Universidade Federal do Rio Grande do Sul
Faculdade de Medicina
Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Tese de Doutorado

CIRURGIA BARIÁTRICA NO TRATAMENTO DA OBESIDADE COM ENFOQUE NO METABOLISMO ÓSSEO E NA INCIDÊNCIA DE CÂNCER

Daniela Schaan Casagrande

Porto Alegre, Junho 2013.

Daniela Schaan Casagrande

Tese de Doutorado

CIRURGIA BARIÁTRICA NO TRATAMENTO DA OBESIDADECOM ENFOQUE NO METABOLISMO ÓSSEO E NA INCIDÊNCIA DE CÂNCER

Tese apresentada como requisito parcial para obtenção do título de Doutor em Ciências Médicas: Endocrinologia, à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia.

Orientadora: Beatriz D'Agord Schaan

Porto Alegre, 2013.

“O desejo ardente pelo conhecimento,
na verdade, é o motivo que atrai e sustenta os
investigadores em seus esforços.
Somente este conhecimento alcançado e, ainda sempre
a voar à frente deles, torna-se o seu único tormento e,
ao mesmo tempo, a sua exclusiva felicidade.
Aqueles que não conhecem o tormento do
desconhecido não podem ter o prazer da descoberta,
que é sem dúvida a mais viva experiência
que os seres humanos podem desfrutar.”

Claude Bernard
Pursuit of knowledge

DEDICATÓRIA

Aos meus Pais, que são as pessoas mais extraordinárias que conheço, e meus fãs incondicionais. Estiveram sempre ao meu lado me incentivando e mostrando alternativas para as dificuldades, nunca deixando que o desânimo me vencesse nos momentos difíceis e comemorando, a cada conquista, como a mais importante vitória do universo.

Ao meu irmão *Guilherme* (in memorian), que me ensinou a lutar pelos meus sonhos, mesmo quando eles parecessem impossíveis e a caminhar em direção da felicidade, vivendo intensamente cada momento.

À Deus, que ilumina, fortalece e direciona meu caminho durante toda a minha vida.

AGRADECIMENTOS

Desejo expressar meus sinceros agradecimentos a todos que contribuíram para a elaboração deste trabalho, em especial:

À minha família: Mãe, Pai, Guilherme (in memorian), André, Luciana, Tatiana, Alexandre, Laura, Rafaela, Mariana, Isabela e Stephen Anderson, que são as pessoas mais importantes na minha vida, e sem o apoio delas, eu não teria chegado até aqui;

À minha orientadora, Profª. Drª. Beatriz D'Agord Schaan, pela inestimável orientação com extrema dedicação, objetividade, carinho e paciência com os meus erros. Por seu apoio na construção de alicerces profissionais sólidos, pelas oportunidades concedidas e, sobretudo, por ter "acreditado em mim";

Ao Prof. Giuseppe Repetto, mestre e amigo, pelo apoio e constante incentivo, não medindo esforços para transmitir seus conhecimentos;

Ao Prof. Dr. Cláudio Corá Mottin, mestre e amigo, pelo apoio e constante incentivo, sendo um interlocutor interessado em participar das minhas inquietações;

Às Drª. Myriam Moretto e Drª.Jacqueline Rizzolli, pelo carinho, amizade, confiança e cumplicidade, estando sempre perto e ajudando nas dificuldades,

Às amigas Márcia Schmitt, Karin Mombach, Raquel Chatkin, Magda Ferreira, Carolina Vargas e Daniela Testoni, pela parceria e convivência, confirmando que, os amigos, são os "irmãos" escolhidos;

À equipe do COM HSL-PUCRS, em especial, às colegas nutricionistas, por colaborarem com seu suporte técnico às minhas investigações;

Às amigas e colegas Rosane Von Muller e Rejane Von Muller juntamente com a equipe administrativa do COM HSL-PUCRS por me ajudarem na parte logística deste trabalho;

À minha tia Maria Teresa Schaan Pessano e à nutricionista Lenice Zarth Carvalho, que me fizeram acreditar na profissão, me ajudando em meus primeiros passos;

Ao Serviço de Endocrinologia do Hospital São Lucas da PUCRS, que através das suas reuniões clínicas, favoreceu a ampliação de meus conhecimentos;

Ao Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul, por ter me acolhido e oportunizado terminar esta etapa;

À *Duke University*, instituição que me acolheu, favorecendo a minha experiência no exterior;

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), por ter acreditado na minha proposta oportunizado o meu estágio no exterior;

Ao Dr. Alfonso Torquatti e toda sua equipe, meu sincero agradecimento;

À Clarice Medeiros Duran por todo apoio na logística de apresentação desta tese;

Às demais pessoas e instituições com as quais interagi neste período que, de alguma forma, contribuíram para a minha formação.

RESUMO

O objetivo dessa tese foi estudar alguns aspectos relacionados aos benefícios e prejuízos da cirurgia bariátrica. Para tanto, dois artigos são apresentados, visando avaliar as alterações no metabolismo ósseo após a cirurgia bariátrica através de um estudo de coorte e a incidência de câncer através de revisão sistemática e meta-análise. O artigo 1 intitulou-se "Alterações na densidade mineral óssea em mulheres após um ano da cirurgia de bypass gástrico" e teve como objetivo avaliar as alterações na densidade mineral óssea (DMO), composição nutricional e marcadores de reabsorção óssea antes e após 1 ano de gastroplastia redutora com derivação gastrojejunal em Y de Roux (GRYR). Foram incluídas 22 mulheres com obesidade classes II-III, idade 37,2 ± 9,6 anos, 86% brancas, 77,2% pré-menopáusicas. O índice de massa corporal pré-operatório (IMC) era 44,4 ± 5,0 Kg/m^2 e após 1 ano, 27,5 ± 4,5 Kg/m^2 (p <0,001). A 25-OH-vitamina D foi semelhante em ambos os momentos [11,7 (9,7-18,0) *vs.* 15,7 (10,2-2,7) pg/dL, p = 0,327]. Houve aumento do paratormônio (45,4 ± 16,7 *vs.* 62,7 ± 28,9 pg/ml, p=0,026) e do N-telopéptido sérico (16,3 ± 3,4 *vs.* 38,2 ± 7,0 nMBCE, p<0,001) no pós-operatório, evidenciando aumento de reabsorção óssea. A DMO diminuiu após a cirurgia na coluna lombar (1,13 ± 0,11 *vs.* 1,04 ± 0,09 g / cm ², p=0,001), colo do fêmur (1,03 ± 0,15 *vs.* 0,94 ± 0,16 g/cm ², p=0,001) e fêmur total (1,07 ± 0,11 *vs.* 0,97 ± 0,15 g/cm ², p=0,003. Concluímos que a deficiência de vitamina D e aumento de reabsorção óssea ocorreram precocemente após a cirurgia bariátrica, sendo parcialmente responsáveis pela redução de DMO observada nas pacientes. O artigo 2 intitulou-se "Incidência de câncer após a cirurgia bariátrica: revisão sistemática e meta-análise" e teve como objetivo fazer uma revisão sistemática com meta-análise de estudos observacionais para avaliar a possível associação da cirurgia bariátrica com o risco de câncer em pacientes no pós-operatório. Utilizamos as bases de dados Medline, Embase e Cochrane Library. De 898 estudos, 13 preencheram os critérios de inclusão (66.636 participantes). Nos estudos controlados, a cirurgia bariátrica foi associada à redução no risco de câncer (OR 0,42, IC 95% 0,24, 0,73, I^2 = 93,3%, P para heterogeneidade <0,001). A taxa de incidência foi de 1,06 casos de câncer por 1000 pessoas-ano (IC 95% 0,64, 1,75, I^2 = 96,0%; P para heterogeneidade <0,001) nos pacientes operados. Análises de sensibilidade por idade e sexo não mostraram diferenças. Na meta-regressão, verificou-se uma relação inversa entre o IMC inicial e a incidência de câncer após a cirurgia (beta coeficiente de -0,233, P <0,05). A cirurgia bariátrica se associa com redução do risco de câncer em indivíduos com obesidade grave. O acompanhamento a longo prazo de indivíduos que se submeteram à cirurgia bariátrica, com a devida publicação dos resultados, é de fundamental importância para determinar o diagnóstico e o tratamento dos possíveis efeitos adversos deste tipo de procedimento, assim como de igual importância é realizar estudos para avaliar o impacto da cirurgia bariátrica sobre o câncer, buscando o melhor equilíbrio entre vantagens e desvantagens.

LISTA DE TABELAS

Artigo 1

Artigo 2

LISTA DE FIGURAS

Artigo 1

Artigo 2

LISTA DE ABREVIATURAS

$1,25(OH)_2D$	1,25-di-hidroxivitamina D
25(OH)D	25-hidroxivitamina D
I^2 test	heterogeneity test
χ^2 test	chi-square test
AGB	*adjustable gastric banding*
ASMBS	*American Society of Metabolic and Bariatric Surgery*
BDS	Beatriz D'Agord Schaan
BMD	*bone mineral density*
BMI	*body mass index*
CAPES	Coordenação de Aperfeiçoamento Pessoal de Nível Superior
CI	*confidence interval*
COM HSL-PUCRS	Centro da Obesidade e Síndrome Metabólica do Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul
DM	diabete mellitus
DSC	Daniela Schaan Casagrande
DXA	*Dual-energy X-ray absorptiometry*
ELISA	*enzyme-linked immunosorbent assay*
GEBECAM	*Brazilian Breast Cancer Study Group*
GRYR	Gastroplastia redutora com derivação gastrojejunal em Y de Roux
HDL-cholesterol	high-density lipoprotein cholesterol
HOMA-IR	*homeostasis model assessment of insulin resistance*
IBGE	Instituto Brasileiro de Geografia e Estatística
IGF-1	fator de crescimento do tipo insulin 1
IGF-BP3	*insulin-like growth factor binding protein -3*
JIB	*bypass jejuno-ileal*
IMC	índice de massa corporal
iPTH	*intact parathyroid hormone*
Kg	Quilograma
Kg/m^2	quilograma por metro quadrado
L1-L4	*lumbar spine* segment L1-L4
LDL-cholesterol	*low-density lipoprotein cholesterol*
MEDLINE	*Medical Literature Analysis and Retrieval System Online*
MAX	*Maximum*
MIN	*Minimum*
MOOSE	*meta-analysis of observational studies in epidemiology*
NHANES	National Health and Nutrition Examination Survey
nMBCE	*nM bone collagen equivalents*
NOS	*Newcastle-Otawa Scale*
NTX-s	*Serum collagen-type I N-telopeptide*
OMS	Organização Mundial de Saúde
OR	*odds ratio*
P25-75	*percentile 25-75*

PCR	proteína C reativa
PTH	Paratormônio
RAS	Roberta Aguiar Sarmento
RP	*Restrictive procedures*
RYGB	*Roux-en-Y gastric bypass*
SBCBM	Sociedade Brasileira de Cirurgia Bariátrica e Metabólica
SD	*standard deviation*
SOS	*Swedish Obese Subjects Study*
SPSS 17.0	*statistical software*
T4	*serum thyroxine*
TNF-alpha	fator de necrose tumoral alpha
TSH	*serum thyrotropin*
UI	unidade internacional
USA	*United States of America*
VIGITEL	Vigilância de fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico
VDR	receptor de vitamina D
VGB	*vertical banded gastroplasty*
Vitamin D	*25-hydroxy-vitamin D*

SUMÁRIO

1 INTRODUÇÃO: CIRURGIA BARIÁTRICA NO TRATAMENTO DA OBESIDADE: BENEFICIOS E PREJUIZOS

A obesidade, atualmente, é um problema de saúde comum e de proporções epidêmicas, atingindo parte significativa da população mundial (Flegal, Carroll et al. 2010). Segundo a Organização Mundial de Saúde (OMS), a obesidade pode ser classificada por meio do índice de massa corporal (IMC), representado pela razão do peso, em quilograma, sobre o quadrado do valor da altura, em metro. De acordo com esse cálculo, o peso normal situa-se entre 18,0 e 24,9 kg/m^2; o sobrepeso, entre 25,0 e 29,9 kg/m^2; a obesidade classe I, entre 30,0 e 34,9 kg/m^2; a obesidade classe II, entre 35,0 e 39,9 kg/m^2; e a obesidade classe III, igual ou acima de 40,0 kg/m^2 (WHO 1995).

A obesidade classe III está associada a uma menor expectativa de vida (Flegal, Kit et al. 2013) e é uma importante causa de morbidade (Bellanger and Bray 2005; Shields, Gorber et al. 2008), determinando excessivos gastos em saúde (Arterburn, Maciejewski et al. 2005). O aumento da morbidade associada à obesidade é particularmente importante por estar relacionado com o aumento no risco de doenças crônicas não transmissíveis (doenças cardiovasculares, diabetes, câncer, entre outras), que são a principal causa de morte no Brasil (72% das mortes em 2007) (Schmidt, Duncan et al. 2011). Osteoartrite de joelho e quadril, (Holliday, McWilliams et al. 2011), gota (Chen, Pan et al. 2013), síndrome da apneia do sono (Simard, Turcotte et al. 2004), refluxo gastroesofágico (Ayazi, Hagen et al. 2009) e doença hepática (Moretto, Kupski et al. 2003) são outras enfermidades frequentemente a ela associadas.

Um estudo prospectivo com 900 mil adultos norte-americanos mostrou maior risco de morte por câncer – 8%, 18%, 32%, e 62%, respectivamente – em mulheres com sobrepeso, obesidade classe I, classe II e classe III, quando comparadas a mulheres com peso normal. Nos homens com obesidade classe I, classe II e classe III, verificou-se aumento da mortalidade de 9%, 20% e 52%, respectivamente, quando comparados com homens de peso normal (Calle, Rodriguez et al. 2003).

A obesidade está relacionada à mortalidade precoce. O estudo de Fontaine *et al*. (Fontaine, Redden et al. 2003), estimando os anos de vida perdidos devido à obesidade, mostrou que, quanto maior o IMC, menor a expectativa de vida. O mesmo se pôde constatar

relativamente à morte por diabetes melito, quando comparados indivíduos com e sem obesidade. Com efeito, indivíduos portadores de obesidade classe I têm 2,8, 4,7, 9,0 vezes mais probabilidade de morrer de diabetes melito do que indivíduos com peso normal, obesidade classe II, obesidade classe III, respectivamente (Rogers, Hummer et al. 2003). Bender et al. mostraram haver maior incidência de mortalidade por alguns tipos de câncer, doenças cardiovasculares e digestivas em indivíduos com obesidade do que em indivíduos sem obesidade (Bender, Zeeb et al. 2006).

Confirmando essa condição de mortalidade associada à obesidade, uma pesquisa que comparou estudos transversais ecológicos da população cubana nos últimos 30 anos constatou uma diminuição da mortalidade por diabetes e doença cardiovascular durante o período de recessão econômica, no qual a escassez de alimentos e o aumento da atividade física colocaram a população em balanço energético negativo (perda média de 4 a 5 kg pela população em geral). Esses mesmos índices aumentaram com a recuperação da economia em 2002, levando, consequentemente, ao aumento do peso e à diminuição da atividade física (Franco, Bilal et al. 2013).

Além das consequências físicas, indivíduos com obesidade enfrentam ainda danos psicológicos, causados, muitas vezes, pela exclusão social e discriminação pela doença (Mond, Rodgers et al. 2007). Estudo comparando as emoções entre indivíduos com e sem obesidade demonstrou que sentimentos como angústia, raiva, nojo, medo e vergonha estão associados à obesidade sendo atenuado na presença de alguma doença física concomitante (Pasco, Williams et al. 2013).

Apesar de os fatores genéticos desempenharem papel importante no ganho de peso, a obesidade é resultado de uma interação complexa desses fatores (van Rossum, Hoebee et al. 2002) com fatores de natureza hormonal (Baessler, Hasinoff et al. 2005), ambiental (Dubois, Ohm Kyvik et al. 2012) e também comportamental (Maher, Mire et al. 2013), como a ingestão de alimentos ricos em gorduras e carboidratos e a inatividade física (Sonestedt, Roos et al. 2009).

Considerando os fatores determinantes acima citados, os quais vêm em ascendência, especialmente no mundo ocidental, a prevalência de obesidade vem crescendo. Nos Estados Unidos, ela atingiu índices superiores a 30% entre 2007 e 2008 (Flegal, Carroll et al. 2010). Acompanhando essa tendência mundial, o Brasil também tem registrado aumento no número de casos de obesidade (13,5% dos adultos brasileiros), como consta da pesquisa realizada pela

VIGITEL em 2009, mediante contatos telefônicos com aproximadamente 41.500 indivíduos (Moura and Claro 2012). Esses números foram confirmados pela Pesquisa de Orçamentos Familiares 2008-2009 do Instituto Brasileiro de Geografia e Estatística (IBGE), em que 12,5% dos homens e 16,9% das mulheres brasileiras encontravam-se com obesidade (Estatística 2010). Atualmente, a obesidade ocorre tanto em países desenvolvidos quanto em países em desenvolvimento (Monteiro, Conde et al. 2002; Chhatwal, Verma et al. 2004).

1.1 TRATAMENTO PARA OBESIDADE - DO MANEJO CLÍNICO À CIRURGIA

Existem vários padrões de tratamento utilizados para a perda de peso em indivíduos com obesidade (Meckling and Sherfey 2007; Calugi, Dalle Grave et al. 2012). A primeira escolha de tratamento é a dietoterapia, em conjunto com o estímulo à atividade física. Sempre que possível, convém associar essa modalidade terápica à terapia comportamental, que incluirá estratégias para reforçar o tratamento dietoterápico e o aumento da atividade física. Se a associação desses tratamentos resultar ineficaz, existe uma recomendação formal de uso de medicamentos antiobesidade (Wadden, Berkowitz et al. 2005). Em pacientes com obesidade classe II e III, contudo, a combinação dos tratamentos comportamental e farmacológico tem tido pouco sucesso (Sjostrom, Rissanen et al. 1998; Ryan, Johnson et al. 2010), visto que a perda de peso promovida pelo uso de medicamentos antiobesidade é, em geral, inferior a 10% do peso corporal e, muitas vezes, acompanhada de reganho de peso (Svetkey, Stevens et al. 2008). Além disso, muitos medicamentos estão associados a efeitos colaterais que limitam o seu uso (Derosa, Cicero et al. 2004). Em última instância, esgotadas as chances de sucesso do tratamento clínico, indica-se o tratamento cirúrgico (Wyatt 2013).

A cirurgia bariátrica é considerada a melhor forma de tratamento da obesidade classe II e III nos pacientes que não apresentam boa resposta ao tratamento clínico, por possibilitar perda de peso e sua manutenção a longo prazo, melhora das comorbidezes (Sjostrom, Lindroos et al. 2004) e redução da mortalidade geral (Sjostrom, Narbro et al. 2007).

A cirurgia bariátrica (*baros* = peso; *iatren* = tratar), por definição, altera a anatomia e a fisiologia do trato digestivo (Herron and Roohipour 2011). Idealmente, esse tratamento deve

oferecer baixo risco de mortalidade e morbidade, redução do excesso de peso superior a 50% (com sua manutenção a longo prazo) em pelo menos 75% dos pacientes, melhora da qualidade de vida com poucos efeitos colaterais, baixa taxa de reoperação por período inferior a dois anos, bem como ser reversível e reprodutível (Manterola, Pineda et al. 2005).

Historicamente, o primeiro procedimento cirúrgico para perda de peso, denominado desvio jejunoileal, foi realizado em 1953. Posteriormente, em razão das complicações hepáticas, metabólicas e nutricionais que acarretava, substituíram-no a gastroplastia em banda vertical, a gastroplastia redutora com derivação gastrojejunal em Y de Roux (GRYR) e a derivação biliodigestiva (Anthone, Lord et al. 2003). A cirurgia bariátrica pode ser subdividida em três grupos, conforme seus mecanismos de ação: restrição, disabsorção ou ambos (DeMaria 2007). Nas cirurgias restritivas, há uma redução da capacidade de ingestão de alimentos, podendo ou não ocorrer interferência no processo de digestão. A banda gástrica ajustável e o *sleeve gastrectomy* (gastroplastia vertical) são exemplos desse tipo de procedimento, onde no primeiro caso, a colocação da banda gástrica não interfere no processo digestivo. Entretanto, há alteração do processo digestivo na cirurgia de *sleeve gastrectomy*, onde o fundo gástrico é retirado, tornando-se uma cirurgia irreversível. Nas cirurgias disabsortivas, há uma pequena restrição gástrica, associada à má absorção intestinal resultante da exclusão da maior parte do intestino delgado do trato digestivo (Buchwald 2005). O *bypass* biliopancreático é exemplo de cirurgia disabsortiva que pode ter duas variações: *Scopinaro* ou *switch* duodenal (Brolin 2002). O desvio jejunoileal é um exemplo de cirurgia totalmente disabsortiva. Não é mais recomendado, como visto, devido à gravidade de seus efeitos colaterais, como deficiências nutricionais severas, entretanto ainda há cirurgiões que o executam (DeMaria 2007). Nas cirurgias mistas, há restrição da capacidade de ingestão de alimentos, com diminuição da capacidade absortiva do trato digestivo. A técnica de GRYR é um exemplo de cirurgia mista e caracteriza-se pela criação de uma pequena bolsa gástrica proximal na pequena curvatura, com a reconstrução do trânsito gastrointestinal fazendo-se por meio de uma alça jejunal em Y de Roux. Consequentemente, a maior parte do estômago, do duodeno e do jejuno proximal é excluída do trânsito alimentar. As medidas das alças biliopancreática e alimentar são variáveis, tendo em média 50 cm e 100 cm, respectivamente. A colocação de um anel de contenção ao redor da pequena bolsa gástrica é realizada por alguns cirurgiões. Tal procedimento pode ser efetuado por videolaparoscopia ou por laparotomia. Alguns autores (Hess and Hess 1998; Rabkin 2004) também consideram a

derivação biliodigestiva uma cirurgia mista; entretanto, a grande maioria a toma por um procedimento primariamente disabsortivo (Buchwald 2005).

Além disso, a cirurgia de bariátrica promove alterações dos hormônios gastrointestinais, variando os mecanismos de ação de acordo com o procedimento cirúrgico realizado (Akkary 2012; Ionut, Burch et al. 2013). A GRYR promove tanto um efeito sacietógeno, quanto incretínico (Geloneze and Pareja 2006).

1.2 CIRURGIA BARIÁTRICA: MODIFICAÇÃO ANATÔMICA COM CONTROLE DE UMA DOENÇA GRAVE

No passado, ninguém poderia imaginar que seus descendentes iriam cortar partes do estômago e intestino para combater o excesso de ingestão alimentar (Pinkney, Johnson et al. 2010). Não se pode afirmar que a obesidade já tenha sido retratada como modelo de beleza. Alguns pesquisadores acreditam que as estatuetas Vênus de Frasassi e Vênus de Willendorf representavam o arquétipo da beleza, fertilidade e fecundidade da mulher no período Paleolítico, entretanto ainda há dúvidas sobre esses conceitos. Olhando essas estatuetas, poderíamos estimar um IMC acima de 30 Kg/m^2, inaceitável atualmente (Bonafini and Pozzilli 2011). O sobrepeso também foi retratado nas pinturas e esculturas do século XVIII, mostrando, pelo menos, uma melhor aceitação de formas mais robustas. - (Bonafini and Pozzilli 2011). Entretanto, com o avanço da medicina e a descoberta da associação entre obesidade e doenças, esse padrão foi se modificando (Holliday, McWilliams et al. 2011; Schmidt, Duncan et al. 2011; Schienkiewitz, Mensink et al. 2012).

Atualmente, a obesidade é vista pela sociedade de várias formas – como doença, falta de cuidado, atitude relapsa, etc. Dependendo de sua gravidade, ela pode levar à exclusão social, além de acarretar uma série de complicações associadas bem conhecidas. Em contrapartida, encontramos também uma realidade oposta, em que a busca da extrema magreza pelas mulheres estabelece um forte e importante paradoxo no mundo contemporâneo: ao mesmo tempo que existem vários fatores contribuindo para o excesso de peso, a sociedade exige, como modelo

ideal de beleza, um corpo bastante magro, muitas vezes inalcançável, para a maioria das mulheres (Bonafini and Pozzilli 2011).

A cirurgia bariátrica é uma importante ferramenta para a consecução do objetivo da perda de peso e está associada ao aumento da expectativa de vida (Sjostrom 2008) e da produtividade (Ewing, Thompson et al. 2011), melhora ou remissão das comorbidezes (Sjostrom, Lindroos et al. 2004; Mottin, Vontobel Padoin et al. 2008) e melhora da qualidade de vida (Arcila, Velazquez et al. 2002), além de contribuir para a redução dos custos da saúde pública (Alexander, Goodman et al. 2008). Em sua meta-análise, Buchwald et al. demonstraram que, dos pacientes submetidos à GRYR, 80% têm perda de 60 a 80% do excesso de peso no primeiro ano de pós-operatório e de 50 a 60% a longo prazo (o excesso de peso define-se pela subtração do peso atual pelo peso ideal, este último determinado pelo IMC de 25 kg/m^2) (Buchwald, Avidor et al. 2004). A eficácia do procedimento cirúrgico resulta de uma interação complexa de fatores como restrição gástrica, má absorção, mudança comportamental e sinais neurais e endócrinos que afetam o apetite e a saciedade (Elder and Wolfe 2007).

1.3 IMPACTO ECONÔMICO DA OBESIDADE

Pessoas com obesidade requerem maiores cuidados especializados e usam mais frequentemente os serviços de saúde (Livingston and Ko 2004). Em estudo realizado com adultos norte-americanos no tocante às suas despesas médicas (consultas, tratamento hospitalar e medicamentos), verificou-se que o total de despesas *per capita* com saúde de indivíduos com obesidade classe III, classe II, classe I e sobrepeso foi, respectivamente, 81%, 65%, 47% e 25% superior ao de adultos com peso normal (Arterburn, Maciejewski et al. 2005). Entretanto, estudos sobre o impacto da cirurgia bariátrica nos custos de saúde mostram resultados diversos (Bockelbrink, Stober et al. 2008; Neovius, Narbro et al. 2012; Weiner, Goodwin et al. 2013).

Muitos estudos registraram diminuição das despesas gastas com saúde após a cirurgia bariátrica, considerando o valor da cirurgia em relação ao custo despendido com o paciente que não sofre o procedimento (Christou, Sampalis et al. 2004; Sampalis, Liberman et al. 2004; Cremieux, Buchwald et al. 2008; Hodo, Waller et al. 2008). No estudo de Sampalis *et al*. foi

demonstrado que o investimento inicial da cirurgia e os custos da internação hospitalar foram compensados pela redução total dos custos de saúde após 3,5 anos do procedimento (Sampalis, Liberman et al. 2004). O mesmo foi evidenciado no estudo de Christou *et al*., que constataram menor índice de internação hospitalar, dias de internação e consultas no grupo operado durante os cinco primeiros anos, em comparação com o grupo de controle (Christou, Sampalis et al. 2004).

Corroborando essa posição, Neovius et al. verificaram significativa diminuição dos custos com consultas médicas (principalmente por doença cardiovascular, diabetes e câncer) e medicamentos no grupo operado, na comparação com o grupo de controle, entre o sétimo e o vigésimo ano de pós-operatório, sem diferenças nos demais custos de saúde. O grupo operado apresentava, em média, 6,3 kg a mais, 1,3 anos a menos, maior índice de tabagismo e diabetes do que o grupo de controle no pré-operatório (Neovius, Narbro et al. 2012).

O uso de medicamentos para as comorbizes associadas à obesidade representa um valor considerável nos custos de saúde. Estudo de Hodo et al. demonstrou que, passados seis meses da cirurgia bariátrica, os pacientes diminuíram em 19%, 54%, 60%, 60% e 51% o uso das medicações para doenças psiquiátricas, doenças cardíacas, diabetes, asma e diuréticos, respectivamente, na comparação com os seis meses que antecederam a cirurgia (Hodo, Waller et al. 2008).

Essa redução de custos de saúde é confirmada pelos dados de Faria et al., que, valendo-se do modelo de Markov, estimaram uma diminuição de 30% nos custos gerais gastos com saúde durante toda a vida do paciente operado, em comparação com o paciente portador de obesidade (Faria, Preto et al. 2013). O modelo de Markov é um modelo estatístico em que o sistema modelado é assumido como um processo de Markov com parâmetros desconhecidos, e o desafio é determinar os parâmetros ocultos a partir dos parâmetros observáveis. Os parâmetros extraídos do modelo podem então ser usados para realizar novas análises, por exemplo, para aplicações de reconhecimento de padrões. Uma limitação para a interpretação desses dados reside no fato de que um modelo de Markov representa um processo cujo comportamento em qualquer ciclo depende somente daquele ciclo (Sonnenberg and Beck 1993), isto é, a transição para um dado estado independe da transição anterior. Em outras palavras, a probabilidade de morte devido a um ataque cardíaco, por exemplo, independe do número de vezes que a pessoa sofreu ataques cardíacos no passado.

Um estudo realizado por nosso grupo, acompanhando 194 pacientes durante três anos após a cirurgia bariátrica, verificou redução dos custos de saúde comparativamente ao período pré-operatório, chegando a registrar queda de 68% nos casos de pacientes que apresentavam duas ou mais comorbidezes no pré-operatório (Sussenbach, Padoin et al. 2012).

Contrapondo-se a essas informações, dados recentes divulgados por Weiner et al. (Weiner, Goodwin et al. 2013) mostram não haver grande benefício financeiro a longo prazo para os pacientes de pós-operatório de cirurgia bariátrica, uma vez que continuam arcando com elevados custos de saúde nesse período. Note-se, no entanto, que os autores avaliaram somente os seis primeiros anos de pós-operatório, em que os custos do procedimento cirúrgico e dos cuidados de pós-operatório tornam esse período mais oneroso (Neovius, Narbro et al. 2012).

As variações entre os estudos podem ser atribuídas a diferenças de rotinas ou tempo de seguimento de pós-operatório, podendo alguns estudos ter como rotina maior ou menor duração de internação hospitalar, acompanhamento de consultas, solicitações de exames, medicações, etc. Outro fator importante a se considerar são as complicações do pós-operatório, que geram maior gasto total e não foram descritas nos estudos. Os estudos de seguimento a longo prazo (mais de dez anos) oferecem uma análise comparativa mais ampla e justa, pois os gastos iniciais do procedimento estarão diluídos nos custos totais do período.

1.4 RISCOS *vs.* BENEFÍCIOS DA CIRURGIA BARIÁTRICA

Além dos benefícios clássicos já abordados acima, que incluem redução significativa do peso (Contreras, Santander et al. 2013), da incidência de diabetes (Mottin, Vontobel Padoin et al. 2008), dos níveis pressóricos (Sjostrom, Lindroos et al. 2004), dos níveis de lipídios (Sjostrom, Lindroos et al. 2004) e de mortalidade (Sjostrom 2008), novos benefícios têm sido relacionados na literatura recentemente. Uma vez que a obesidade está associada a um maior risco de neoplasias malignas (Crujeiras, Cueva et al. 2012; Schlesinger, Aleksandrova et al. 2013), é de esperar que seu tratamento resulte na redução desse risco, o que tem sido sugerido em estudos recentes (McCawley, Ferriss et al. 2009; Sjostrom, Gummesson et al. 2009).

Entretanto, esses benefícios podem vir acompanhados de prejuízos, alguns simples e de fácil manejo, e outros mais complexos, trazendo maiores riscos à saúde, e até a morte (deficiências nutricionais, síndrome de *dumping*, síndrome de hipoglicemia hiperinsulinêmica, náuseas, vômitos e diarréias, etc.) (Kellogg, Bantle et al. 2008; Aasheim, Johnson et al. 2011; Sarwer, Moore et al. 2012; Thurnheer, Bisang et al. 2012).

A perda de massa óssea no pós-operatório é um prejuízo importante da cirurgia, já tendo sido relatada e evidenciada por diversos autores, incluindo nosso grupo. Entretanto, um manejo e tratamento adequados podem minimizar suas consequências (Coates, Fernstrom et al. 2004; Fleischer, Stein et al. 2008; Carrasco, Ruz et al. 2009; Casagrande, Repetto et al. 2012).

A deficiência de vitamina D é uma condição carencial comum tanto na obesidade quanto no pós-operatório da cirurgia bariátrica. Atualmente, estudos indicam que a deficiência de vitamina D está relacionada com uma série de doenças além da osteoporose (Mata-Granados, Cuenca-Acevedo et al. 2010; Narula, Tauseef et al. 2013), entre elas as doenças cardiovasculares (Vacek, Vanga et al. 2012), e com o desenvolvimento de câncer (Samimi, Touze et al. 2013). O diagnóstico e tratamento da deficiência de vitamina D são extremamente importantes, haja vista a piora do estado geral de saúde na sua escassez.

A seguir, serão detalhadas essas três condições importantes (incidência de câncer, deficiência de vitamina D e perda de massa óssea), mostrando-se o benefício do procedimento cirúrgico e os riscos associados ao pós-operatório.

1.4.1 Incidência de câncer

A obesidade pode resultar na piora do tratamento e prognóstico do câncer, aumentando a mortalidade a ele relacionada (Chang, Schechter et al. 2012; Connor, Baumgartner et al. 2013). A associação entre a obesidade e o risco de câncer envolve alterações metabólicas e endócrinas, que induzem à produção de peptídeos e hormônios esteroides (Calle, Rodriguez et al. 2003).

Muitos tipos de câncer estão associados a alterações dos hormônios esteroides, especialmente aqueles tipos considerados hormônios-dependentes, como os cânceres de endométrio (Dossus, Lukanova et al. 2013), mama (Kaaks, Berrino et al. 2005), útero (Zhao,

Yoshida et al. 2013), ovário (Lee, Rosen et al. 2005) e próstata (Salonia, Abdollah et al. 2013). Além disso, existe uma associação estabelecida entre inflamação e câncer (Chang, Kuo et al. 2012).

A obesidade também está associada à inflamação crônica derivada do tecido adiposo branco, que leva à liberação de citocinas pró-inflamatórias tais como o fator de necrose tumoral alfa (TNF-alpha), a proteína C reativa (PCR) e muitas interleucinas (Vendrell, Maymo-Masip et al. 2010; La Vignera, Condorelli et al. 2011). Essas citocinas pró-inflamatórias agem nos tecidos e células e estão associadas ao câncer devido a seus efeitos diretos e indiretos sobre as células inatas e adaptativas do sistema imunológico, à homeostase desordenada dos tecidos e ao aumento do estresse oxidativo (Lyon, McCain et al. 2008).

Alguns estudos mostraram que a cirurgia bariátrica resulta na diminuição de marcadores de estresse oxidativo e de inflamação sistêmica (Uzun, Zengin et al. 2004; Holdstock, Lind et al. 2005; Vazquez, Pazos et al. 2005), o que poderia contribuir para reduzir o risco de câncer após o procedimento (Christou, Lieberman et al. 2008).

Sabe-se que existe uma forte associação entre resistência à insulina e câncer (Colangelo, Gapstur et al. 2002; Jee, Ohrr et al. 2005). Quanto maior a resistência à insulina, maior o nível de insulina circulante, o que pode potencializar os efeitos anabólicos e mediar a proliferação celular e a progressão do câncer (Capasso, Esposito et al. 2013). Níveis de insulina aumentados têm sido associados com câncer de cólon (Colangelo, Gapstur et al. 2002), mama (Oh, Park et al. 2011), pâncreas (Berrington de Gonzalez, Yun et al. 2008) e endométrio (Wang, Rohan et al. 2011). Entre os importantes efeitos da cirurgia bariátrica, pode-se citar a melhora ou remissão do diabetes (Mottin, Vontobel Padoin et al. 2008) e da resistência à insulina (Lee, Chong et al. 2011).

A cirurgia bariátrica pode melhorar ou curar a esteatose, a esteato-hepatite em muitos pacientes (Mottin, Moretto et al. 2005), por diminuir o estresse oxidativo (Kisakol, Guney et al. 2002; Uzun, Zengin et al. 2004) e aumentar os níveis e a atividade dos antioxidantes (Uzun, Zengin et al. 2004). Dados recentes apontam que a obesidade e o diabetes são fatores de risco para o desenvolvimento do carcinoma hepatocelular (Polesel, Zucchetto et al. 2009), pois geralmente estão associados à doença gordurosa não alcoólica hepática, que pode progredir para a esteatose não alcoólica, a cirrose e o próprio carcinoma hepatocelular. Esses mecanismos da

carcinogênese incluem esteatose relacionada à obesidade, peroxidação lipídica e aumento do estresse oxidativo (Oliveira, Faintuch et al. 2005).

Os níveis de leptina costumam ser altos em indivíduos obesos, podendo estimular a proliferação de células cancerosas e, assim, contribuir para a carcinogênese (Fenton, Hord et al. 2005). Após a cirurgia bariátrica são verificados níveis baixos de leptina (Geloneze, Tambascia et al. 2001), o que talvez explique a menor incidência de câncer na população submetida ao procedimento (Adams, Stroup et al. 2009; Sjostrom, Gummesson et al. 2009).

Em suma, a cirurgia bariátrica pode exercer papel protetor contra o câncer (Sjostrom, Gummesson et al. 2009), devido à melhora da resistência à insulina (Ballantyne, Farkas et al. 2006) e da síndrome metabólica (Gracia-Solanas, Elia et al. 2011), à diminuição do estresse oxidativo e da inflamação (Joao Cabrera, Valezi et al. 2010) e à modulação benéfica dos esteroides sexuais (Bastounis, Karayiannakis et al. 1998; Rosenblatt, Faintuch et al. 2012), dos hormônios intestinais (le Roux, Aylwin et al. 2006), das adipocinas (Trakhtenbroit, Leichman et al. 2009) e do sistema imunológico (Viardot, Lord et al. 2010).

1.4.2 Deficiência de vitamina D

A vitamina D (colecalcidiol) é um hormônio fundamental para a absorção do cálcio e a manutenção do esqueleto (Norman 2008). É adquirida pela dieta por meio da ingestão de alimentos ricos em óleo de peixe, fígado e ovos. A maior fonte, porém, decorre da ativação na pele (derme e epiderme), a partir da exposição aos raios ultravioleta B (UVB), quando o composto 7-dehidrocolesterol se transforma em vitamina D. Essa forma, cuja ativação não é metabólica, necessita da função hepática e renal preservada. É transportada pela corrente sanguínea até o fígado, onde sofre uma hidroxilação no carbono 25, gerando 25 hidroxivitamina D - 25(OH)D - ou calcidiol. Para se tornar ativa, a 25(OH)D necessita ainda de uma hidroxilação na posição 1, que ocorre nas mitocôndrias dos túbulos contornados proximais do rim, sob a ação da enzima 1αhidroxilase, transformando-se em 1,25-diidroxivitamina D ($1,25(OH)_2D$) ou calcitriol (hormônio 1.000 vezes mais potente que seu precursor, o calcidiol) (Holick 1995).

A deficiência da vitamina D leva a uma diminuição da absorção intestinal do cálcio e, consequentemente, à hipocalcemia. Esta, no entanto, é breve, pois em seguida surge um hiperparatireoidismo compensatório, com aumento da mobilização do cálcio ósseo e diminuição da depuração renal do cálcio, juntamente com o aumento na depuração do fosfato. Ao mesmo tempo, ocorre uma hipofosfatemia, gerada pela absorção intestinal de fosfato diminuída. Esse mecanismo compensatório pode deixar de existir devido à gravidade e/ou duração da doença. Nessa fase, o metabólito ativo da vitamina D – $1,25(OH)_2D$ – pode estar normal ou elevado. Os níveis séricos de cálcio geralmente se encontram dentro ou muito próximo da normalidade, há hipofosfatemia e níveis baixos de vitamina D; a fosfatase alcalina pode estar aumentada, e há perda de massa óssea com risco aumentado de fraturas, situação em que os marcadores de reabsorção óssea estão elevados. Níveis constantes e suficientes de vitamina D são, portanto, fundamentais para a manutenção da massa óssea (Premaor and Furlanetto 2006).

A deficiência de vitamina D ou hipovitaminose D é um problema de saúde pública mundial (Mithal, Wahl et al. 2009), podendo ser definida por valores séricos de 25(OH)D inferiores a 20 ng/ml (50 nmol/L) (Talaei, Yadegari et al. 2012). Entretanto, ainda não há uma definição aceita globalmente sobre qual seria o valor de normalidade de 25(OH)D. Diversos estudos tentaram definir um ponto de corte ideal de 25(OH)D, baseados em sua concentração plasmática, abaixo do qual os valores séricos de PTH elevam-se. No entanto, essa concentração plasmática tem variado em cada país onde foi pesquisada (Lips, Duong et al. 2001). Em crianças e jovens, demonstrou-se que, com a dosagem de 25(OH)D de 70 nmol/L, quase sempre se observa supressão do PTH (Vieth, Ladak et al. 2003). No Brasil, estudo com jovens entre 17 e 35 anos mostrou que o ponto de corte era de 74,5 nmol/L (Maeda, Kunii et al. 2007). Nos idosos acima de 70 anos, é provável que seja necessário elevar essa concentração plasmática para mais próximo de 100 nmol/L para se conseguir suprimir o PTH (Vieth, Ladak et al. 2003). A classificação desenvolvida por Freaney e cols. tem sido amplamente utilizada para definir o *status* de 25(OH)D e refere como concentrações plasmáticas desejáveis acima de 100 nmol/L (ou 40 ng/mL) (Freaney, McBrinn et al. 1993).

Dados do *National Health and Nutrition Examination Survey 2005-2006* (NHANES 2005-2006) relativos a 4.485 participantes adultos norte-americanos mostraram prevalência da deficiência de vitamina D ($25(OH)D \leq 20ng/mL$) em 42% da população estudada, com os maiores índices sendo registrados entre os afrodescendentes (82,1%) e os hispânicos (69,2%)

(Forrest and Stuhldreher 2011). A deficiência de vitamina D também é prevalente em indivíduos com obesidade classe III, atingindo de 40 a 80% dessa população (Flancbaum, Belsley et al. 2006; Casagrande, Repetto et al. 2010; Johnson, Hofso et al. 2012).

Estudo prévio de nosso grupo evidenciou prevalência de deficiência de vitamina D de 80% em indivíduos com obesidade classe III, os quais apresentavam valores normais de cálcio e magnésio, mas níveis de PTH mais elevados, embora sem significância estatística, do que aqueles indivíduos sem deficiência de vitamina D (Casagrande, Repetto et al. 2010). A causa da deficiência de vitamina D nessa população poderia relacionar-se com uma menor exposição solar desses indivíduos, menor ingestão de alimentos fonte de vitamina D ou mesmo com o sequestro de vitamina D pelo tecido adiposo (Holick and Chen 2008).

Os tecidos do cérebro, da próstata, da mama, do cólon, entre outros, assim como as células do sistema imunológico, têm um receptor de vitamina D (VDR) que responde à forma ativa da vitamina D. Alguns desses tecidos e células expressam a enzima 25-hidroxivitamina D-1α-hidroxilase, que converte 25(OH)D em $1,25(OH)_2D$ (Dusso, Brown et al. 2005). A - $1,25(OH)_2D$ - exerce efeitos em células que não estão envolvidas na homeostase do cálcio. A ligação do VDR com a forma ativa da vitamina D, $1,25(OH)_2D$, produz múltiplos efeitos celulares, incluindo a indução de diferenciação e apoptose, a inibição da proliferação, a angiogênese e o potencial metastático (Diaz, Paraskeva et al. 2000; Evans, Shchepotin et al. 2000). Portanto, a vitamina D pode desempenhar papel importante na etiologia e no tratamento do câncer. A deficiência de vitamina D está associada a diversos tipos de câncer (Churilla, Brereton et al. 2012; Friedman, DeMichele et al. 2012; Roskies, Dolev et al. 2012). Além disso, os níveis séricos de 25(OH)D são significativamente mais elevados em pacientes com câncer de mama em estágio precoce do que naqueles com doença avançada ou metastática (Palmieri, MacGregor et al. 2006).

1.4.3 Perda de massa óssea

O cálcio é o mineral mais abundante do corpo humano (39% em relação a outros minerais), correspondendo a 1-2% do peso corporal, 99% nos ossos e 1% no sangue, espaço

extracelular e células de tecidos moles. Sua função relaciona-se ao crescimento e desenvolvimento dos ossos e dentes, estabilização das membranas de células excitáveis (músculos e nervos), participação no processo de coagulação sanguínea e na atividade de diversas enzimas (Grüdtner, Weingrill et al. 1997). Tradicionalmente considera-se que a quantidade ideal deste mineral na dieta seja aquela que conduza a um pico de massa óssea adequado na criança e adolescente, mantenha-o no adulto e minimize a perda na senilidade (NIH 1994). Seu mecanismo de absorção é complexo, envolvendo especialmente a vitamina D, ATPase, fosfatase alcalina intestinal, fatores que aumentam ou diminuem sua solubilidade, proteína ligadora de cálcio no enterócito, e proteína ligadora de cálcio no plasma. O transporte celular de cálcio é maior no duodeno e jejuno proximal, e menor no cólon proximal, pouco ocorrendo no jejuno distal e no íleo (Grüdtner, Weingrill et al. 1997).

A avaliação da massa óssea é um método utilizado na prática clínica diária para identificação de osteopenia e osteoporose. Entretanto, sabe-se que a densidade mineral óssea (DMO) é uma medida estática e, portanto, não reflete alterações dinâmicas do tecido ósseo. A remodelação é um fenômeno que ocorre ao longo da vida, sendo fundamental para renovação do esqueleto e preservação de sua qualidade. Em situações fisiológicas, a reabsorção e a formação são fenômenos acoplados e dependentes, e o predomínio de um sobre o outro pode resultar em ganho ou perda de massa óssea. Fosfatase alcalina total, fosfatase alcalina óssea, osteocalcina, pró-peptídeo do colágeno tipo I são marcadores de formação óssea; cálcio urinário, hidroxiprolina urinária, fosfatase ácida tartarato-resistente, moléculas interligadoras do colágeno tipo I (piridinolina, deoxipiridinolina, telopeptídeos aminoterminais (N-telopeptídeo) e carboxiterminais (C-telopeptídeo) do colágeno tipo I) são marcadores de reabsorção óssea (Saraiva and Lazaretti-Castro 2002). Importante ressaltar também que o principal desfecho da osteoporose são as fraturas, e sua ocorrência depende de múltiplos outros fatores, além da perda de DMO. Dentre os mais relevantes cita-se idade, sexo, uso de glicocorticóides, artrite reumatóide, doenças que se relacionam com reabsorção óssea aumentada, história familiar de osteoporose, tabagismo, ingestão de álcool, IMC, risco de queda, fraqueza muscular, entre outros (Ensrud, Lui et al. 2009).

A obesidade já foi tida como um fator de proteção para a osteoporose (Albala, Yanez et al. 1996). Entretanto, estudos recentes questionam essa posição e indicam que o aumento do tecido adiposo não é sempre benéfico para a estrutura óssea (Janicka, Wren et al. 2007),

considerando a obesidade como fator de risco para fraturas (Greco, Fornari et al. 2010). Estudo observacional mostrou que indivíduos com obesidade têm menor DMO do que esperado para a sua faixa etária (Greco, Fornari et al. 2010). Outros autores, avaliando homens e mulheres com idades entre 25-64 anos mostraram que o tecido adiposo foi inversamente associado com a DMO total do corpo e do quadril, o que foi independente do peso, nível de atividade física e idade (Hsu, Venners et al. 2006). Outro estudo recente, que utilizou tomografia computadorizada para avaliação da gordura visceral e DMO, mostrou que a gordura na medula óssea se correlacionava positivamente com a gordura visceral e negativamente com o fator de crescimento da insulina tipo 1 (IGF-1) em mulheres com obesidade (Bredella, Torriani et al. 2011), sugerindo que os efeitos prejudiciais da gordura visceral sobre a saúde óssea podem ser mediados, em parte, pelo acúmulo de gordura na medula óssea, estabelecendo elo entre obesidade central e osteoporose (Bredella, Torriani et al. 2011).

Mulheres com sobrepeso e obesidade apresentam menores taxas de marcadores de formação óssea, como indicado pelos níveis circulantes de colágeno tipo 1, comparadas às mulheres com peso normal, mostrando que IMC está inversamente associado com níveis de colágeno tipo I, que é um marcador de formação óssea. Entretanto, neste estudo mulheres com obesidade tinham DMO maior do que mulheres com peso normal e com sobrepeso (Papakitsou, Margioris et al. 2004).

A cirurgia bariátrica produz uma perda de peso importante, sobretudo no primeiro ano após a operação. Considerando-se os mecanismos acima citados, a perda de massa óssea pode se iniciar já nos primeiros meses de pós-operatório. Em mulheres que foram submetidas à GRYR, foram observados altos valores de C-telopeptideo sérico, com diminuição de 25(OH)D e aumento de PTH no primeiro ano de pós-operatório, indicando elevada remodelação óssea, deficiência de vitamina D e hiperparatireoidismo secundário (El-Kadre, Savassi-Rocha et al. 2004).

A obesidade e a síndrome metabólica produzem efeitos potencialmente prejudiciais na saúde óssea, com grande incidência de fraturas osteoporóticas e fragilidade da estrutura óssea em adultos (jovens e idosos) com aumento da adiposidade visceral (von Muhlen, Safii et al. 2007; Gilsanz, Chalfant et al. 2009). Adiponectina é um hormônio proteico secretado pelos adipócitos e modula vários processos metabólicos (regula a homeostase de energia e tem efeitos anti-inflamatório e anti-aterogênico). No estudo de Lenchik et al. foi demonstrado que a adiponectina

está inversamente associada à gordura visceral e à DMO, não demonstrando a mesma relação com a gordura subcutânea (Lenchik, Register et al. 2003).

Assim como a obesidade está relacionada à saúde óssea, a perda de peso também pode produzir efeitos prejudiciais no osso (Hinton, Rector et al. 2012) – de fato, evidências demonstram relação entre perda de peso e perda óssea em vários sítios (Andersen, Wadden et al. 1997; Salamone, Cauley et al. 1999). Em função disso, a avaliação óssea no pré-operatório da cirurgia bariátrica deve ser criteriosa e de rotina, pois, como já foi descrito, a deficiência de vitaminas e minerais poderá comprometer a saúde óssea no pós-operatório (Casagrande, Repetto et al. 2010).

As técnicas cirúrgicas que causam disabsorção constituem alto fator de risco para desenvolvimento de doenças ósseas (Riedt, Brolin et al. 2006). Entretanto, há vários estudos demonstrando alterações no metabolismo ósseo em técnicas puramente restritivas (Pugnale, Giusti et al. 2003; Giusti, Gasteyger et al. 2005; Nogues, Goday et al. 2010). Ainda não está claro se o aumento nos marcadores de remodelação óssea representa um efeito adverso da cirurgia bariátrica, ou se reflete um ajuste fisiológico devido às mudanças no peso e, consequentemente, na carga carregada. Nos dois casos, o aumento da remodelação óssea produz um efeito catabólico no osso, onde a remodelação é maior do que a formação óssea (Brzozowska, Sainsbury et al. 2013).

A deficiência de vitaminas e minerais que afeta os pacientes no pós-operatório da cirurgia bariátrica é responsável pelos danos causados no metabolismo ósseo. Uma suplementação adequada com um rigoroso acompanhamento no pós-operatório poderia mudar esse desfecho, evitando a doença óssea (Brzozowska, Sainsbury et al. 2013). A Sociedade Americana de Cirurgia Bariátrica e Metabólica (ASMBS – American Society of Metabolic and Bariatric Surgery) recomenda uma suplementação de 1.200 a 2.000 mg de citrato de cálcio e de 400 a 800 UI de vitamina D por dia para a prevenção de doença óssea no pós-operatório. Não obstante, sugere o monitoramento e eventual alteração na suplementação recomendada (Aills, Blankenship et al. 2008).

1.4.3 Risco de fraturas na obesidade e após cirurgia bariátrica

Baixo peso corporal é fator de risco para fraturas, principalmente em idosos, o que pode ser o resultado de vários fatores, incluindo baixa DMO, aumento do risco de quedas resultante da fraqueza muscular e menor quantidade de tecidos moles que podem proteger contra o impacto de uma queda. Por outro lado, recentemente, especial atenção tem sido dada para a ocorrência de fraturas em indivíduos com sobrepeso ou obesidade (Nielson, Srikanth et al. 2012).

A associação entre o IMC e o risco de fraturas é complexa, pois difere conforme os locais do esqueleto e é modificada pela interação entre IMC e DMO. Em recente revisão sistemática com meta-análise de estudos observacionais, totalizado 398.610 mulheres acompanhadas, baixos valores de IMC foram associados com maior risco de fratura de quadril e menor risco de fraturas osteoporóticas, fratura de tíbia e fíbula, antebraço distal e braço (resultados ajustados para DMO). Já valores elevados de IMC foram associados com maior risco de fratura na parte superior do braço (úmero e cotovelo) e todas as fraturas osteoporóticas (Johansson, Kanis et al. 2013). Em relação à fratura de quadril, outra recente revisão sistemática com meta-análise realizada com 15 estudos de coorte (3.126.313 adultos), mostrou que indivíduos obesos possuem menor risco desse tipo de fratura (RR 0,48; IC 95% 0,39 – 0,58; P< 0,001) e que a obesidade parece ser um fator protetor para fratura de quadril (Tang, Liu et al. 2013).

O tipo de obesidade conforme a distribuição da gordura corporal também tem sido analisado. Em mulheres, ao final de cinco anos de seguimento, para cada 1 kg a menos na gordura abdominal, observou-se associação com um risco 50% maior de qualquer tipo de fratura (HR 1,50; IC 95% 1,10-2,05) após ajuste para idade, densidade mineral óssea do colo femoral, quedas, estatura, atividade física e fraturas prévias (Yang, Nguyen et al. 2013).

Poucos estudos têm demonstrado a ocorrência de fraturas após a cirurgia bariátrica. Um estudo da *Mayo Clinic*, apresentado na 91ª Reunião Anual da Sociedade de Endocrinologia, relatou aumento no risco de fraturas em pacientes submetidos à cirurgia bariátrica, em comparação com o que seria esperado para pessoas da população em geral com a mesma idade (Haglind, Kennel et al. 2009). Já estudo de coorte retrospectivo não encontrou aumento do risco de fraturas em 2.079 pacientes submetidos à cirurgia bariátrica, em comparação com grupo controle (8,8 *versus* 8,2 por 1.000 pessoas-ano; RR 0,89; IC 95% 0,60-1,33). A cirurgia bariátrica também não afetou o risco de fraturas osteoporóticas e não osteoporóticas. No entanto, observou-se uma tendência para um aumento no risco de fratura após três a cinco anos pós-

operatórios, bem como em pacientes que tiveram uma maior diminuição no IMC após a cirurgia, mas isso não foi significativo (Lalmohamed, de Vries et al. 2012).

2 JUSTIFICATIVA

A cirurgia bariátrica é considerada o tratamento mais eficaz para pacientes com obesidade. Entretanto, seus efeitos colaterais, causados pela desnutrição secundária ao procedimento, pela suplementação de vitaminas e de minerais inadequada ou inexistente e por alterações fisiológicas promovidas pela cirurgia podem acarretar piora do estado de saúde a longo prazo. Por outro lado, a cirurgia bariátrica produz efeitos benéficos metabólicos, perda de peso e melhora ou remissão de doenças associadas à obesidade.

Dessa forma, é importante estudar as alterações metabólicas, como as do metabolismo ósseo, e suas consequências antes e depois do procedimento considerando que a disabsorção de nutrientes proposta pela cirurgia bariátrica possa interferir nesses resultados no pós-operatório.

Dado que a obesidade está associada à maior incidência de muitas neoplasias malignas, o estudo da incidência de câncer no pós-operatório da cirurgia bariátrica tem sido muito explorado, mas não havia até recentemente revisão sistemática sobre o tema.

Considerando essas duas lacunas da literatura, são propostos um estudo de coorte para investigar o metabolismo ósseo após a cirurgia bariátrica e também uma revisão sistemática com meta-análise para o estudo da incidência de câncer no pós-operatório da cirurgia bariátrica.

3 OBJETIVOS

Os objetivos desta tese foram:

1) Verificar o perfil nutricional, os aspectos metabólicos e a densidade mineral óssea da coluna lombar e do fêmur de pacientes com obesidade mórbida antes e após um ano da gastroplastia redutora com derivação gastrojejunal em Y de Roux;

2) Avaliar a incidência de câncer em indivíduos submetidos à cirurgia bariátrica, comparando-os com indivíduos obesos mediante uma revisão sistemática com meta-análise.

4 ARTIGOS

4.1 ARTIGO 1

CHANGES IN BONE MINERAL DENSITY IN WOMEN FOLLOWING ONE YEAR GASTRIC BYPASS SURGERY

Daniela Schaan Casagrande, Giuseppe Repetto, Claudio Corá Mottin,
Jatin Shah, Ricardo Pietrobon, Mathias Worni, Beatriz D. Schaan

Obesity surgery. 2012 Aug;22(8):1287-92. doi: 10.1007/s11695-012-0687-z.

Changes in bone mineral density in women following one year gastric bypass surgery

Daniela Schaan Casagrande, MS[1,2,3]. Giuseppe Repetto, MD[4]. Claudio Corá Mottin, MD, PhD[2,4]. Jatin Shah, BAMS[3]. Ricardo Pietrobon MD, PhD[3]. Mathias Worni, MD[3]. Beatriz D. Schaan, MD, PhD[1].

1. Postgraduate Program in Medical Sciences: Endocrinology and Metabolism, Universidade Federal do Rio Grande do Sul, Hospital de Clinicas de Porto Alegre, Brazil.
2. Obesity and Metabolic Sindrome Center of Hospital São Lucas, Pontificia Universidade Católica do Rio Grande do Sul (COM HSL-PUCRS), Porto Alegre, Brazil.
3. Research on Research Group, Department of Surgery, Duke University Medical Center, Durham, NC, USA.
4. Faculty of Medicine, Hospital Sao Lucas, Pontificia Universidade Catolica do Rio Grande do Sul, Porto Alegre, Brazil.

Corresponding author and reprint request:
Beatriz D'Agord Schaan
Endocrine Division - Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos 2350, prédio 12, 4º andar - 90035-003 Porto Alegre, RS
e-mail: beatrizschaan@gmail.com
Fax: (51) 3359-8127

Financial disclosure/funding support:
This work was supported by grant from The Brazilian Federal Agency for Support and Evaluation of Graduate Education - Capes and PBBEP3-131567 from the Swiss National Science Foundation (MW). The authors have no other potential conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Key words:

Morbid obesity, Metabolic bone disease, Bone turnover, Vitamin D deficiency, Osteoporosis, Bariatric Surgery, Bone Metabolism

Abstract

Background: Roux-en-Y gastric bypass (RYGB) surgery is the gold standard surgical treatment for obesity. However, unintended nutritional deficiencies following this surgery are common, including changes in bone metabolism.

Objective: We assessed changes in bone mineral density (BMD), nutritional compounds and bone resorption markers before and 1-year following RYGB surgery.

Methods: Our study included 22 female patients with class II/III obesity. A clinical questionnaire, a 24-h recall and blood and urine samples and Dual-energy X-ray absorptiometry (DXA) were provided.

Results: Mean age was 37.2 ± 9.6 years, 86% were Caucasian and 77.2% were premenopausal. Mean preoperative body mass index (BMI) was 44.4 ± 5.0 Kg/m^2 and 27.5 ± 4.5 Kg/m^2 at the 1-year follow-up ($p<0.001$). 25-OH-vitamin D-levels were similar in both periods [11.7 (9.7-18.0) *vs* 15.7 (10.2-2.7) pg/dL, p= 0.327]. Serum N-telopeptide (16.3 ± 3.4 *vs* 38.2 ± 7.0 nMBCE, $p<0.001$) and parathyroid hormone (45.4 ± 16.7 *vs* 62.7 ± 28.9 pg/mL, p=0.026) increased after RYGB surgery, reflecting bone resorption. BMD decreased after RYGB surgery in the lumbar spine (1.13 ± 0.11 *vs* 1.04 ± 0.09 g/cm², p=0.001), femoral neck (1.03 ± 0.15 *vs* 0.94 ± 0.16 g/cm², p= 0.001), and total femur (1.07 ± 0.11 *vs* 0.97 ± 0.15 g/cm², p=0.003).

Conclusion: Decreased BMD in the lumbar spine, femoral neck and total femur is detectable in women one year after RYGB surgery. Calcium malabsorption, caused by vitamin D deficiency and increased bone resorption, is partially responsible for these outcomes and should be targeted in future clinical trials.

Introduction

Obesity has dramatically increased over the last several years throughout the world (Rokholm, Baker et al. 2010), and reached a prevalence of about 30% in the United States in 2008 (Flegal, Carroll et al. 2010) and 13.5% in Brazil in 2009 (Moura and Claro 2011). Currently, bariatric surgery is the most effective treatment to lose weight, improve quality of life, and reduce morbidity and mortality among obese individuals who could not achieve weight loss with lifestyle interventions and/or anti-obesity medication (Colquitt, Picot et al. 2009). Roux-en-

Y gastric bypass (RYGB) surgery is considered the gold standard surgical treatment for these patients, because it leads to less severe malabsorption and malnutrition than traditional malabsorptive procedures (i.e., jejuno-ileal bypass) (Barrow 2002; Garcia, Long et al. 2009) and to significantly higher excess weight loss than pure restrictive procedures (Campos, Rabl et al. 2011). However, unintended nutritional deficiencies following gastric bypass surgery are a major adverse outcome, including changes in bone metabolism (Fleischer, Stein et al. 2008; Gehrer, Kern et al. 2010; Higa, Ho et al. 2010; Sinha, Shieh et al. 2011). Weight loss induced by malabsorptive procedures can be accompanied by increased levels of parathyroid hormone (PTH), resulting from an inadequate intake and absorption of calcium and vitamin D (Riedt, Cifuentes et al. 2005). Increased PTH and decreased vitamin D are known to cause osteoporosis (Mezquita-Raya, Munoz-Torres et al. 2001) and are highly prevalent after any kind of caloric restriction (Ricci, Heymsfield et al. 2001). This is most prominent if routine exercise is not associated with dietary interventions (Villareal, Shah et al. 2008).

Although some previous studies show a decrease in bone mineral density in the first year following bariatric surgery (Fleischer, Stein et al. 2008; Mahdy, Atia et al. 2008; Vilarrasa, San Jose et al. 2011), others show that RYGB is associated with high bone resorption and hyperparathyroidism, without a reduction in bone mineral density measured in the lumbar spine and femoral neck (Valderas, Velasco et al. 2009).

The aim of this 1-year follow-up study in obese women undergoing RYGB is twofold: first, to quantify the change in bone mineral density using dual-emission X-ray absorptiometry (DXA), the standard technique for bone mineral density measurement in non-obese women, and second, to assess changes in bone serum markers and nutritional components between preoperative and 1-year follow-up measurements.

Methods

We performed a prospective cohort study of patients undergoing RYGB surgery. All patients were recruited from the outpatient clinic of the Obesity and Metabolic Syndrome Center of Hospital São Lucas of Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), in Porto Alegre, Brazil. The Internal Review Board of Hospital São Lucas of PUCRS approved the study and all subjects gave written informed consent before participating in it (protocol 06/02985). The RYGB patients were recruited between January 2007 and July 2008 and met

inclusion criteria to undergo bariatric surgery (patients who maintain BMI >40 kg/m2, or a BMI >35 kg/m2 with at least 1 comorbidity) (1992). Patients were excluded if they had preoperative gut malabsorption syndrome, any gastric, kidney, or liver disease, or if they used any medication affecting bone metabolism (e.g. glucocorticoids, calcium supplements, vitamin D derivate, diuretics, and anti-epileptic drugs). All RYGB procedures were performed at the Obesity and Metabolic Syndrome Center of Hospital São Lucas of Pontificia Universidade Católica do Rio Grande do Sul. All procedures entailed the creation of a 30 ml gastric pouch, a 150 cm "Roux limb" (alimentary limb) and a 50 cm biliopancreatic limb.

Patient clinical history, blood samples, anthropometric measurements (body weight, height, abdominal and hip circumference), dietary intake (obtained through 24-h recall) and dual-emission X-ray absorptiometry (DXA) were collected before and one year following the RYGB procedure. Nutrient analysis of the 24-h recall were performed using the food analysis software Dietwin® Professional 2.0 (Brubins and Dataweb Tecnologia, Porto Alegre, Brazil). The percent of excess weight loss was calculated using the following formula (Deitel and Greenstein 2003): percent excess weight loss = [(operative weight – follow-up weight)/operative excess weight] x 100, where: excess weight = actual weight - ideal weight.

Bone mass density, was measured using DXA (Hologic QDR-4500 Acclaim, Boston, MA) at the lumbar spine (L1-L4), the total femur and the femoral neck in all subjects. Low bone density was defined as a Z-score lower than −2.0 for premenopausal women, and a T-score lower than −1.0 for postmenopausal women, at any of the sites of bone mineral density studied (Baim, Binkley et al. 2008).

Insulin and PTH were measured by the chemiluminescence method (Advia Centaur, Bayer Corporation, Tarrytown, NY). Serum and urinary calcium, alkaline phosphatase, liver enzymes, fasting plasma glucose, creatinine and albumin were measured by the dry chemical system (Fusion FS 5.1, Johnson & Johnson, Buckinghamshire, United Kingdom). Serum thyroxin (T4), thyrotropin (TSH), and 17β-estradiol were measured using a chemiluminescence immunoassay (Vitros ECi Immunodiagnostic System, Ortho-Clinical Diagnostics, Rochester, NY). Insulin resistance was assessed by the HOMA-IR (homeostasis model assessment of insulin resistance) in individuals who were not on hypoglycemic agents or insulin, as described using the formula: HOMA1-IR = fasting plasma insulin (μU/ml) x fasting plasma glucose (mM/22.5) (Matthews, Hosker et al. 1985). Serum 25-hydroxyvitamin D levels were determined

by radioimmunoassay, based on an antibody with specificity for 25-OH-D (DiaSorin, Stillwater, MN). Serum collagen-type I N-telopeptide (NTX-s) was measured by means of the enzyme-linked immunosorbent assay (ELISA), using the Osteomark NTx® serum test (Whampole Laboratories Inc., Princeton, NJ). The manufacturer's recommendation of reference values for women ranges from 6.2 to 19.0 nM bone collagen equivalents (nM BCE). Some tests were used only as criterion for exclusion and were not included in the results.

Statistical Analysis

Data are expressed as counts and relative frequencies, means and standard deviations or medians and interquartile ranges (P25-75), where appropriate. Fisher's exact test was used to compare categorical variables; the paired *t*-test was used to compare pre- and postoperative outcomes of continuous variables. P values below 0.05 were considered statistically significant; all tests were performed two-sided. All analyses were performed using SAS Enterprise Guide 4.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Initially, 33 patients were included in this prospective study, but only 22 patients (67%) completed the 1-year follow up examinations. Patients dropped out of the study for the following reasons: 6 patients missed follow-up appointments, 4 patients refused the DXA and bone marker measurements at the 1-year follow-up, and one woman died from a pulmonary embolism. To evaluate the significance of the attrition rate (33% of our patients), we compared the initial clinical data of the 11 patients who dropped out of our study to the inicial clinical data of the 22 patients who remained in our study. The clinical characteristics (age, BMI, blood pressure levels) and laboratory test results (fasting plasma glucose, HOMA-IR, lipid levels) were similar ($p<0.05$) between the groups.

The mean preoperative age of the 22 women was 37.2 ± 9.9 years, most were Caucasian (n=19; 86%), and premenopausal (n=17; 77.2%). The mean BMI was 44.4 ± 5.0 Kg/m^2 prior to RYGB surgery and 27.5 ± 4.5 Kg/m^2 at the 1-year follow-up ($p<0.001$). The mean percent excess weight loss was 89.2 ± 18.1 %. The general clinical characteristics of the subjects studied before and after the procedure are summarized in Table 1.

The mean serum albumin level remained unchanged over the first year. Fasting plasma glucose and HOMA-IR decreased significantly in the same period of observation.

Differences in the nutritional composition of the pre- and postoperative period are presented in Table 2. Overall, we observe a significant decrease in total energy intake from 3,197 to 1,257 kilocalories ($p< 0.001$). Reported carbohydrates, lipids, phosphorus, and calcium intake decreased at the 1-year follow-up period, while cholecalciferol intake remained unchanged over time. Although, the total amount of protein intake in grams decreased from 141.1 to 68.1 ($p< 0.001$), protein as a percentage of total diet increased from 18.7 to 22.4% ($p<0.050$).

Preoperative and 1-year follow-up summaries of bone serum and urine markers are provided in Table 3. No differences were detected in the group's 25-OH-vitamin D, alkaline phosphatase, serum calcium or 24-hour urinary calcium levels. Increases in NTX-s levels reflect evidence of bone resorption ($P<0.001$).

The BMD, measured with the DXA method, significantly decreased after the RYGB surgery (lumbar spine 1.13 ± 0.11 *vs.* 1.04 ± 0.09 g/cm², $p<0.001$; femoral neck: 1.03 ± 0.15 *vs.* 0.94 ± 0.16 g/cm², $p= 0.001$; total femur: 1.07 ± 0.11 *vs.* 0.97 ± 0.15 g/cm², $p=0.003$), as reflected in Figure 1. One year following RYGB surgery, the mean percentage of bone mineral loss was 7.26% ($p<0.001$) in the lumbar spine, 8.59% ($p= 0.001$) in the total femur and 8.78% ($p=0.003$) in the femoral neck.

Discussion

In this study, we simultaneously compare bone mineral density, bone resorption markers, nutritional components, and metabolic markers prior to and following RYGB surgery. We provide compelling evidence that bone mineral density compared to the preoperative period decreased after the 1-year follow-up in all evaluated bone segments. The decrease in BMD was accompanied by a decrease in bone serum resorption markers and low vitamin D levels, indicating increased turnover, and overall resorption, of bone substance. However, the lower energy intake, weight loss and metabolic improvements attained were beneficial for the patients.

Bone mass density in the lumbar spine, femoral neck, and total femur decreased by an average of 8.2% a year following bariatric surgery. Our findings are in accordance with a recent study performed by Vilarrasa *et al.* that monitored 59 patients before and after RYGB surgery. They report a decrease of BMD in the femoral neck of about 10%, but only a 3% decrease of

BMD in the column one year after RYGB surgery (Vilarrasa, Gomez et al. 2009). In addition, Fleisher *et al.* support the decrease in BMD in the femoral neck (9.2%) and the total hip (8.0%), but similarly do not confirm the decrease of BMD in the lumbar spine one year after RYGB surgery (Fleischer, Stein et al. 2008). A potential explanation for why they were unable to detect a decrease of BMD in the lumbar spine might be associated with the DXA instrument. DXA may be unable to accurately measure changes in adipose tissue density and distribution following bariatric surgery, as previously described by Tothill *et al*. (Tothill 2005).

To adequately evaluate bone metabolism after surgery, it is crucial to measure BMD, the specific bone serum markers, vitamin D levels, and also calcium and phosphorus intake. We found that NTX-s and PTH levels were increased one year following RYGB surgery compared to preoperative measurements. The high level of NTX-s, a very specific marker for bone resorption, indicates bone mineral loss (Eastell, Mallinak et al. 2000; Yoshimura, Muraki et al. 2011). This loss may either be caused by low calcium and phosphorus intake or absorption (Singhellakis, Malandrinou et al. 2011) or inadequate bone metabolism (Flores, Osaba et al. 2010; Williams 2011). We believe the combination of both factors is responsible for bone mineral loss in RYGB patients. Other studies used NTX-u (NTX measured in the urine) instead of NTX-s to show increased bone resorption (Fleischer, Stein et al. 2008; Nogues, Goday et al. 2010; Sinha, Shieh et al. 2011), but serum-based markers of bone turnover (NTX-s) tend to show less variability compared to the urine-based markers (NTX-u) (Eastell, Mallinak et al. 2000). Further, Eastell *et al.* showed that NTX-s can be a good marker for the monitoring of bone resorption (Eastell, Mallinak et al. 2000).

As we previously reported, most of our patients had a deficiency of serum vitamin D levels in the preoperative period (Casagrande, Repetto et al. 2010), which were lower than the initial vitamin D levels recorded in other research (Fleischer, Stein et al. 2008; Gemmel, Santry et al. 2009; Vilarrasa, Gomez et al. 2009). In the post-operative period, the vitamin D levels of our patients increased by 50% through the use of a multivitamin supplement and regular doses of cholecalciferol. However, these levels were still lower than those observed in the postoperative period of the previously mentioned studies (Fleischer, Stein et al. 2008; Vilarrasa, Gomez et al. 2009). We suspect a few reasons account for the lower vitamin D levels found in our patients. First, characteristics of patients vary from study to study, and different serum vitamin D levels vary across differing age groups, genders, body fat distributions, and smoking habits (Lee,

O'Keefe et al. 2008). Second, it is known that vitamin D levels are associated with sun exposure, which is often lower in obese patients due to a lack of outdoor activity (Saraiva, Cendoroglo et al. 2005; Silva, Camargos et al. 2008). Third, obese patients often suffer from systemic inflammation, which may interfere with vitamin D metabolism (Wortsman, Matsuoka et al. 2000; Lee, O'Keefe et al. 2008). This research reinforces the importance of strict supplementation of vitamin D in the postoperative period following RYGB surgery, in doses well above the recommended daily allowance (Aills, Blankenship et al. 2008) to achieve beneficial effects on BMD (Jackson, LaCroix et al. 2006).

Additionally, the intake of calcium and phosphorus among our patients following surgery did significantly decrease below the recommended daily intake (Aills, Blankenship et al. 2008), and this is another important risk factor in BMD loss (Whitehead and Fleming 2000). Other studies confirm decreased intake of calcium following RYGB surgery, which can persist up to eight years after the surgery (Ott, Fanti et al. 1992; Colossi, Casagrande et al. 2008; Duran de Campos, Dalcanale et al. 2008). In contrast, Fleischer *et al*. showed that with additional micronutrient supplementation, an increase of calcium and phosphorus intake can be achieved (Fleischer, Stein et al. 2008).

We would like to acknowledge the limitations of our study. As with other prospective studies in bariatric surgery evaluating BMD, the sample size of our study is limited. The primary limitation to patient participation relates to the fact that DXA equipment is often unable to measure patients exceeding a weight of 150 kg. Furthermore, we experienced a high post-surgery attrition rate, which is similar to other obesity studies (Karlsson, Taft et al. 2003; Garb, Welch et al. 2009). Moreover, a high prevalence of vitamin D deficiency was observed in the preoperative evaluation, which could account, at least in part, for the bone mineral density reduction observed in our bariatric surgery patients. However, the clinical characteristics and lab results of both groups were similar, which reinforces our belief that our findings were not skewed by patient attrition.

Conclusion

Our study provides preliminary evidence that women with class II and III obesity may have early increases in bone resorption and bone mineral density loss one year following RYGB

surgery. Calcium malabsorption caused by vitamin D deficiency and increased bone resorption are partially responsible for these outcomes, and thus, should be measured in future clinical trials involving larger number of patients submitted to bariatric surgery. We suggest that routine follow-up measurements should be performed to monitor changes in patient bone metabolism and bone mineral density over time.

Acknowledgments:

We thank Dr. Melissa Markoski from Instituto de Cardiologia do Rio Grande do Sul / Fundação Universitária de Cardiologia, Porto Alegre, Brazil for the bone resorption markers' measurements.

References

1. Rokholm, B., J.L. Baker, and T.I. Sorensen, *The levelling off of the obesity epidemic since the year 1999--a review of evidence and perspectives.* Obes Rev, 2010. **11**(12): p. 835-46.
2. Flegal, K.M., et al., *Prevalence and trends in obesity among US adults, 1999-2008.* JAMA, 2010. **303**(3): p. 235-41.
3. Moura, E.C. and R.M. Claro, *Estimates of obesity trends in Brazil, 2006-2009.* Int J Public Health, 2011.
4. Colquitt, J.L., et al., *Surgery for obesity.* Cochrane Database Syst Rev, 2009(2): p. CD003641.
5. Barrow, C.J., *Roux-en-Y gastric bypass for morbid obesity.* AORN J, 2002. **76**(4): p. 590, 593-604; quiz 606-8.
6. Garcia, O.P., K.Z. Long, and J.L. Rosado, *Impact of micronutrient deficiencies on obesity.* Nutr Rev, 2009. **67**(10): p. 559-72.
7. Campos, G.M., et al., *Better weight loss, resolution of diabetes, and quality of life for laparoscopic gastric bypass vs banding: results of a 2-cohort pair-matched study.* Arch Surg, 2011. **146**(2): p. 149-55.
8. Fleischer, J., et al., *The decline in hip bone density after gastric bypass surgery is associated with extent of weight loss.* J Clin Endocrinol Metab, 2008. **93**(10): p. 3735-40.
9. Sinha, N., et al., *Increased PTH and 1.25(OH)(2)D Levels Associated With Increased Markers of Bone Turnover Following Bariatric Surgery.* Obesity (Silver Spring), 2011.
10. Higa, K., et al., *Laparoscopic Roux-en-Y gastric bypass: 10-year follow-up.* Surg Obes Relat Dis, 2010.

11. Gehrer, S., et al., *Fewer nutrient deficiencies after laparoscopic sleeve gastrectomy (LSG) than after laparoscopic Roux-Y-gastric bypass (LRYGB)-a prospective study.* Obes Surg, 2010. **20**(4): p. 447-53.

12. Riedt, C.S., et al., *Overweight postmenopausal women lose bone with moderate weight reduction and 1 g/day calcium intake.* J Bone Miner Res, 2005. **20**(3): p. 455-63.

13. Mezquita-Raya, P., et al., *Relation between vitamin D insufficiency, bone density, and bone metabolism in healthy postmenopausal women.* J Bone Miner Res, 2001. **16**(8): p. 1408-15.

14. Ricci, T.A., et al., *Moderate energy restriction increases bone resorption in obese postmenopausal women.* Am J Clin Nutr, 2001. **73**(2): p. 347-52.

15. Villareal, D.T., et al., *Effect of weight loss and exercise therapy on bone metabolism and mass in obese older adults: a one-year randomized controlled trial.* J Clin Endocrinol Metab, 2008. **93**(6): p. 2181-7.

16. Mahdy, T., et al., *Effect of Roux-en Y gastric bypass on bone metabolism in patients with morbid obesity: Mansoura experiences.* Obes Surg, 2008. **18**(12): p. 1526-31.

17. Vilarrasa, N., et al., *Evaluation of bone mineral density loss in morbidly obese women after gastric bypass: 3-year follow-up.* Obes Surg, 2011. **21**(4): p. 465-72.

18. Valderas, J.P., et al., *Increase of bone resorption and the parathyroid hormone in postmenopausal women in the long-term after Roux-en-Y gastric bypass.* Obes Surg, 2009. **19**(8): p. 1132-8.

19. *Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement.* Am J Clin Nutr, 1992. **55**(2 Suppl): p. 615S-619S.

20. Deitel, M. and R.J. Greenstein, *Recommendations for reporting weight loss.* Obes Surg, 2003. **13**(2): p. 159-60.

21. Baim, S., et al., *Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference.* J Clin Densitom, 2008. **11**(1): p. 75-91.

22. Matthews, D.R., et al., *Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man.* Diabetologia, 1985. **28**(7): p. 412-9.

23. Vilarrasa, N., et al., *Evaluation of bone disease in morbidly obese women after gastric bypass and risk factors implicated in bone loss.* Obes Surg, 2009. **19**(7): p. 860-6.

24. Tothill, P., *Dual-energy x-ray absorptiometry measurements of total-body bone mineral during weight change.* J Clin Densitom, 2005. **8**(1): p. 31-8.

25. Yoshimura, N., et al., *Biochemical markers of bone turnover as predictors of osteoporosis and osteoporotic fractures in men and women: 10-year follow-up of the Taiji cohort.* Mod Rheumatol, 2011.

26. Eastell, R., et al., *Biological variability of serum and urinary N-telopeptides of type I collagen in postmenopausal women.* J Bone Miner Res, 2000. **15**(3): p. 594-8.

27. Singhellakis, P.N., et al., *Vitamin D deficiency in white, apparently healthy, free-living adults in a temperate region.* Hormones (Athens), 2011. **10**(2): p. 131-43.

28. Flores, L., et al., *Calcium and vitamin D supplementation after gastric bypass should be individualized to improve or avoid hyperparathyroidism.* Obes Surg, 2010. **20**(6): p. 738-43.

29. Williams, S.E., *Metabolic bone disease in the bariatric surgery patient.* J Obes, 2011. **2011**: p. 634614.

30. Nogues, X., et al., *[Bone mass loss after sleeve gastrectomy: a prospective comparative study with gastric bypass]*. Cir Esp, 2010. **88**(2): p. 103-9.

31. Casagrande, D.S., et al., *Bone mineral density and nutritional profile in morbidly obese women.* Obes Surg, 2010. **20**(10): p. 1372-9.

32. Gemmel, K., et al., *Vitamin D deficiency in preoperative bariatric surgery patients.* Surg Obes Relat Dis, 2009. **5**(1): p. 54-9.

33. Lee, J.H., et al., *Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor?* J Am Coll Cardiol, 2008. **52**(24): p. 1949-56.

34. Saraiva, G.L., et al., *Influence of ultraviolet radiation on the production of 25 hydroxyvitamin D in the elderly population in the city of Sao Paulo (23 degrees 34'S), Brazil.* Osteoporos Int, 2005. **16**(12): p. 1649-54.

35. Silva, B.C., et al., *[Prevalence of vitamin D deficiency and its correlation with PTH, biochemical bone turnover markers and bone mineral density, among patients from ambulatories]*. Arq Bras Endocrinol Metabol, 2008. **52**(3): p. 482-8.

36. Wortsman, J., et al., *Decreased bioavailability of vitamin D in obesity.* Am J Clin Nutr, 2000. **72**(3): p. 690-3.

37. Aills, L., et al., *ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient.* Surg Obes Relat Dis, 2008. **4**(5 Suppl): p. S73-108.

38. Jackson, R.D., et al., *Calcium plus vitamin D supplementation and the risk of fractures.* N Engl J Med, 2006. **354**(7): p. 669-83.

39. Whitehead, C.C. and R.H. Fleming, *Osteoporosis in cage layers.* Poult Sci, 2000. **79**(7): p. 1033-41.

40. Duran de Campos, C., et al., *Calcium intake and metabolic bone disease after eight years of Roux-en-Y gastric bypass.* Obes Surg, 2008. **18**(4): p. 386-90.

41. Ott, M.T., et al., *Biochemical Evidence of Metabolic Bone Disease in Women Following Roux-Y Gastric Bypass for Morbid Obesity.* Obes Surg, 1992. **2**(4): p. 341-348.

42. Colossi, F.G., et al., *Need for multivitamin use in the postoperative period of gastric bypass.* Obes Surg, 2008. **18**(2): p. 187-91.

43. Karlsson, J., et al., *Psychosocial functioning in the obese before and after weight reduction: construct validity and responsiveness of the Obesity-related Problems scale.* Int J Obes Relat Metab Disord, 2003. **27**(5): p. 617-30.

44. Garb, J., et al., *Bariatric surgery for the treatment of morbid obesity: a meta-analysis of weight loss outcomes for laparoscopic adjustable gastric banding and laparoscopic gastric bypass.* Obes Surg, 2009. **19**(10): p. 1447-55.

Tables and Figure:

Table 1. Clinical and metabolic characteristics of the subjects studied. (n=22)

Characteristic	Preoperative	1-year follow-up	p-value
Weight (kg)	114.0 ± 12.8	70.7 ± 11.2	< 0.001
BMI (kg/m^2)	44.4 ± 5.0	27.5 ± 4.5	< 0.001
Waist circumference (cm)	122.7 ± 9.5	88.7 ± 9.0	< 0.001
Hip (cm)	133.4 ± 8.4	103.6 ± 8.3	< 0.001
Serum albumin (g/dL)	4.2 ± 0.3	4.1 ± 0.3	0.155
Fasting plasma glucose (mg/dL)	93.6 ± 8.8	78.1 ± 6.9	< 0.001
HOMA-IR	5.6 ± 2.9	1.3 ± 0.6	< 0.001

Results are expressed as mean ± SD. BMI: body-mass index; HOMA-IR: homeostasis model assessment insulin resistant. The value of P is the minimum level of significance of the paired *t*-test for the comparison between pre *vs.* post-operative Roux-en-Y gastric bypass.

Table 2. Nutritional composition of the diet (n=22)

Variable	Preoperative	1-year follow-up	p-value
Total energy value (kcal)	3,197 ± 1340	1,257 ± 290	< 0.001
Protein (g)	141.1 ± 48.7	68.1 ± 20.3	< 0.001
Protein (%)	18.7 ± 4.4	22.4 ± 6.8	< 0.050
Carbohydrate (g)	388.8 ± 178.8	140.6 ± 45.6	< 0.001
Carbohydrate (%)	48.2 ± 7.8	44.4 ± 7.5	0.160
Lipid (g)	119.7 ± 57.4	46.9 ± 18.0	< 0.001
Lipid (%)	33.1 ± 6.1	33.2 ± 8.6	0.962
Cholecalciferol (mcg)	1.9 (1.2-2.4)	2.1 (1.3-3.2)	0.871
Phosphorus (mg)	1717.0 ± 662.0	917.0 ± 255.0	< 0.001
Calcium (mg)	857.0 (608.0-1,471.0)	500.0 (402.0-656.0)	< 0.001

Results are expressed as mean ± SD or median (P 25-75). The value of P is the minimum level of significance of the paired *t*-test for the comparison between pre *vs.* post-operative Roux-en-Y gastric bypass.

Table 3. Characterization of the subjects studied according to their bone metabolism.

Variable	Preoperative	1-year follow-up	p-value
Serum calcium (mg/dL)	9.3 ± 0.5	9.20 ± 0.4	0.418
24-hour urinary calcium (mg/24 h)	167.0 (83.7-279.2)	156.0 (115.7-227.5)	0.395
25-OH-vitamin D (pg/dL)	11.7 (9.7-18.0)	15.7 (10.3-23.7)	0.327
Alkaline phosphatase (U/L)	96.7 ± 46.3	78.9 ± 24.7	0.113
PTH (pg/mL)	45.5 ± 16.8	62.7 ± 28.9	0.026
NTX-s (nM BCE)	16.4 ± 3.5	38.2 ± 7.1	< 0.001

Results are expressed as mean ± SD or median (P 25-75). iPTH: parathyroid hormone. NTX-s: serum collagen-type I N-telopeptide. nM BCE: nM bone collagen equivalents. BMD: bone mineral density. The value of P is the minimum level of significance of the paired *t*-test for the comparison between pre *vs.* post-operative Roux-en-Y gastric bypass.

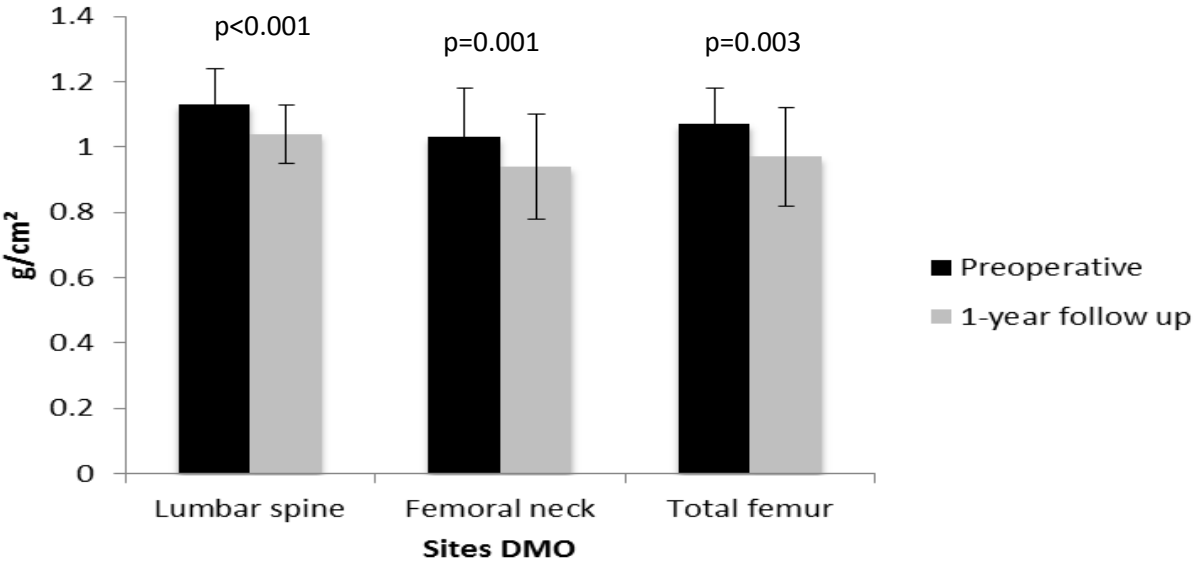


Figure 1: Comparison of the bone mineral density in the lumbar spine, femoral neck and total femur preoperative versus the 1-year follow up. The measurement of the bone mineral density (BMD) was performed by dual energy X-ray absorptiometry. The value of P is the minimum level of significance of the paired *t*-test for the comparison between pre *vs.* post-operative Roux-en-Y gastric bypass.

4.2 ARTIGO 2

INCIDENCE OF CANCER FOLLOWING BARIATRIC SURGERY: SYSTEMATIC REVIEW AND META-ANALYSIS

Daniela Schaan Casagrande, Daniela Dornelles Rosa, Daniel Umpierre, Roberta Aguiar Sarmento, Clarissa Garcia Rodrigues, Ricardo Pietrobon, Beatriz D. Schaan

Incidence of cancer following bariatric surgery: Systematic review and meta-analysis

Daniela Schaan Casagrande, MS, PhD [1,2,3]. Daniela Dornelles Rosa, MD, PhD [4]. Daniel Umpierre, PhD [5]. Roberta Aguiar Sarmento, MS [1]. Clarissa Garcia Rodrigues [3]. Ricardo Pietrobon, MD, PhD, MBA [3]. Beatriz D. Schaan, MD, PhD [1,5].

1. Postgraduate Program in Medical Sciences: Endocrinology and Metabolism, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.
2. Obesity and Metabolic Syndrome Center of Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (COM HSL-PUCRS), Porto Alegre, Brazil.
3. Research and Innovation Coaching Program, Department of Surgery, Duke University Medical Center, Durham, USA.

4. Oncology Unit, Hospital Moinhos de Vento, Porto Alegre, Brazil; Brazilian Breast Cancer Study Group (GBECAM).

5. Postgraduate Program in Health Sciences: Cardiovascular Sciences, Universidade Federal do Rio Grande do Sul, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.

Corresponding author and reprint request:

Beatriz D'Agord Schaan
Endocrine Division - Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos 2350, prédio 12, 4º andar - 90035-003 Porto Alegre, RS
e-mail: beatrizschaan@gmail.com
Phone/Fax: +55 (51) 3359-8127

Financial disclosure/funding support:

This work was supported by a grant from The Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES). The authors have no potential conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Abstract

We conducted a systematic review of observational studies to evaluate the association of bariatric surgery with the risk of cancer in postoperative patients. Data sources were Medline, Embase and Cochrane Library. From 951 references, 13 studies met the inclusion criteria (54,257 participants). We employed a meta-analysis to assess the risk of developing cancer following bariatric surgery by comparing the surgery groups *vs.* control groups of controlled studies and also described the incidence of cancer in the surgery groups within both controlled and uncontrolled studies. In controlled studies, bariatric surgery was associated with a reduction in the risk of cancer (OR 0.42; 95% confidence interval 0.24, 0.73; I^2=93.3%; P for heterogeneity <0.001). Cancer incidence density rate was 1.06 cases per 1000 person-years (95% confidence interval 0.64, 1.75; I^2=96.0%; P for heterogeneity < 0.001) within the surgery groups. The results of our sensitivity analysis of age and gender yield no differences. In the meta-regression, we found an inverse relationship between baseline body mass index and cancer incidence after the surgery (beta coefficient -0.233, P< 0.05). Bariatric surgery is associated with reduced cancer risk in severely obese individuals. However, considering the heterogeneity among the studies, conclusions should be drawn with care.

Keywords

Cancer, morbid obesity, bariatric surgery, gastric bypass, obesity

Introduction

Data from the National Health and Nutrition Examination Survey (NHANES) reviews that the prevalence of obesity in adults is increasing every year in the United States (1), as well as worldwide (2). Severe obesity shortens life expectancy, is a significant cause of morbidity, and mortality, and raises healthcare expenditures in North America (1). In addition, obesity and weight gain increase the risk for several diseases, including cancer (3), and can lead to poor treatment outcomes, and increased cancer-related mortality (4, 5). The association between obesity and cancer risk involves metabolic and endocrine effects of obesity that induce the production of peptide and steroid hormones (6).

The treatment of obesity includes lifestyle changes (nutritional education, behavioral counseling, physical activity), pharmacological agents and, in severe obesity, bariatric surgery (7, 8). Bariatric surgery has been shown to produce significant long-term weight loss (9) and reduction of mortality rates (10) for patients with severe obesity. Although obesity is clearly linked to the development of cancer, to the best of our knowledge, it remains unclear whether weight loss obtained through bariatric surgery influences cancer incidence. It is also unknown if a relationship exists between body mass index (BMI) before surgery and cancer risk in the postoperative period. Previous studies have suggested that there is a relationship between bariatric surgery and reduced cancer risk (11, 12). A retrospective study, authored by McCawley et al.(11), that analyzed 1482 women who underwent bariatric surgery found breast and endometrial cancers as the most common types of cancer in these women, and suggested that bariatric surgery may have decreased the development of cancer in this population. However, it is unknown whether the lower cancer rates following bariatric surgery were related to the metabolic changes associated with weight loss, or if lower BMIs following surgery would result in earlier diagnosis and improved cancer treatment outcomes (13).

Accordingly, in order to summarize the relationship between postoperative weight loss and its potential association with cancer, we conducted a systematic review with meta-analysis focused on the incidence of cancer in patients following bariatric surgery.

Methods

Protocol and Registration

This systematic review is reported in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (14).

Eligibility Criteria

Studies were selected if they included both a cancer diagnosis following bariatric surgery as well as the following eligibility criteria: patients ≥ 18 years of age who were measured with a BMI ≥ 35 kg/m^2. We tabulated all cancer cases as well as the adequacy of controls related to our eligibility criteria. Exclusion criteria for studies included patients who were diagnosed with cancer in the pre or perioperative periods.

Information Sources

We searched the following electronic databases covering their initial periods up to June 2013: MEDLINE (accessed by PubMed), EMBASE and Cochrane Central Register of Controlled Trials. We did not use limits for dates or language when conducting the search.

Search Strategy

We searched the terms abdominal fat / obesity, morbid / obesity / obesity, abdominal / adiposity / weight gain / intra-abdominal fat / overnutrition / bariatric surgery / bariatrics / gastroplasty / gastric balloon / gastric bypass / anastomosis, Roux-en-Y / biliopancreatic diversion / jejunoileal bypass / bariatric medicine / gastric banding / laparoscopic adjustable gastric banding / cancer and related terms. We used the search strategy that PubMed employed to create its cancer subset (see Appendix: Pubmed search strategy).

Study selection

Two reviewers (D.S.C. and R.A.S.) independently analyzed the titles and abstracts retrieved from the literature search. All articles that failed to meet the inclusion criteria were excluded. All selected articles were analyzed, and eligible articles were identified. Disagreements between reviewers were resolved by a third reviewer's opinion (B.D.S).

Data extraction and quality assessment

Two reviewers (D.S.C. and R.A.S.) independently extracted data from each study. Extracted data were: year of publication, authors, geographic location of the first author, study design, the type of bariatric procedure, sample size, participant characteristics, cancer incidence, type of cancer, post surgical analysis when cancer was diagnosed, incidence of diabetes, and deaths related to cancer. A third reviewer (B.D.S.) assessed all studies for completeness of criteria.

To avoid double counting patients who were included in multiple reports authored by the same individuals or working groups, patient recruitment periods were assessed and, if necessary, authors were contacted to provide clarity. Authors were also contacted to obtain important additional data that were omitted from their publications.

The Newcastle-Ottawa Scale was adapted for our study, and it was used independently by two reviewers (D.S.C. and R.A.S.) to assess the quality of the studies (15).

Data synthesis and analysis

A pooled odds ratio (OR) was calculated to assess the association between cancer and bariatric surgery in the controlled studies. The meta-analyses were carried out using the random effects model, because significant heterogeneity was found among the studies.

We also used the surgery group from the controlled and uncontrolled studies to estimate the incidence density rate of cancer following bariatric surgery. To estimate this incidence density rate, we multiplied the total sample size by the follow-up period to calculate the denominator. We made logit transformations to address the asymmetrical distribution. The logit model was weighted by the inverse of the logit's variance. Also, we explored heterogeneity between studies by removing each study from the analysis to check if any particular study drove heterogeneity. Moreover, predefined subgroup analyses were performed according to age (dichotomized in two groups, < 45.0 and > 45.1 years old), and gender (dichotomized in two groups, < 79.9 and > 80.0 % of women), to assess if these variables were potential sources of heterogeneity. Furthermore, meta-regression analyses were performed to investigate other potential sources of heterogeneity. The variables used in this analysis were BMI and the time frame for a follow up examination when cancer was diagnosed.

In meta-analyses, the Cochran χ^2 and the I^2 tests were used to evaluate heterogeneity among studies. A p value below 0.05 was considered significant in the Cochran test (16). In the I^2 test, values below 25% reflected low heterogeneity, values between 25% and 50% reflected moderate heterogeneity, and values exceeding 50% reflected high heterogeneity (17).

The statistical analyses were performed with Stata 11.0 software (Stata Corp, College Station, TX), and the second version of the Comprehensive Meta-analysis ^{TM} software for the incidence meta-analysis.

Results

Overall, 951 studies were initially identified, from which 49 duplicates were excluded. After initial title and abstract screening, 774 citations were excluded, leaving 128 articles for retrieval. Full text assessment of these articles resulted in 20 eligible studies (9, 13, 18-31). In cases where results for the same population were reported more than once, we selected the most recent results, thus excluding seven additional articles (9, 13, 24, 26, 31-33). Among the retrieved studies, there were no randomized clinical trials. The remaining 13 articles, published between 1997 and 2011, were separated in two groups: (i) controlled studies (11, 12, 18, 19) and (ii) uncontrolled studies (20-23, 25, 27-30). Three uncontrolled studies were excluded from the meta-analysis (20, 28, 30) because these articles reported deaths caused by cancer, not providing incident cancer. The agreement between reviewers was estimated by the Kappa coefficient (Kappa = 0.835). A flowchart of study search and selection is shown in figure 1.

Studies' characteristics

Table 1 shows the characteristics of the four selected controlled studies, which included 11,087 patients who underwent bariatric surgery (surgery group) and 20,720 patients who did not undergo surgery (control group). Two studies were carried out in the United States (11, 18), one in Canada (19) and one in Sweden (12). The percentage of cancer related mortality was reported in one study (18), being 0.62% in the surgery group and 1.13% in the control group.

Table 2 shows the characteristics of 9 selected uncontrolled studies, which included 22,450 individuals in the surgery group. Five studies were carried out in the United States (22, 23, 27, 29, 30), two in Sweden (21, 25), one in Australia (20), and one in Switzerland (28). The percentage of cancer related mortality ranged from 0.26% to 2.65% in four studies (20, 22, 28, 30), and five studies did not report death (21, 23, 25, 27, 29).

Association between cancer risk and bariatric surgery

Controlled studies showed that bariatric surgery was associated with a reduction in the risk of cancer (figure 2; OR 0.42; 95% confidence interval [CI] 0.24, 0.73; I^2=93.3%; P for heterogeneity <0.001). In an exploratory attempt to identify the sources of heterogeneity among these studies, we removed one study (11) which was performed solely with women, though the results of this study were not different (OR 0.53; confidence interval [CI] 0.32, 0.88; I^2=91.5%;

P for heterogeneity=0.014). When we removed another study (19), in which the control group was taken from a hospital population, no heterogeneity was observed and the association between bariatric surgery and low cancer risk was maintained (OR 0.74; confidence interval [CI] 0.65, 0.85; I^2=0%; P for heterogeneity<0.512).The strategy above displays the high heterogeneity of the primary meta-analysis. After removing each study that eliminated heterogeneity, there was no need to perform sensitivity analysis or meta-regression in the controlled studies.

The cancer incidence density rate was 1.06 cases per 1000 persons-year (confidence interval [CI] 0.64, 1.75 cases per 1000 persons-year; I^2=96.0%; P for heterogeneity < 0.001) measured across 9 studies, utilizing the surgery groups from the controlled and uncontrolled studies (Figure 3). We know that this estimate is low, as the years subsequent to the follow-up period for cancer patients should be omitted from the denominator. Therefore, the real denominator should be lower than the value we used. To assess the impact of this on our results, we assumed that the cancer patients did not contribute to the denominator (the denominator was calculated by subtracting the number of cancer cases from the total number of patients, and then multiplying this difference by the average follow-up period, implying that cancers were diagnosed at follow-up times equal to zero). Using this denominator, the cancer incidence density was 1.08 cases per 1,000 persons-year (confidence interval [CI] 0.65, 1.80 cases per 1000 persons-year), and this implies that the real value of incidence is between 1.06 and 1.08 persons-year. We excluded one study (11) in the meta-analysis that did not report data over the follow up.

No reduction in heterogeneity was observed upon removing each study. Sensitivity analyses were carried out to explore the heterogeneity. The results did not change when analyzed by age or gender in either the surgery groups of both the controlled and uncontrolled studies. Since these analyses resulted in no change in heterogeneity, they were omitted. In an additional attempt to identify sources of heterogeneity across the studies, we performed a meta-regression analysis using BMI and the time period to cancer diagnosis as covariates for the surgery group from both the controlled and uncontrolled studies. We found no difference in the results of meta-regression that used time to cancer diagnosis as a covariate. However, in the meta-regression

using the BMI as a covariate, we found a decrease in cancer incidence as BMI increased (beta coefficient -0.233, $P < 0.05$).

Quality assessment

Although we achieved a reasonable degree of quality through the inclusion/exclusion criteria, there was some variation between the quality assessments (15). Based on a sample selection, three studies received four-star ratings (11, 12, 19), four studies received three-star ratings (18, 22, 23, 27), three studies received two-star ratings (25, 28, 29) and three studies received one-star ratings (20, 21, 30). In terms of comparability, three studies received two-star ratings (12, 18, 19), one study received a one-star rating (11), and 9 uncontrolled studies received no stars. This variation was due to differences in accounting for confounding factors. For the quality of studies' assessment, six studies received two-star ratings (20, 22, 23, 27, 29, 30), and seven studies received three-star ratings (11, 12, 18, 19, 21, 25, 28). In total, four studies received high quality ratings of seven to nine stars (11, 12, 18, 19), five studies received medium quality rates of five to six stars (22, 23, 25, 27, 28), and four studies received low quality ratings of four stars or below (20, 21, 29, 30) (Table 3).

Discussion

This systematic review demonstrates that in severely obese patients bariatric surgery is associated with a reduction in the incidence of cancer. Importantly, this effect of bariatric surgery was found within both controlled and uncontrolled studies. Of the 13 studies included in our analyses, four controlled studies showed a significant reduction in the risk of cancer, with ORs ranging from 0.12 to 0.88. Data from the surgery group from controlled and uncontrolled studies displayed a cancer incidence density rate of 1.06 cases per 1000 person-years in a follow up period of 2 to 23 years.

Cancer rates in obese people are generally higher, as displayed in a study (34) of an Austrian population (5.43 cases per 1000 person-years) and in a study (35) of a Swedish population (5.8 cases per 1000 person-years), as well as in a systematic review and meta-analysis (36) of data from a global population (2.12 cases per 1000 person-years). Therefore, the cancer incidence density rate of 1.06 cases per 1000 person-years obtained in the present meta-analysis

displays that severely obese individuals undergoing bariatric surgery may reduce their risk for cancer, with incidence density rates similar to those found in non-obese people (36).

Reducing weight likely reduces high cancer rates associated with obesity (37, 38), but the method employed to achieve target weight can change this perspective. For example, trials that used specific pharmacological interventions (39, 40) achieved weight reduction, but mortality/cardiovascular outcomes were increased, revealing the need for treatments that obtain both goals: weight loss and lower mortality rates. Moreover, no cancer incidence reduction was showed in population-wide weight reduction induced by imposed dietary restrictions in non-severely obese people (41).

Data from three cohorts showed that intentional (non-surgical) weight loss is associated with lower cancer rates (38), but it is likely that multiple methods were used to achieve targeted weight loss in this study, so it is difficult to draw precise conclusions about the most efficacious non-surgical method. Our results show that reducing body weight through bariatric surgery is associated with reduced cancer rates, though we could not found mortality data specifically linked to cancer. This is supported by Birks' meta-analysis of studies that showed an association between lower cancer rates and people who intentionally lost weight through bariatric surgery (38). Moreover, when examining the relationship between bariatric surgery and cancer rates, it is challenging to separate the effects of the surgery from the multiple associated changes it yields.

It is important to consider that bariatric surgery is more frequently performed on young subjects (42), while cancer is more frequently observed in aged people (43). Moreover, the long lead-time for the appearance of cancer cases is too long to expect sufficient numbers of studies to be available at present. However, obesity is a risk factor for cancer development, and it likely precedes the diagnosis of several cases (34). Performing a surgical procedure of the magnitude of bariatric surgery raises the awareness and possible diagnosis of cancer among these patients (12)

It remains unknown whether metabolic changes related to weight loss result in lower rates of cancer development. It is also unknown if a lower BMI simply allows for better assessment and treatment, or if it actually related to lower cancer incidence. These data are supported by well-known pathophysiological disturbances of obesity, such as chronic inflammation (44) and hormonal changes (6). Pro-inflammatory cytokines act on tissues and

cells, resulting in cancer development through direct and indirect effects on innate and adaptive immune cells, imbalances in tissue homeostasis and increased oxidative stress (45). People with obesity have increased estrogen levels, due to the conversion of circulating androgens by increased aromatase activity in peripheral adipocytes; increased adrenal and ovarian secretion of hormones, and decreased progesterone production due to decreased ovulation (6). In addition, increased insulin levels cause the inhibition of sex hormone-binding globulin synthesis by the liver, increasing free steroid hormone levels. Overall, the increased unopposed estrogen can promote cancer in hormonally responsive tissues (6, 46). Therefore, there is an established mechanistic association between inflammation and hormonal imbalance brought on obesity and cancer (47). Reversal of these inflammatory and hormonal disturbances can be expected with the weight loss from bariatric surgery, as decreases in both oxidative stress and systemic inflammatory markers were reported (48), and there is consistent evidence that the incidence of cancer is reduced (38, 49). Beyond obesity risk, the excess of visceral adiposity, type 2 diabetes, insulin resistance, chronic inflammation and metabolic syndrome are all associated with cancer, independent of body size (50).

A strength of our systematic review is its inclusion of uncontrolled studies, adding information to the research provided by Birks et al (38). Traditionally, controlled studies are viewed as providing higher quality evidence than uncontrolled studies. However, the controls for bariatric patients are likely imperfect, as it is difficult to find appropriate matches of their clinical conditions. Thus, patients undergoing bariatric surgery may comprise a medically fitter population as compared to those who did not undergo surgery.

A variety of strategies explored the high heterogeneity levels observed in our meta-analyses, investigating potential sources of variation among the studies. In the controlled studies, heterogeneity was accounted for by removing the McCawley et al. (11) study, which excluded men, and also by removing of the Christou et al. (19) study, which used a hospital population as its control group. Upon removing these two studies from the meta-analysis, no heterogeneity was observed (I^2=0%). Although the specific population characteristics of these studies accounted for high heterogeneity, these two studies were strictly inside the previously determined inclusion criteria, and thus they were included in the primary meta-analysis.

In the surgery group from the controlled and uncontrolled studies, we observed no reduction in heterogeneity upon removing each study or in performing sensitivity analysis. Further, the meta-regression analysis showed a decrease in cancer incidence when high baseline BMI values were present. This is in accordance to the results of Renehan et al. (36), as their meta-analysis displayed an increased risk of cancer with increased BMI. We would anticipate a larger magnitude of intervention effects in populations with higher baseline derangements (51, 52). Finally, the high levels of heterogeneity observed may be due to different study designs, differences in the populations studied, or differences in a variety of other characteristics (e.g., genetic background, varied bariatric procedures) across studies. Indeed, it is likely that one or more of these factors that were beyond our control account for a portion of the heterogeneity observed among studies.

Limitations

Limitations are present in this study. In the absence of randomized controlled trials, we dealt with distinct data that expressed cancer incidence and death registries. As is inherent in observational studies, data from registries can be biased, so the information compiled in this meta-analysis may also have a bias. Therefore, our derived estimates may potentially influence our results. Although such bias would impact both surgical and non-surgical samples, the control groups were carefully selected in two studies (12, 18). Due to observational designs, the surgery group may have been healthier than the patients who were not offered surgery and were used as controls. In addition, the generalization of our findings is somewhat hampered by the geographical origin of our included studies, as they were primarily performed in the United States and Europe.

Among the limitations of the literature in bariatric surgery and cancer, we could not explore the potential effects of different bariatric procedures, which promote distinct action mechanisms on various target populations. Likewise, we were unable to obtain BMI and weight data at cancer diagnosis in the studies included in our review. Risk factors for cancer such as family history, smoking, gender, physical inactivity, alcoholism and malnutrition were also unavailable. In conjunction with the surgery outcomes, we underscore that pre and post-surgery dietary patterns could contribute to our analyses. Moreover, the number of cancer cases were too low to allow analyses by organ or type, especially those cancers related to obesity and smoking.

Finally, the follow-up after bariatric surgery is often poor and that patients may not disclose a cancer diagnosis during follow-up.

Conclusion

Bariatric surgery is associated with reduced cancer risk in morbidly obese people. Considering the heterogeneity among the studies and the other limitations cited above, conclusions should be drawn with care. We suggest that variables associated with cancer be measured in prospective bariatric surgery trials, and that cancer rates are assessed as a primary outcome

Acknowledgments:

This study was supported by grant from The Brazilian Federal Agency for Support and Evaluation of Graduate Education. We thank Dr. Lars Sjostrom, who provided complementary data of his study. We also thank Dr. Rodrigo Ribeiro, who helped in our statistical analyses, and Stephen Anderson, who helped with our English review.

Financial disclosure/funding support:

This work was supported by a grant from The Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES). The authors have no potential conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Supplementary information is available at the journal's website.

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA : the journal of the American Medical Association. 2010;303(3):235-41. Epub 2010/01/15.

2. Rokholm B, Baker JL, Sorensen TI. The levelling off of the obesity epidemic since the year 1999--a review of evidence and perspectives. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2010;11(12):835-46. Epub 2010/10/27.

3. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JFJ. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control. 2006;17(7):901-9.

4. Parekh N, Chandran U, Bandera EV. Obesity in cancer survival. Annual review of nutrition. 2012;32:311-42. Epub 2012/05/01.

5. Kaidar-Person O, Bar-Sela G, Person B. The two major epidemics of the twenty-first century: obesity and cancer. Obesity surgery. 2011;21(11):1792-7. Epub 2011/08/16.

6. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4(8):579-91.

7. Eckel RH. Clinical practice. Nonsurgical management of obesity in adults. N Engl J Med. 2008;358(18):1941-50.

8. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database Syst Rev. 2009(2):CD003641.

9. Christou NV, Sampalis JS, Liberman M, Look D, Auger S, McLean AP, et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. Annals of surgery. 2004;240(3):416-23; discussion 23-4. Epub 2004/08/21.

10. Sjostrom L. Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. International journal of obesity (2005). 2008;32 Suppl 7:S93-7. Epub 2009/01/16.

11. McCawley GM, Ferriss JS, Geffel D, Northup CJ, Modesitt SC. Cancer in obese women: potential protective impact of bariatric surgery. Journal of the American College of Surgeons. 2009;208(6):1093-8. Epub 2009/05/30.

12. Sjostrom L, Gummesson A, Sjostrom CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. The lancet oncology. 2009;10(7):653-62. Epub 2009/06/27.

13. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. The New England journal of medicine. 2007;357(8):753-61. Epub 2007/08/24.

14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA : the journal of the American Medical Association. 2000;283(15):2008-12. Epub 2000/05/02.

15. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp[cited 2013 Feb 05] [updated 02/05/2013; cited 2013 Feb 05, 2013]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. Epub 2003/09/06.

18. Adams TD, Stroup AM, Gress RE, Adams KF, Calle EE, Smith SC, et al. Cancer incidence and mortality after gastric bypass surgery. Obesity. 2009;17(4):796-802.

19. Christou NV, Lieberman M, Sampalis F, Sampalis JS. Bariatric surgery reduces cancer risk in morbidly obese patients. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2008;4(6):691-5. Epub 2008/11/26.

20. Clough A, Layani L, Shah A, Wheatley L, Taylor C. Laparoscopic gastric banding in over 60s. Obesity surgery. 2011;21(1):10-7. Epub 2010/05/22.

21. Forsell P, Hellers G. The Swedish Adjustable Gastric Banding (SAGB) for morbid obesity: 9 year experience and a 4-year follow-up of patients operated with a new adjustable band. Obesity surgery. 1997;7(4):345-51. Epub 1997/08/01.

22. Gagne DJ, Papasavas PK, Maalouf M, Urbandt JE, Caushaj PF. Obesity surgery and malignancy: our experience after 1500 cases. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2009;5(2):160-4. Epub 2008/10/14.

23. Gusenoff JA, Koltz PF, O'Malley WJ, Messing S, Chen R, Langstein HN. Breast cancer and bariatric surgery: temporal relationships of diagnosis, treatment, and reconstruction. Plastic and reconstructive surgery. 2009;124(4):1025-32. Epub 2009/11/26.

24. Marsk R, Freedman J, Tynelius P, Rasmussen F, Naslund E. Antiobesity surgery in Sweden from 1980 to 2005: a population-based study with a focus on mortality. Annals of surgery. 2008;248(5):777-81. Epub 2008/10/25.

25. Ostlund MP, Lu Y, Lagergren J. Risk of obesity-related cancer after obesity surgery in a population-based cohort study. Annals of surgery. 2010;252(6):972-6. Epub 2010/06/24.

26. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. The New England journal of medicine. 2007;357(8):741-52. Epub 2007/08/24.

27. Srikanth MS, Fox SR, Oh KH, Ward K, Sun H, Keskey T, et al. Renal cell carcinoma following bariatric surgery. Obesity surgery. 2005;15(8):1165-70. Epub 2005/10/04.

28. Steffen R, Potoczna N, Bieri N, Horber FF. Successful multi-intervention treatment of severe obesity: a 7-year prospective study with 96% follow-up. Obes Surg. 2009;19(1):3-12. Epub 2008/09/17.

29. Sugerman HJ, Sugerman EL, Wolfe L, Kellum JM, Jr., Schweitzer MA, DeMaria EJ. Risks and benefits of gastric bypass in morbidly obese patients with severe venous stasis disease. Annals of surgery. 2001;234(1):41-6. Epub 2001/07/20.

30. Sultan S, Gupta D, Parikh M, Youn H, Kurian M, Fielding G, et al. Five-year outcomes of patients with type 2 diabetes who underwent laparoscopic adjustable gastric banding. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2010;6(4):373-6. Epub 2010/07/16.

31. Neovius M, Narbro K, Keating C, Peltonen M, Sjoholm K, Agren G, et al. Health care use during 20 years following bariatric surgery. JAMA : the journal of the American Medical Association. 2012;308(11):1132-41. Epub 2012/09/20.

32. Burza MA, Pirazzi C, Maglio C, Sjoholm K, Mancina RM, Svensson PA, et al. PNPLA3 I148M (rs738409) genetic variant is associated with hepatocellular carcinoma in obese individuals. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2012;44(12):1037-41. Epub 2012/06/19.

33. Maglio C, Ericson U, Burza MA, Mancina RM, Pirazzi C, Assarsson JA, et al. The IRS1 rs2943641 variant and risk of future cancer among morbidly obese individuals. The Journal of clinical endocrinology and metabolism. 2013;98(4):E785-9. Epub 2013/02/19.

34. Rapp K, Schroeder J, Klenk J, Stoehr S, Ulmer H, Concin H, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer. 2005;93(9):1062-7. Epub 2005/10/20.

35. Lukanova A, Bjor O, Kaaks R, Lenner P, Lindahl B, Hallmans G, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. International journal of cancer Journal international du cancer. 2006;118(2):458-66. Epub 2005/07/29.

36. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-78. Epub 2008/02/19.

37. Byers T, Sedjo RL. Does intentional weight loss reduce cancer risk? Diabetes, obesity & metabolism. 2011;13(12):1063-72. Epub 2011/07/08.

38. Birks S, Peeters A, Backholer K, O'Brien P, Brown W. A systematic review of the impact of weight loss on cancer incidence and mortality. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2012;13(10):868-91. Epub 2012/06/08.

39. Topol EJ, Bousser MG, Fox KA, Creager MA, Despres JP, Easton JD, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet. 2010;376(9740):517-23. Epub 2010/08/17.

40. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. The New England journal of medicine. 2010;363(10):905-17. Epub 2010/09/08.

41. Franco M, Bilal U, Ordunez P, Benet M, Morejon A, Caballero B, et al. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends. BMJ. 2013;346:f1515. Epub 2013/04/11.

42. DeMaria EJ, Pate V, Warthen M, Winegar DA. Baseline data from American Society for Metabolic and Bariatric Surgery-designated Bariatric Surgery Centers of Excellence using the Bariatric Outcomes Longitudinal Database. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2010;6(4):347-55. Epub 2010/02/24.

43. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA: a cancer journal for clinicians. 2010;60(5):277-300. Epub 2010/07/09.

44. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. European cytokine network. 2006;17(1):4-12. Epub 2006/04/15.

45. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nature reviews Cancer. 2006;6(1):24-37. Epub 2006/01/07.

46. Modesitt SC, Huang B, Shelton BJ, Wyatt S. Endometrial cancer in Kentucky: the impact of age, smoking status, and rural residence. Gynecologic oncology. 2006;103(1):300-6. Epub 2006/04/25.

47. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7. Epub 2002/12/20.

48. Ashrafian H, Ahmed K, Rowland SP, Patel VM, Gooderham NJ, Holmes E, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. Cancer. 2011;117(9):1788-99. Epub 2011/04/22.

49. Parker ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2003;27(12):1447-52. Epub 2003/11/25.

50. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes care. 2012;35(11):2402-11. Epub 2012/10/25.

51. DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. Diabetic medicine : a journal of the British Diabetic Association. 2010;27(3):309-17. Epub 2010/06/12.

52. Unick JL, Beavers D, Jakicic JM, Kitabchi AE, Knowler WC, Wadden TA, et al. Effectiveness of lifestyle interventions for individuals with severe obesity and type 2 diabetes: results from the Look AHEAD trial. Diabetes Care. 2011;34(10):2152-7. Epub 2011/08/13.

Table 1 - Characteristics of cancer incidence related to bariatric surgery in the controlled studies

				Surgery group								Control Group							
Study	Bariatric Procedure	Total Follow-up (months)	Surgery follow-up when cancer was diagnosed (months)	no.	Age (years)	BMI (Kg/m^2)	Women (%)	no. cancer	% DM	Cancer type	Cancer death	no.	Age (years)	BMI (Kg/m^2)	Women (%)	no. cancer	% DM	Cancer type	Cancer death
Adams 2009 [18]	RYGB	276	147.6	6596	38.9 (10.3)	44.9 (7.6)	86.0	254	NA	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28	41	9442	39.1 (10.7)	47.4 (6.5)	83	477	NA	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28	107
Christou 2008 [19]	RYGB / VBG	197	NA	1035	45.1 (11.6)	> 40.0	65.6	21	NA	5, 8, 12, 14, 17, 21, 24, 25	NA	5746	46.7 (13.1)	> 40.0	64	487	NA	NA	NA
McCawley 2009 [11]	RYGB / AGB / VBG	NA	50.4	1446	41.7 (18-69)[a]	> 40.0	100.0	17	22.5	1, 5, 12, 13, 14, 16, 17, 30	NA	3495	46.9	> 40.0	100	203	NA	NA	NA
Sjostrom 2009 [12]	RYGB / AGB / VBG	130	NA	2010	47.2 (5.9)	41.7[b]	70.6	117	7.4	3,5,6,8,9,12, 14,15,16,17, 19,20,21,28, 29	NA	2037	48.7 (6.3)	40.9[b]	71	169	6.1	3,5,6,8,9,12, 14,15,16,17, 19,20,21,28, 29	NA

Results are expressed as mean ± SD or median (P 25–75); NA – data is not available; no. – number of participants; no. cancer - number of participants with cancer; % Women – percentage of women; %DM – percentage of participants with diabetes mellitus; RYGB – Roux-en-Y gastric bypass; VBG - vertical banded gastroplasty; AGB – adjustable gastric banding

[a] mean (min-max)

[b] weighted mean

Cancer type: 1.Head and neck cancer (oral cavity, pharynx, larynx); 2.Esophagus; 3.Stomach; 4.Small intestine; 5.Colorectal; 6.Liver; 7.Galbladder; 8.Pancreas; 9.Trachea, lung and bronchus; 10.Soft tissue (sarcomas); 11.Heart; 12.Melanoma; 13.Skin non-melanoma; 14.Breast; 15.Cervix; 16.Ovary; 17.Endometrial (uterine corpus); 18.Vulva and vagina; 19.Prostate; 20.Urinary Bladder; 21.Kidney and pelvis; 22.Brain; 23.Thyroid; 24.Lymphoma; 25.Myeloma; 26,Leucemia; 27.Throphoblastic disease; 28.Other; 29. Hematopoietic; 30. Unknown Primary; 31. Obesity related and all cancer; 32. Carcinoma

Table 2 - Characteristics of cancer incidence related to bariatric surgery in the uncontrolled studies

	Surgery group										
Study	Bariatric Procedure	Total Follow-up (months)	Surgery follow-up when cancer was diagnosed (months)	no.	Age (years)	BMI (Kg/m^2)	Women (%)	no. cancer	% DM	Cancer type	Cancer death
Clough 2011[20]	RYGB	25.5	NA	113	63.6 (60-73)[a]	42.2 (NA)	56.6	NA	36.4	NA	3
Forsell & Hellers 1997 [21]	AGB	48.0	24	50	41 (19-60)[a]	46.0 (33-59)[a]	70.0	1	NA	22	NA
Gagne 2009 [22]	RYGB / Laparoscopic conversion of VBG to RYGB	102.0	26	1524	NA	NA	NA	16	NA	4, 5, 8, 12, 14, 17, 20, 21, 22, 24, 26	4
Gusenoff 2009 [23]	NA	180.0	NA	2878	NA	NA	NA	13	NA	14	NA
Ostlund 2010 [25]	RYGB / AGB / VBG	108.0	1 ≥ 120	13123	NA	NA	77.0	296	NA	31	NA
Srikanth 2005 [27]	RYGB / AGB / VBG	132.0	27	2287	43.4 (29-52)[a]	49.4 (43-60)[a]	NA	5	NA	21	NA
Steffen 2009 [28]	RYGB / AGB	84.0	NA	404	42.7(10)	42.6 (4)	77.0	NA	14.2	32	2
Sugerman 2001[29]	RYGB	216.0	36 and 156	1976	44.0 (10)	61.0 (12)	83.4	2	14.7	5, 24	NA
Sultan 2010 [30]	RYGB	60.0	NA	95	49.3 (21-68)[a]	46.3 (7)	52.0	NA	100.0	NA	2

Results are expressed as mean ± SD or median (P 25–75); NA – data is not available; no. – number of participants; no. cancer - number of participants with cancer; %DM – percentage of participants with diabetes mellitus; VBG - vertical banded gastroplasty; AGB – adjustable gastric banding; JIB – bypass jejuno-ileal; RP - restrictive procedures;
[a] mean (min-max)

Cancer type: 1.Head and neck cancer (oral cavity, pharynx, larynx); 2.Esophagus; 3.Stomach; 4.Small intestine; 5.Colorectal; 6.Liver; 7.Galbladder; 8.Pancreas; 9.Trachea, lung and bronchus; 10.Soft tissue (sarcomas); 11.Heart; 12.Melanoma; 13.Skin non-melanoma; 14.Breast; 15.Cervix; 16.Ovary; 17.Endometrial (uterine corpus); 18.Vulva and vagina; 19.Prostate; 20.Urinary Bladder; 21.Kidney and pelvis; 22.Brain; 23.Thyroid; 24.Lymphoma; 25.Myeloma; 26,Leucemia; 27.Throphoblastic disease; 28.Other; 29. Hematopoietic; 30. Unknown Primary; 31. Obesity related and all cancer; 32. Carcinoma

Table 3– Quality assessment of the studies

	Newcastle – Ottawa Scale			
Study (setting)	**Selection (max. 4*)**	**Comparability (max. 2*)**	**Assessment (max. 3*)**	**Total stars**
Adams 2009 [18]	***	**	***	**8**
Christou 2008 [19]	****	**	***	**9**
McCawley 2009 [11]	****	*	***	**8**
Sjostrom 2009 [12]	****	**	***	**9**
Clough 2011[20]	*	-	**	**3**
Forsell & Hellers 1997 [21]	*	-	***	**4**
Gagne 2009 [22]	***	-	**	**5**
Gusenoff 2009 [23]	***	-	**	**5**
Ostlund 2010 [25]	**	-	***	**5**
Srikanth 2005 [27]	***	-	**	**5**
Steffen 2009 [28]	**	-	***	**5**
Sugerman 2001 [29]	**	-	**	**4**
Sultan 2010 [30]	*	-	**	**3**

Stars (*) were awarded for selection, comparability and assessment according to adapt to Newcastle-Otawa criteria (15)

Figure1. Flowchart shows a literature search for studies attempting to identify an association of cancer with bariatric surgery

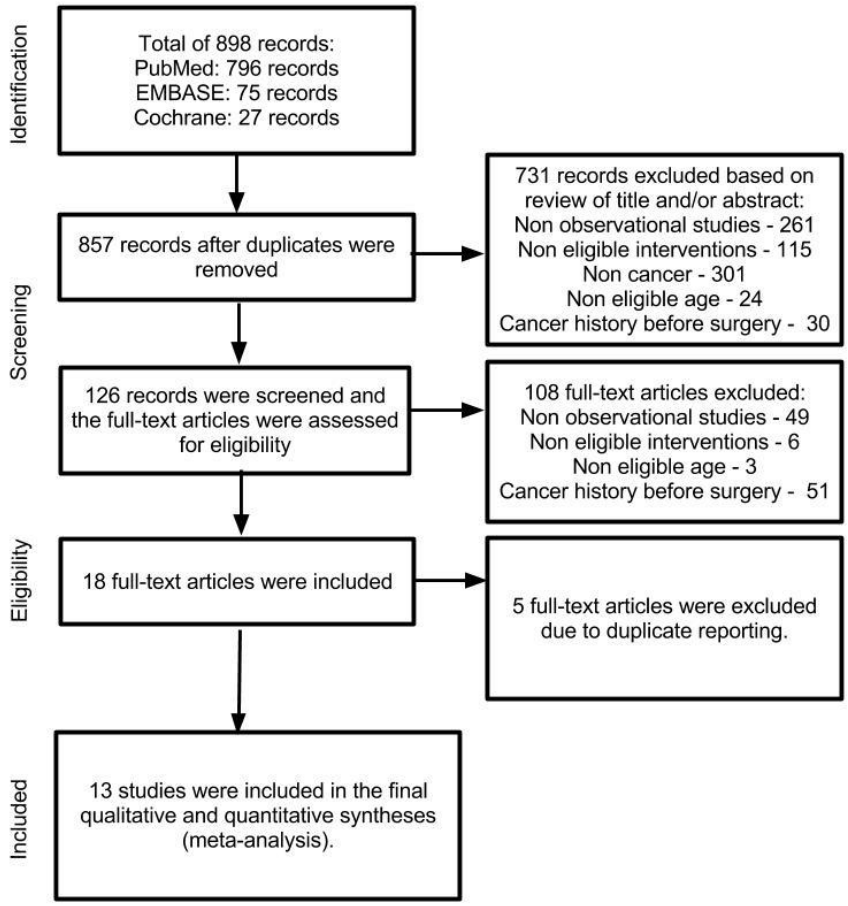


Figure 2. Association between cancer risk and bariatric surgery in controlled studies

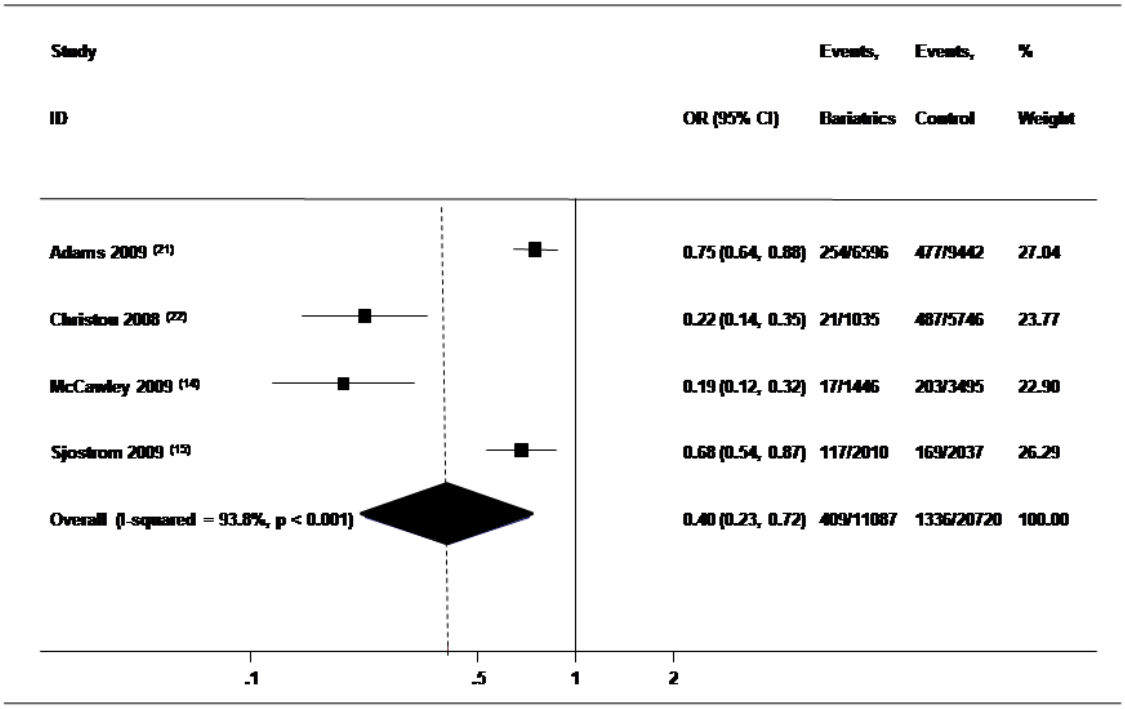
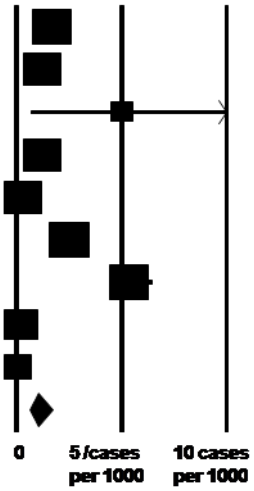


Figure 3. Studies displaying the incidence density rate of cancer following bariatric surgery

Study name	Statistics for each study			Event rate and 95% CI
	Event rate	Lower limit	Upper limit	
Adams 2009 [21]	1,67	1,48	1,89	
Christou 2008 [22]	1,24	0,81	1,89	
Forsell & Hellers 1997 [24]	5,00	0,70	34,61	
Gagne 2009 [25]	1,24	0,76	2,02	
Gusenoff 2009 [26]	0,30	0,17	0,52	
Ostlund 2010 [28]	2,51	2,24	2,81	
Sjostrom 2009 [15]	5,37	4,48	6,44	
Srikanth 2005 [30]	0,20	0,08	0,48	
Sugerman 2001 [32]	0,06	0,01	0,22	
	1,06	0,64	1,75	



Appendix: PubMed search strategy

(("Abdominal Fat"[Mesh] OR "Abdominal Obesities"[tw] OR "Abdominal Obesity"[tw] OR "Central Obesity"[tw] OR "Obesity, Central"[tw] OR "Obesity, Morbid"[Mesh] OR "Morbid Obesities"[TW] OR "Obesities, Morbid"[TW] OR "Morbid Obesity"[TW]) OR ("Obesity"[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Adiposity"[Mesh] OR "Weigh Gain"[Mesh] OR "Intra-Abdominal Fat"[Mesh] OR "Overnutrition"[Mesh])) AND cancer [sb] AND (("Bariatric Surgeries"[tw] OR "Bariatric surgery"[MeSH Terms] OR "Bariatrics"[MeSH Terms] OR Gastroplasties[tw] OR "Vertical-Banded Gastroplasty"[tw] OR "Vertical Banded Gastroplasty"[tw] OR "Vertical-Banded Gastroplasties"[tw] OR "Gastroplasty"[MeSH Terms] OR "Gastric balloon"[MeSH Terms] OR "Gastric Balloons"[tw] OR "Gastric Bubble"[tw] OR "Gastric Bubbles"[tw] OR "Garren-Edwards Gastric Bubble"[tw] OR "Garren Edwards Gastric Bubble"[tw] OR "Ballobes Balloon"[tw] OR "Gastric Bypass"[MeSH Terms] OR "Bypass, Gastric"[tw] OR "Roux-en-Y Gastric Bypass"[tw] OR "Gastric Bypass, Roux-en-Y"[tw] OR "Roux en Y Gastric Bypass"[tw] OR "Greenville Gastric Bypass"[tw] OR "Gastroileal Bypass"[tw] OR "Gastrojejunostomy"[tw] OR "Gastrojejunostomies"[tw] OR "Anastomosis, Roux-en-Y"[MeSH Terms] OR "Anastomosis, Roux en Y"[tw] OR "Roux-en-Y Loop"[tw] OR "Roux en Y Loop"[tw] OR "Roux-en-Y Loops"[tw] OR "Roux-en-Y Anastomosis"[tw] OR "Roux en Y Anastomosis"[tw] OR "Roux-en-Y Anastomoses"[tw] OR "Roux-en-Y Diversion"[tw] OR "Roux en Y Diversion"[tw] OR "Roux-en-Y Diversions"[tw] OR "Biliopancreatic Diversion"[MeSH Terms] OR "Biliopancreatic Diversions"[tw] OR "Biliopancreatic Bypass"[tw] OR "Bilio-Pancreatic Bypass"[tw] OR "Bilio Pancreatic Bypass"[tw] OR "Bilio-Pancreatic Diversion"[tw] OR "Bilio Pancreatic Diversion"[tw] OR "Jejunoileal Bypass"[MeSH Terms] OR "Bypass, Jejunoileal"[tw] OR "Jejunoileal Bypasses"[tw] OR "Jejuno-Ileal Bypass"[tw] OR "Jejuno Ileal Bypass"[tw] OR "Jejuno-Ileal Bypasses"[tw] OR "Ileojejunal Bypass"[tw] OR "Intestinal Bypass"[tw] OR "Intestinal Bypasses"[tw] OR "duodenal switch"[tw] OR Bariatric Medicine[Mesh] OR bariatrics)

5 CONSIDERAÇÕES FINAIS

Nesta tese foi demonstrado que a cirurgia bariátrica tem como efeito colateral a perda de massa óssea no primeiro ano de pós-operatório. Por outro lado, indivíduos que se submeteram à cirurgia bariátrica tiveram menor incidência de câncer no pós-operatório, mostrando ser esse procedimento cirúrgico um fator de proteção contra o câncer.

Cumpre ressaltar que, no estudo do metabolismo ósseo, consideramos somente o primeiro ano de cirurgia, durante o qual a perda de peso é mais acelerada, com aumento de marcadores de remodelação óssea e consequente perda de massa óssea. Entretanto, não estudamos a perda de massa óssea subsequente, em que há uma estabilização do peso e, possivelmente, melhora da absorção de nutrientes. O fato é que demonstramos que a remodelação óssea evidenciada no primeiro ano de pós-operatório é importante e deve ser monitorada e devidamente tratada.

Na revisão sistemática com meta-análise da incidência de câncer em pacientes em pós-operatório de cirurgia bariátrica, também pudemos concluir que os indivíduos com obesidade classe II e III que se submeteram a esse procedimento tiveram benefícios. Entretanto, não conseguimos definir os fatores ou condições que protegem mais, assim como o tipo de câncer que é mais beneficiado. Essas dúvidas foram colocadas como uma limitação dos estudos avaliados, demonstrando haver necessidade de mais estudos sobre câncer em indivíduos em pós-operatório de cirurgia bariátrica.

O acompanhamento a longo prazo de indivíduos que se submeteram à cirurgia bariátrica, com a devida publicação dos resultados, será de fundamental importância para determinar o diagnóstico e o tratamento dos possíveis efeitos colaterais, assim como de igual importância será a realização de estudos para avaliar o impacto da cirurgia bariátrica sobre o câncer, buscando o melhor equilíbrio entre vantagens e desvantagens.

REFERENCIAS BIBLIOGRÁFICAS

AASHEIM, E. T. et al. Vitamin status after gastric bypass and lifestyle intervention: a comparative prospective study. **Surg. Obes. Relat. Dis.**, v. 8, n. 2, p. 169-175, 2012.

ADAMS, T. D. et al. Cancer incidence and mortality after gastric bypass surgery. **Obesity**, v. 17, n. 4, p. 796-802, 2009.

AILLS, L. et al. ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient. **Surg. Obes. Relat. Dis.**, v. 4, n. 5 Suppl, p. S73-S108, 2008.

ALBALA, C. et al. Obesity as a protective factor for postmenopausal osteoporosis. **Int. J. Obes. Relat. Metab. Disord.**, v. 20, n. 11, p. 1027-1032, 1996.

ALEXANDER, J. W. et al. The impact of medicaid status on outcome after gastric bypass. **Obes. Surg.**, v. 18, n. 10, p. 1241-1245, 2008.

ANDERSEN, R. E.; Wadden, T. A.; Herzog, R. J. Changes in bone mineral content in obese dieting women. **Metabolism**, v. 46, n. 8, p. 857-861, 1997.

ANTHONE, G. J. et al. The duodenal switch operation for the treatment of morbid obesity. **Ann. Surg.**, v. 238, n, 4, p. 618-627, 2003.

ARCILA, D. et al. Quality of life in bariatric surgery. **Obes. Surg.**, v. 12, n. 5, p. 661-665, 2002.

ARTERBURN, D. E.; MACIEJEWSKI, M. L.; TSEVAT, J. Impact of morbid obesity on medical expenditures in adults. **Int. J. Obes.**, London, v. 29, n. 3, p. 334-339, 2005.

AYAZI, S. et al. Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. **J. Gastrointest. Surg.**, v. 13, n. 8, p. 1440-1447, 2009.

BAESSLER, A. et al. Genetic linkage and association of the growth hormone secretagogue receptor (ghrelin receptor) gene in human obesity. **Diabetes**, v. 54, n. 1, p. 259-267, 2005.

BALLANTYNE, G. H. et al. Short-term changes in insulin resistance following weight loss surgery for morbid obesity: laparoscopic adjustable gastric banding versus laparoscopic Roux-en-Y gastric bypass. **Obes. Surg.**, v. 16, n. 9, p. 1189-1197, 2006.

BASTOUNIS, E. A. et al. Sex hormone changes in morbidly obese patients after vertical banded gastroplasty. **Europ. Surg. Res.**, v. 30, n. 1, p. 43-47, 1998.

BELLANGER, T. M.; BRAY, G. A. Obesity related morbidity and mortality. **J. La State Med. Soc.**, v. 157, n.1, p. S42-S49, 2005.

BENDER, R. et al. Causes of death in obesity: relevant increase in cardiovascular but not in all-cancer mortality. **J. Clin. Epidemiol.**, v. 59, n. 10, p. 1064-1071, 2006.

BERRINGTON DE GONZALEZ, A. et al. Pancreatic cancer and factors associated with the insulin resistance syndrome in the Korean cancer prevention study. **Cancer Epidemiol. Biomark. Prev.**, v. 17, n. 2, p. 359-364, 2008.

BOCKELBRINK, A. et al. Evaluation of medical and health economic effectiveness of bariatric surgery (obesity surgery) versus conservative strategies in adult patients with morbid obesity. **GMS Health Technol. Assess.**, v. 4, p. Doc06, 2008.

BONAFINI, B. A.; POZZILLI, P. Body weight and beauty: the changing face of the ideal female body weight. **Obes. Rev.**, v. 12, n. 1, p. 62-65, 2011.

BREDELLA, M. A. et al. Vertebral bone marrow fat is positively associated with visceral fat and inversely associated with IGF-1 in obese women. **Obesity**, v. 19, n. 1, p. 49-53, 2011.

BROLIN, R. E. Bariatric surgery and long-term control of morbid obesity. **JAMA**, v. 288, n. 22, p. 2793-2796, 2002.

BRZOZOWSKA, M. M. et al. Bariatric surgery, bone loss, obesity and possible mechanisms. **Obes. Rev.**, v. 14, n. 1, p. 52-67, 2013.

BUCHWALD, H. Consensus conference statement. Bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. **Surg. Obes. Relat. Diseases**, v. 1, n. 3, p. 371-381, 2005.

BUCHWALD, H. et al. Bariatric surgery: A systematic review and meta-analysis. **J. Am. Med. Assoc.**, v. 292, n. 14, p. 1724-1737, 2004.

CALLE, E. E. et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. **N. Engl. J. Med.**, v. 348, n. 17, p. 1625-1638, 2003.

CALUGI, S. et al. Weight loss and clinical characteristics of young adults patients seeking treatment at medical centers: data from the QUOVADIS Study. **Eat Weight Disord.**, v. 17, n. 4, p. e314-e319, 2012.

CAPASSO, I. et al. Homeostasis model assessment to detect insulin resistance and identify patients at high risk of breast cancer development: national cancer institute of Naples experience. **J. Exp. Clin. Cancer Res.**, v. 32, n. 1, p. 14, 2013.

CARRASCO, F. et al. Changes in bone mineral density, body composition and adiponectin levels in morbidly obese patients after bariatric surgery. **Obes. Surg.**, v. 19, n. 1, p. 41-46, 2009.

CASAGRANDE, D. S. et al. Changes in bone mineral density in women following 1-year gastric bypass surgery. **Obes. Surg.**, v. 22, n. 8, p. 1287-1292, 2012.

CASAGRANDE, D. S. et al. Bone mineral density and nutritional profile in morbidly obese women. **Obes. Surg.**, v. 20, n. 10, p. 1372-1379, 2010.

CHANG, P. Y. et al. Association and prognostic value of serum inflammation markers in patients with leukoplakia and oral cavity cancer. **Clin. Chem. Lab. Med.**, v. 51, n. 6, p. 1291-1300, 2013.

CHANG, Y. et al. Collaborative modeling of the impact of obesity on race-specific breast cancer incidence and mortality. **Breast Cancer Res. Treat.**, v. 136, n. 3, p. 823-835, 2012.

CHEN, J. H. et al. Impact of obesity and hypertriglyceridemia on gout development with or without hyperuricemia: a prospective study. **Arthritis Care Res.**, v. 65, n. 1, p. 133-140, 2013.

CHHATWAL, J.; VERMA, M.; RIAR, S. K. Obesity among pre-adolescent and adolescents of a developing country (India). **Asia Pac. J. Clin. Nutr.**, v. 13, n. 3, p. 231-235, 2004.

CHRISTOU, N. V. et al. Bariatric surgery reduces cancer risk in morbidly obese patients. **Surg. Obes. Relat. Dis.**, v. 4, n. 6, p. 691-695, 2008.

CHRISTOU, N. V. et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. **Ann. Surg.**, v. 240, n. 3, p. 416-423, discussion 423-424, 2004.

CHURILLA, T. M. et al. Vitamin D deficiency is widespread in cancer patients and correlates with advanced stage disease: a community oncology experience. **Nutr. Cancer**, v. 64, n. 4, p. 521-525, 2012.

COATES, P. S. et al. Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. **J. Clin. Endocrinol. Metab.**, v. 89, n. 3, p. 1061-1065, 2004.

COLANGELO, L. A. et al. Colorectal cancer mortality and factors related to the insulin resistance syndrome. **Cancer Epidemiol. Biomark. Prev.**, v. 11, n. 4, p. 385-391, 2002.

CONNOR, A. E. et al. Obesity and risk of breast cancer mortality in hispanic and non-hispanic white women: the New Mexico women's health study. **J. Womens Health**, v. 22, n. 4, p. 368-377, 2013.

CONTRERAS, J. E. et al. Correlation between age and weight loss after bariatric surgery. **Obes. Surg.**, 2013. [Epub ahead of print]

CREMIEUX, P. Y. et al. A study on the economic impact of bariatric surgery. **Am. J. Managed Care**, v. 14, n. 9, p. 589-596, 2008.

CRUJEIRAS, A. B. et al. Association of breast cancer and obesity in a homogeneous population from Spain. **J. Endocrinol. Invest.**, v. 35, n. 7, p. 681-685, 2012.

DEMARIA, E. J. Bariatric surgery for morbid obesity. **New Engl. J. Med.**, v. 356, n. 21, p. 2176-2183, 2007.

DEROSA, G. et al. Comparison of metabolic effects of orlistat and sibutramine treatment in Type 2 diabetic obese patients. **Diabetes Nutr. Metab**., v. 17, n. 4, p. 222-229, 2004.

DIAZ, G. D. et al. Apoptosis is induced by the active metabolite of vitamin D3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: possible implications for prevention and therapy. **Cancer Res.**, v. 60, n. 8, p. 2304-2312, 2000.

DOSSUS, L. et al. Hormonal, Metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort - A factor analysis. **Am. J. Epidemiol.**, v. 177, n. 8, p. 787-799, 2013.

DUBOIS, L. et al. Genetic and environmental contributions to weight, height, and BMI from birth to 19 years of age: an international study of over 12,000 twin pairs. **PLoS ONE**, v. 7, n. 2, p. e30153, 2012.

DUSSO, A. S.; Brown, A. J.; Slatopolsky, E. Vitamin D. **Am. J. Physiol. Renal. Physiol.**, v. 289, n. 1, p. F8-28, 2005.

ELDER, K. A.; Wolfe, B. M. Bariatric surgery: a review of procedures and outcomes. **Gastroenterol.**, v. 132, n. 6, p. 2253-2271, 2007.

EVANS, S. R. et al. 1,25-dihydroxyvitamin D3 synthetic analogs inhibit spontaneous metastases in a 1,2-dimethylhydrazine-induced colon carcinogenesis model. **Int. J. Oncol.**, v. 16, n. 6, p. 1249-1254, 2000. ,

EWING, B. T. et al. A cost-benefit analysis of bariatric surgery on the South Plains region of Texas. **Obes. Surg.**, v. 21, n. 5, p. 644-649, 2011.

FARIA, G. R.; PRETO, J. R.; COSTA-MAIA, J. Gastric bypass is a cost-saving procedure: results from a comprehensive markov model. **Obes. Surg.**, v. 23, n. 4., p. 460-466, 2013.

FENTON, J. I. et al. Leptin, insulin-like growth factor-1, and insulin-like growth factor-2 are mitogens in ApcMin/+ but not Apc+/+ colonic epithelial cell lines. **Cancer Epidemiol. Biomark. Prev.**, v. 14, n. 7, p. 1646-1652, 2005.

FLANCBAUM, L. et al. Preoperative nutritional status of patients undergoing roux-en-Y gastric bypass for morbid obesity. **J. Gastroint. Surg.**, v. 10, n. 7, p. 1033-1037, 2006.

FLEGAL, K. M. et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. **JAMA**, v. 309, n. 1, p. 71-82, 2013.

FLEGAL, K. M. et al. Prevalence and trends in obesity among US adults, 1999-2008. **JAMA**, v. 303, n. 3, p. 235-241, 2010.

FLEISCHER, J. et al. The decline in hip bone density after gastric bypass surgery is associated with extent of weight loss. **J. Clin. Endocrinol. Metab.**, v. 93, n. 10, p. 3735-3740, 2008.

FONTAINE, K. R. et al. Years of life lost due to obesity. **JAMA**, v. 289, n. 2, p. 187-193, 2003.

FORREST, K. Y.; Stuhldreher, W. L. Prevalence and correlates of vitamin D deficiency in US adults. **Nutr. Res.**, v. 31, n. 1, 2011.

FRANCO, M. et al. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: repeated cross sectional surveys and ecological comparison of secular trends. **BMJ**, v. 346, p. F1515, 2013.

FRIEDMAN, C. F. et al. Vitamin d deficiency in postmenopausal breast cancer survivors. **J. Wom. Health**, v. 21, n. 4, p. 456-462, 2012.

GELONEZE, B. et al. Serum leptin levels after bariatric surgery across a range of glucose tolerance from normal to diabetes. **Obes. Surg.**, v. 11, n. 6, p. 693-698, 2001.

GILSANZ, V. et al. Reciprocal relations of subcutaneous and visceral fat to bone structure and strength. **J. Clin. Endocrinol. Metab.**, v. 94, n. 9, p. 3387-3393, 2009.

GIUSTI, V. et al. Gastric banding induces negative bone remodelling in the absence of secondary hyperparathyroidism: potential role of serum C telopeptides for follow-up. **Int. J. Obes.**, Londres, v. 29, n. 12, p. 1429-1435, 2005.

GRACIA-SOLANAS, J. A. et al. Metabolic syndrome after bariatric surgery. Results depending on the technique performed. **Obes. Surg.**, v. 21, n. 2, p. 179-185, 2011.

GRECO, E. A. et al. Is obesity protective for osteoporosis? Evaluation of bone mineral density in individuals with high body mass index. **Int. J. Clin. Pract.**, v. 64, n. 6, p. 817-820, 2010.

HERRON, D. M.; ROOHIPOUR, R. Bariatric surgical anatomy and mechanisms of action. **Gastrointest. Endosc. Clin. N. Am.**, v. 21, n, 2, p. 213-228, 2011.

HESS, D. S.; HESS, D. W. Biliopancreatic diversion with a duodenal switch. **Obes. Surg.**, v. 8, n. 3, p. 267-282, 1998.

HINTON, P. S. et al. Weight-loss-associated changes in bone mineral density and bone turnover after partial weight regain with or without aerobic exercise in obese women. **Eur. J. Clin. Nutr.**, v. 66, n. 5, p. 606-612, 2012.

HODO, D. M. et al. Medication use after bariatric surgery in a managed care cohort. **Surg. Obes. Relat. Dis.**, v. 4, n. 5, p. 601-607, 2008.

HOLDSTOCK, C. et al. CRP reduction following gastric bypass surgery is most pronounced in insulin-sensitive subjects. **Int. J. Obes.**, v. 29, n. 10, p. 1275-1280, 2005.

HOLICK, M. F.; Chen,T. C. Vitamin D deficiency: a worldwide problem with health consequences. **Am. J. Clin. Nutr.**, v. 87, n. 4, p. 1080S-1086S, 2008.

HOLLIDAY, K. L. et al. Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. **Osteoarthritis Cartil.**, v. 19, n. 1, p. 37-43, 2011.

HSU, Y. H. et al. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. **Am. J. Clin. Nutr.**, v. 83, n. 1, p. 146-154, 2006.

IBGE. **Estatística:** pesquisa de orçamentos familiares 2008-2009. Brasília: IBGE, 2010.

JANICKA, A. et al. Fat mass is not beneficial to bone in adolescents and young adults. **J. Clin. Endocrinol. Metab.**, v. 92, n. 1, p. 143-147 2007. **92**(1): p. 143-7.

JEE, S. H. et al. Fasting serum glucose level and cancer risk in Korean men and women. **JAMA**, v. 293, n. 2, p. 194-202, 2005.

JOAO CABRERA, E. et al. Reduction in plasma levels of inflammatory and oxidative stress indicators after Roux-en-Y gastric bypass. **Obes. Surg.**, v. 20, n. 1, p. 42-49, 2010.

JOHNSON, L. K. et al. Impact of gender on vitamin D deficiency in morbidly obese patients: a cross-sectional study. **Eur. J. Clin. Nutr.**, v. 66, n. 1, p. 83-90, 2012.

KAAKS, R. et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). **J. Natl. Cancer Inst.**, v. 97, n. 10, p. 755-765, 2005.

KELLOGG, T. A. et al. Postgastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet. **Surg. Obes. Relat. Dis.**, v. 4, n. 4, p. 492-499, 2008.

KISAKOL, G. et al. Effect of surgical weight loss on free radical and antioxidant balance: A preliminary report. **Obes. Surg.**, v. 12, n. 6, p. 795-800, 2002.

LA VIGNERA, S. et al. Obesity is associated with a higher level of pro-inflammatory cytokines in follicular fluid of women undergoing medically assisted procreation (PMA) programs. **Eur. Rev. Med. Pharmacol. Sci.**, v. 15, n. 3, p. 267-273, 2011.

LE ROUX, C. W. et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. **Ann. Surg.**, v. 243, n. 1, p. 108-114, 2006.

LEE, P. et al. Expression of progesterone receptor is a favorable prognostic marker in ovarian cancer. **Gynecol. Oncol.**, v. 96, n. 3, p. 671-677, 2005.

LEE, W. J. et al. Diabetes remission and insulin secretion after gastric bypass in patients with body mass index <35 kg/m2. **Obes. Surg.**, v. 21, n. 7, p. 889-895, 2011.

LIPS, P. et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. **J. Clin. Endocrinol. Metab.**, v. 86, n. 3, p. 1212-1221, 2001.

LIVINGSTON, E. H.; KO, C. Y. Socioeconomic characteristics of the population eligible for obesity surgery. **Surgery**, v. 135, n. 3, p. 288-296, 2004.

LYON, D. E. et al. Cytokine comparisons between women with breast cancer and women with a negative breast biopsy. **Nurs. Res.**, v. 57, n. 1, p. 51-58, 2008.

MAHER, C. A. et al. The independent and combined associations of physical activity and sedentary behavior with obesity in adults: NHANES 2003-06. **Obesity**, 2013.[Epub ahead of print]

MANTEROLA, C. Surgery for morbid obesity: selection of operation based on evidence from literature review. **Obes. Surg.**, v. 15, n. 1, p. 106-113, 2005.

MATA-GRANADOS, J. M. et al. Vitamin D deficiency and high serum levels of vitamin A increase the risk of osteoporosis evaluated by Quantitative Ultrasound Measurements (QUS) in postmenopausal Spanish women. **Clin. Biochem.**, v. 43, n. 13-14, p. 1064-1068, 2010.

MCCAWLEY, G. M. et al. Cancer in obese women: potential protective impact of bariatric surgery. **J. Am. Coll. Surg.**, v. 208, n. 6, p. 1093-1098, 2009.

MECKLING, K. A.; SHERFEY, R. A randomized trial of a hypocaloric high-protein diet, with and without exercise, on weight loss, fitness, and markers of the Metabolic Syndrome in overweight and obese women. **Appl. Physiol. Nutr. Metab.**, v. 32, n. 4, p. 743-752, 2007.

MITHAL, A. et al. Global vitamin D status and determinants of hypovitaminosis D. **Osteoporos. Int.**, v. 20, n. 11, p. 1807-1820, 2009.

MOND, J. M. et al. Obesity and impairment in psychosocial functioning in women: the mediating role of eating disorder features. **Obesity**, v. 15, n. 11, p. 2769-2779, 2007.

MONTEIRO, C. A.; CONDE, W. L.; POPKIN, B. M. Is obesity replacing or adding to undernutrition? Evidence from different social classes in Brazil. **Public Health Nutr.**, v. 5, n. 1A, p. 105-112, 2002.

MORETTO, M. et al. Hepatic steatosis in patients undergoing bariatric surgery and its relationship to body mass index and co-morbidities. **Obes. Surg.**, v. 13, n. 4, p. 622-624, 2003.

MOTTIN, C. C. et al. Behavior of type 2 diabetes mellitus in morbid obese patients submitted to gastric bypass. **Obes. Surg.**, v. 18, n. 2, p. 179-181, 2008.

MOTTIN, C. C. et al. Histological behavior of hepatic steatosis in morbidly obese patients after weight loss induced by bariatric surgery. **Obes. Surg.**, v. 15, n. 6, p. 788-793, 2005.

MOURA, E. C.; CLARO, R. M. Estimates of obesity trends in Brazil, 2006-2009. **Int. J. Public Health**, v. 57, n. 1, p. 127-133, 2012.

NARULA, R. et al. Vitamin d deficiency among postmenopausal women with osteoporosis. **J. Clin. Diagn. Res.**, v. 7, n. 2, p. 336-338, 2013.

NEOVIUS, M. et al. Health care use during 20 years following bariatric surgery. **JAMA**, v. 308, n. 11, p. 1132-1141, 2012.

NOGUES, X. et al. Bone mass loss after sleeve gastrectomy: A prospective comparative study with gastric bypass. **Cirug. Espan.**, v. 88, n. 2, p. 103-109, 2010.

NORMAN, A. W. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. **Am. J. Clin. Nutr.**, v. 88, n. 2, p. 491S-499S, 2008.

OH, S. W. et al. Adipokines, insulin resistance, metabolic syndrome, and breast cancer recurrence: a cohort study. **Breast Cancer Res.**, v. 13, n. 2, p. R34, 2011.

OLIVEIRA, C. P. et al. Lipid peroxidation in bariatric candidates with nonalcoholic fatty liver disease (NAFLD) - preliminary findings. **Obes. Surg.**, v. 15, n. 4, p. 502-505, 2005.

OTT, M. T. et al. Biochemical evidence of metabolic bone disease in women following Roux-Y gastric bypass for morbid obesity. **Obes. Surg.**, v. 2, n. 341-348, 1992.

PALMIERI, C. et al. Serum 25-hydroxyvitamin D levels in early and advanced breast cancer. **J. Clin. Pathol.**, v. 59, n. 12, p. 1334-1336, 2006.

PAPAKITSOU, E. F. et al. Body mass index (BMI) and parameters of bone formation and resorption in postmenopausal women. **Maturitas**, v. 47, n. 3, p. 185-193, 2004.

PASCO, J. A. et al. Obesity and the relationship with positive and negative affect. **Aust. N. Z. J. Psychiatry**, v. 47, n. 5, p. 477-482, 2013.

PINKNEY, J. H.; JOHNSON, A. B.; GALE, E. A. The big fat bariatric bandwagon. **Diabetologia**, v. 53, n. 9, p. 1815-1822, 2010.

POLESEL, J. et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. **Ann. Oncol.**, v. 20, n. 2, p. 353-357, 2009.

PREMAOR, M. O.; Furlanetto, T. W. Vitamin D deficiency in adults: to better understand a new presentation of an old disease. **Arq. Bras. Endocrinol. Metabol.**, v. 50, n. 1, p. 25-37, 2006.

PUGNALE, N. et al. Bone metabolism and risk of secondary hyperparathyroidism 12 months after gastric banding in obese pre-menopausal women. **Int. J. Obes. Relat. Metab. Disord.**, v. 27, n. 1, p. 110-116, 2003.

RABKIN, R. A. The duodenal switch as an increasing and highly effective operation for morbid obesity. **Obes. Surg.**, v. 14, n. 6, p. 861-865, 2004.

RASERA, I. Derivação gástrica em "Y de Roux". **Einsten**, v. 1, p. S97-S102, 2006.

RIEDT, C. S. et al. True fractional calcium absorption is decreased after Roux-en-Y gastric bypass surgery. **Obesity**, v. 14, n. 11, p. 1940-1948, 2006.

ROGERS, R. G.; HUMMER, R. A.; KRUEGER, P. M. The effect of obesity on overall, circulatory disease- and diabetes-specific mortality. **J. Biosoc. Sci.**, v. 35, n. 1, p. 107-129, 2003.

ROSENBLATT, A.; FAINTUCH, J.; CECCONELLO, I. Sexual hormones and erectile function more than 6 years after bariatric surgery. **Surg. Obes. Relat. Dis.**, 2012. [Epub ahead of print]

ROSKIES, M. et al. Vitamin D deficiency as a potentially modifiable risk factor for thyroid cancer. **J. Otolaryngol. Head Neck Surg.**, v. 41, n. 3, p. 160-163, 2012.

RYAN, D. H. et al. Nonsurgical weight loss for extreme obesity in primary care settings: results of the Louisiana Obese Subjects Study. **Arch. Intern. Med.**, v. 170, n. 2, p. 146-154, 2010.

SALAMONE, L. M. et al. Effect of a lifestyle intervention on bone mineral density in premenopausal women: a randomized trial. **Am. J. Clin. Nutr.**, v. 70, n. 1, p. 97-103, 1999.

SALONIA, A. et al. Preoperative sex steroids are significant predictors of early biochemical recurrence after radical prostatectomy. **World J. Urol.**, v. 31, n. 2, p. 275-280, 2013.

SAMIMI, M. et al. Vitamin D deficiency is associated with greater tumor size and poorer outcome in Merkel cell carcinoma patients. **J. Eur. Acad. Dermatol. Venereol.**, 2013. [Epub ahead of print]

SAMPALIS, J. S. et al. The impact of weight reduction surgery on health-care costs in morbidly obese patients. **Obes. Surg.**, v. 14, n. 7, p. 939-947, 2004.

SARWER, D. B. et al. A pilot study investigating the efficacy of postoperative dietary counseling to improve outcomes after bariatric surgery. **Surg. Obes. Relat. Dis.**, v. 8, n. 5, p. 561-568, 2012.

SCHIENKIEWITZ, A.; MENSINK, G. B.; SCHEIDT-NAVE, C. Comorbidity of overweight and obesity in a nationally representative sample of German adults aged 18-79 years. **BMC Public Health**, v. 12, p. 658, 2012.

SCHLESINGER, S. et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. **Int. J. Cancer**, v. 132, n. 3, p. 645-657, 2013.

SCHMIDT, M. I. et al. Chronic non-communicable diseases in Brazil: burden and current challenges. **Lancet**, v. 377, n. 9781, p. 1949-1961, 2011.

SHIELDS, M.; GORBER, S. C.; TREMBLAY, M. S. Effects of measurement on obesity and morbidity. **Health Rep.**, v. 19, n. 2, p. 77-84, 2008.

SIMARD, B. et al. Asthma and sleep apnea in patients with morbid obesity: outcome after bariatric surgery. **Obes. Surg.**, v. 14, n. 10, p. 1381-1388, 2004.

SJOSTROM, L. Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. **Int. J. Obes.**, v. 32, n. suppl 7, p. S93-S97, 2008.

SJOSTROM, L. et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. **The Lancet Oncology**, v. 10, n. 7, p. 653-662, 2009.

SJOSTROM, L. et al. Effects of bariatric surgery on mortality in Swedish obese subjects. **New Engl. J. Med.**, v. 357, n. 8, p. 741-752, 2007.

SJOSTROM, L. et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. **New Engl. J. Med.**, v. 351, n. 26, p. 2683-2693, 2004.

SJOSTROM, L. et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. **Lancet**, v. 352, n. 9123, p. 167-172, 1998.

SONESTEDT, E. et al. Fat and carbohydrate intake modify the association between genetic variation in the FTO genotype and obesity. **Am. J. Clin. Nutr.**, v. 90, n. 5, p. 1418-1425, 2009.

SONNENBERG, F. A.; Beck, J. R. Markov models in medical decision making: a practical guide. **Med. Decis. Making.**, v. 13, n. 4, p. 322-338, 1993.

SUSSENBACH, S. P. et al. Economic benefits of bariatric surgery. **Obes. Surg.**, v. 22, n. 2, p. 266-270, 2012.

SVETKEY, L. P. et al. Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial. **JAMA**, v. 299, n. 10, p. 1139-1148, 2008.

TALAEI, A. et al. Prevalence and cut-off point of vitamin D deficiency among secondary students of Arak, Iran in 2010. **Indian J. Endocrinol. Metab.**, v. 16, n. 5, p. 786-790, 2012.

THURNHEER, M. et al. A novel distal very long Roux-en Y gastric bypass (DVLRYGB) as a primary bariatric procedure-complication rates, weight loss, and nutritional/metabolic changes in the first 355 patients. **Obes. Surg.**, v. 22, n. 9, p. 1427-1436, 2012.

TRAKHTENBROIT, M. A. et al. Body weight, insulin resistance, and serum adipokine levels 2 years after 2 types of bariatric surgery. **Am. J. Med.**, v. 122, n. 5, p. 435-442, 2009.

UZUN, H. et al. Changes in leptin, plasminogen activator factor and oxidative stress in morbidly obese patients following open and laparoscopic Swedish adjustable gastric banding. **Obes. Surg.**, v. 14, n. 5, p. 659-665, 2004.

VACEK, J. L. et al. Vitamin D deficiency and supplementation and relation to cardiovascular health. **Am. J. Cardiol.**, v. 109, n. 3, p. 359-363, 2012.

VAN ROSSUM, C. T. et al. Genetic factors as predictors of weight gain in young adult Dutch men and women. **Int. J. Obes. Relat. Metab. Disord.**, v. 26, n. 4, p. 517-528, 2002.

VAZQUEZ, L. A. et al. Effects of changes in body weight and insulin resistance on inflammation and endothelial function in morbid obesity after bariatric surgery. **J. Clin. Endocrinol. Metab.**, v. 90, n. 1, p. 316-322, 2005.

VENDRELL, J. et al. Tumor necrosis-like weak inducer of apoptosis as a proinflammatory cytokine in human adipocyte cells: up-regulation in severe obesity is mediated by inflammation but not hypoxia. **J. Clin. Endocrinol. Metab.**, v. 95, n. 6, p. 2983-2992, 2010.

VIARDOT, A.; Lord, R. V.; Samaras, K. The effects of weight loss and gastric banding on the innate and adaptive immune system in type 2 diabetes and prediabetes. **J. Clin. Endocrinol. Metab.**, v. 95, n. 6, p. 2845-2850, 2010.

VON MUHLEN, D. et al. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. **Osteoporos. Int.**, v. 18, n. 10, p. 1337-1344, 2007.

WADDEN, T. A. et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. **N. Engl. J. Med.**, v. 353, n. 20, p. 2111-2120, 2005.

WANG, T. et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. **Cancer Epidemiol. Biomark. Prev.**, v. 20, n. 5, p. 971-977, 2011.

WEINER, J. P. et al. Impact of bariatric surgery on health care costs of obese persons: a 6-year follow-up of surgical and comparison cohorts using health plan data. **JAMA Surg.**, p. 1-8, 2013. [Epub ahead of print]

WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. **World Health Organ. Tech. Rep. Ser.**, v. 854, p. 1-452, 1995.

WYATT, H. R. Update on treatment strategies for obesity. **J. Clin. Endocrinol. Metab.**, v. 98, n. 4, p. 1299-1306, 2013.

ZHAO, Z. et al. 18F-FES and 18F-FDG PET for differential diagnosis and quantitative evaluation of mesenchymal uterine tumors: correlation with immunohistochemical analysis. **J. Nucl. Med.**, v. 54, n. 4, p. 499-506, 2013.

CIP - Catalogação na Publicação

Casagrande, Daniela Schaan
Cirurgia bariátrica no tratamento da obesidade com enfoque no metabolismo ósseo e na incidência de câncer / Daniela Schaan Casagrande. -- 2013.
96 f.

Orientadora: Beatriz D'Agord Schaan.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2013.

1. Cirurgia bariátrica. 2. metabolismo ósseo. 3. câncer. 4. nutrição. I. Schaan, Beatriz D'Agord, orient. II. Título.

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