redução da pressão arterial (90).

Se a exposição inadequada ao sol é um mecanismo importante pelo qual os níveis séricos de 25OHD diminuem na obesidade, devemos suspeitar que, em indivíduos obesos, não apenas os níveis de 25OHD são reduzidos, mas que outras anormalidades prejudiciais à saúde são concomitantes, como baixos níveis de óxido nítrico séricos, e que apenas a suplementação de vitamina D não poderia corrigí-las.

Em um estudo transversal no sul do Brasil, a alta prevalência de hipovitaminose D foi documentada e pode ser atribuída tanto a aumento do tecido adiposo quanto à

baixa exposição solar de indivíduos obesos (91). Levando isso em consideração, foi recomendado que todos os pacientes submetidos à CB recebessem suplementação de vitamina D antes mesmo dos procedimentos bariátricos (92). Porto Alegre, cidade daquele estudo, está na latitude -30º e, em latitudes positivas equivalentes, a síntese de vitamina D pela pele durante o inverno foi considerada nula (93).

Quanto à etnia, Dix e cols. (87), correlacionaram dados referentes à cor da pele e os níveis séricos de 25OHD em participantes obesos. Como resultado encontraram associação da cor natural da pele com a variação dos níveis de 25OHD, sugerindo que a cor natural da pele determine resposta nos níveis séricos de 25OHD quando ocorre a exposição solar.

II – 1.3.3 Vitamina D, Cirurgia Bariátrica e Atividade Física

Wicherts e col. mostraram que níveis de 25OHD abaixo de 20 ng/ml estavam associados com baixo desempenho físico e um grande declínio deste desempenho, na população idosa holandesa. tanto em homens quanto em mulheres. Como quase 50% da população tinha níveis séricos de 25OHD abaixo de 20 ng/ml, os autores sugeriram que estratégias de saúde pública deveriam ser dirigidas para este grupo (94).

Por outro lado, em outro estudo, níveis séricos adequados de 25OHD, ingestão de cálcio e obesidade menos grave correlacionaram-se positivamente com a melhora do desempenho muscular em participantes fisicamente ativos. Foi sugerido a partir destes dados, que determinando os níveis de 25OHD poderíamos ter um marcador de melhora do desempenho muscular, especialmente em adultos mais velhos, saudáveis com atividade física mais baixa. Os mesmos autores, no mesmo estudo, também sugerem que as concentrações de 25OHD e cálcio podem prevenir a fadiga muscular (95).

Ensaio clínico que comparou dois grupos de pacientes submetidos à CB (RYGB e SG), um grupo tratado com suplementação de vitamina D e cálcio no pré e pós-operatório e prescrição de atividade física e outro grupo com acompanhamento pós-operatório sem suplementação ou prescrição de atividade física constatou que os pacientes suplementados e fisicamente ativos apresentaram redução da perda de massa óssea e magra em relação aos pacientes não suplementados e fisicamente inativos (96).

### II - 1.3.4 Vitamina D, Cirurgia Bariátrica, Síndrome Metabólica e Doença Cardiovascular

Síndrome Metabólica é o termo que corresponde à associação de fatores que aumentam o risco cardiovascular e inclui o aumento da circunferência da cintura, hiperglicemias, dislipidermias e HAS (97).

Uma associação de baixos níveis séricos de 25OHD com aumento da prevalência de DM, HAS, doença cardiovascular e risco cardiovascular também foi descrita por vários autores (98–100), muitos dos quais creditam essa relação à menor ação da vitamina D nessas condições, o que poderia resultar nas respostas alteradas dos tecidos endoteliais, células musculares lisas e cardiomiócitos (101,102).

As doenças cardiovasculares em geral são uma importante causa de morbimortalidade em pacientes obesos (103–105) e muitos dos efeitos da CB na mortalidade desses pacientes parecem ser devidos à diminuição do risco cardiovascular (106,107). Essa redução pode ser decorrente da melhora, após a cirurgia, tanto dos mediadores clássicos de risco cardiovascular, como pressão arterial e perfil lipídico, quanto por alterações em mediadores não-clássicos, como glicemia, HbA1c, quantidade de tecido adiposo visceral e perfil inflamatório (105–108).

A relação entre hipovitaminose e a obesidade com o risco de doença cardiovascular sugere que uma exploração mais aprofundada dos riscos à saúde associados ao estado de hipovitaminose D que ocorre na obesidade, e os possíveis determinantes do risco cardiovascular, devam ser pesquisados.

Níveis baixos de 25OHD sérica estão associados à diminuição da massa muscular em alguns estudos (109) e é provável que a diminuição da massa muscular tenha impacto no uso periférico de glicose (110,111), principalmente quando há resistência à insulina, como ocorre na obesidade (112,113).

Um estudo com 11.092 adultos não diabéticos sem história de doença cardiovascular, no Estudo de Risco de Aterosclerose em Comunidades (ARIC) (114), identificou a HbA1c como fator de risco para doença cardiovascular e morte, mesmo antes do diagnóstico de DM e após a correção para glicemia em jejum (114). O estudo ARIC foi realizado em uma população de norte-americanos, brancos e negros, excluindo participantes com outra declaração de cor (114).

Associação inversa dos níveis séricos de 25OHD e HbA1c também foi encontrada no estudo de Hutchinson e cols. (115) na população nórdica, em sua maioria caucasiana, não diabética, que incluía obesos e não obesos. Neste estudo, os pacientes com DM foram excluídos apenas por um questionário respondido pelos participantes. Kositsawat e cols. (116) que avaliaram dados do NHANES na população adulta dos Estados Unidos da América com participantes com e sem obesidade e DM, também observaram associação de HbA1c com 25OHD. Nos dados do NHANES, a mesma associação somente não se repetiu na análise dos participantes mais jovens, de 18 a 34 anos.

Meta-análise que incluiu 35 estudos encontrou associação entre níveis séricos mais altos de 25OHD e menores níveis pressóricos, além de chance reduzida de HAS (117). Um estudo em população do nordeste brasileiro encontrou associação inversa entre os níveis de 25OHD e colesterol total, e LDL-colesterol, mostrando que há relação entre baixos níveis séricos de 25OHD e perfil aterogênico. Este mesmo trabalho não encontrou associação entre 25OHD e síndrome metabólica ou seus componentes (118).

## II – 2 JUSTIFICATIVA

A obesidade está associada a baixos níveis séricos de 25OHD (13,119), porém os estudos são controversos em relação ao efeito da CB nos níveis séricos de 25OHD (120,121).

Alguns mecanismos poderiam explicar a associação entre obesidade e 25OHD baixa, entre eles um menor tempo de exposição solar dos pacientes obesos devido aos estigmas sociais relacionados à obesidade; sequestro da vitamina D circulante pelo tecido adiposo e a diluição simples da vitamina D pelo excesso de gordura visceral (15,119). Níveis baixos de 25OHD também têm sido associados com DM e HAS (101,116,122–125).

A relação entre os níveis de 25OHD e obesidade e o risco de doenças cardiovasculares (13) sugere a necessidade de uma exploração dos riscos associados aos níveis baixos de 25OHD entre os obesos e, por consequência, após a CB. Além disso, apesar das hipóteses de diluição ou sequestro da vitamina D no tecido adiposo, e da maior necessidade de exposição à radiação ultravioleta para obtenção dos mesmos níveis séricos de 25OHD nas mulheres obesas comparadas com as não-obesas (74), a relação da exposição solar e níveis de 25OHD e complicações esqueléticas e não esqueléticas necessita de mais investigação.

## II – 3 PROBLEMAS

Há diferença entre os níveis séricos de 25OHD em mulheres na pré e pós-menopausa e homens com obesidade graus II e III, sem DM, em comparação com mulheres na pré e pós-menopausa e homens que se submeteram à CB?

Há associação dos níveis séricos de 25OHD com exposição solar, obesidade, síndrome metabólica e seus componentes, CB e nível de atividade física em mulheres e homens com obesidade graus II e III, sem DM, em pré- e pós-operatório de CB?

## II – 4 HIPÓTESES

### II – 4.1 HIPÓTESES NULAS

Os níveis séricos de 25OHD são semelhantes em mulheres na pré e pós-menopausa e homens com obesidade graus II e III, sem DM, em comparação com mulheres na pré e pós-menopausa e homens após CB.

Os níveis séricos de 25OHD não se associam com exposição solar, obesidade, síndrome metabólica e seus componentes, CB e nível de atividade física em mulheres e homens com obesidade graus II e III, sem DM, em pré- e pós-operatório de CB.

### II – 4.2 HIPÓTESES ALTERNATIVAS

Os níveis séricos de 25OHD são maiores em mulheres na pré e pós-menopausa e homens com obesidade graus II e III, sem DM, em comparação com mulheres na pré e pós-menopausa e homens após CB.

Os níveis séricos de 25OHD se associam com exposição solar, obesidade, síndrome metabólica e componentes, CB e nível de atividade física em mulheres e homens com obesidade graus II e III, sem DM, antes e após CB.

## II – 5 OBJETIVOS

### II – 5.1 OBJETIVO GERAL

Avaliar e comparar os níveis séricos de 25OHD em mulheres na pré- e pós-menopausa e homens com obesidade graus II e III, sem DM, antes e após CB.

### II – 5.2 OBJETIVOS ESPECÍFICOS

Avaliar a associação dos níveis séricos de 25OHD com obesidade, síndrome metabólica e seus componentes, CB, nível de atividade física e exposição solar em mulheres e homens com obesidade graus II e III, sem DM, tanto em pré, como em pós-CB.

## REFERÊNCIAS BIBLIOGRÁFICAS


1. Ministério da Saúde. Vigitel Brasil 2019 [Internet]. Vigitel Brasil 2019 : vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico : estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados . 2020. 139 p. Available from: https://www.saude.gov.br/images/pdf/2020/April/27/vigitel-brasil-2019-vigilancia-fatores-risco.pdf
2. Astrup A, Bügel S. Overfed but undernourished: recognizing nutritional inadequacies/deficiencies in patients with overweight or obesity. Int J Obes [Internet]. 2019;43(2):219–32. Available from: http://dx.doi.org/10.1038/s41366-018-0143-9
3. Callaghan BC, Gao LL, Li Y, Zhou X, Reynolds E, Banerjee M, et al. Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. Ann Clin Transl Neurol. 2018;5(4):397–405.
4. Nienov OH, Matte L, Dias LS, Schmid H. Peripheral polyneuropathy in severely obese patients with metabolic syndrome but without diabetes: Association with low HDL-cholesterol. Rev Assoc Med Bras. 2017;63(4):324–31.
5. Dias LS, Nienov OH, Machado FD, Ramos CP, Rodrigues D, Menguer RK, et al. Polyneuropathy in Severely Obese Women Without Diabetes: Prevalence and Associated Factors. Obes Surg [Internet]. 2018; Available from: http://link.springer.com/10.1007/s11695-018-03627-0
6. Russell JW, Feldman EL. Impaired glucose tolerance--does it cause neuropathy? Muscle Nerve. 2001;24(9):1109–12.
7. Becker D a., Balcer LJ, Galetta SL. The neurological complications of nutritional

deficiency following bariatric surgery. J Obes. 2012;2012.

8. Abarbanel JM, Berginer VM, Osimani a, Solomon H, Charuzi I. Neurologic complications after gastric restriction surgery for morbid obesity. Neurology. 1987;37(2):196–200.

9. Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, Norell JE, Dyck PJB. A controlled study of peripheral neuropathy after bariatric surgery. Neurology. 2004;63(8):1462–70.

10. Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, Norell JE, Dyck PJB, Dyck JB. Good nutritional control may prevent polyneuropathy after bariatric surgery. Muscle Nerve. 2010;42(5):709–14.

11. Punchai S, Hanipah ZN, Meister KM, Schauer PR, Brethauer SA, Aminian A. Neurologic Manifestations of Vitamin B Deficiency after Bariatric Surgery. Obes Surg. 2017;27(8):2079–82.

12. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary P a., Albers JW, et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type1 diabetes: Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med. 2012;29(7):937–44.

13. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72(3):690–3.

14. Klinedinst BS, Meier NF, Larsen B, Wang Y, Yu S, Mochel JP, et al. Walking in the Light: How History of Physical Activity, Sunlight, and Vitamin D Account for Body Fat—A UK Biobank Study. Obesity. 2020;28(8):1428–37.

15. Drincic AT, Armas L a. G, Van Diest EE, Heaney RP. Volumetric Dilution, Rather Than Sequestration Best Explains the Low Vitamin D Status of Obesity.

Obesity [Internet]. 2012;20(7):1444–8. Available from: http://dx.doi.org/10.1038/oby.2011.404/nature06264

16. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on Clinical pr. Vol. 71, Hypertension. 2018. 13–115 p.
17. Callaghan BC, Xia R, Banerjee M, De Rekeneire N, Harris TB, Newman AB, et al. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. Diabetes Care. 2016;39(5):801–7.
18. Welbourn R, Hollyman M, Kinsman R, Dixon J, Cohen R, Morton J, et al. Bariatric-Metabolic Surgery Utilisation in Patients With and Without Diabetes: Data from the IFSO Global Registry 2015–2018. Obes Surg [Internet]. 2021 Feb 27; Available from: http://link.springer.com/10.1007/s11695-021-05280-6
19. Brasil CF de M. Resolução CFM nº 2.131/2015. Diário Of da União. 2016;1.
20. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357(8):741–52.
21. Landais A. Neurological Complications of Bariatric Surgery. Obes Surg. 2014;
22. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
23. Schmid H, Goelzer Neto CF, Dias LS, Weston AC, Espindola MB, Pioner SR, et

al. Metabolic syndrome resolution by Roux-en-Y gastric bypass in a real world: a case control study. Rev Assoc Med Bras. 2015;61(2):161–9.

24. Goelzer Neto CF. Avaliação das respercussões das terapêuticas clínica e cirúrgica da obesidade mórbida em um centro de tratamento multidisciplinar. Fundação Universidade Federal de Ciências da Saúde de Porto Alegre; 2012.

25. Dias LS. Neuropatia diabética e instabilidade ao andar em uma população de pacientes com Diabetes Mellitus tipo 2 - associação com sintomas depressivos. Fundação Universidade Federal de Ciências da Saúde de Porto Alegre; 2013.

26. Matte L. Prevalencia de neuropatia diabética somática em obesos com síndrome metabólica. Universidade Federal de Ciências da Saúde de Porto Alegre; 2012.

27. Rickers L, McSherry C. Bariatric surgery: nutritional considerations for patients. Nurs Stand. 2012;26(49):41–8.

28. Mechanick JI, Kushner RF, Sugerman HJ, Michael Gonzalez-Campoy J, Collazo-Clavell ML, Spitz AF, et al. American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic and Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatri. Obesity. 2009;17(1):S3–72.

29. Koffman BM, Greenfield LJ, Ali II, Pirzada N a. Neurologic complications after surgery for obesity. Muscle Nerve. 2006;33(2):166–76.

30. Coupaye M, Breuil MC, Rivière P, Castel B, Bogard C, Dupré T, et al. Serum vitamin D increases with weight loss in obese subjects 6 months after roux-en-y gastric bypass. Obes Surg. 2013;23(4):486–93.

31. Scarano V, Milone M, Minno MND Di, Panariello G, Bertogliatti S, Terracciano M, et al. Late micronutrient deficiency and neurological dysfunction after

laparoscopic sleeve gastrectomy : a case report. Eur J Clin Nutr. 2012;66(1):645–8.

32. Durán B, Ruíz De Angulo D, Parrilla P. Beriberi: An uncommon complication of sleeve gastrectomy. Surg Obes Relat Dis. 2015;11(6):e53–5.

33. Kröll D, Laimer M, Borbély YM, Laederach K, Candinas D, Nett PC. Wernicke Encephalopathy: a Future Problem Even After Sleeve Gastrectomy? A Systematic Literature Review. Obes Surg. 2016;26(1):205–12.

34. Medina ARDL, Noguera-Rojas W, Anitúa-Valdovinos MDM, Muñoz-Joachim C. Acute postgastric reduction surgery neuropathy and severe malnutrition after sleeve gastrectomy for morbid obesity. Surg Obes Relat Dis. 2011;7(1):119–21.

35. Mundi MS, Lorentz P a., Swain J, Grothe K, Collazo-Clavell M. Moderate physical activity as predictor of weight loss after bariatric surgery. Obes Surg. 2013;23(10):1645–9.

36. Zalesin KC, Franklin B a., Miller WM, Nori Janosz KE, Veri S, Odom J, et al. Preventing Weight Regain After Bariatric Surgery: An Overview of Lifestyle and Psychosocial Modulators. Am J Lifestyle Med. 2010;4(2):113–20.

37. Sjöström L, Lindroos A, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004 Dec 11;351(26).

38. Dixit S, Maiya AG, Shastry B a. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: A single blind, parallel group randomized controlled trial. J Diabetes Complications. 2013;2–9.

39. Ruhland JL, Shields RK. The effects of a home exercise program on impairment and health-related quality of life in persons with chronic peripheral neuropathies.

Phys Ther. 1997;77(10):1026–39.

40. Klaus BD. Peripheral neuropathy. Nurse Pract. 1996;21(6):130–1.

41. Dyck P, Davies J, Wilson D, Service E, Melton L, Pc O. Risk Factors for Severity of Diabetic Polyneuropathy. Diabetes Care. 1999;22(9):1479–86.

42. Neumann C, Branchtein L, Schmid H. Severe autonomic neuropathy: How many symptoms? [1]. Diabetes Care. 1995;18(1):133–4.

43. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacol Ther. 2008;120(1):1–34.

44. Pop-Busui R, Boulton AJMM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017;40(January):136–54.

45. Ziegler D. Painful diabetic neuropathy: advantage of novel drugs over old drugs? Diabetes Care. 2009;32(2).

46. Dyck PJ, Litchy WJ, Lehman K a, Hokanson JL, Low P a, O'Brien PC. Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. Neurology. 1995;45(6):1115–21.

47. Cai Z, Yang Y, Zhang J. A systematic review and meta-analysis of the serum lipid profile in prediction of diabetic neuropathy. Sci Rep [Internet]. 2021;11(1):1–20. Available from: https://doi.org/10.1038/s41598-020-79276-0

48. Young MJ, Boulton AJM, Macleod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36:150–4.

49. Carlsson LMS, Sjöholm K, Karlsson C, Jacobson P, Andersson-Assarsson JC, Svensson PA, et al. Long-term incidence of microvascular disease after bariatric surgery or usual care in patients with obesity, stratified by baseline glycaemic

status: a post-hoc analysis of participants from the Swedish Obese Subjects study. Lancet Diabetes Endocrinol [Internet]. 2017;5(4):271–9. Available from: http://dx.doi.org/10.1016/S2213-8587(17)30061-X

50. Callaghan BC, Xia R, Reynolds E, Banerjee M, Rothberg AE, Burant CF, et al. Exploring the association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. JAMA Neurol [Internet]. 2016 Dec 1;73(12):1468. Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2016.3745

51. Coleman KJ, Haneuse S, Johnson E, Bogart A, Fisher D, O'Connor PJ, et al. Long-term microvascular disease outcomes in patients with type 2 diabetes after bariatric surgery: Evidence for the legacy effect of surgery. Diabetes Care. 2016;39(8):1400–7.

52. Yang Z, Chen R, Zhang Y, Huang Y, Hong T, Sun F, et al. Scoring systems to screen for diabetic peripheral neuropathy. Cochrane Database Syst Rev. 2014;(3).

53. Yang Z, Zhang Y, Chen R, Huang Y, Ji L, Sun F, et al. Simple tests to screen for diabetic peripheral neuropathy. Cochrane Database Syst Rev. 2014;(2).

54. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: Clinical manifestations and current treatments. Lancet Neurol. 2012;11(6):521–34.

55. Han T, Bai J, Liu W, Hu Y. A systematic review and meta-analysis of -lipoic acid in the treatment of diabetic peripheral neuropathy. Eur J Endocrinol. 2012;167(4):465–71.

56. Low PA, Nickander KK, Tritschler HJ. The role of oxidative stress and antioxidante treatment in experimental diabetic neuropathy. Diabetes.

1997;46(9).

57. Wiggin TD, Sullivan K a, Pop-busui R, Amato A, Sima A a F, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes. 2009;58(July):1634–40.

58. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: A clinical perspective. Vol. 33, Diabetes Care. 2010. p. 434–41.

59. Cameron NE, Cotter M a. Metabolic and vascular factors in the pathogenesis of diabetic neuropathy. Diabetes. 1997;46 Suppl 2:S31–7.

60. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, et al. Diabetic polyneuropathies: Update on research definition, diagnostic criteria and estimation of severity. Vol. 27, Diabetes/Metabolism Research and Reviews. 2011. p. 620–8.

61. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Prevalence of polyneuropathy in prediabetes and diabetes is associated with abdominal obesity and macroangiopathy: The Monica/Kora Augsburg surveys S2 and S3. Diabetes Care. 2008;31(3):464–9.

62. Callaghan BC, Feldman EL. Measuring neuropathy in obese populations: Challenge accepted. Reply to “Diagnostic accuracy of neuropathy tests in obese population remains elusive.” Clin Neurophysiol [Internet]. 2018;129(7):1504–5. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2000732007&from=export

63. Hanewinckel R, Drenthen J, Ligthart S, Dehghan A, Franco OH, Hofman A, et al. Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: A prospective population-based cohort study. J Neurol Neurosurg

Psychiatry. 2016;87(12):1336–42.

64. Han L, Ji L, Chang J, Wen J, Zhao W, Shi H, et al. Peripheral neuropathy is associated with insulin resistance independent of metabolic syndrome. Diabetol Metab Syndr. 2015;7(1):1–6.

65. Azmi S, Ferdousi M, Liu Y, Adam S, Iqbal Z, Dhage S, et al. Bariatric surgery leads to an improvement in small nerve fibre damage in subjects with obesity. Int J Obes [Internet]. 2021 Jan 27; Available from: http://www.nature.com/articles/s41366-020-00727-9

66. Bacci V, Silecchia G. Vitamin D status and supplementation in morbid obesity before and after bariatric surgery. Expert Rev Gastroenterol Hepatol. 2016;6:781.

67. Kim D, Kim J. Association between serum 25-hydroxyvitamin D levels and adiposity measurements in the general Korean population. Nutr Res Pract. 2016;10(2):206–11.

68. Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, et al. Major osteoporotic fragility fractures: Risk factor updates and societal impact. World J Orthop. 2016;7(3):171–81.

69. Julián C, Lentjes MA, Huybrechts I, Luben R, Wareham N, Moreno LA, et al. Fracture risk in relation to serum 25-hydroxyvitamin D and physical activity: results from the EPIC-Norfolk cohort study . J Bone Min Res. 2016;1–17.

70. Curtis EM, Moon RJ, Dennison EM, Harvey NC, Cooper C. Recent advances in the pathogenesis and treatment of osteoporosis. Clin Med (Northfield Il). 2016;16(4):360–4.

71. Moran DS, McClung JP, Kohen T, Lieberman HR. Vitamin D and physical performance. Sport Med. 2013;43(7):601–11.

72. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of

vitamin D supplementation on muscle strength: A systematic review and meta-analysis. Osteoporos Int. 2011;22(3):859–71.

73. Choi JE, Ainsworth BE. Associations of food consumption, serum vitamins and metabolic syndrome risk with physical activity level in middle-aged adults: the National Health and Nutrition Examination Survey (NHANES) 2005–2006. Public Health Nutr. 2016;19(8):1–10.

74. Carrelli A, Bucovsky M, Horst R, Cremers S, Zhang C, Bessler M, et al. Vitamin D Storage in Adipose Tissue of Obese and Normal Weight Women. J Bone Miner Res. 2017;32(2):237–42.

75. Piccolo BD, Hall LM, Stephensen CB, Gertz ER, Van Loan MD. Circulating 25-Hydroxyvitamin D Concentrations in Overweight and Obese Adults Are Explained by Sun Exposure, Skin Reflectance, and Body Composition. Curr Dev Nutr. 2019;3(7):1–12.

76. Gallagher JC, Yalamanchili V, Smith LM. The effect of vitamin d supplementation on serum 25OHD in thin and obese women. J Steroid Biochem Mol Biol. 2013;136:195–200.

77. Johnson JM, Maher JW, DeMaria EJ, Downs RW, Wolfe LG, Kellum JM. The long-term effects of gastric bypass on vitamin D metabolism. Ann Surg [Internet]. 2006;243(5):701–4; discussion 704-5. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1570540&tool=pmcentrez&rendertype=abstract

78. Shah M, Simha V, Garg A. Review: Long-term impact of bariatric surgery on body weight, comorbidities, and nutritional status. J Clin Endocrinol Metab. 2006;91(11):4223–31.

79. Peterli R, Borbély Y, Kern B, Gass M, Peters T, Thurnheer M, et al. Early results

of the swiss multicentre bypass or sleeve study (SM-BOSS): A prospective randomized trial comparing laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. Ann Surg. 2013;258(5):690–5.

80. Mason C, Xiao L, Imayama I, Duggan C, Wang CY, Korde L, et al. Vitamin D3 supplementation during weight loss: a double-blind randomized controlled trial. Am J Clin Nutr. 2014;99(5):1015–25.

81. Zuk A, Fitzpatrick T, Rosella LC. Effect of Vitamin D3 Supplementation on Inflammatory Markers and Glycemic Measures among Overweight or Obese Adults: A Systematic Review of Randomized Controlled Trials. López Lluch G, editor. PLoS ONE [Electronic Resour. 2016 Apr;11(4):e0154215.

82. Yin X, Yan L, Lu Y, Jiang Q, Pu Y, Sun Q. Correction of hypovitaminosis D does not improve the metabolic syndrome risk profile in a Chinese population: a randomized controlled trial for 1 year. Asia Pac J Clin Nutr2. 2016;25(1):71–7.

83. Larsen SC, Ängquist L, Moldovan M, Huikari V, Sebert Y, Cavadino A, et al. Serum 25-hydroxyvitamin D status and longitudinal changes in weight and waist circumference: Influence of genetic predisposition to adiposity. PLoS One. 2016;11(4):1–18.

84. Leary PF, Zamfirova I, Au J, McCracken WH. Effect of latitude on vitamin D levels. J Am Osteopath Assoc. 2017;117(7):433–9.

85. Brouwer-Brolsma EM, Bischoff-Ferrari HA, Bouillon R, Feskens EJM, Gallagher CJ, Hypponen E, et al. Vitamin D: Do we get enough?: A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. Osteoporos Int. 2013;24(5):1567–77.

86. van der Rhee H, de Vries E, Coomans C, van de Velde P, Willem Coebergh J.

Sunlight: For Better or For Worse? A Review of Positive and Negative Effects of Sun Exposure. Cancer Res Front [Internet]. 2016 May 1;2(2):156–83. Available from: http://cancer-research-frontiers.org/2016-2-156/

87. Dix CF, Bauer JD, Martin I, Rochester S, Romero BD, Prins JB, et al. Association of sun exposure, skin colour and body mass index with vitamin D status in individuals who are morbidly obese. Nutrients. 2017;9(10):1–15.

88. Salehpour A, Hosseinpanah F, Shidfar F, Vafa M, Razaghi M, Dehghani S, et al. A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. Nutr J [Internet]. 2012;11(1):1. Available from: Nutrition Journal

89. Fleury N, Geldenhuys S, Gorman S. Sun exposure and its effects on human health: Mechanisms through which sun exposure could reduce the risk of developing obesity and cardiometabolic dysfunction. Int J Environ Res Public Health. 2016;13(10).

90. Halliday GM, Byrne SN. An unexpected role: UVA-induced release of nitric oxide from skin may have unexpected health benefits. J Invest Dermatol [Internet]. 2014;134(7):1791–4. Available from: http://dx.doi.org/10.1038/jid.2014.33

91. Vivan MA, Kops NL, Fülber ER, de Souza AC, Fleuri MASB, Friedman R. Prevalence of Vitamin D Depletion, and Associated Factors, among Patients Undergoing Bariatric Surgery in Southern Brazil. Obes Surg. 2019;29(10):3179–87.

92. Cole AJ, Beckman LM, Earthman CP. Vitamin D status following bariatric surgery: implications and recommendations. 2014;(September).

93. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney

RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.

94. Wicherts IS, Van Schoor NM, Boeke AJP, Visser M, Deeg DJH, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab. 2007;92(6):2058–65.

95. Al-Eisa ES, Alghadir AH, Gabr SA. Correlation between vitamin d levels and muscle fatigue risk factors based on physical activity in healthy older adults. Clin Interv Aging. 2016;11:513–22.

96. Muschitz C, Kocijan R, Haschka J, Zendeli A, Pirker T, Geiger C, et al. The Impact of Vitamin D, Calcium, Protein Supplementation, and Physical Exercise on Bone Metabolism after Bariatric Surgery: The BABS Study. J Bone Miner Res. 2016;31(3):672–82.

97. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International . Circulation. 2009;120(16):1640–5.

98. Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease : dose-response meta-analysis of prospective studies 1 – 3. 2017;25:4–7.

99. McMullan CJ, Borgi L, Curhan GC, Fisher N, Forman JP. The effect of Vitamin D on renin-angiotensin system activation and blood pressure: A randomized control trial. J Hypertens. 2016;35(4):822–9.

100. Al-Ishaq RK, Kubatka P, Brozmanova M, Gazdikova K, Caprnda M, Büsselberg

D. Health implication of vitamin D on the cardiovascular and the renal system. Arch Physiol Biochem [Internet]. 2019;0(0):1–15. Available from: https://doi.org/10.1080/13813455.2019.1628064

101. Jorde R, Schirmer H, Wilsgaard T, Joakimsen RM, Mathiesen EB, Njølstad I, et al. Polymorphisms related to the serum 25-Hydroxyvitamin D level and risk of Myocardial infarction, diabetes, cancer and mortality. The Tromsø study. PLoS One. 2012;7(5).

102. Vaidya A, Sun B, Larson C, Forman JP, Williams JS. Vitamin D3 therapy corrects the tissue sensitivity to angiotensin II akin to the action of a converting enzyme inhibitor in obese hypertensives: An interventional study. J Clin Endocrinol Metab. 2012;97(7):2456–65.

103. Masters RK, Powers DA, Link BG. Obesity and US mortality risk over the adult life course. Am J Epidemiol. 2013;177(5):431–42.

104. Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: The framingham heart study. Circulation. 2009;119(24):3078–84.

105. Fan X, Wang J, Song M, Giovannucci EL, Ma H, Jin G, et al. Vitamin D status and risk of all-cause and cause-specific mortality in a large cohort: results from the UK Biobank. J Clin Endocrinol Metab. 2020;25(October):1–14.

106. Romeo S, Maglio C, Burza MA, Pirazzi C, Sjöholm K, Peltonen M, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. Diabetes Care. 2012;35(12):2613–7.

107. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric Surgery and Long-Term Cardiovascular Events. Surv Anesthesiol. 2012;56(6):327–8.

108. Johnson RJ, Johnson BL, Blackhurst DW, Bour ES, Cobb IV WS, Carbonell AM, et al. Bariatric surgery is associated with a reduced risk of mortality in morbidly obese patients with a history of major cardiovascular events. Am Surg. 2012;78(6):685–92.

109. Halfon M, Phan O, Theta D. Vitamin D: A review on its effects on muscle strength, the risk of fall, and frailty. Biomed Res Int. 2015;2015.

110. Pendergrass M, Bertoldo A, Bonadonna R, Nucci G, Mandarino L, Cobelli C, et al. Muscle glucose transport and phosphorylation in type 2 diabetic , obese nondiabetic , and genetically predisposed individuals. Am J Physiol Metab. 2007;292:92–100.

111. Abdul-Ghani MA, Defronzo RA. Pathogenesis of insulin resistance in skeletal muscle. J Biomed Biotechnol. 2010;

112. Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, de Rekeneire N, et al. Excessive Loss of Skeletal Muscle Mass in Older Adults With Type 2 Diabetes. Diabetes Care. 2009;32(11):1993–7.

113. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia Exacerbates Obesity-Associated Insulin Resistance and Dysglycemia : Findings from the National Health and Nutrition Examination Survey III. PLoS Med. 2010;5(5).

114. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(21):2030–1.

115. Hutchinson MS, Figenschau Y, Njølstad I, Schirmer H, Jorde R. Serum 25-hydroxyvitamin D levels are inversely associated with glycated haemoglobin (HbA1c). The Tromsø Study. Scand J Clin Lab Invest. 2011;71(5):399–406.

116. Kositsawat J, Freeman VL, Gerber BS, Geraci S. Association of A1C Levels

With Vitamin D Status in U.S. Adults. Diabetes Care [Internet]. 2010;33(6):1236–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20215453

117. Vimaleswaran KS, Cavadino A, Berry DJ, Power C, Hyppönen E, Jorde R, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: A mendelian randomisation study. Lancet Diabetes Endocrinol. 2014;2(9):719–29.

118. Curvello-Silva KL, Oliveira NA, Silva TSS, Sousa CD, Daltro C. Association Between Cardiovascular Risk Factors and 25(OH)D Levels in Obese Patients. Metab Syndr Relat Disord. 2020;XX(Xx):1–5.

119. Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes. 2011;36(3):387–96.

120. Fox A, Slater C, Ahmed B, Ammori BJ, Senapati S, Akhtar K, et al. Vitamin D Status After Gastric Bypass or Sleeve Gastrectomy over 4 Years of Follow-up. 2019;

121. Benenati N, Brocci FT, MacCora C, Neri O, Bufano A, Paolini B, et al. Italian Society of Obesity IX National Congress. Eat Weight Disord - Stud Anorexia, Bulim Obes [Internet]. 2018 Oct 3;23(5):705–29. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L624716778

122. Manousopoulou A, Al-Daghri NM, Garbis SD, Chrousos GP. Vitamin D and cardiovascular risk among adults with obesity: A systematic review and meta-analysis. Eur J Clin Invest. 2015;45(10):1113–26.

123. Vaidya A, Forman JP, Hopkins PN, Seely EW, Williams JS. 25-Hydroxyvitamin

D is associated with plasma renin activity and the pressor response to dietary sodium intake in Caucasians. JRAAS - J Renin-Angiotensin-Aldosterone Syst. 2011;12(3):311–9.

124. Williams ED, Rawal L, Oldenburg BF, Renwick C, Shaw JE, Tapp RJ. Risk of cardiovascular and all-cause mortality: Impact of impaired health-related functioning and diabetes - The Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Diabetes Care. 2012;35(5):1067–73.

125. Leu Agelii M, Lehtinen-Jacks S, Zetterberg H, Sundh V, Björkelund C, Lissner L. Low vitamin D status in relation to cardiovascular disease and mortality in Swedish women – Effect of extended follow-up. Nutr Metab Cardiovasc Dis [Internet]. 2017;27(12):1143–51. Available from: https://doi.org/10.1016/j.numecd.2017.10.013

**Artigo 1: Prevalence of Peripheral Polyneuropathy before and after Roux-en-Y Gastric Bypass and Sleeve Gastrectomy**

Artigo submetido ao periódico *Obesity Surgery*, classificado pela A2 na área de Medicina III pelo Web-Qualis da Plataforma Sucupira e Fator de Impacto 3.412 pelo JCR (do inglês, *Journal Citation Report*).

# Prevalence of Peripheral Polyneuropathy before and after Roux-en-Y Gastric Bypass and Sleeve Gastrectomy

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**Main Text Word Count:** 3085 words

**Acknowledgments**

To Obesity Treatment Center's team from Santa Casa de Misericórdia de Porto Alegre and CNPq/CAPES, that provided fellowships' grants for FDM and OHN.

**Abstract**

Introduction: Peripheral polyneuropathy (PPN) can occur in Diabetes Mellitus (DM), obesity and after bariatric surgery (BS).

Objective: To evaluate PPN prevalence before (PreBS-PPN) and after BS (PostBS-PPN) and to look for variables that may be independently associated with both.

Methods: In this cross-sectional study, we evaluated 1467 participants with obesity and without DM before and 10.4 ± 6.8 months after Roux-en-Y Gastric Bypass (RYGB), or Sleeve Gastrectomy (SG). The Michigan Neuropathy Screening Instrument and the International Physical Activity Questionnaire were used to define the presence of PPN and the Metabolic Equivalent Tasks (MET) spent per week, respectively. Using Poisson regression models with a robust estimator, the prevalence of PreBS-PPN and PostBS-PPN were analyzed as dependent variables.

Results: Prevalence of PostBS-PPN (10.5%) was lower than PreBS-PPN (20.4%, $p < 0.001$), with a prevalence of 12.7% post-RYGB and 8.4% post-SG ($p = 0.072$). In the univariate analysis, PreBS-PPN was associated with postmenopausal status (PMS), older age, and taller height. In twelve regression models, we found an independent association of PreBS-PPN with older age, PMS and taller height. PostBS-PPN prevalence was associated with a higher fasting glycemia and stature, and a lower MET on univariate analysis, and with higher fasting glycemia, stature and RYGB in four multivariate regression models.

Conclusion: PPN occurs frequently in subjects with obesity without DM and is lower after BS. SG is not likely to be harmful in the development of neuropathy. Studies of PPN incidence and persistence after BS should clarify these factors**.**

**Key points**

- Polyneuropathy prevalence is higher in obesity than post bariatric surgery
- Polyneuropathy in obesity and post bariatric surgery is associated with stature
- Polyneuropathy is more prevalent after RYGB than after SG

## Introduction

The effects of obesity and bariatric surgery on the occurrence of peripheral polyneuropathy (PPN) are currently not clear. In some recent studies, obesity was associated with PPN [1–4], regardless of the presence of Diabetes Mellitus (DM). Factors that were associated with the occurrence of PPN were very similar to those described in DM [1,3,5,6]. However, serious deficiencies in a wide range of micronutrients are present in patients with severe obesity [7], which could also contribute to the development of PPN. Because of this, it has been recommended to consider obesity as a potential cause of PPN in patients without diabetes and to study

treatment strategies for this important metabolic alteration [3,8]. Bariatric surgery (BS) may be a potential treatment strategy, since it is very effective at producing weight loss and decreasing morbidity and mortality related to severe obesity [9].

PPN has previously been considered to be a complication of BS by some authors [10,11], but in more recent publications, PPN seems to regress at follow-up of patients who have undergone Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) [5,6,12].

When we evaluated women with grade II or III obesity and without DM, an 11.6% prevalence of PPN and an independent association with age and/or the post-menopausal state (postMS) was found [1]. Few studies evaluating PPN prevalence in non-diabetic subjects after BS have been published, with most of them being retrospective in nature [10,11,13]. A systematic review and meta-analysis, which included four prospective studies with 292 participants with PPN found an improvement in PPN after BS [5].

Using a widely-validated method, the Michigan Neuropathy Screening Instrument (MNSI), we evaluated the presence of PPN and factors that could be independently associated with the presence of PPN in patients from a BS center. The subjects had grade II or III obesity or underwent BS (RYGB or SG) after a previous history of grade II or III obesity.

**Methods**

A cross-sectional study, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14], was performed in participants with grade II or III obesity from two bariatric centers and post-bariatric subjects from a single center. The participants were evaluated for the presence of PPN using the MNSI, adopting a cut-off point of $\geq 2.5$ and at least one symptom, which has a specificity of 79% and a sensitivity of 61% [15]. The data collection occurred between January 2016 and March 2020.

Participants diagnosed with DM in the preoperative period or with conditions known to cause PPN, such as vitamin B12 deficiency (< 210 pg/mL), or alcohol abuse (assessed using the CAGE questionnaire [16]), were excluded from the analyses.

As shown in Flowchart 1, 1905 participants consented to participate in the study. Of these, 438 were excluded for having one or more exclusion factors. Of the remaining, 721 were in pre-surgical follow-up, 746 were in post-surgical follow-up (354 and 392 respectively underwent the laparoscopic procedure RYGB and SG). The median postoperative time was 8.0 months (interquartile range of 5.4 to 14.0 months).

The care protocol of the centers where the patients were followed up includes the administration of multivitamins daily and injections of vitamin B12 as needed, to maintain normal serum levels. All patients received nutritional monitoring and were advised to begin physical activities. The routine monitoring at the centers includes laboratory tests of the glycemic, lipid, and vitamin B12 profile. Anthropometric measurements were taken on the same day as the PPN assessment.

The assessment of physical activity was carried out through the International Physical Activity Questionnaire (IPAQ) - short version [17], which allows the computation of

Metabolic Equivalents Task (MET) (MET-min/week) using the formula proposed by Ainsworth [18]. Hypertension was classified according to the criteria of the American Heart Association, with participants classified as having stage 1 or 2 hypertension being considered hypertensive, and participants classified as normal or elevated as normotensive [19]. Metabolic syndrome (MetSynd) was defined according to the International Diabetes Federation criteria [20]. Pre-diabetes (PreDM) was defined as HbA1c between 5.7 and 6.4%, according to American Diabetes Association [21].

For post-BS participants, the measure chosen to assess weight loss was the percentage of total weight loss (%TWL) and TWL ≥ 20% was considered to indicate that the surgical target was achieved [22].

Statistical analysis

Statistical analysis was performed using SPSS® software version 18, dividing the participants into two groups, pre-BS and post-BS. Continuous variables were tested using the Shapiro-Wilk test to define their distribution. Due to their non-parametric distribution, these variables were described using the median and interquartile range, and their association with the prevalence of PPN was tested using the Mann-Whitney U test. The association of the prevalence of PPN with pre (PreMS) and postMS, smoking, preDM, type of surgery, hypertension, and TWL ≥ 20%, was assessed using Pearson's chi-square test or Fisher's exact test.

To define which variables were independently associated with the prevalence of PPN in both groups, Poisson regression models with a robust estimator were proposed, with presence of PPN as a dependent variable. These models included, in addition to variables where $p < 0.2$ occurred in the univariate analysis, serum vitamin B12 levels and smoking, as these factors are well known to be associated with PPN [23].

Sample size calculation

For the sample size calculation, results from previous work from our group were used, which determined the PPN prevalence among participants with grade II and III obesity with MetSynd and without DM, finding a prevalence of 11% [24]. The sample size calculation was conducted using the PSS Health on-line version, set to detect a difference of 7% in PPN prevalence, with a power of 95% and a significance level of 5%. This resulted in a calculated sample size of 876 subjects, 438 pre-BS and 438 post-BS. Accounting for 10% losses, the sample size should be at least of 964 subjects.

Ethical aspects

This study was approved by the Research Ethics Committees of the two Hospitals, the first under number 3,537,318, and of second, under number 1,600,535. All participants signed an informed consent form when entering the study.

**Results**

In the present study, the prevalence of PostBS-PPN was lower than PreBS-PPN, 10.5% versus 20.4% ($p < 0.001$, Fisher’s exact test).

PreBS-PPN

In the univariate assessment, postMS, older age and greater height were associated with PreBS-PPN ($p<0.05$). There was no association between preBS-PPN and smoking, hypertension, MetSynd, lipid profile or MET. PreDM, serum vitamin B12 levels, fasting blood glucose, waist circumference and weight showed a borderline significant p-value ($p< 0.2$) (Table 1).

The multivariate analysis included the variables: smoking, PostMS, age, height, preDM, serum levels of vitamin B12, fasting blood glucose, waist circumference and body weight. In the eight proposed regression models, menopause, older age and greater height were independently associated with preBS-PPN (Table 2). Being in postMS increased the chance of preBS-PPN by 3.2 to 3.3 times (models 1, 2, 3 and 4). An increase of one centimeter in height increased the chance of preBS-PPN by 1.5 to 3.8% (models 1, 2, 3, 4, 5 and 6). With every year of increase in age, the chance of preBS-PPN increased by 3.2 to 3.4% (models 5, 6, 7 and 8).

PostBS-PPN

In the univariate analysis, postBS-PPN was associated with higher serum fasting blood glucose levels, greater height and lower MET ($p<0.05$). There was a tendency ($p<0.2$) for association with PostMS, hypertension, RYGB, age, post-BS time, serum triglyceride levels and weight (Table 3).

The multivariate analysis included the variables: fasting glucose, height, MET, postMS, hypertension, TWL ≥ 20%, type of surgery, age, post-BS time, serum triglyceride levels, weight, serum levels of vitamin B12, and smoking. In four proposed models, fasting blood glucose, preMS and postMS, height, RYGB and MET were independently associated with PostBS-PPN (Table 4). Compared with men, women had more chance of postBS-PPN: postMS women had a 3.7 to 3.8 times higher chance of postBS-PPN (models 1 and 2), whereas preMS women had twice the chance of postBS-PPN than men (models 1 and 2). For every centimeter increase in height, the chance of postBS-PPN increased by 7.9 to 8.2% (models 1, 2, 3 and 4). The RYGB type of surgery increased the chance of postBS-PPN by 67.3 to 70.2% (models 1, 2 3 and 4). MET had no effect on the chances of postBS-PPN. For every mg/dl increase in glycemia, the chance of postBS-PPN increased by 2.9% (models 1 and 2).

**Discussion**

The present study included participants with grade II and III obesity, and individuals with a history with the same degree of obesity but who had undergone BS of the RYGB and SG types around 1 year prior. These groups showed a significant difference in the prevalence of PPN, 20.4% and 10.5%, respectively. An independent association of grade II and III obesity in the absence of DM, with age, postMS and greater height were observed in twelve multivariate regression models.

In individuals with historical characteristics similar to those of the group with obesity who underwent BS, the prevalence of PPN was lower, and independently associated with the same factors as obesity (higher stature and postMS), but also with higher fasting blood glucose, preMS and RYGB surgery.

The results described here are in agreement with our previous studies and recent data presented by other authors [3,4,8,25], which showed that the prevalence of PPN in the population is associated with DM, obesity, aging, greater height, hyperglycemia, dyslipidemia and greater number of components of MetSynd [4,8,25]. In the present study, the inclusion of only individuals with grade II and III obesity and without DM allowed us to identify the characteristics of PPN in people with obesity. This was not possible in most of the studies listed above, in which there were limitations related to the presence of other metabolic changes that predispose to neuropathy, such as hyperglycemia and DM [4,8,24]. The fact that the prevalence of PPN was lower after BS, that is, after the weight loss induced by surgery, is also in line with the hypothesis that obesity may be associated with the appearance of PPN [3].

In the patients with obesity and without DM in the present study, the independent association of PPN with greater height is in line with the result observed by Callaghan et al. [3] in an epidemiological, cross-sectional study of 4002 Chinese participants. These authors sought an association of the components of MetSynd with PPN and showed that an altered MNSI exam was associated with age, sex and height, in addition to body weight and elevated glycemic status in the DM range, but not pre-DM. This study identified obesity and diabetes (but not pre-DM) as the main metabolic drivers of PPN [3].

In a publication of 2019 [1], we added the postMS to the previously described factors associated with the PPN related to grade II and III obesity. We confirm this in the present study, showing an independent association of Pre-BS PPN with postMS [1].

A lower prevalence of PPN was found after BS than before BS (10.5% and 20.4%, respectively; $p < 0.001$). In the analysis of factors associated with PPN after BS, there was an independent and direct association with being of the female sex (preMS and postMS) and height, but also with fasting blood glucose and RYGB surgery, but not with the SG procedure. As previously mentioned, PPN has historically been considered an important neurological complication of BS in the literature [10,11,13], but later studies with small samples and including participants with preDM and DM, have recently shown the opposite result [5,6].

The association we report of postBS-PPN with a high fasting glucose level may be related to an altered glycemic state resistant to BS, which could occur in individuals with lower pancreatic reserve. This was not evaluated in the present study. On the other hand, the association with RYGB, a more disabsorptive surgery than SG, suggests that postBS-PPN occurs secondary to an inadequate replacement of micronutrients in the late postoperative period. It is probable that postBS nutritional replacement has been improved over the history of BS worldwide, especially for restrictive surgeries, which would lead to a lower prevalence of postBS-PPN. The suggestion that this was occurring in patients at the Mayo Clinic was made by Thaisetthawatkul et al [10,11].

In the present study, by excluding patients with vitamin B12 deficiency and adding serum B12 levels as a factor in the multivariate regression, it was possible to partially assess another factor potentially involved with PPN, both in the sample of participants with obesity and after BS. Vitamin B12 levels had no impact on PPN, suggesting that adequate vitamin B12 supplementation occurred in participants of the present study.

In agreement with the results presented here using the MNSI for PPN detection, we found the systematic review by Aghili et al [5] and the four studies included in this meta-analysis [5,25–28], all evaluating PPN using the Neuropathy Symptoms Score and with the NDS. In the most recently published study, Azmi et al. (2021) evaluated 26 participants with obesity and 20 controls before and 12 months after BS and observed an improvement in factors such as weight, HbA1c, lipids, and symptoms of neuropathy, in addition to deficits in small fibers [6]. In another study, by Punchai et al. (2017), neurological manifestations of vitamin B12 deficiency after BS were more frequent after RYGB than after SG, as seen in our study [13].

Among the main limitations of our work are the low number of male participants and the short follow-up, when potentially patients are more motivated to take supplements earlier on, as opposed to long term when more nutrient deficiencies could be apparent. The strengths of the study include that there is very little data on factors associated with PPN in obesity in the literature, with controversial results, and small numbers of participants.

An explanation for the association of the PPN with female sex may be the low proportion of men included in the study (17.5%). As the number of men seeking BS is usually less than that of women [29], studies with a randomly-selected population of participants from bariatric treatment centers will likely always be disproportionately female.

## Conclusion

A high prevalence of PPN was found in patients with grades II and III obesity. It was lower among participants who underwent BS. This result indicates that obesity and the factors associated with it probably could have a role in PPN development, and that the weight loss and change of lifestyle induced by BS may benefit patients with PPN associated with obesity.

Author's 1 conflict of interest: none

Author's 2 conflict of interest: none

Author's 3 conflict of interest: none

## References

1. Dias LS, Nienov OH, Machado FD, Ramos CP, Rodrigues D, Menguer RK, et al. Polyneuropathy in Severely Obese Women Without Diabetes: Prevalence and Associated Factors. Obes Surg [Internet]. Obesity Surgery; 2018; Available from: http://link.springer.com/10.1007/s11695-018-03627-0

2. Nienov OH, Matte L, Dias LS, Schmid H. Peripheral polyneuropathy in severely obese patients with metabolic syndrome but without diabetes: Association with low HDL-cholesterol. Rev Assoc Med Bras. 2017;63:324–31.

3. Callaghan BC, Gao LL, Li Y, Zhou X, Reynolds E, Banerjee M, et al. Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. Ann Clin Transl Neurol. 2018;5:397–405.

4. Hanewinckel R, Drenthen J, Ligthart S, Dehghan A, Franco OH, Hofman A, et al. Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: A prospective population-based cohort study. J Neurol Neurosurg Psychiatry. 2016;87:1336–42.

5. Aghili R, Malek M, Tanha K, Mottaghi A. The Effect of Bariatric Surgery on Peripheral Polyneuropathy: a Systematic Review and Meta-analysis. Obes Surg [Internet]. Obesity Surgery; 2019;29:3010–20. Available from: http://link.springer.com/10.1007/s11695-019-04004-1

6. Azmi S, Ferdousi M, Liu Y, Adam S, Iqbal Z, Dhage S, et al. Bariatric surgery leads to an improvement in small nerve fibre damage in subjects with obesity. Int J Obes [Internet]. 2021; Available from: http://www.nature.com/articles/s41366-020-00727-9

7. Astrup A, Bügel S. Overfed but undernourished: recognizing nutritional inadequacies/deficiencies in patients with overweight or obesity. Int J Obes [Internet]. Springer US; 2019;43:219–32. Available from: http://dx.doi.org/10.1038/s41366-018-0143-9

8. Callaghan BC, Xia R, Banerjee M, De Rekeneire N, Harris TB, Newman AB, et al. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. Diabetes Care. 2016;39:801–7.

9. Carlsson LMS, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson P-A, Taube M, et al. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. N Engl J Med. 2020;383:1535–43.

10. Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, Norell JE, Dyck PJB, Dyck JB. Good nutritional control may prevent polyneuropathy after bariatric surgery. Muscle Nerve. 2010;42:709–14.

11. Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, Norell JE, Dyck PJB. A controlled study of peripheral neuropathy after bariatric surgery. Neurology. 2004;63:1462–70.

12. Coleman KJ, Haneuse S, Johnson E, Bogart A, Fisher D, O'Connor PJ, et al. Long-term microvascular disease outcomes in patients with type 2 diabetes after bariatric surgery: Evidence for the legacy effect of surgery. Diabetes Care. 2016;39:1400–7.

13. Punchai S, Hanipah ZN, Meister KM, Schauer PR, Brethauer SA, Aminian A. Neurologic Manifestations of Vitamin B Deficiency after Bariatric Surgery. Obes Surg. Obesity Surgery; 2017;27:2079–82.

14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9.

15. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type1 diabetes: Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med. 2012;29:937–44.

16. Buchsbaum DG. Screening for Alcohol Abuse Using CAGE Scores and Likelihood Ratios. Ann Intern Med [Internet]. 1991;115:774. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-115-10-774

17. Pardini R, Matsudo S, Matsudo V, Andrade E, Braggion G, Andrade D. Validação do questionário internacional de nível de atividade física ( IPAQ - versão 6 ): estudo piloto em adultos jovens brasileiros. Rev Bras Ciência e Mov. 2001;9:45–51.

18. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32:S498–516.

19. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on Clinical pr. Hypertension. 2018.

20. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International . Circulation. 2009;120:1640–5.

21. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes d 2019. Diabetes Care. 2019;42:13–28.

22. Corcelles R, Boules M, Froylich D, Hag A, Daigle CR, Aminian A, et al. Total Weight Loss as the Outcome Measure of Choice After Roux-en-Y Gastric Bypass. Obes Surg [Internet]. Obesity Surgery; 2016;26:1794–8. Available from: http://dx.doi.org/10.1007/s11695-015-2022-y

23. Pop-Busui R, Boulton AJMM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017;40:136–54.

24. [organização] U de B-H de C de PA. PSS Health: Power and Sample Size for Health Researchers. [Internet]. [cited 2021 Feb 17]. Available from: https://hcpa-unidade-bioestatistica.shinyapps.io/PSS_Health

25. Han L, Ji L, Chang J, Wen J, Zhao W, Shi H, et al. Peripheral neuropathy is associated with insulin resistance independent of metabolic syndrome. Diabetol Metab Syndr. 2015;7:1–6.

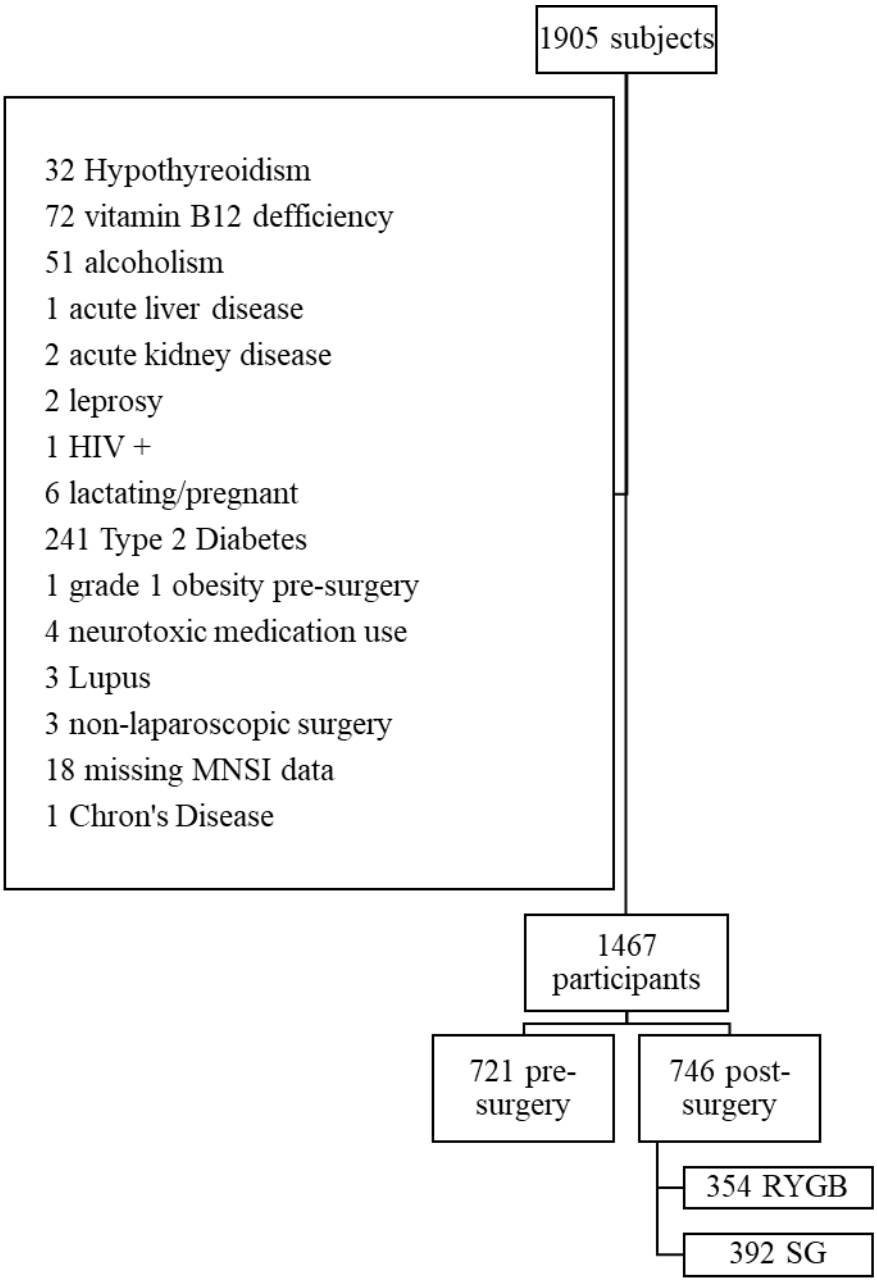
26. Müller-Stich BP, Billeter AT, Fleming T, Fischer L, Büchler MW, Nawroth PP. Nitrosative stress but not glycemic parameters correlate with improved neuropathy in

nonseverely obese diabetic patients after Roux-Y gastric bypass. Surg Obes Relat Dis [Internet]. Elsevier; 2015;11:847–54. Available from: http://dx.doi.org/10.1016/j.soard.2014.12.007

27. Müller-Stich BP, Fischer L, Kenngott HG, Gondan M, Senft J, Clemens G, et al. Gastric bypass leads to improvement of diabetic neuropathy independent of glucose normalization - Results of a prospective cohort study (DiaSurg 1 Study). Ann Surg. 2013;258:760–6.

28. Casellini CM, Parson HK, Hodges K, Edwards JF, Lieb DC, Wohlgemuth SD, et al. Bariatric surgery restores cardiac and sudomotor autonomic C-fiber dysfunction towards normal in obese subjects with type 2 diabetes. PLoS One. 2016;11:1–18.

29. Welbourn R, Hollyman M, Kinsman R, Dixon J, Cohen R, Morton J, et al. Bariatric-Metabolic Surgery Utilisation in Patients With and Without Diabetes: Data from the IFSO Global Registry 2015–2018. Obes Surg [Internet]. Obesity Surgery; 2021; Available from: http://link.springer.com/10.1007/s11695-021-05280-6




Flowchart 1 Inclusion and exclusion of participants who gave consent to the study.

Table 1 Evaluation of 721 participants with obesity before BS and its association with presence of PPN +. Qualitative variables are expressed by frequency and tested by Fisher's Exact Test and quantitative variables are expressed by median and interquartile interval and tested by Mann-Whitney.

| | PreBS without PPN (n=574) | PreBS with PPN (n=147) | p-value |
|---|---|---|---|
| Smoke (n=720) | 24 (4.2%) | 6 (4.1%) | 1.000 |
| PreDM (A1c 5.7-6.4%) (n=691) | 120 (21.9%) | 40 (28.0%) | 0.147 |
| Menopausal status | | | 0.001* |
| Male | 122 (21.3%) | 35 (23.8%) | |
| Pre-menopausal | 403 (70.2%) | 84 (57.1%) | |
| Post-menopausal | 49 (8.5%) | 28 (19.0%) | |
| Hypertension (n=718) | 422 (73.8%) | 112 (76.7%) | 0.524 |
| Metabolic Syndrome (n=638) | 511 (92.9%) | 127 (92.0%) | 0.715 |
| Number of Metabolic Syndrome Components (n=550/138) | 3.0 (2.0; 3.0) | 3.0 (2.0; 3.0) | 0.540 |
| Vitamin B12 (pg/mL) (n=522/135) | 397.5 (313.0; 502.0) | 431.1 (321.2; 534.2) | 0.170 |
| Fasting Glucose (mg/dL) (n=550/140) | 92.0 (85.0; 99.0) | 94.0 (87.0; 101.5) | 0.067 |
| HbA1c (%) (n=507/127) | 5.4 (5.1; 5.6) | 5.5 (5.2; 5.7) | 0.058 |
| Age (years) | 35.0 (29.0; 41.0) | 39.0 (31.5; 46.0) | <0.001* |
| Stature (cm) | 164.0 (159.0; 169.0) | 166.0 (159.5; 174.0) | 0.012* |
| Waist Circumference (cm) (n=572/147) | 111.8 (104.0; 120.0) | 113.0 (106.0; 125.0) | 0.093 |

| | | | |
|---|---|---|---|
| Triglycerides (mg/dL) (n=550/144) | 128.0 (89.0; 173.0) | 128.0 (94.5; 161.5) | 0.989 |
| HDL-Cholesterol (mg/dL) (n=543/143) | 47.0 (40.0; 56.0) | 45.6 (39.5; 54.5) | 0.742 |
| LDL-Cholesterol (mg/dL) (n=541/143) | 112.0 (94.0; 135.4) | 115.2 (96.4; 133.1) | 0.769 |
| MET (MET-min/week) (n=570/146) | 405.0 (132.0; 980.0) | 392.3 (80.0; 847.5) | 0.414 |
| Weight (kg) | 113.0 (101.5; 127.0) | 115.3 (101.3; 136.5) | 0.126 |
| BMI ($kg/m^2$) | 41.8 (38.8; 45.6) | 42.3 (38.9; 46.5) | 0.384 |
| Non-HDL-Cholesterol (mg/dL) (n=542/143) | 138.0 (118.0; 165.0) | 146.0 (120.0; 163.0) | 0.699 |

*Statistical significance accepted when p-value <0.05.

PreBS PPN: Pre-bariatric surgery Peripheral Polyneuropathy; PreDM: prediabetes; HbA1c: glycated hemoglobin; HDL-Cholesterol: High-Density Lipoprotein Cholesterol; LDL-Cholesterol: Low-Density Lipoprotein Cholesterol; MET: Metabolic Equivalent; BMI: Body Mass Index; Non-HDL-Cholesterol: Non-High-Density Lipoprotein Cholesterol

Table 2 Poisson Regression Models with a robust estimator with PreBS PPN prevalence as dependent variable.

| Independent Variables | Model 1 (n=640) p=0.002* OR (CI95%) | p-value | Model 2 (n=640) p=0.004* OR (CI95%) | p-value |
|---|---|---|---|---|
| PreDM (HbA1c 5.7-6.4%) (n,%) | 1.301 (0.920; 1.841) | 0.137 | NA | NA |
| Fasting Glucose (mg/dL) | NA | NA | 1.007 (0.993; 1.020) | 0.345 |
| Smoke (n,%) | 1.088 (0.514; 2.300) | 0.826 | 1.114 (0.528; 2.349) | 0.777 |
| Status Menopausal (n, %) | | | | |
| Post-menopause | 3.273 (1.881; 5.693) | <0.001* | 3.236 (1.863; 5.621) | <0.001* |
| Pre-menopause | 1.410 (0.872; 2.280) | 0.161 | 1.397 (0.864; 2.261) | 0.173 |
| Male | 1 | | 1 | |
| Age (years) | NA | NA | NA | NA |
| Vitamin B12 (pg/mL) | 1.000 (0.999; 1.001) | 0.612 | 1.000 (0.999; 1.001) | 0.696 |
| Stature (cm) | 1.038 (1.014; 1.063) | 0.002* | 1.036 (1.012; 1.061) | 0.003* |
| Waist Circumference (cm) | 1.005 (0.993; 1.017) | 0.436 | 1.006 (0.993; 1.020) | 0.359 |
| Weight (kg) | NA | NA | NA | NA |
| Independent Variables | Model 3 (n=640) p=0.002* OR (CI95%) | p-value | Model 4 (n=640) p=0.003* OR (CI95%) | p-value |
| PreDM (HbA1c 5.7-6.4%) (n,%) | 1.278 (0.908; 1.799) | 0.160 | NA | NA |
| Fasting Glucose (mg/dL) | NA | NA | 1.006 (0.993; 1.023) | 0.380 |
| Smoke (n,%) | 1.073 (0.508; 2.267) | 0.853 | 1.095 (0.520; 2.308) | 0.811 |
| Status Menopausal (n, %) | | | | |
| Post-menopause | 3.310 (1.923; 5.699) | <0.001* | 3.269 (1.900; 5.625) | <0.001* |
| Pre-menopause | 1.396 (0.869; 2.241) | 0.168 | 1.376 (0.856; 2.214) | 0.188 |
| Male | 1 | | 1 | |
| Age (years) | NA | NA | NA | NA |
| Vitamin B12 (pg/mL) | 1.000 (0.999; 1.001) | 0.571 | 1.000 (0.999; 1.001) | 0.642 |
| Stature (cm) | 1.032 (1.005; 1.060) | 0.020* | 1.030 (1.003; 1.057) | 0.028* |
| Waist Circumference (cm) | NA | NA | NA | NA |
| Weight (kg) | 1.005 (0.998; 1.012) | 0.142 | 1.006 (0.999; 1.013) | 0.102 |

| Independent Variables | Model 5 (n=640) p=0.002* | | Model 6 (n=640) p=0.003* | |
|---|---|---|---|---|
| | OR (CI95%) | p-value | OR (CI95%) | p-value |
| PreDM (HbA1c 5.7-6.4%) (n,%) | 1.241 (0.879; 1.753) | 0.220 | NA | NA |
| Fasting Glucose (mg/dL) | NA | NA | 1.004 (0.991; 1.018) | 0.545 |
| Smoke (n,%) | 1.039 (0.492; 2.193) | 0.920 | 1.055 (0.500; 2.226) | 0.888 |
| Status Menopausal (n, %) | NA | NA | NA | NA |
| Post-menopause | | | | |
| Pre-menopause | | | | |
| Male | | | | |
| Age (years) | 1.032 (1.017; 1.047) | <0.001* | 1.032 (1.017; 1.047) | <0.001* |
| Vitamin B12 (pg/mL) | 1.000 (0.999; 1.001) | 0.818 | 1.000 (0.999; 1.001) | 0.877 |
| Stature (cm) | 1.027 (1.007; 1.047) | 0.008* | 1.025 (1.006; 1.045) | 0.011* |
| Waist Circumference (cm) | 1.000 (0.988; 1.013 | 0.941 | 1.001 (0.989; 1.014) | 0.829 |
| Weight (kg) | NA | NA | NA | NA |
| Independent Variables | Model 7 (n=640) p=0.001* | | Model 8 (n=640) p=0.001* | |
| | OR (CI95%) | p-value | OR (CI95%) | p-value |
| PreDM (HbA1c 5.7-6.4%) (n,%) | 1.184 (0.843; 1.663) | 0.331 | NA | NA |
| Fasting Glucose (mg/dL) | NA | NA | 1.002 (0.989; 1.016) | 0.716 |
| Smoke (n,%) | 1.017 (0.484; 2.136) | 0.964 | 1.029 (0.490; 2.158) | 0.940 |
| Status Menopausal (n, %) | NA | NA | NA | NA |
| Post-menopause | | | | |
| Pre-menopause | | | | |
| Male | | | | |
| Age (years) | 1.033 (1.018; 1.049) | <0.001* | 1.034 (1.019; 1.049) | <0.001* |
| Vitamin B12 (pg/mL) | 1.000 (0.999; 1.001) | 0.833 | 1.000 (0.999; 1.001) | 0.874 |
| Stature (cm) | 1.017 (0.995; 1.039) | 0.128 | 1.015 (0.994; 1.037) | 0.157 |
| Waist Circumference (cm) | NA | NA | NA | NA |
| Weight (kg) | 1.006 (0.998; 1.013) | 0.128 | 1.006 (0.989; 1.016) | 0.716 |

*Statistical significance accepted when p-value <0.05.

PreDM: prediabetes

Table 3 Evaluation of qualitative variables from 746 participants after BS and its association with presence of postBS PPN. Qualitative variables are expressed by frequency and tested by Fisher's Exact Test or Pearson's and quantitative variables are expressed by median and interquartile interval and tested by Mann-Whitney

| | PostBS without PPN (n=668) | PostBS with PPN (n=78) | p-value |
|---|---|---|---|
| Smoke (n, %) | 26 (3.9%) | 5 (6.4%) | 0.360[F] |
| PreDM (HbA1c 5.7-6.4%) (n, %) (n=689) | 19 (3.1%) | 3 (4.3%) | 0.583[P] |
| Menopausal status (n, %) | | | 0.069[F] |
| Male | 114 (17.1%) | 17 (21.8%) | |
| Pre-menopausal | 460 (68.9%) | 44 (56.4%) | |
| Post-menopausal | 94 (14.1%) | 17 (21.8%) | |
| Hypertension (n, %) (n=744) | 172 (25.8%) | 28 (35.9%) | 0.078[F] |
| Metabolic Syndrome (n, %) (n=721) | 209 (32.4%) | 29 (38.7%) | 0.300[F] |
| Number of Metabolic Syndrome Components (n, %) (n=646/75) | 1.0 (1.0; 2.0) | 1.0 (1.0; 2.0) | 0.268 |
| TWL ≥20% (n, %) | 622 (93.7%) | 67 (87.0%) | 0.054[F] |
| Type of Surgery (n, %) | | | 0.072[F] |
| RYGB | 309 (46.3%) | 45 (57.7%) | |
| SG | 359 (53.7%) | 33 (42.3%) | |
| Vitamin B12 (pg/mL) (n=608/71) | 474.0 (355.0; 694.0) | 467.0 (355.0; 645.3) | 0.993 |
| Fasting Glucose (mg/dL) (n=614/69) | 82.0 (78.0; 87.0) | 84.0 (79.4; 89.0) | 0.016* |

| | | | |
|---|---|---|---|
| HbA1c (%) (n=485/55) | 5.1 (4.9; 5.3) | 5.1 (4.9; 5.4) | 0.980 |
| Age (years) | 37.0 (31.0; 43.0) | 37.0 (32.0; 48.0) | 0.114 |
| Time post-surgery (months) | 7.9 (5.4; 13.7) | 9.4 (5.5; 17.9) | 0.173 |
| Stature (cm) | 163.0 (159.0; 168.0) | 166.5 (160.5; 174.5) | <0.001* |
| Waist Circumference (cm) (n=664/78) | 86.0 (80.0; 94.0) | 87.0 (81.0; 95.0) | 0.445 |
| Triglycerides (mg/dL) (n=584/64) | 78.0 (61.0; 95.0) | 80.0 (68.0; 106.0) | 0.068 |
| HDL-Cholesterol (mg/dL) (n=574/62) | 49.0 (42.0; 57.0) | 46.7 (38.0; 62.0) | 0.892 |
| LDL-Cholesterol (mg/dL) (n=566/63) | 92.4 (75.6; 115.6) | 88.0 (73.7; 111.8) | 0.697 |
| MET (MET-min/week) (n=661/78) | 750.0 (280.0; 1582.5) | 500.0 (165.0; 1200.0) | 0.033* |
| Weight (kg) | 77.2 (68.9; 87.2) | 79.4 (70.6; 91.8) | 0.096 |
| BMI (kg/m²) | 26.3 (29.0; 31.9) | 28.6 (26.1; 32. 1) | 0.633 |
| Total Weight Loss (%) (%TWL) (n=666/77) | 29.8 (24.5; 35.6) | 30.4 (25.4; 35.3) | 0.592 |
| Non-HDL Cholesterol (mg/dL) (n=569/62) | 108.0 (89.0; 134.0) | 106.5 (88.0; 135.0) | 0.806 |

* Statistical significance accepted when p-value <0.05.

PostBS PPN: Peripheral Polyneuropatia post-bariatric surgery; PreDM: prediabetes; TWL: Total Weight Loss; RYGB: Roux-en-Y Gastric Bypass; SG: Sleeve Gastrectomy. HbA1c: glycated hemoglobin; HDL-Cholesterol: High-Density Lipoprotein Cholesterol; LDL-Cholesterol: Low-Density Lipoprotein Cholesterol; MET: Metabolic Equivalent; BMI: Body Mass Index; Non-HDL-Cholesterol: Non-High-Density Lipoprotein Cholesterol.

Table 4 Poisson Regression Models with a robust estimator with Post-BS PPN prevalence as the dependent variable.

| Independent Variables | Model 1 (n=621) p<0.001* | | Model 2 (n=621) p<0.001* | |
|---|---|---|---|---|
| | OR (CI95%) | p-value | OR (CI95%) | p-value |
| Fasting Glucose (mg/dL) | 1.029 (1.002; 1.057) | 0.036* | 1.029 (1.000; 1.058) | 0.046* |
| Smoke (n, %) | 0.929 (0.231; 3.737) | 0.918 | 0.956 (0.257; 3.862) | 0.949 |
| Status Menopausal (n, %) | | | | |
| Post-menopause | 3.840 (1.706; 8.644) | 0.001* | 3.765 (1.670; 8.487) | 0.001* |
| Pre-menopause | 2.097 (1.073; 4.099) | 0.030* | 2.082 (1.065; 4.069) | 0.032* |
| Male | 1 | | 1 | |
| Age (years) | NA | NA | NA | NA |
| Hypertension (n, %) | 1.068 (0.647; 1.764) | 0.796 | 1.073 (0.642; 1.794) | 0.788 |
| Vitamin B12 (pg/mL) | 1.000 (0.999; 1.001) | 0.779 | 1.000 (0.999; 1.001) | 0.770 |
| Stature (cm) | 1.079 (1.036; 1.123) | <0.001* | 1.082 (1.044; 1.121) | <0.001* |
| TWL>20% (n, %) | NA | NA | 0.708 (0.334; 1.504) | 0.369 |
| Weight (kg) | 1.003 (0.982; 1.025) | 0.761 | NA | NA |
| Triglycerides (mg/dL) | 1.005 (0.999; 1.012) | 0.121 | 1.005 (0.999; 1.011) | 0.093 |
| Time post-surgery (months) | 1.015 (0.992; 1.038) | 0.194 | 1.015 (0.993; 1.038) | 0.176 |
| Type of Surgery (n, %) | | | | |

| | | | | |
|---|---|---|---|---|
| RYGB | 1.673 (1.041; 2.687) | 0.033* | 1.682 (1.049; 2.698) | 0.031* |
| SG | 1 | | 1 | |
| MET (MET-min/week) | 1.000 (1.000; 1.000) | 0.050 | 1.000 (1.000; 1.000) | 0.052 |
| Independent Variables | Model 3 (n=621) p=0.003* | | Model 4 (n=621) p=0.002* | |
| | OR (CI95%) | p-value | OR (CI95%) | p-value |
| Fasting Glucose (mg/dL) | 1.029 (1.000; 1.060) | 0.052 | 1.029 (0.999; 1.061) | 0.060 |
| Smoke (n, %) | 0.951 (0.243; 3.717) | 0.942 | 0.976 (0.249; 3.826) | 0972 |
| Status Menopausal (n, %) | NA | NA | NA | NA |
| Post-menopause | | | | |
| Pre-menopause | | | | |
| Male | | | | |
| Age (years) | 1.012 (0.986; 1.038) | 0.377 | 1.010 (0.984; 1.036) | 0.447 |
| Hypertension (n, %) | 1.111 (0.672; 1.839) | 0.681 | 1.115 (0.667; 1.863) | 0.679 |
| Vitamin B12 (pg/mL) | 1.000 (0.999; 1.001) | 0.862 | 1.000 (0.999; 1.001) | 0.867 |
| Stature (cm) | 1.050 (1.014; 1.089) | 0.007* | 1.051 (1.023; 1.080) | <0.001* |
| TWL>20% (n, %) | NA | NA | 0.714 (0.336; 1.517) | 0.381 |
| Weight (kg) | 1.001 (0.979; 1.024) | 0.806 | NA | NA |
| Triglycerides (mg/dL) | 1.006 (1.000; 1.012) | 0.062 | 1.006 (1.000; 1.012) | 0.059 |
| Time post-surgery (months) | 1.013 (0.991; 1.036) | 0.237 | 1.014 (0.993; 1.037) | 0.193 |

| | | | | |
|---|---|---|---|---|
| Type of Surgery (n, %) | | | | |
| RYGB | 1.683 (1.051; 2.695) | 0.030* | 1.702 (1.063; 2.724) | 0.027* |
| SG | 1 | | 1 | |
| MET (MET-min/week) | 1.000 (1.000; 1.000) | 0.050 | 1.000 (1.000; 1.000) | 0.049* |

*Statistical significance accepted when p-value <0.05.

TWL: Total Weight Loss.

**Artigo 2: Serum levels of 25-hydroxyvitamin D, sun exposure and physical activity of subjects from a bariatric center in Southern Brazil: a cross-sectional study**

Artigo submetido ao periódico *Obesity Surgery*, classificado pela A2 na área de Medicina III pelo Web-Qualis da Plataforma Sucupira e Fator de Impacto 3.412 pelo JCR.

**Serum levels of 25-hydroxyvitamin D, sun exposure and physical activity of subjects from a bariatric center in Southern Brazil: a cross-sectional study**

**Vit D, Sun & Physical Activity**

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**Acknowledgments**

To Obesity Treatment Center's team from Santa Casa de Misericórdia de Porto Alegre and CNPq/CAPES, that provided fellowships' grants for FDM and OHN.

**Abstract**

Objective: To assess whether serum levels of 25-hydroxyvitamin D (25OHD) in obesity and after a bariatric surgery (BS) were associated with sun exposure time (SET), season of evaluation and physical activity (PA).

Design: Cross-sectional study.

Patients: 481 participants with Grade II and III obesity and 340 subjects post-BS (median of 6.7; 5.1–12.6 months) without use of specific supplementation of vitamin D from a Center of BS were included.

Measurements: 25OHD serum levels, anthropometric data, metabolic syndrome components, PA and SET were measured. Associations were analyzed according to 25OHD quartiles with an ordinal logistic regression model. PA was measured by using the International Physical Activity Questionnaire (IPAQ).

Results: In subjects with severe obesity from Southern Brazil, on univariate analysis, being in the lower quartile of 25OHD was associated with increased weight, body mass index and waist circumference, sample collection at winter/autumn, lower metabolic equivalent for PA and lower total and weekend SET. After the bariatric procedure, 25OHD levels were higher when compared to levels of pre-surgery patients ($p<0.001$). On six ordinal logistic regression models, using 25(OH)D levels divided by quartiles as the dependent variable, associations with lower levels occurred for higher weight-related measures and lower SET in all models ($p<0.001$).

Conclusion: Decreased 25OHD levels in obesity and after a BS are probably in part related to low SET. In order to prevent complications related to low SET and maintain normal serum levels of 25OHD, people with obesity and post-BS should be encouraged to increase SET.

**Key points**

- Lower 25OHD levels are associated with higher body weight and BMI

- Decreased 25OHD in obesity and in post-BS subjects is associated with a low SET

- Hypovitaminosis D is more prevalent in severe obesity compared to a post BS status

**Introduction**

For a long time, a large body of literature reporting association between a high bone mineral density (BMD) with a high BMI, PA and sun exposure time (SET) suggested that high BMI, PA and ultraviolet radiation (UVR) had protective effects on the skeleton [1–4]. Recently, however, it has been shown that the effect of a high BMI is complicated by the effect of obesity in decreasing serum levels of 25-hydroxyvitamin D (25OHD) and in increasing levels of parathyroid hormone (PTH), especially in the postmenopausal state. In those women, BMI was positively correlated with BMD and PTH but negatively correlated with vitamin D [3]. Low PA has also been associated with low serum levels 25OHD [5].

Low serum levels of 25OHD in obesity are, at least in part, the effect of decreased bioavailability of vitamin D due to its deposition in body fat compartments [6]. Since blood vitamin D3 concentrations 24 h after whole-body irradiation are lower in subjects with obesity when compared with lean subjects, lower UVR action after exposure of the skin, as well as decreased SET, both described in obese individuals [6,7] could also be mechanisms by which serum levels of vitamin D decrease. Recommendations for using high doses of vitamin D in obesity are related to the above information as well as to clinical observations [8]. Besides that, evaluations of SET and PA and its relations with levels of vitamin D in people with obesity are very scarce in the literature. SET and PA were able to increase 25OHD levels in lean subjects [9], while there remains controversy about its effect in obesity [5].

After bariatric surgery (BS), osteoporosis is expected in the long-term follow-up, according to some authors [10], but not to others [11,12], and serum levels of vitamin D increase while the patients lose weight [13], but decrease in the long-term follow-up, especially if the patients were submitted to the roux en-Y gastric bypass (RYGB) compared to sleeve gastrectomy (SG) [12].

Skin exposure to UVR triggers the release of vitamin D but also of nitric oxide (NO) from dermal storage sites into the bloodstream [14]. If inadequate SET is an important mechanism by which serum levels of 25OHD decrease in obesity, we should suspect that in people with obesity not only are the vitamin D levels decreased but that other abnormalities that might be detrimental to health, like low levels of serum NO, are also occurring and only the ingestion of vitamin D could not replace it.

In a cross-sectional study in southern Brazil, a high prevalence of hypovitaminosis D was previously documented [15]. Taking the data above into account, we thought that it would be very useful to determine levels of 25OHD, SET and PA in individuals with grades II and III obesity, who are candidates for BS, as well as in subjects who were submitted to BS. By defining SET and PA in these individuals, we could also find whether low serum levels of 25OHD are associated with less SET and /or PA.

**Materials and Methods**

A cross-sectional study with a prospective collection of data was conducted on 821 participants from the Obesity Treatment Center of our hospital, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [16].

From April 2016 to October 2019, 481 participants with Grade II and III obesity, as

well as 340 post-BS subjects, 9.14 ± 5.45 months post-BS, were evaluated in preoperative/ postoperative monitoring of BS during routine consultations with a multidisciplinary service team. After the BS, all patients received a prescription of 1 pill a day of Complex of Vitamins – Centrum® or similar, all of them containing no more than 200 UI of cholecalciferol. A flow chart (figure 1) shows all inclusions and exclusions that occured.

Anthropometric data, blood pressure, medical record data, questionnaires and laboratory tests were collected. The level of PA was assessed using the International Physical Activity Questionnaire (IPAQ) [17], which allowed the calculation of metabolic equivalents (MET) using the formula proposed by Ainsworth [18] and the period of PA per week. Regarding their SET, participants also answered one or three questions (in Portuguese): 1. Do you usually expose yourself to the sunlight? 2. If yes, how many hours during weekdays? 3. If yes, how many hours during weekends? Using the answers, SET per week (SET-Total) and SET during weekends (SET-Wend) were calculated. The use of sunscreen was not questioned.

In order to define the season of the year to which the questionnaire reports referred, the fate of collection of blood samples was chosen and this was classified as winter/autumn or summer/spring.

Dosages of 25OHD were all performed using chemiluminescence methods in the laboratories that the patients chose (serum levels of 25OHD are routinely tested in patients of the service before and after BS). The presence of arterial hypertension was defined according to the criteria of the American College of Cardiology/American Heart Association [19].

Data such as blood pressure, lipids, HbA1c, glucose, body weight (BW) and waist

circumference (WC) were measured for defining the presence or not of obesity and metabolic syndrome (MS). Prediabetes was defined as HbA1c ≥ 5.6% to 6.4%, according to ADA (20).

Data analysis was performed using the SPSS statistical software, version 18. A significant difference was considered when the p-value was ≤0.05. To define their normality, continuous variables were tested by the Shapiro–Wilk test. As the distribution of the 25OHD serum levels was not parametric and its correlation with variables was not linear, we used the division of groups into 25OHD quartiles to assess possible associations. Variables of anthropometric data, MET, duration of PA, SET-Total and SET-Wend, MS presence, and prediabetes presence were tested in a search for associations with the different quartiles of 25OHD. The possibility of associations between 25OHD quartiles with gender, menopause, and ethnicity was also verified by using Pearson's chi-squared test or Fisher's exact test. To clarify which variables were independently associated with the distribution of 25OHD in quartiles, an ordinal logistic regression was performed, with 25OHD quartiles as a dependent variable and other variables as independent variables. After the analysis, the log-odds obtained from the logistic regression were converted to odds ratios.

Sample calculation

As a secondary study, the sample calculation was made after the data collection by using a sample of 40 participants in a pilot study. The sample size required for this analysis was calculated using the WinPEPI® version 11.65 tool, using the 25OHD quartiles and the variable SET-Total. According to this calculation, a sample of 20 participants per quartile would be needed to find a difference of 0.5 hours per week in the SET-Total levels.

**Results**

The mean serum levels of 25OHD in the 821 participants included in the study was 25.1 ± 8.7 ng/ml.

According to Table 1, lower values for serum levels of 25OHD were observed in participants with obesity in a presurgical follow-up (22.3, 17.3–28.0 ng/ml) compared with participants who came 9.14 ± 5.45 months after BS (27.4, 21.5–33.0 ng/ml, $p<0.001$). Prevalence of hypovitaminosis D (serum levels of 25OHD <20 ng/ml) in the presurgical group was of 36.0 % and in the group who was submitted to the BS it was lower, 19.4 % ($p<0.001$). Sufficient 25OHD levels were observed in 20% of the presurgical group and in 40.2% of the post-bariatric participants ($p<0.001$). Also in Table 1, it is possible to see that by using a univariate analysis and comparing the pre-bariatric group with the post, MET, duration of PA, SET-Total and SET-Wend were higher for the post-bariatric group ($p<0.001$).

The 25OHD distribution in quartiles is showed on tables 2 and 3. In the univariate analysis of factors associated with the serum levels of 25OHD divided into quartiles, there was an association with the weight distribution ($p<0.001$), the BMI ($p<0.001$), the WC ($p<0.001$), the MET ($p=0.026$), the SET-Total ($p<0.001$) and the SET-Wend ($p<0.001$). There was a tendency towards the association of the quartiles with the age ($p=0.193$) (Table 2).

In a post hoc analysis, BW, BMI and WC were higher in the first three quartiles of vitamin D, compared to the fourth quartile. For the values of MET, SET-Total and SET-Wend, higher values were observed in the fourth quartile of vitamin D, that is, there was a greater MET and a greater SET associated with values of 25OHD considered normal (Table 2). On Table 3 we show there was association of the lowest quartiles with a

prediabetes (p<0.001), collection of 25OHD in winter / autumn (p=0.002), metabolic syndrome (p<0.001) and previous BS (p <0.001).

In multivariate analysis, six models of ordinal logistic regression were proposed, with 25OHD quartiles as the dependent variable and with BW, BMI, male gender, previous BS in the last year, SET-Total and SET-Wend, MET, prediabetes, white ethnicity and MS as independent variables (Table 4). The models were formulated so that there was no collinearity between variables in the same model. Of the variables tested, association with the distribution of 25OHD in quartiles was inverse for weight, BMI and male gender, and direct for the occurrence of previous BS. In the same analysis, SET-Total and SET-Wend were also directly associated with the distribution of 25OHD in quartiles.

**Discussion**

In a cross-sectional study in subjects with Grades II and III of obesity in southern Brazil, latitude of -29 to -30º, we showed a high prevalence of hypovitaminosis D and an independent association of low levels of 25OHD with a history of lower SET, being male, and having a high BMI and BW. A previous BS (9.1 ± 5.4 months before) was independently associated with higher serum levels of 25OHD. PA defined by MET used per week was not independently related. Subjects submitted to BS had a lower prevalence of hypovitaminosis D when compared to the pre-bariatric group as well as a lower BMI and higher SET and MET.

In order to give an interpretation of the results that we found, we should consider that vitamin D supply could be achieved from various sources, including cutaneous synthesis, food sources, and mobilization from vitamin D body stores. The impact of different sources on 25OHD levels appears to be influenced by individual and

environmental factors [21,22]. As reflected by the seasonal variation of 25OHD levels, cutaneous synthesis of vitamin D induced by UV-B appears to be the major source of 25OHD in most individuals [23]. In the present study, 25OHD levels of subjects who collected the blood samples during the winter were lower and those who had lower BW induced by BS, when compared to the participants with severe obesity, had higher values of serum 25OHD levels, probably even with low SET.

According to several authors, the most probable explanation for the variation of serum vitamin D related to the BW derives from the lipophilic nature of vitamin D, leading to an increased deposit in adipose tissue in obesity and therefore lower circulating levels of 25OHD [24,25].

We think that the findings with most impact that were produced in the present study, however, were the facts that nine months after BS 25OHD levels were normal, and that obese and post-BS individuals differ in their 25OHD serum levels according SET habits independently of their PA: higher/normal levels of vitamin D could be found when the SET was high and in those who were submitted to RYGB and SG, without difference of results between the two procedures. Our results are in accordance with some others who evaluated subjects with obesity as well as lean persons but not with the study by Dix et al. (2017), who evaluated subjects with obesity and post-BS subjects [26].

Overall, approximately one-third of the prevalence of vitamin D deficiency may be attributable to obesity [23]. Several studies suggest that an increase in BMI leads to lower 25OHD concentrations and that population-level interventions in order to support a reduction of BW are expected to decrease the prevalence of hypovitaminosis D [9,24].

Like ours, several studies show low serum levels of 25OHD in subjects with severe obesity [9,27,28] and because BS could decrease absorption of calcium, phosphorus and

vitamin D [29]), which could increase the chance of osteoporosis, supplementation of the diet with vitamin D with 25OHD levels monitored is recommended by specialists before as well as after a BS, especially after the RYGB [12]. Since we showed that normal levels of vitamin D can be found in 20.0% of subjects with severe obesity only through sun exposure in latitudes of -29 to -30°, we think that this recommendation should also be included in the prescriptions made to all subjects with obesity as well as after the BS, with 25OHD levels being monitored. Subjects with obesity are more prone to osteoporosis, bone fractures as well as high periods for recovering from that [12], and having serum 25OHD over 30 ng/ml can probably be protective for these morbidities.

Sun exposure is FREE, and aside from its well-known effects on increasing bioavailability of vitamin D with positive effects on bone and mineral metabolism, SET may also play another important role in extra-skeletal processes. Several other effects aside from vitamin D synthesis are induced by exposition to UVR. The human skin is the largest storage of NO and its derivatives. Irradiation with relevant doses of UVR-A induces translocation of NO into the circulation, leading to vasodilatation, reduced vascular resistance, and a reduction in blood pressure [30].

Our study has some limitations regarding the subjectivity of the endpoints since we applied questionnaires for defining PA and SET of the participants. Other limitations are the fact that we did not measure the amount of vitamin D consumed in the diet and that serum levels of 25OHD were measured in different laboratories, according to the participants' preference. As positive points, related to what we can find in the literature we have the fact that little is known about the effect of SET in a high number of subjects with severe obesity and after BS who are not using supplementation with vitamin D with different dosages: none of the presurgical participants of the present study were using vitamin D as a supplement and after BS all the participants were

receiving a prescription with only 200 UI of vitamin D.

## Conclusion

Decreased 25OHD serum levels in people with obesity and after BS are probably related to low SET and to the winter season, but not to physical activity. In order to prevent complications related obesity and SET and maintain normal serum levels of 25OHD people with obesity and after a BS should be encouraged to increase their SET.

## Statements regarding ethics

This study used the data obtained in a study that aimed to assess the prevalence of peripheral polyneuropathy after bariatric surgery (BS) and was approved by the Research Ethics Committee of Santa Casa de Misericórdia de Porto Alegre under number 1,442,347.

## Conflict of Interest Disclosure Statement

The authors declare they have no conflict of interest.

## References

1. McGee DL. Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol. 2005;15:87–97.

2. Wardlaw GM. Putting body weight and osteoporosis into perspective. Am J Clin Nutr. 1996;63:6–9.

3. Kharroubi A, Saba E, Smoom R, Bader K, Darwish H. Serum 25-hydroxyvitamin D and bone turnover markers in Palestinian postmenopausal osteoporosis and normal women. Arch Osteoporos. Archives of Osteoporosis; 2017;12.

4. Kelley GA, Kelley KS, Kohrt WM. Exercise and bone mineral density in premenopausal women: A meta-analysis of randomized controlled trials. Int J Endocrinol. 2013;2013.

5. Klinedinst BS, Meier NF, Larsen B, Wang Y, Yu S, Mochel JP, et al. Walking in the Light: How History of Physical Activity, Sunlight, and Vitamin D Account for Body Fat—A UK Biobank Study. Obesity. 2020;28:1428–37.

6. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72:690–3.

7. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: Nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007;85:860–8.

8. Salehpour A, Hosseinpanah F, Shidfar F, Vafa M, Razaghi M, Dehghani S, et al. A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. Clin Nutr Interface Between Metab Diet, Dis. 2013;3–20.

9. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000;72:690–3.

10. Migliaccio S, Di A, Chiara N, Scappaticcio L, Savastano S. Obesity and hypovitaminosis D : causality or casualty ? Int J Obes Suppl [Internet]. Springer US; 2019;3:20–31.

11. Liu C, Wu D, Zhang JF, Xu D, Xu WF, Chen Y, et al. Changes in Bone Metabolism in Morbidly Obese Patients After Bariatric Surgery: A Meta-Analysis. Obes Surg. 2016;26:91–7.

12. Khalid SI, Omotosho PA, Spagnoli A, Torquati A. Association of Bariatric Surgery With Risk of Fracture in Patients With Severe Obesity. JAMA Netw open. 2020;3:e207419.

13. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-

hydroxyvitamin D in healthy volunteers. PLoS One. 2014;9.

14. Fleury N, Geldenhuys S, Gorman S. Sun exposure and its effects on human health: Mechanisms through which sun exposure could reduce the risk of developing obesity and cardiometabolic dysfunction. Int J Environ Res Public Health. 2016;13.

15. Vivan MA, Kops NL, Fülber ER, de Souza AC, Fleuri MASB, Friedman R. Prevalence of Vitamin D Depletion, and Associated Factors, among Patients Undergoing Bariatric Surgery in Southern Brazil. Obes Surg. 2019;29:3179–87.

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9.

17. Pardini R, Matsudo S, Matsudo V, Andrade E, Braggion G, Andrade D. Validação do questionário internacional de nível de atividade física ( IPAQ - versão 6 ): estudo piloto em adultos jovens brasileiros. Rev Bras Ciência e Mov. 2001;9:45–51.

18. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32:S498–516.

19. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on Clinical pr. Hypertension. 2018.

20. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2019. Diabetes Care. 2019;42:13-28.

21. Leary PF, Zamfirova I, Au J, McCracken WH. Effect of latitude on vitamin D levels. J Am

Osteopath Assoc. 2017;117:433–9.

22. Brouwer-Brolsma EM, Bischoff-Ferrari HA, Bouillon R, Feskens EJM, Gallagher CJ, Hypponen E, et al. Vitamin D: Do we get enough?: A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. Osteoporos Int. 2013;24:1567–77.

23. Trummer C, Pandis M, Verheyen N, Grübler MR, Gaksch M, Obermayer-Pietsch B, et al. Beneficial effects of UV-radiation: Vitamin D and beyond. Int J Environ Res Public Health. 2016;13:1–16.

24. Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes. Nature Publishing Group; 2011;36:387–96.

25. Vanlint S. Vitamin D and obesity. Nutrients. 2013;5:949–56.

26. Dix CF, Bauer JD, Martin I, Rochester S, Romero BD, Prins JB, et al. Association of sun exposure, skin colour and body mass index with vitamin D status in individuals who are morbidly obese. Nutrients. 2017;9:1–15.

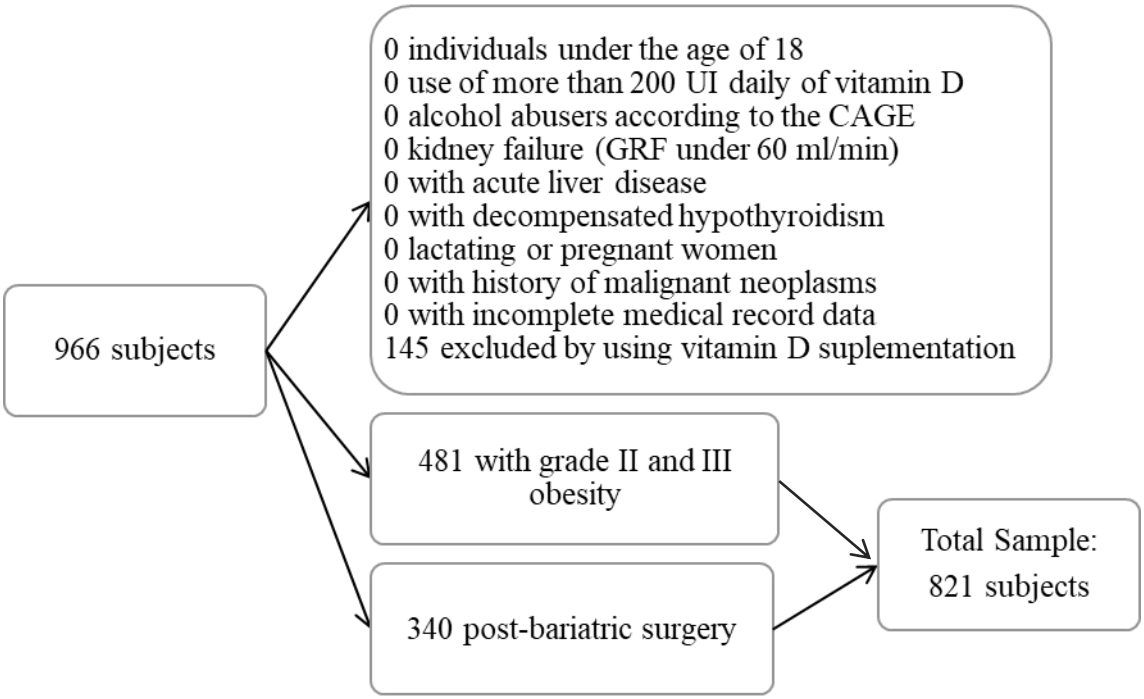
27. Salehpour A, Hosseinpanah F, Shidfar F, Vafa M, Razaghi M, Dehghani S, et al. A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. Nutr J [Internet]. Nutrition Journal; 2012;11:1.

28. Pereira-Santos M, Costa PRF, Assis AMO, Santos CAST, Santos DB. Obesity and vitamin D deficiency: A systematic review and meta-analysis. Obes Rev. 2015;16:341–9.

29. Ybarra J, Sánchez-Hernández J, Gich I, De Leiva A, Rius X, Rodríguez-Espinosa J, et al. Unchanged hypovitaminosis D and secondary hyperparathyroidism in morbid obesity after bariatric surgery. Obes Surg [Internet]. 2005 [cited 2019 Jan 20];15:330–5.

30. Halliday GM, Byrne SN. An unexpected role: UVA-induced release of nitric oxide from skin may have unexpected health benefits. J Invest Dermatol [Internet]. Elsevier Masson SAS; 2014;134:1791–4

Figure 1. Flowchart showing inclusion and exclusion of subjects into the study.




CAGE: Cut-off, Annoyed, Guilty and Eye-opener; GFR: Glomerular Filtration Rate

Table 1. Characteristics of the participants with obesity Grade II and III and of the participants submitted to the bariatric surgery.

| | Obese (n=481) | Post-BS (n=340) | p-value |
|---|---|---|---|
| Vitamin D Deficiency (<20 ng/ml) | 173 (36.0%) | 66 (19.4%) | <0.001*[F] |
| Vitamin D Sufficiency (>30 ng/ml) | 96 (20.0%) | 143 (42.1%) | <0.001*[F] |
| 25(OH)D (ng/ml) | 22.4 (17.3; 28.0) | 27.5 (21.6; 33.0) | <0.001*[M] |
| Age (years) | 36.0 (30.; 43.0) | 37.0 (31.0; 45.0) | 0.150 [M] |
| Weight (kg) | 113.4 (101.1; 129.2) | 79.7 (70.8; 92.8) | <0.001* [M] |
| BMI (kg/cm²) | 41.6 (38.7; 45.2) | 29.8 (26.8; 33.1) | <0.001* [M] |
| Waist Circumference (cm) | 112.0 (104.0; 122.0) | 89.0 (82.0; 98.0) | <0.001* [M] |
| Energy expenditure (MET-min/week) | 365.0 (120; 768.8) | 834.0 (320.0; 1680.0) | <0.001* [M] |
| Physical Activity Total Time (h/week) | 1.7 (0.5; 3.3) | 4.0 (2.0; 7.2) | <0.001*[M] |
| SET-Total (hours/week) | 2.1 (0.0; 7.0) | 3.5 (0.6; 7.5) | <0.001* [M] |
| SET-Wend (hours/day) | 0.2 (0.0; 1.0) | 0.5 (0.0; 1.5) | 0.001* [M] |

BMI: Body Mass Index; MET: Metabolic Equivalent Task; SET-Total: Total Sun Exposition Time; SET-Wend: Sun Exposition Time on Weekends.

*Statistical significance accepted when p-value ≤ 0.05.

Table 2 Distribution of continuous variables of anthropometric data, physical activity, and sun exposure habits between the quartiles of serum 25OHD levels.

| | 1st quartile (<19.0 ng/mL) | 2nd quartile (19.0 – 24.5 ng/mL) | 3rd quartile (24.5 – 30.3 ng/mL) | 4th quartile (>30.3 ng/mL) | p-value |
|---|---|---|---|---|---|
| Age (years) | 36.0 (30.0; 42.0) | 37.0 (32.0; 47.0) | 36.0 (31.0; 44.0) | 37.0 (30.0; 44.0) | 0.193 |
| Weight (kg) | 107.0 (93.4; 129.5) [a] | 102.0 (91.1; 115.9) [a] | 102.4 (82.0; 114.4) [a] | 88.6 (74.0; 108.0) [b] | <0.001* |
| BMI (kg/cm²) | 40.5 (35.7; 45.0) [a] | 39.2 (34.0; 42.3) [a,b] | 38.3 (30.8; 42.5) [b] | 32. 3 (28.1; 39.6) [c] | <0.001* |
| Waist Circumference (cm) | 109.3 (100.0; 121.0) [a] | 106.0 (96.0; 115.0) [b] | 103.0 (91.0; 112.0) [b] | 95.0 (84.0; 107.0) [c] | <0.001* |
| HbA1c (%) | 5.4 (5.1; 5.7)[a] | 5.4 (5.1; 5.7)[a] | 5.3 (5.0; 5.6)[a] | 5.2 (5.0; 5.4)[b] | <0.001* |
| Energy expenditure (MET-min/week)** | 418.0 (148.5; 891.0) [a] | 556.0 (262.8; 1084.5) [a,b] | 447.5 (148.5; 1215.0) [a,b] | 609.8 (220.0; 1410.0) [b] | 0.026* |
| SET-Total (hours/week) | 0.6 (0.0; 5.8) [a] | 3.0 (0.0; 7.0) [a,b] | 3.5 (0.0; 8.8) [b,c] | 3.5 (1.1; 9.0) [c] | <0.001* |
| SET-Wend (hours/day) | 0.0 (0.0; 1.0) [a] | 0.3 (0.0; 1.0) [a,b] | 0.3 (0.0; 1.3) [b,c] | 0.5 (0.0; 2.0) [c] | <0.001* |

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MET: Metabolic Equivalent Task; SET-Total: Total Solar Exposition Time; SET-Wend: Solar Exposition Time on Weekends; HbA1c: Glycated hemoglobin A.

*Statistical significance accepted when p-value ≤ 0.05 on Kruskal-Wallis' test.

Different superscript letters ([a, b, c]) on variable values indicate a statistically significant difference (p-value ≤ 0.05) found using the Dunn–Bonferroni post hoc test. When the same superscript letter indicates no statistically significant difference (p>0.05) found using the Dunn–Bonferroni post hoc test.

** Results with MET and duration of PA were similar and for this reason only MET was presented on the table.

Table 3 Frequencies of categorical variables of high glycemic status, collection of blood for measurements in winter/autumn, ethnicity, metabolic syndrome, previous bariatric surgery and male sex according to 25(OH)D serum level quartiles.

| | 1st quartile (<19.0 ng/mL) | 2nd quartile (19.0 – 24.5 ng/mL) | 3rd quartile (24.5 – 30.3 ng/mL) | 4th quartile (>30.3 ng/mL) | Fisher's Exact Test p-value |
|---|---|---|---|---|---|
| Prediabetes (n, %) | 60 (26.4) | 55 (29.9) | 47 (22.8) | 24 (11.8) | <0.001 |
| Season (winter/autumn) (n, %) | 126 (56.8) | 91 (50.3) | 85 (42.3) | 77 (39.5) | 0.002* |
| Ethnicity (white) (n, %) | 178 (78.4) | 149 (81.0) | 158 (76.7) | 163 (79.9) | 0.749 |
| Metabolic Syndrome (n, %) | 186 (81.9) | 149 (81.4) | 157 (77.3) | 123 (60.6) | <0.001* |
| Post-surgery (n, %) | 59 (26.0) | 88 (42.7) | 88 (42.7) | 128 (62.7) | <0.001* |
| Sex (male) (n, %) | 69 (30.4) | 50 (23.3) | 35 (17.5) | 47 (26.3) | 0.072 |

*Statistical significance accepted when p-value ≤ 0.05.

BMI: Body Mass Index; MET: Metabolic Equivalent Task; SET-Total: Total Solar Exposition Time; SET-Wend: Solar Exposition Time on Weekends; NA: Not Applicable.

Table 4 Ordinal logistic regression model with the 25(OH)D levels divided by quartiles as the dependent variable.

| | Model 1 p<0.001* (n=812) | | Model 2 p<0.001* (n=817) | | Model 3 p<0.001* (n=817) | |
|---|---|---|---|---|---|---|
| Independent variables | OR (CI95%) | p-value | OR (CI95%) | p-value | OR (CI95%) | p-value |
| Weight (kg) | NA | NA | 0.990 (0.983; 0.997) | 0.008* | NA | NA |
| BMI (kg/cm²) | NA | NA | NA | NA | 0.970 (0.948; 0.993) | 0.011* |
| Sex (Male) | 0.674 (0.499; 0.912) | 0.010* | 0.847 (0.600; 1.196) | 0.345 | 0.719 (0.530; 0.975) | 0.034* |
| Post-surgery | 2.555 (1.853; 3,522) | <0.001* | 1.863 (1.296; 2.677) | 0.001* | 1.793 (1.213; 2.649) | 0.003* |
| SET-Total (h/week) | 1.037 (1.021; 1.053) | <0.001* | 1.037 (1.021; 1.052) | <0.001* | 1.037 (1.021; 1.052) | <0.001* |
| SET-Wend (h/day) | NA | NA | NA | NA | NA | NA |
| Energy expenditure (MET-min/week) | 1.000 (1.000; 1.000) | 0.691 | 1.000 1.000 1.000 | 0.768 | 1.000 (1.000; 1.000) | 0.778 |
| Prediabetes | NA | NA | 0.815 (0.593; 1.121) | 0.208 | 0.821 (0.597; 1.130) | 0.226 |
| Ethnicity (White) | 0.965 (0.711; 1.309) | 0.818 | 0.913 (0.671; 1.241) | 0.559 | 0.894 (0.657; 1.217) | 0.478 |
| Metabolic Syndrome | 0.883 (0.619; 1.260) | 0.493 | NA | NA | NA | NA |
| | Model 4 p<0.001* (n=812) | | Model 5 p<0.001* (n=817) | | Model 6 p<0.001* (n=817) | |
| Independent variables | OR (CI95%) | p-value | OR (CI95%) | p-value | OR (CI95%) | p-value |
| Weight (kg) | NA | NA | 0.990 (0.983; 0.997) | 0.006* | NA | NA |
| BMI (kg/cm²) | NA | NA | NA | NA | 0.969 (0.946; 0.992) | 0.008* |
| Sex (Male) | 0.699 (0.518; 0.942) | 0.019* | 0.883 (0.627; 1.242) | 0.474 | 0.746 (0.552; 1.008) | 0.057 |
| Post-surgery | 2.550 (1.850; 3.514) | <0.001* | 1.858 (1.293; 2.671) | 0.001* | 1.773 (1.201; 2.620) | 0.004* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SET-Total (h/week) | NA | | NA | NA | | NA | NA | | NA |
| SET-Wend (h/day) | 1.246 | (1.136; 1.367) | <0.001* | 1.246 | (1.135; 1.367) | <0.001* | 1.248 | (1.138; 1.370) | <0.001* |
| Energy expenditure (MET-min/week) | 1.000 | (1.000; 1.000) | 0.668 | 1.000 | (1.000; 1.000) | 0.738 | 1.000 | (1.000; 1.000) | 0.746 |
| Prediabetes | NA | | NA | 0.850 | (0.619; 1.168) | 0.317 | 0.857 | (0.623; 1.179) | 0.344 |
| Ethnicity (White) | 0.949 | (0.700; 1.288) | 0.738 | 0.904 | (0.665; 1.229) | 0.519 | 0.884 | (0.650; 1.203) | 0.434 |
| Metabolic Syndrome | 0.888 | (0.623; 1.267) | 0.514 | NA | | NA | NA | | NA |

*Statistical significance accepted when p-value ≤ 0.05.

BMI: Body Mass Index; MET: Metabolic Equivalent Task; SET-Total: Total Solar Exposition Time; SET-Wend: Solar Exposition Time on Weekends; NA: Not Applicable.

## Artigo 3: 25-hydroxyvitamin D, sun exposure and glycated hemoglobin in obese people without diabetes in Southern Brazil: a cross-sectional study

Artigo submetido ao periódico *Journal of Diabetes and its Complications*, classificado pela A2 na área de Medicina II pelo Web-Qualis da Plataforma Sucupira e Fator de Impacto 2.781 pelo JCR

**25-hydroxyvitamin D, sun exposure and glycated hemoglobin in obese people without diabetes in Southern Brazil: a cross-sectional study**

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**Highlights**

- In young people with severe obesity, low SET, 25OHD and high HbA1c are associated
- BMI and glycemia are associated with 25OHD quartiles
- Higher SET is associated with lower HbA1c in obese people without Diabetes

**Abstract**

Aims: We assessed whether serum levels of 25 hydroxyvitamin D (25OHD) were associated with solar exposition time (SET), HbA1c, as no classical and classical cardiovascular risk (CVR) markers in obese candidates for bariatric surgery.

Methods: Cross-sectional study with 511 participants with obesity grades II and III without diabetes, no use of antihypertensive medication, median of 33 years of age.

Measurements: 25OHD and its association with blood pressure, serum glucose and lipids, anthropometric data, physical activity, SET and CVR (Cardiac Risk Ratio, CRR, and Framingham 30 years score) measures.

Results: On a global analysis BMI and glycemia were associated with 25OHD quartiles ($p=0.037$ and $p=0.017$) and SET was increased on higher 25OHD quartiles ($p<0.001$). On the regression model, only SET and HbA1c were independently associated with 25OHD serum levels ($p<0.001$).

Conclusion: In severely obese young individuals in southern Brazil, there is an association between being in the higher quartiles of 25OHD with lower levels of HbA1c and with higher hours of SET. As an increase in HbA1c is a no classical CVR marker, low serum levels of 25OHD and/ or low SET might be related to an increase in HbA1c and CVR of obese people even without Diabetes.

Key-Words

25-hydroxyvitamin D; glycated hemoglobin A; obesity; vitamin D; cardiovascular disease

**Acknowledgements**

To the Obesity Treatment Center's team from Santa Casa de Misericórdia de Porto Alegre, who allowed us to carry out the study and to CNPq/Capes, that provided the fellowship grants.

## 1. Introduction

Obesity has been associated with low serum vitamin D levels 1,2. One of the mechanisms by which this relationship has been explained is the occurrence of vitamin D sequestration by adipose tissue in addition to frequent low sun exposure practiced by obese individuals 1–3.

An association of low serum vitamin D levels with increased prevalence of diabetes, hypertension, cardiovascular disease and cardiovascular risk was also described by several authors4–9, many of whom credit this relationship to the lower action of vitamin D in these conditions, which could result in altered responses of endothelial tissues, smooth muscle cells and cardiomyocytes5–7.

Cardiovascular diseases in general are an important cause of morbidity and mortality in obese patients10–12 and many of the effects of bariatric surgery on the mortality of these patients appear to be due to the decrease in cardiovascular risk13,14. This decrease could be due to the improvement, after surgery, of both the classic mediators of cardiovascular risk, such as blood pressure and lipid profile, as well as to

changes in non-classic mediators such as glycemia/glycated hemoglobin, amount of visceral adipose tissue and inflammatory profile12–15.

The relationship between both hypovitaminosis D and obesity with the risk of cardiovascular disease suggests that further exploration of the health risks associated with the state of hypovitaminosis D which occurs in obesity, and possible determinants of cardiovascular risk, should be sought.

In a cross-sectional study in Southern Brazil, the high prevalence of hypovitaminosis D has been previously documented and could be attributed to both the increase in adipose tissue and to the low sun exposure of obese individuals16. Taking that into account it was recommended that all patients undergoing bariatric surgery, should receive vitamin D supplementation even before bariatric procedures17. Porto Alegre, the city of that study and also of our study, is at -30° latitude18 and at equivalent positive latitudes, close to 30°, during winter synthesis of vitamin D by the skin was described as practically null17.

In the present study, our objective was to verify possible associations between serum levels of 25 OHD with classic (CVR-C) and non-classic (CVR-NC) cardiovascular risk factors, in individuals with grades II and III obesity, non-diabetics, candidates to bariatric surgery.

## 2. Materials and Methods

A cross-sectional study was conducted on 511 participants from the Obesity Treatment Center of Santa Casa de Misericórdia in Porto Alegre, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement19.

### 2.1 Population and sample

Grade II and III obese participants were evaluated in preoperative monitoring of bariatric surgery during routine consultations with a multidisciplinary service team. The team components were a surgeon, an endocrinologist, a general practitioner, a psychiatrist, a psychologist, and a nutritionist.

#### 2.1.1 Inclusion criteria

Obese participants, men and women, without diabetes, were included from April 2016 to October 2019.

#### 2.1.2 Exclusion criteria

Individuals under the age of 18, using antihypertensive drugs, alcohol abusers according to the CAGE questionnaire20, with kidney failure (GFR under 60 ml/min), with acute liver disease, with decompensated hypothyroidism, lactating and pregnant

women, history of malignant neoplasms and incomplete medical record data were excluded. Of the 703 participants enrolled in the study, 192 were excluded for using antihypertensive drugs.

2.2 Data collect

Anthropometric data, blood pressure, medical record data and laboratory tests were collected. The level of physical activity was assessed using the International Physical Activity Questionnaire (IPAQ)21, which allowed the calculation of metabolic equivalents (MET) using the formula proposed by Ainsworth22. Participants also answered questions regarding their sun exposure habits.

Dosages of 25-hydroxyvitamin D (25OHD) were all performed using chemiluminescence methods but in different laboratories (serum levels of 25OHD are routinely tested on patients of the service). The presence of arterial hypertension was defined according to the criteria of the American College of Cardiology/American Heart Association23.

Cardiovascular risk was assessed using C-CVR, such as age, blood pressure, smoking, LDL-cholesterol, Cardiac Risk Ratio (CRR) defined by the ratio of total cholesterol to HDL24, Framingham score for 30 years11, and NC-CVR, such as HbA1c, blood glucose, triglycerides, BMI and waist circumference.

2.4 Recommendations received by patients

Patients with vitamin D deficiency received a replacement prescription of at least 1000 IU/day and when the blood samples used for the study were collected patients were not yet on replacement.

2.5 Ethical aspects

This study used the data obtained in a study that aimed to assess the prevalence of peripheral polyneuropathy after bariatric surgery, being approved by the Research Ethics Committee of Santa Casa de Misericórdia de Porto Alegre under number 1,442,347.

2.6 Statistical analysis

Data analysis was performed using the SPSS statistical software, version 18. A significant difference was admitted when the p-value was $\leq 0.05$. Continuous variables were tested by Shapiro-Wilk to define their normality. As the distribution of the 25OHD serum levels was not parametric and its correlation with variables was not linear, we used the division of groups into 25OHD quartiles to assess possible associations. In order to define if CVR-C and CVR-NC were associated with 25 OHD levels, by using the Kruskal Wallis test, the continuous variables of anthropometric data, pressure measurements (systolic blood pressure, SBP, and diastolic blood pressure, BPD),

physical activity (MET), solar exposure time (SET), cardiovascular risk (Framingham and CRR) lipid and glycemic profile were tested in a search for association with the different quartiles of 25OHD. The possibility of associations between 25OHD quartiles with gender, menopause, smoking, ethnicity, hypertension, cardiovascular risk, vitamin supplementation was also verified using Pearson's chi-square test or Fisher's exact test. To clarify which variables were independently associated with the distribution of 25OHD in quartiles, an ordinal logistic regression was performed, with 25OHD quartiles as a dependent variable and SBP, waist circumference, CRR, SET and HbA1c as independent variables. After the analysis, the log-odds obtained from the logistic regression were converted to Odds Ratio.

2.7 Sample calculation

The sample size required for this analysis was calculated using the WinPEPI® version 11.65 tool, based on the study by Hutchinson et al (2011)25, which assessed the association of vitamin D levels divided into quartiles and the HbA1c level in 8,643 participants. According to this calculation, a sample of 343 participants would be needed to find a difference of 0.05 points in the levels of HbA1c.

3. Results

Data obtained from the 511 obese non-diabetic participants included in the study showed a hypovitaminosis D prevalence of 79.5%. Between them, 406 subjects had serum levels of 25OHD ≤30 ng/dl and 34.2% (n=175) had serum levels of 25OHD ≤20 ng / ml.

Among the 511 participants, the median of 25OHD was 22.65 ng/ml and their quartiles were divided as follows: in the first quartile values below 17.6 ng/ml, in the second quartile, from 17.6 to 22.65 ng/ml, third quartile, from 22.65 to 29.0 ng/ml and in the fourth quartile, values above 29.0 ng/ml. There was an association between BMI and the distribution of 25OHD in quartiles (p=0.037), however, in the pairwise analysis it was not possible to define which quartiles were different in relation to BMI.

SET was associated with the 25OHD quartiles (p<0.001), being lower in the first quartile compared to the others. Serum blood glucose levels were associated with the distribution of 25OHD (p=0.017), but in the pairwise analysis it was not possible to establish which quartiles had different blood glucose values. Weight, waist circumference, SBP, DBP, HbA1c (p=0.116, 0.058, 0.058, 0.106, 0.066, respectively) presented p-values considered borderline (Table 1).

Among the categorical variables evaluated (Table 2), only ethnicity showed borderline p-values (p=0.123 and p=149, respectively).

To define which variables were independently associated with the distribution of 25OHD in quartiles, the ordinal logistic regression model was used. The choice of variables for the model was made from the p-value (less than 0.2) or according to the

objective of the study. Among the variables related to blood pressure with p less than 0.2, SBP and DBP, we chose to include SBP in the model because it is the measure considered most related to cardiovascular risk26.

Also for composing the model, among anthropometric variables weight, BMI and waist circumference, the choice was the waist circumference due to the known relationship between abdominal fat, therefore waist circumference, and cardiovascular risk26 and among the variables of glycemic profile, glycemia and HbA1c, the variable chosen was HbA1c because it better reflects cardiovascular risk. Among the risk scores, Framingham 30 years and CRR, the inclusion of Framingham would imply the exclusion of all variables used for its calculation in logistic regression, and therefore the CRR was chosen. Among factors that influence serum vitamin D levels such as time of sun exposure, ethnicity the variable chosen to compose the model was the time of sun exposure: ethnicity was not considered a reliable variable because in our multiethnic sample (In Brazil it is very difficult to define whites and non-whites).

Results of the ordinal logistic regression model proposed for the 25OHD quartiles ($p<0.001$) (Table 3), which included the variables SBP, waist circumference, CRR, SET, and HbA1c, showed that there was an independent association with HbA1c ($p=0.048$) and SET ($p<0.001$). Despite not being independently associated, the CRR presented a borderline p-value ($p=0.055$). Thus, considering the first quartile of less than 17.6 ng/mL of 25OHD values and that values of the other variables of the model remained the same, the increase of one hour per week in the time of sun exposure was associated with an increase of 4.8% in the chance of being in the second, third or fourth quartiles of 25OHD (OR 1.048 95% CI 1.002; 1,075). Likewise, also considering that other model variables did not change, a 1% increase in HbA1c from 4.5% was associated with a 42% decrease in the chance to be in the second, third or fourth quartiles of 25OHD (OR 0.580 95% CI 0.339; 0.995).

## 4. Discussion

In the present study, we sought to verify the possible association between serum 25OHD levels and CVR-C and CVR-NC factors in candidates to the bariatric procedure. In this sample of subjects with severe obesity and without diabetes, in Southern Brazil, we found a high prevalence (34.2%) of hypovitaminosis D. We also observed that low levels of serum vitamin D were associated with low SET and with high levels of HbA1c, findings that suggest that vitamin D could act as a marker but not necessarily as a casualty factor for glycemic responses in these subjects. According to this possibility, there are evidences that both obesity and vitamin D deficiency are risk factors for occurrence of diabetes 27, some observations similar to ours 6,16,25 and the fact that supplementations with vitamin D did not have effect on the incidence of cardiovascular disease 28.

Low serum vitamin D levels are associated with decreased muscle mass in several studies29 and a decrease in muscle mass is likely to have an impact on the

peripheral use of glucose30,31, especially when there is insulin resistance as occurs in obesity32,33. The findings we present could partly explain the predisposition of individuals with hypovitaminosis D and obesity to higher HbA1c values, higher CVR and even Diabetes. It is also possible that other factors that could increase after sun exposition but not vitamin D are protecting for increases in serum levels of A1c. If this is the case, we cannot expect that supplementation with vitamin D is going to prevent CVR.

According to our results are some similar studies but not with all the measured parameters that we used and measured. In a Brazilian population, but of residents from Northeastern Brazil, the region with the highest incidence of sun exposure, it was showed a median for 25OHD levels of 25.9 ng/ml but in that study, there was no assessment of glycemic parameters. In another study also from Brazil, carried out in obese people but with the inclusion of subjects with diabetes, and without measure of SET, Vivan et al (2019), found an average value of 25OHD of 19.2 ng/ml, a value even lower than that observed in our study16, and that hypovitaminosis D was associated with BMI and HbA1c, a result similar to that observed by us.

A study of 11,092 non-diabetic adults with no history of cardiovascular disease, in the Atherosclerosis Risk in Communities (ARIC) Study34, identified HbA1c as a risk factor for cardiovascular disease and death, even before the diagnosis of diabetes and after correction for fasting blood glucose34. The ARIC Study was conducted in a population of North Americans, whites and blacks, excluding participants with another color statement34.

An inverse association of serum levels of 25OHD and HbA1c was also found in the study by Hutchinson et al.25, in the Nordic population, mostly Caucasian, non-diabetic, which included obese and non-obese individuals. In this study, patients with diabetes were excluded only by a questionnaire answered by the participants. Kositsawat et al.6, who evaluated data from the National Health Nutrition Examination Survey, NHANES, in the adult population of the United States of America, with participants with and without obesity and diabetes, also observed an association of HbA1c with 25OHD. In the NHANES data, the same association was found and it was not repeated only in the analysis among the youngest participants, aged 18 to 34 years. To our knowledge, our work is the first study to evaluate the association of serum levels of 25OHD, SET and HbA1c in young obese, non-diabetic participants in Brazil.

Our study has some limitations regarding the CVR scores used because they were not standardized for our ethnic group35. Another limitation is the fact that serum levels of 25OHD were measured in different laboratories, according to the participants' preference.

## 5. Conclusions

Based on our results, due to the finding of an independent association of 25OHD serum levels with HbA1c and with sun exposure, it is possible that 25 OHD when used as a marker of sun exposure/diet (with no additional supplementation of vitamin D) is a marker of an effect that modifies the risk of having a high HbA1c and maybe Diabetes Mellitus and cardiovascular disease. This possible effect might be related to other health effects produced in parallel with sun exposure and not directly by the serum 25OHD levels. Evaluation of the effect of correcting serum vitamin D levels by exposure to the sun on HbA1c and CVR markers should be performed.

## 6. References

1. Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes. 2011;36(3):387-396. doi:10.1038/ijo.2011.119

2. Vranić L, Mikolašević I, Milić S. Vitamin D deficiency: Consequence or cause of obesity? Medicina (B Aires). 2019;55(541). doi:10.3390/medicina55090541

3. Kull M, Kallikorm R, Lember M. Body mass index determines sunbathing habits: Implications on vitamin D levels. Intern Med J. 2009;39(4):256-258. doi:10.1111/j.1445-5994.2009.01900.x

4. Manousopoulou A, Al-Daghri NM, Garbis SD, Chrousos GP. Vitamin D and cardiovascular risk among adults with obesity: A systematic review and meta-analysis. Eur J Clin Invest. 2015;45(10):1113-1126. doi:10.1111/eci.12510

5. Jorde R, Schirmer H, Wilsgaard T, et al. Polymorphisms related to the serum 25-Hydroxyvitamin D level and risk of Myocardial infarction, diabetes, cancer and mortality. The Tromsø study. PLoS One. 2012;7(5). doi:10.1371/journal.pone.0037295

6. Kositsawat J, Freeman VL, Gerber BS, Geraci S. Association of A1C Levels With Vitamin D Status in U.S. Adults. Diabetes Care. 2010;33(6):1236-1238. doi:10.2337/dc09-2150.The

7. Vaidya A, Forman JP, Hopkins PN, Seely EW, Williams JS. 25-Hydroxyvitamin D is associated with plasma renin activity and the pressor response to dietary sodium intake in Caucasians. JRAAS - J Renin-Angiotensin-Aldosterone Syst. 2011;12(3):311-319. doi:10.1177/1470320310391922

8. Williams ED, Rawal L, Oldenburg BF, Renwick C, Shaw JE, Tapp RJ. Risk of cardiovascular and all-cause mortality: Impact of impaired health-related functioning and diabetes - The Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Diabetes Care. 2012;35(5):1067-1073. doi:10.2337/dc11-1288

9. Leu Agelii M, Lehtinen-Jacks S, Zetterberg H, Sundh V, Björkelund C, Lissner L. Low vitamin D status in relation to cardiovascular disease and mortality in Swedish

women – Effect of extended follow-up. Nutr Metab Cardiovasc Dis. 2017;27(12):1143-1151. doi:10.1016/j.numecd.2017.10.013

10. Masters RK, Powers DA, Link BG. Obesity and US mortality risk over the adult life course. Am J Epidemiol. 2013;177(5):431-442. doi:10.1093/aje/kws325

11. Pencina MJ, D'Agostino RB, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: The framingham heart study. Circulation. 2009;119(24):3078-3084. doi:10.1161/CIRCULATIONAHA.108.816694

12. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: A meta-analysis of prospective cohort studies. Int J Cardiol. 2013;168(5):4761-4768. doi:10.1016/j.ijcard.2013.07.230

13. Romeo S, Maglio C, Burza MA, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. Diabetes Care. 2012;35(12):2613-2617. doi:10.2337/dc12-0193

14. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric Surgery and Long-Term Cardiovascular Events. Surv Anesthesiol. 2012;56(6):327-328. doi:10.1097/sa.0b013e3182752111

15. Johnson RJ, Johnson BL, Blackhurst DW, et al. Bariatric surgery is associated with a reduced risk of mortality in morbidly obese patients with a history of major cardiovascular events. Am Surg. 2012;78(6):685-692. doi:10.1177/000313481207800623

16. Vivan MA, Kops NL, Fülber ER, de Souza AC, Fleuri MASB, Friedman R. Prevalence of Vitamin D Depletion, and Associated Factors, among Patients Undergoing Bariatric Surgery in Southern Brazil. Obes Surg. 2019;29(10):3179-3187. doi:10.1007/s11695-019-03963-9

17. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-1930. doi:10.1210/jc.2011-0385

18. Porto-Alegre PM de. Conheça Porto Alegre. Published 2020. https://prefeitura.poa.br/gp/projetos/conheca-porto-alegre

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-349. doi:10.1016/j.jclinepi.2007.11.008

20. Buchsbaum DG. Screening for Alcohol Abuse Using CAGE Scores and Likelihood Ratios. Ann Intern Med. 1991;115(10):774. doi:10.7326/0003-4819-115-10-774

21. Pardini R, Matsudo S, Matsudo V, Andrade E, Braggion G, Andrade D. Validação do questionário internacional de nível de atividade física ( IPAQ - versão 6 ): estudo piloto em adultos jovens brasileiros. Rev Bras Ciência e Mov. 2001;9(3):45-51. doi:http://dx.doi.org/10.18511/rbcm.v9i3.393

22. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(9 SUPPL.):S498-S516. doi:10.1097/00005768-200009001-00009

23. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Pr. Vol 71.; 2018. doi:10.1161/HYP.0000000000000065

24. Kinosian B, Glick H, Preiss L, Puder KL. Cholesterol and coronary heart disease: predicting risks in men by changes in levels and ratios. J Investig Med. 1995;43(5):443-450. doi:10.1016/1062-1458(96)86726-2

25. Hutchinson MS, Figenschau Y, Njølstad I, Schirmer H, Jorde R. Serum 25-hydroxyvitamin D levels are inversely associated with glycated haemoglobin (HbA1c). The Tromsø Study. Scand J Clin Lab Invest. 2011;71(5):399-406. doi:10.3109/00365513.2011.575235

26. Marino M, Li Y, Pencina MJ, D'Agostino RB, Berkman LF, Buxton OM. Quantifying cardiometabolic risk using modifiable non-self-reported risk factors. Am J Prev Med. 2014;47(2):131-140. doi:10.1016/j.amepre.2014.03.006

27. Gagnon C, Lu ZX, Magliano DJ, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: Results from a national, population-based prospective study (the Australian diabetes, obesity and lifestyle study). Diabetes Care. 2011;34(5):1133-1138. doi:10.2337/dc10-2167

28. Manson JE, Cook NR, Lee I-M, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2019;380(1):33-44. doi:10.1056/NEJMoa1809944

29. Halfon M, Phan O, Theta D. Vitamin D: A review on its effects on muscle strength, the risk of fall, and frailty. Biomed Res Int. 2015;2015. doi:10.1155/2015/953241

30. Pendergrass M, Bertoldo A, Bonadonna R, et al. Muscle glucose transport and phosphorylation in type 2 diabetic , obese nondiabetic , and genetically predisposed individuals. Am J Physiol Metab. 2007;292:92-100. doi:10.1152/ajpendo.00617.2005.

31. Abdul-Ghani MA, Defronzo RA. Pathogenesis of insulin resistance in skeletal muscle. J Biomed Biotechnol. Published online 2010. doi:10.1155/2010/476279

32. Park SW, Goodpaster BH, Lee JS, et al. Excessive Loss of Skeletal Muscle Mass in Older Adults With Type 2 Diabetes. Diabetes Care. 2009;32(11):1993-1997. doi:10.2337/dc09-0264.

33. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia Exacerbates Obesity-Associated Insulin Resistance and Dysglycemia : Findings from the National Health and Nutrition Examination Survey III. PLoS Med. 2010;5(5). doi:10.1371/journal.pone.0010805

34. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(21):2030-2031. doi:10.1056/NEJMc1003829

35. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American college of cardiology/American heart association task force on practice guidelines. Circulation. 2014;129(25 SUPPL. 1). doi:10.1161/01.cir.0000437741.48606.98

Declarations of interest: none.

Credit Author Statement

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Table 2 Distribution of continuous variables of anthropometric data, blood pressure, laboratory results, physical activity and sun exposure habits between the serum 25OHD levels quartiles.

| | 1st quartile (0 – 17.6 ng/mL) | 2nd quartile (17.6 – 22.65 ng/mL) | 3rd quartile (22.65 – 29.0 ng/mL) | 4th quartile (>29.0 ng/mL) | p-value Kruskal-Wallis |
|---|---|---|---|---|---|
| Age (years) | 34.0 (29.5; 40.0) | 35.0 (30.0; 39.5) | 35.0 (30.5; 39.5) | 32.0 (28.0; 38.0) | 0.853 |
| Stature (cm) | 165.0 (159.0; 171.0) | 163.0 (158.5; 167.0) | 165.0 (161.0; 168.5) | 164.0 (157.0; 170.0) | 0.720 |
| Weight (kg) | 110.8 (101.8; 134.9) | 110.5 (99.9; 120.2) | 113.3 (104.0; 123.0) | 112.4 (101.0; 118.0) | 0.116 |
| BMI[a] (kg/cm²) | 41.4 (39.5; 45.7) | 41.3 (39.0; 44.7) | 42.0 (39.1; 43.6) | 40.8 (38.4; 44.2) | 0.037* |
| Waist Circumference (cm) | 110.0 (103.3; 120.8) | 110.5 (104.5; 118.0) | 111.0 (104.5; 117.5) | 108.0 (101.0; 118.0) | 0.058 |
| SBP[b] (mmHg) | 126.0 (118.0; 135.5) | 127.5 (119.0; 133.5) | 123.0 (116.0; 132.0) | 126.0 (118.0; 135.0) | 0.058 |
| DBP[c] (mmHg) | 85.0 (8.0; 92.5) | 86.0 (81.0; 90.0) | 85.0 (77.5; 90.5) | 85.0 (79.0; 91.0) | 0.106 |
| MET[d] (n=494) (n=509) | 262.5 (89.5; 666.0) | 406.3 (172.0; 856.0) | 306.0 (99.0; 713.3) | 396.0 (120.0; 1059.0) | 0.252 |
| SET[e] (hours/week) (n=335) | 0.0(0.0; 3.1) [a] | 0.0 (0.0; 6.1) [a,c] | 2.3 (0.0; 7.0) [b,c] | 3.5 (0.0; 14.0) [b,c] | <0.001* |
| Cardiac Risk Ratio (n=502) | 4.0 (3.3; 4.9) | 4.1 (3.3; 5.1) | 4.0 (3.3; 4.7) | 3.9 (3.1; 4.7) | 0.351 |
| Framingham 30 years (n=501) | 18.0 (12.5; 27.5) | 16.0 (10.0; 25.0) | 16.0 (11.0; 23.5) | 14.0 (9.0; 22.0) | 0.511 |
| Glycemia (mg/dL) (n=504) | 93.0 (85.5; 98.0) | 92.5 (85.0; 100.0) | 91.0 (84.0; 97.0) | 89.6 (83.0; 96.0) | 0.017* |
| HbA1c[f](%) (n=469) | 5.4 (5.3; 5.6) | 5.4 (5.2; 5.7) | 5.3 (5.1; 5.6) | 5.3 (5.1; 5.5) | 0.066 |
| Cholesterol (mg/dL) (n=506) | 192.5 (170.5; 212.0) | 194.5 (168.5; 223.2) | 186.0 (165.5; 210.5) | 185.0 (159.0; 210.0) | 0.792 |
| HDL-Cholesterol[g] (mg/dL) (n=502) | 46.2 (40.2; 52.0) | 47.8 (39.5; 54.5) | 47.0 (39.0; 55.0) | 48.0 (41.0; 55.0) | 0.789 |
| LDL-Cholesterol[h] (mg/dL) (n=504) | 111.5 (95.7; 135.6) | 119.8 (94.1; 143.4) | 108.6 (95.4; 127.9) | 109.6 (86.0; 126.0) | 0.515 |
| Triglycerides (mg/dL) (n=506) | 136.0 (83.0; 182.0) | 129.0 (90.0; 175.5) | 120.0 (88.5; 174.0) | 108.0 (85.0; 151.0) | 0.511 |

a: Body Mass Index; b: Sistolic Blood Pressure; c: Diastolic Blood Pressure; d: Metabolic Equivalent; e: Solar Exposition Time; f: Glycated hemoglobina A; g: High Density Lipoprotein – Cholesterol; h: Low Density Lipoprotein – Cholesterol.

*Statistical significance accepted when p-value ≤ 0.05.

Superscript letters on variables values indicate the diferences (p-value ≤ 0.05) found on Dunn-Bonferroni post-hoc test.

Table 3 Frequencies of categorical variables of sex, smoke, hypertension, vitamin D supplementation and ethnicity accordingly with 25(OH)D serum levels quartiles.

| | 1st quartile (0 – 17.6 ng/ml) | 2nd quartile (17.6 – 22.65 ng/ml) | 3rd quartile (22.65 – 29.0 ng/ml) | 4th quartile (>29.0 ng/ml) | p-value |
|---|---|---|---|---|---|
| Sex (female) | 92 (74.8%) | 107 (81.7%) | 117 (80.7) | 89 (79.5%) | 0.544[a] |
| Menopause | 8 (6.5%) | 8 (6.1%) | 7 (4.8%) | 5 (4.5%) | 0.803 [b] |
| Smoke | 7 (6.4%) | 6 (5.0%) | 10 (7.5%) | 7 (6.5%) | 0.916 [a] |
| Hypertension | | | | | 0.203 [a] |
| Normal | 24 (19.5%) | 18 (13.7%) | 40 (27.6%) | 24 (21.4%) | |
| Elevated | 10 (8.1%) | 14 (10.7%) | 10 (6.9%) | 12 (10.7%) | |
| Stage 1 | 40 (32.5%) | 54 (41.2%) | 54 (37.2%) | 40 (35.7%) | |
| Stage 2 | 49 (39.8%) | 45 (34.4%) | 41 (28.3%) | 36 (32.1%) | |
| Ethnicity | | | | | 0.149 [a] |
| White | 91 (74.0%) | 111 (84.7%) | 115 (79.3%) | 93 (83.0%) | |
| Non-white | 32 (26.0%) | 20 (15.3%) | 30 (20.7%) | 19 (17.0%) | |

*Statistical significance accepted when p-value ≤ 0.05.

[a] Person's Chi-square p-value; [b] Fisher's Exact Test p-value.

Table 4 Ordinal Logistic Regression Model with the 25(OH)D levels divided by quartiles as dependent variable and systolic blood pressure, waist circumference, cardiac risk ratio, solar exposition time and HbA1c as independent variables, with log transformation to odds ratio.

| | Model p<0.001* (n=309) | |
|---|---|---|
| Independent variables | OR (CI95%) | p-value |
| SBP[a] (mmHg) | 0.995 (0.979; 1.011) | 0.520 |
| Waist Circumference (cm) | 0.992 (0.976; 1.009) | 0.372 |
| Cardiac Risk Ratio | 0.841 (0.704; 1.004) | 0.055 |
| Solar Exposition Time | 1.048 (1.002; 1.075) | <0.001* |
| HbA1c[b] (%) | 0.580 (0.339; 0.995) | 0.048* |

*Statistical significance accepted when p-value ≤ 0.05.

[a] Systolic Blood Pressure; [b] glycated hemoglobina A.

## CONSIDERAÇÕES FINAIS

Os resultados apresentados nos artigos que compõe trabalho são frutos de dados de um projeto de pesquisa que buscou avaliar a prevalência de PNP em mulheres pré e pós-menopáusicas e homens, sem diabetes, com obesidade grau II e III antes e após a CB. Grande parte dos objetivos gerais e específicos propostos inicialmente foi respondida até aqui. Outros pontos ainda carecem de futuras investigações.

Neste trabalho, a prevalência de PNP foi maior nos participantes com obesidade quando comparados aos participantes após-CB. Tanto na obesidade, quanto após a CB, a PNP se associou com maior estatura e, após a CB, foi mais prevalente no RYGB do que no SG. Ao avaliarmos os níveis séricos de 25OHD, encontramos associação de menores níveis séricos de 25OHD e maior peso corporal e IMC. A hipovitaminose D foi mais prevalente entre os participantes com obesidade, em comparação com os participantes submetidos à CB e, nos dois grupos, se associou com baixo tempo de exposição solar.

Considerando os dados disponíveis para este estudo e os resultados encontrados, a avaliação da associação entre 25OHD, PNP e CB nos parece de interesse. Uma das propostas é a continuidade da análise do banco de dados atual, além de propor novos estudos que avaliem estes fatores com mais tempo de acompanhamento pós-CB.

Preliminarmente, em dados não apresentados neste trabalho, temos encontrado níveis mais altos de 25OHD nos neuropatas antes da cirurgia, o que não se repete após o procedimento bariátrico. Essa associação ainda não foi explorada, já que a literatura disponível até o momento não prevê essa associação.

Este trabalho contribui de modo expressivo para a formação do conhecimento acerca dos níveis de 25OHD, exposição solar e atividade física e prevalência de PNP em mulheres

pré e pós-menopáusicas e homens com obesidade graus II e III, sem diabetes, antes e após a CB.

## PERSPECTIVAS FUTURAS

A continuidade da avaliação dos dados disponíveis deste estudo nos parece evidentemente necessária para o esclarecimento das lacunas da literatura, além das questões levantadas pelos nossos trabalhos. Caso a volta à coleta de dados, interrompida precocemente devido à pandemia de Covid-19, um aumento do tamanho da amostra poderia esclarecer questões referentes à possível associação entre os níveis séricos de 25OHD e PPN.