FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA
CIÊNCIAS CIRÚRGICAS

CARLOS AUGUSTO SCUSSEL MADALOSSO

EFEITO DO BYPASS GÁSTRICO NA DOENÇA DO REFLUXO GASTROESOFÁGICO EM PACIENTES COM OBESIDADE MÓRBIDA

Orientador: **Prof. Dr. Richard Ricachenevski Gurski**

Coorientador: **Prof. Dr. Fernando Fornari**

Porto Alegre, RS, Brasil

2009

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

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Dissertação apresentada como requisito para obtenção do título de Mestre em Ciências Médicas

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À minha mulher Alexandra, que me proporcionou o conforto de seu amor e compreensão pela minha ausência

Aos meus filhos Bruno e Bianca, que são a razão de tudo

Aos meus pais, Carlos e Celina, pelo amor, incentivo e exemplo.

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LISTA DE ABREVIATURAS

AED	amplitude esofágica distal
DRGE	doença do refluxo gastroesofágico
EB	esôfago de Barrett
EDA	endoscopia digestiva alta
EIE	esfíncter inferior do esôfago
GYR	gastroplastia vertical com bandagem por anel de silastic e derivação jejunal em Y-de-Roux
HCPA	Hospital de Clínicas de Porto Alegre
HSVP	Hospital São Vicente de Paulo
IBP	inibidores da bomba de prótrons
IMC	índice de massa corporal
MEI	motilidade esofágica ineficaz
RxEE	estudo radiológico com contraste baritado de esôfago e estômago
UFRGS	Universidade Federal do Rio Grande do Sul

LISTA DE ABREVIATURAS EM INGLÊS

ACT	acid contact time
DEA	distal esophagus amplitude
EGJ	esophagogastric junction
GEPG	gastroesophageal pressure gradient
GERD	gastroesophageal reflux disease
GERD-SQ	gastroesophageal reflux disease symptoms questionnaire
HbA1C	glycohemoglobin
HDS	heartburn during sleep
IEM	ineffective esophageal motility
LES	lower esophageal sphincter
PPI	protron pump inhibitor
SHH	Sliding hiatal hernia
TRLES	transient relaxation of the lower esophagus sphincter
WC	waist circumpherence
WHR	waist/hip ratio

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RESUMO DA DISSERTAÇÃO

A doença do refluxo gastroesofágico (DRGE) é caracterizada por sintomas desconfortáveis e/ou complicações que são causadas pelo refluxo de conteúdo gástrico para o esôfago. Em nosso estudo de revisão verificamos que, no Brasil, a prevalência de DRGE é de aproximadamente 7%, sendo a pirose semanal verificada de 4,6% a 31%. A DRGE determina redução de qualidade de vida e elevado custo social e econômico. Quanto à etiologia, uma associação causal entre fatores ambientais, comportamentais e genéticos tem sido proposta. A crescente prevalência de obesidade coincide com um aumento da frequência de DRGE, expressa pela maior ocorrência de sintomas ou lesão esofágica, como esofagite de refluxo (ER), esôfago de Barrett (EB) e adenocarcinoma do esôfago. Estudos populacionais podem subestimar a prevalência da DRGE em obesos em consequência da redução da percepção de sintomas nesse grupo de doentes.

Nosso primeiro estudo verifica o desempenho do Consenso de Montreal no diagnóstico de DRGE em pacientes candidatos à cirurgia bariátrica. Nesse estudo, 75 pacientes consecutivos foram avaliados sintomaticamente, por endoscopia digestiva alta e pHmetria de 24h sem uso de IBP. Dois algoritmos diagnósticos foram testados: o primeiro consistiu na abordagem padrão, em que qualquer sintoma esofágico, síndromes esofágicas com injúria pela endoscopia ou exposição ácida aumentada à pHmetria de 24h eram considerados diagnósticos; o segundo aplicava a abordagem recomendada pelo Consenso de Montreal, pelo qual apenas sintomas desconfortáveis e achados endoscópicos eram considerados. Nossos achados demonstram acurácia e especificidade elevadas, porém com baixo valor preditivo negativo (47%).

Os tratamentos utilizados na DRGE são o medicamentoso e o cirúrgico. Este último consiste na fundoplicatura associada à hiatoplastia com índices de sucesso próximo a

90%. Contudo, em indivíduos com obesidade mórbida (OM) a recidiva da DRGE após cirurgia antirrefluxo ocorre em cerca de um terço dos pacientes. Recentemente, a gastroplastia vertical com reconstrução em Y-de-Roux (GYR), padrão-ouro no tratamento da OM, tem sido proposta como alternativa no tratamento da DRGE.

Nosso segundo estudo teve por foco a terapêutica cirúrgica da DRGE em obesos mórbidos. Assim, avaliou o efeito da (GYR) por meio de parâmetros subjetivos e objetivos de DRGE em obesos mórbidos. A análise foi realizada em 86 pacientes consecutivos, que foram investigados no pré-operatório e seis meses após a GYR. Os pacientes foram submetidos à avaliação subjetiva, através de sintomas, e objetiva, com endoscopia e pHmetria de 24h. Além disso, foram avaliados radiologicamente para a presença de hérnia hiatal e submetidos à manometria esofágica para estudo de alterações de motilidade esofágica. Com os dois estudos, chegamos às seguintes conclusões: 1. A abordagem pelo Consenso de Montreal limita a identificação de DRGE em obesos mórbidos, sendo, assim, recomendada a investigação mesmo em pacientes sem sintomas desconfortáveis de DRGE; 2. Sintomas de DRGE, exposição ácida do esôfago e injúria mucosa do esôfago apresentam resposta favorável com a GYR; 3. A melhora radiológica é observada em metade dos pacientes, estando relacionada com alívio de sintomas; 4. Não há melhora dos distúrbios motores do esôfago com a GYR. 5. Resultados a longo prazo são necessários para confirmar essa operação como técnica de escolha para tratar DRGE mesmo em indivíduos com obesidade leve.

ARTIGO de Revisão –Versão em Português em processo de submissão

DOENÇA DO REFLUXO GASTROESOFÁGICO E OBESIDADE : FISIOPATOLOGIA, DIAGNÓSTICO E TRATAMENTO

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Título abreviado: DRGE e obesidade

RESUMO

Ao longo dos últimos duzentos anos, as doenças inflamatórias do esôfago têm sido amplamente estudadas. Os avanços nos métodos diagnósticos proporcionaram uma melhor compreensão da doença do refluxo gastroesofágico. Ainda no início do século XX já havia sido demonstrada radiologicamente a ocorrência do refluxo. A caracterização de sintomas da DRGE com achados endoscópicos foi estabelecida ainda na década de 1930 . No campo terapêutico, a hiatoplastia e, mais tarde, a fundoplicatura foram as alternativas terapêuticas utilizadas desde a metade do século até a introdução da cimetidina e, uma década mais tarde, dos inibidores de bomba de prótons (IBP). Os bons resultados com esses medicamentos limitaram a cirurgia apenas aos casos mais complexos. Com o advento da cirurgia minimamente invasiva, a utilização da fundoplicatura passou a ter um novo crescimento de indicações. Finalmente, recentes publicações têm sugerido a realização da gastroplastia com derivação jejunal em Y-de-Roux como opção em indivíduos obesos.

DRGE e obesidade são doenças prevalentes. Dados epidemiológicos têm demonstrado que essa associação, bastante importante, não é apenas coincidência, e vários mecanismos fisiopatológicos podem explica-la. Aumento de pressão abdominal, determinando um gradiente pressórico gastroesofágico positivo, maior secreção gástrica e biliar, maior ocorrência de relaxamentos transitórios do esfíncter inferior do esôfago, menor capacidade de clareamento esofágico, assim como retenção gástrica proximal, são alguns dos eventos envolvidos na maior prevalência de DRGE nesses indivíduos.

Embora alguns estudos tenham demonstrado resultados satisfatórios com a fundoplicatura laparoscópica em obesos, elevadas taxas de recidiva foram demonstradas. Recentemente, procedimentos empregados para tratamento de obesidade

mórbida têm sido avaliados quanto ao seu impacto na DRGE, e sua resposta adequada tem levado a que muitos grupos considerem a opção cirúrgica como uma nova modalidade de tratamento cirúrgico em indivíduos obesos com DRGE. Assim, este estudo tem por objetivo revisar os principais aspectos dessa associação no que diz respeito à fisiopatologia, ao tratamento e prognóstico.

PALAVRAS-CHAVE:

Doença do refluxo gastroesofágico, Consenso de Montreal, obesidade mórbida, gastroplastia com derivação em Y-de-Roux

INTRODUÇÃO

A DRGE é caracterizada por sintomas desconfortáveis e/ou complicações causadas pelo refluxo de conteúdo gástrico para o esôfago. No Brasil, a prevalência de DRGE, quando caracterizada por pirose semanal, é de 4,6% a 31% (1-3). A DRGE determina redução de qualidade de vida e elevado custo social e econômico (4). Nos Estados Unidos, 14 bilhões de dólares são gastos anualmente com investigação e tratamento da DRGE (5). Quanto à etiologia, uma associação causal entre fatores ambientais, comportamentais e genéticos tem sido proposta (6-8). Contudo, o aumento da prevalência de obesidade explica, pelo menos em parte, o aumento da DRGE.

Obesidade e sobrepeso encontram-se hoje em níveis epidêmicos(9) e são importantes fatores de risco para sintomas de DRGE, esofagite de refluxo (ER) (10-13), esôfago de Barrett (EB) (14) e adenocarcinoma do esôfago (15). A crescente prevalência de obesidade coincide com um aumento da frequência de DRGE. Estudos populacionais podem subestimar a prevalência da DRGE em obesos em consequência da redução da percepção de sintomas viscerais, que é característica desse grupo de doentes (16, 17).

Os tratamentos utilizados na DRGE são o medicamentoso e o cirúrgico. Este último consiste na fundoplicatura associada à hiatoplastia, com índices de sucesso próximo a 90%. Contudo, em indivíduos com obesidade mórbida seu resultado tem sido limitado (18). Recentemente, a gastroplastia vertical com reconstrução em Y-de-Roux (GYR), tradicionalmente utilizada para tratamento da obesidade mórbida, tem sido proposta como alternativa no tratamento da DRGE (19-23).

HISTÓRICO

Os primeiros relatos de esofagite vêm do segundo século, quando Cláudio Galeno fez a primeira observação de inflamação do esôfago. Quinze séculos mais tarde, Quincke descreveu esofagite em necropsias e Frank (1792), inflamação em esôfago proximal e faringe. Rokitansky fez a primeira associação causal com ácido (24) e, nessa época, Paracelsus indicava tratamento dos problemas causados pelos sucos digestivos com a utilização de pó de pérolas. Morell Mackenzie, em 1884, introduziu o conceito de esofagite como inflamação idiopática e aguda das membranas mucosas do esôfago, que determinava odinofagia severa e, frequentemente, afagia (25). Walter B. Cannon, professor de fisiologia de Harvard, estudou a deglutição de bismuto em gatos sem sedação. O autor observou que havia regurgitação do estômago para o esôfago, seguida de súbito movimento peristáltico que devolvia o material refluído novamente para o estômago. Neste estudo Cannon definiu o esfíncter inferior do esôfago (EIE), o qual foi denominado "esfíncter cárdico". A existência do EIE foi negada pela maioria dos autores, inclusive por Norman Barrett (26). Em 1906, Wilder Tileston, patologista, definiu a úlcera péptica do esôfago como nova entidade. Asher Winkelstein, em 1934, fez a primeira associação entre sintomas e achados endoscópicos e descreveu resposta sintomática adequada, porém temporária, com bicarbonato de sódio (26).

Em 1946, Philip Allison introduziu o conceito de hérnia hiatal e sua técnica de hiatoplastia tornou-se o procedimento padrão da DRGE (27). Em 1956, Nissen propôs a gastropexia e, mais tarde, a fundoplicatura longa para tratamento da hérnia de hiato. A endoscopia digestiva alta flexível foi introduzida por Hirschowitz em

1957 (28). Ingelfinger, em 1958, foi o primeiro a considerar a importância do pinçamento diafragmático na prevenção de DRGE (29), teoria que seria comprovada trinta anos mais tarde (30). Bernstein e Baker, ao final da década de 1950, demonstraram que a infusão de ácido na mucosa esofágica era capaz de induzir pirose em pacientes sem lesão esofágica . Foi esta a primeira observação de esofagite não erosiva. Belsey, baseado nos achados de Ingelfinger, passou a defender a necessidade de manter a fundoplicatura abaixo do diafragma (31), e dez anos mais tarde, Donahue propôs a técnica de Nissen frouxo e curto (32). Ainda nesse período foi descrita a classificação de esofagite por Savary-Miller em 1978 e, em 1999, a de Los Angeles (33).

Em 1975, com a cimetidina (34) e, na década de 1980, com os inibidores da bomba de prótrons (IBP), a cirurgia da DRGE ficou restrita aos casos mais complexos. Ainda nessa época, surgiu a pH-metria de 24h (35), que permitiu associar sintomas típicos e reconhecer sintomas atípicos ao evento refluxo independentemente da presença de esofagite. A cirurgia teve novo impulso com Dallemagne (36) e Geagea, (37) a partir da descrição da técnica videolaparoscópica. Em 2003 foi desenvolvido o sistema Bravo – livre de cateter (38). No ano seguinte, surgia a impedancio-pH-metria esofágica, para o estudo de fluxo esofágico independentemente de seu pH, sentido ou estado físico (39). Recentemente, a GYR foi proposta com a finalidade de tratar DRGE em pacientes obesos (19-23). Em 2006 ficou estabelecido o Consenso de Montreal com o objetivo de estabelecer diretrizes conceituais de sintomas, achados endoscópicos de DRGE e abordagem diagnóstica (40).

EPIDEMIOLOGIA

A falta de consenso na definição da DRGE limitou a obtenção de estudos

epidemiológicos comparáveis. Por exemplo, na última década, a prevalência de

DRGE variou de 5% até 42% (6, 41-43). Essa discrepância pode ser justificada por diferenças populacionais, metodológicas e conceituais. Além disso, muitos estudos foram conduzidos pela aplicação de questionários ou enquetes por telefone ou correio; por isso, o indiscutível voluntarismo na adesão a esses estudos dificultou a generalização dos resultados (41, 43-45). Mesmo entrevistas presenciais não estão imunes a esses vieses. Em um estudo original de Harvard foi demonstrado que a correta compreensão do termo "pirose" ocorria em 65% dos pacientes que apresentavam sintomas e apenas em 22% nos assintomáticos (46). No Brasil, um estudo em indivíduos com mais de 16 anos de 22 metrópoles brasileiras evidenciou prevalência de pirose semanal de 4,6% (2), e em estudo da população de Pelotas – RS, em indivíduos acima de 20 anos, essa prevalência chegou a 18,2% (3).

A caracterização da DRGE pelo Consenso de Montreal é baseada em sintomas ou injúria esofágicos (40). Dados referentes à presença de ER ou EB em pacientes assintomáticos são, obviamente, desconhecidos. Em recente estudo coreano, com 25.000 indivíduos submetidos à avaliação endoscópica de rotina, 42% da população com esofagite erosiva não apresentava sintomas (47). Em uma série de 75 candidatos à cirurgia bariátrica, injúria esofágica foi identificada em 24% dos pacientes sem sintomas desconfortáveis para DRGE (16).

Raça

El Serag e cols., em uma enquete por correio com 915 funcionários do Veterans Affairs - Texas, onde a população negra é de 43%, encontraram uma prevalência de pirose semanal de 27% em caucasianos e de 23% em negros, não sendo possível caracterizar diferenças de prevalência entre essas raças (41). Porém, numa análise retrospectiva de estudos endoscópicos foi observada uma menor prevalência de

complicações da DRGE em negros e asiáticos orientais do que em caucasianos (2,8% e 0% vs 35%; p<0,001) (46).

Fatores genéticos, ambientais e comportamentais

Obesidade é um fator de risco para DRGE. Corley e cols. demonstraram que a elevação do índice de massa corporal (IMC) em obesos determina um aumento desproporcional de sintomas de DRGE em brancos do sexo masculino, quando comparados a negros de mesmo sexo (48). Porém, a obesidade é também determinada por um padrão genético, cuja influência foi reforçada em estudo inglês que evidenciou uma maior prevalência de DRGE em gêmeos idênticos em comparação com bivitelínicos (49) e também em indivíduos com história familiar de DRGE (6). A pequena influência ambiental e comportamental pode ser justificada pelo fato de que não foi observada significância na associação entre cônjuges ou entre gêmeos dizigóticos (49, 50). Dore e cols., em estudo de 300 pacientes e 200 controles, avaliaram a influência de atividade física, álcool, café, chocolate, refrigerante, tabaco, grandes volumes alimentares, obesidade e escolaridade. Neste estudo apenas IMC, sexo feminino e baixo nível de instrução estiveram positivamente associados à DRGE (7).

Sexo e Idade

A associação entre DRGE e sexo é controversa. Foi demonstrada associação positiva com sexo masculino (48-51), feminino (7, 45), ou ausência de relação entre sexo (51-53). O uso de contraceptivos orais e gravidez também foram favoravelmente relacionados à DRGE (54, 55), justificando, em parte, a predominância do sexo

feminino em alguns estudos. O sexo masculino esteve positivamente relacionado à esofagite de refluxo (47, 56). Foi observada uma distribuição etária unimodal, com pico > 55 anos (45, 57, 58), ou bimodal, com picos entre 15-20 e >60anos (7).

FISIOPATOLOGIA DA DRGE

Os mecanismos envolvidos na fisiopatologia da DRGE são multifatoriais e complexos. A competência do mecanismo antirefluxo, clareamento esofágico, a resistência da mucosa ao conteúdo gastroduodenal e a ocorrência de relaxamento transitório do EIE são eventos intimamente relacionados à ocorrência de RGE. Em adição, a presença de hérnia hiatal e retenção gástrica proximal têm grande influência na promoção dos eventos de refluxo, havendo também forte associação ao surgimento de complicações.

COMPETÊNCIA DO MECANISMO ANTI-REFLUXO

As estruturas anatômicas da junção esôfagogástrica que determinam a barreira antirrefluxo são o EIE (componente intrínseco) e a crura diafragmática (componente extrínseco). O componente extrínseco atua sobre o esôfago graças à ancoragem do ligamento frenoesofágico, que mantém a junção esôfagogástrica em posição intra-abdominal. Em condições normais, o EIE apresenta cerca de 4 cm, sendo pinçado pela crura em cerca de 2 cm. Além disso, ocorrem mudanças estruturais da musculatura esofágica no nível do EIE, caracterizadas por aumento em sua espessura à ecoendoscopia (59, 60). Ainda, na porção inferior do esôfago existem fibras oblíquas ou em forma de “C”, oriundas do estômago, as quais determinam um mecanismo valvular e são essenciais na contenção do refluxo gastroesofágico (61),

pois pressionam o esôfago distal, aumentando a pressão do EIE (62). Korn e cols. demonstraram correlação positiva entre a gravidade da DRGE e a dilatação do cárdia, esta consequente a deslocamentos de grupos musculares do EIE, principalmente de fibras oblíquas (63).

CLAREAMENTO ESOFÁGICO

O refluxo gastroesofágico é um evento fisiológico comum em pessoas saudáveis. Neste caso, a capacidade do esôfago de livrar-se da agressão do suco gastroduodenal é essencial para a proteção da mucosa. Os mecanismos que determinam o clareamento esofágico são a ação da gravidade, deglutição de saliva e peristalse esofágica (64-66). A saliva determina diluição e neutralização do material refluído (64, 67) e contém fator de crescimento epitelial que pode contribuir na regeneração da mucosa (68). Durante o sono, o clareamento esofágico é reduzido em razão da menor frequência de deglutições (69) e também da redução na produção de saliva (70, 71).

A motilidade esofágica ineficaz (MEI) é um evento patológico que determina redução da amplitude das ondas peristálticas do terço inferior do esôfago, sendo definida como deglutições líquidas ineficazes iguais ou maiores que 30 % (72). Fibbe cols. demonstraram que pacientes com DRGE associada à MEI são mais sintomáticos e apresentam esofagite mais intensa (73), embora esses achados sejam contestados (74). Sifrim e cols. verificaram que somente nos casos de MEI severa houve prolongamento do clareamento esofágico (75, 76). Se a MEI é causa ou conseqüência da agressão da mucosa pelo ácido não se sabe, porém estudos experimentais oferecem boas evidências causais, já que, aumentando a exposição esofágica ao ácido, é possível induzir alterações motoras (77); por outro lado,

melhora do distúrbio motor após tratamento da DGRE permanece indefinida (73, 78-81).

RESISTÊNCIA MUCOSA AO CONTEÚDO GASTRODUODENAL

Estudos experimentais demonstraram que, quando a mucosa esofágica é exposta ao ácido clorídrico isolado, apenas em pH < 1,3 ocorre lesão mucosa (82). A adição de pepsina, mesmo em doses baixas, determina lesão importante (83-85), e pacientes com pH esofágico < 2 e >7 apresentam maiores graus de esofagite (86). Uma das primeiras observações de que as secreções duodenais podem induzir sintomas foi relatado em pacientes gastrectomizados (87) e a ocorrência de refluxo duodenogástrico ocorre também em pacientes com trato gastrointestinal intacto, podendo determinar complicações mais graves nos pacientes com DRGE (88). Finalmente, em recente estudo, Farré cols. demonstraram, por meio de microscopia eletrônica, que a dilatação do espaço intercelular pode ser induzida por ácidos biliares, levando ao aumento da permeabilidade da mucosa e, consequentemente, da sua sensibilidade (89).

RELAXAMENTO TRANSITÓRIO DO EIE

O relaxamento transitório do EIE caracteriza-se por um prolongado período de relaxamento do EIE (entre 10 e 60 segundos), que, em estudo experimental, esteve associado ao relaxamento da crura diafragmática (90, 91). Mittal e cols demonstraram que, após anulação do tônus do EIE por atropina (92) ou por estimulação faríngea (93), o refluxo gastroesofágico somente ocorreu em períodos coincidentes com o relaxamento da crura diafragmática. O relaxamento transitório do

EIE, provavelmente, é o mecanismo mais frequente associado ao refluxo gastroesofágico em pacientes sem grandes hérnias hiatais (94); é consequente à distensão gástrica, sendo observado tanto em indivíduos normais como naqueles com DRGE (95, 96). Recente teoria sugere que a contração longitudinal e ascendente da musculatura do esôfago distal determina deslocamento e afastamento do EIE e da crura e, nos casos de hérnia hiatal, projeção torácica da junção esofagogástrica. Assim, a contratura da musculatura longitudinal do esôfago seria a responsável pelo relaxamento transitório do EIE e por criar um ambiente favorável ao refluxo gastroesofágico (97).

HÉRNIA HIATAL

Por muitas décadas a DRGE foi sinônimo de hérnia hiatal, estando associada a sintomas, esofagite de refluxo e esôfago de Barrett (98-100), com associação positiva entre o seu tamanho e a gravidade da DRGE (101, 102). Prevalência de 94% de hérnia de hiato em pacientes com esofagite de refluxo (103) e de 96% naqueles com esôfago de Barrett (104) tem sido demonstrada. A capacidade da hérnia de hiato em promover refluxo gastroesofágico pode ser explicada por, pelo menos, duas hipóteses: primeira, o deslocamento da junção esôfagogástrica para o tórax leva à perda do reforço muscular do EIE gerado pela crura diafragmática; segunda, a presença de hérnia hiatal determina redução da eficiência do clareamento esofágico (105).

RETENÇÃO GÁSTRICA PROXIMAL

A associação entre distensão gástrica e eventos de retenção gástrica proximal tem

sido observada. Holloway e cols., analisando manometricamente o esôfago no período pós-prandial, observaram que a distensão gástrica determina episódios de relaxamento transitório do EIE sem, contudo, alterar seu tônus basal (96). Penagini e cols. identificaram que pacientes com DRGE comparados a um grupo controle apresentaram maior dificuldade para recuperar o tônus do estômago proximal após alimentação (106) e houve associação positiva entre retenção gástrica proximal e DRGE (30, 107). Porém, tem sido demonstrado que o pH gástrico aumenta com a retenção gástrica proximal, havendo correlação inversa com o número de episódios de refluxo ácido (108, 109). Assim, futuros estudos são necessários para estabelecer o papel da retenção gástrica proximal na DRGE.

CONSENSO DE MONTREAL E DEFINIÇÕES DA DRGE

DRGE tem sido definida pelo consenso brasileiro de DRGE como "afecção crônica decorrente do fluxo retrógrado de parte do conteúdo gastro-duodenal para o esôfago e/ou órgãos adjacentes ao mesmo, acarretando variável espectro de sintomas e/ou sinais esofagianos e/ou extra-esofagianos, associados ou não a lesões teciduais"(110). Sintomas típicos da DRGE, como pirose e regurgitação, são ocasionais para muitos indivíduos, podendo não afetar a sua qualidade de vida. Nesta situação não fica caracterizada morbidez do refluxo. Em 2006, 44 conceituados especialistas de 18 países obtiveram um grau de entendimento baseado em evidências da DRGE, o qual foi denominado Consenso de Montreal (40). Esse foi alcançado por meio de votações anônimas e sequenciais, permitindo, assim, que durante todo o processo revisões sistemáticas fossem realizadas, garantindo a cada participante mudança de sentença sem constrangimento. Após quatro votações, alcançou-se um grau de entendimento comum em muitos pontos essenciais para a

compreensão da DRGE. Abaixo estão descritas definições importantes obtidas por esse consenso.

Em relação às síndromes da DRGE, ficaram caracterizadas: as síndromes esofágicas - sintomáticas (síndrome típica de refluxo ou síndrome de dor torácica relacionada ao refluxo gastroesofágico) ou com lesão esofágica (ER, estenose péptica, EB e adenocarcinoma esofágico); síndromes extraesofágicas - com associações já estabelecidas (tosse, laringite, asma ou erosão dental relacionados ao refluxo) ou com associações propostas (faringite, sinusite, fibrose pulmonar idiopática e otite média recurrente) – (Figura 1).

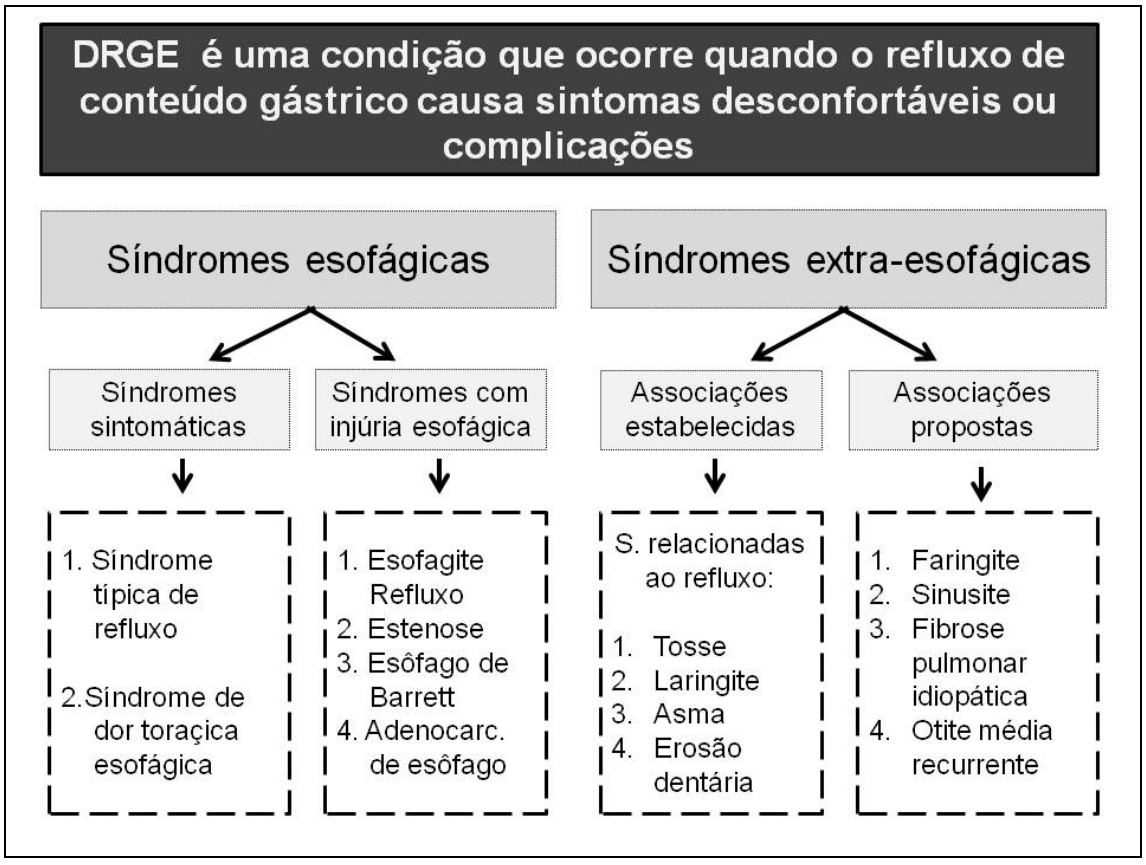


Figura 1. Consenso de Montreal e definições das síndromes esofágicas e extraesofágicas da DRGE(40).

A DRGE é caracterizada como afecção decorrente de aumento da exposição da

mucosa do esôfago ao conteúdo gástrico, determinando sintomas desconfortáveis ou complicações. Sintomas incomodativos são definidos pelo paciente como aqueles que comprometem seu bem-estar. São sintomas típicos a pirose e a regurgitação. Desse estudo citam-se ainda pontos de elevada concordância ou elevado grau de evidência em relação à síndrome esofágica sintomática: pirose é a sensação de queimação retroesternal e regurgitação é a percepção de refluxo de conteúdo gástrico para a boca ou a hipofaringe. Pirose e regurgitação são sintomas característicos da DRGE, que é a causa mais comum de pirose. Sintomas também podem ser causados por refluxo levemente ácido ou conteúdo gasoso. Pirose pode se dever a outras causas que não a DRGE, porém sua prevalência é desconhecida. A DRGE pode ser diagnosticada apenas por sintomas típicos, dispensando exames adicionais. A DRGE não erosiva, também denominada "doença do refluxo endoscopicamente negativa", é definida pela presença de sintomas incomodativos do refluxo na ausência endoscópica de soluções de continuidade da mucosa do esôfago. Dor epigástrica pode ser o mais proeminente sintoma de DRGE. Distúrbios do sono frequentemente estão associados à DRGE. Dor torácica não distinta da dor cardíaca isquêmica pode ser determinada por DRGE, mesmo quando não é acompanhada de pirose ou regurgitação. Distúrbios motores de esôfago podem determinar dor, que simula dor cardíaca isquêmica por um mecanismo separado do refluxo gastroesofágico, embora essa situação seja menos frequente. Disfagia é a percepção de dificuldade de passagem do alimento da boca para o estômago, considerada como incomodativa quando determina mudança de seus padrões alimentares ou causa impactação alimentar. A disfagia persistente, progressiva ou incomodativa é um sintoma de alarme para estenose ou câncer de esôfago que merece investigação.

Em relação às lesões esofágicas, obteve-se elevado grau de concordância ou

evidência nas complicações esofágicas da DRGE, que são ER , hemorragia, estenose, EB e adenocarcinoma. A ER é definida endoscopicamente por rupturas epiteliais na mucosa esofágica distal e, embora a frequência e intensidade da pirose estejam correlacionadas com a lesão mucosa, nenhuma delas prediz a severidade do dano mucoso de modo acurado. O consenso propõe a utilização da classificação de Los Angeles para caracterização e graduação de ER.

QUESTIONÁRIOS DE QUALIDADE DE VIDA

Grande parte dos estudos de DRGE na última década foram baseados na presença e evolução das alterações endoscópicas da mucosa esofágica (111); porém, com a adoção do Consenso de Montreal, tornou-se necessária a confirmação e graduação do caráter desconfortável dos sintomas. Dada a subjetividade para a caracterização do impacto dos sintomas no bem-estar dos pacientes, questionários de qualidade de vida tornaram-se ferramentas essenciais para clínicos e pesquisadores. Esses instrumentos possibilitam quantificar por meio de escores o caráter incomodativo dos sintomas. Velanovich e cols. construíram e validaram uma escala baseada em sintomas típicos para a DRGE (112). Fornari e cols. traduziram, adaptaram e validaram este questionário de qualidade de vida para a língua portuguesa, além de torná-lo mais abrangente ao adicionar a variável regurgitação (113), adequando-o às definições das síndromes esofágicas sintomáticas determinadas pelo Consenso de Montreal.

DIAGNÓSTICO

A propedêutica diagnóstica do paciente com DRGE deve ser baseada em sintomas e centrada no paciente (40). Pirose e regurgitação são suficientemente descritivas para

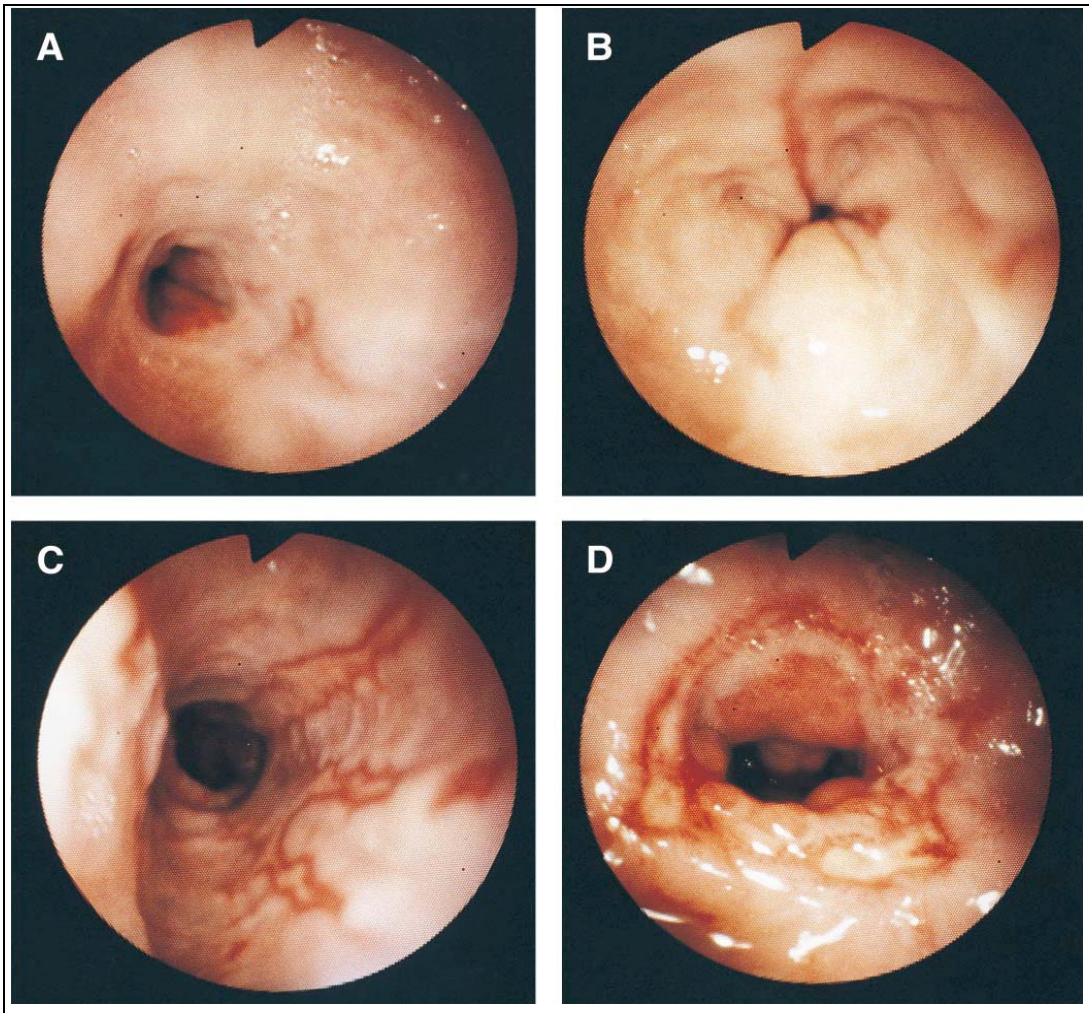
estabelecer diagnóstico e dispensam exames complementares quando em primeiro nível de atenção. A presença desses sintomas típicos tem especificidade para DRGE de 89 e 95%, respectivamente, contudo apresentam baixa sensibilidade (38 e 6%), justificando a necessidade de estudos complementares (114). Esses são utilizados para confirmação diagnóstica, detecção de complicações e avaliação de resposta terapêutica. São importantes também na avaliação de pacientes com sintomas atípicos, visto que predominam em uma quarta parte dos pacientes com DRGE (115). Os exames complementares comumente utilizados são endoscopia digestiva alta (EDA), Rx baritado de esôfago e estômago (RxEE), monitoramento do pH esofágico (pH-metria de 24h) e o teste terapêutico com medicamentos ácido-supressores.

ENDOSCOPIA DIGESTIVA ALTA

A endoscopia digestiva alta possibilita a identificação de alterações mucosas como ER, EB ou adenocarcinoma de esôfago. Contudo, a EDA apresenta baixa sensibilidade na detecção de DRGE. Na avaliação de pacientes com pirose diária, ER é identificada em pouco mais de 30% (116, 117). A ER foi estratificada em graus de gravidade, sendo classificada de A (menos grave) a D (mais grave) (33), como demonstrado na Figura 2(118). Mais de 50% dos pacientes com sintomas de DRGE não apresentam lesões esofágicas à endoscopia, caracterizando-se, assim, a doença do refluxo endoscopicamente negativa (116, 117). Essa condição é definida, endoscopicamente como aquela em que sintomas típicos da DRGE são causados pela presença de ácido intraesofágico, contudo sem determinar lesão mucosa (40, 119). No entanto, nem sempre os sintomas são consequentes ao ácido.

Martinez demonstrou que em apenas 45% dos casos de doença do refluxo endoscopicamente negativa a pH-metria de 24h foi positiva; a acidificação do

esôfago por refluxo gastroesofágico induziu sintomas em 50% desses pacientes, ao passo que nos pacientes com doença do refluxo endoscopicamente negativa e com pH-metria de 24h negativa os sintomas foram percebidos em apenas 18%(120).



Adaptado de Armstrong et. Al (118)

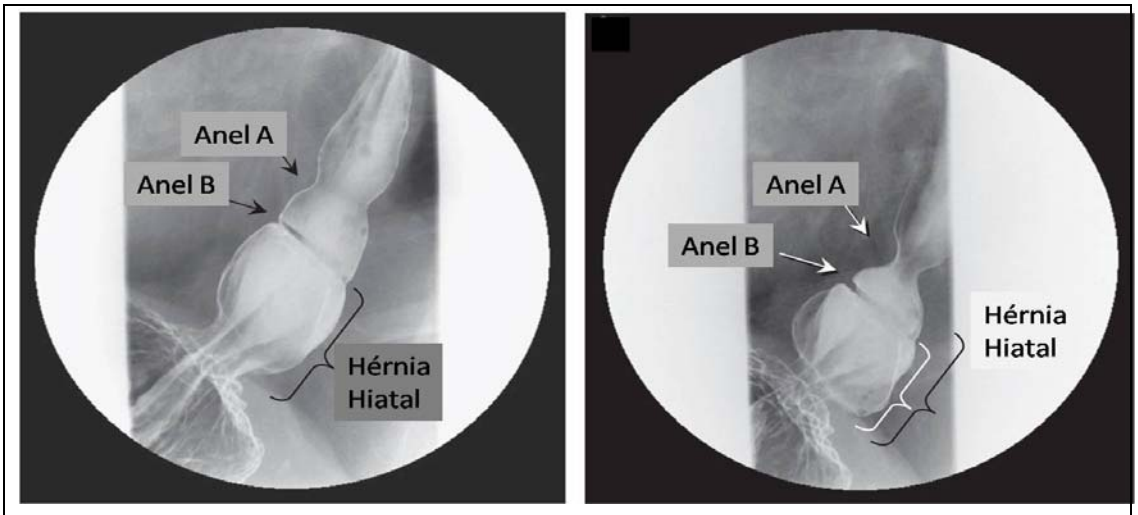
Figura 2 Classificação de Los Angeles, A) erosões menores que 5mm, não confluentes, B) erosões maiores que 5 mm, mas não confluentes, C) erosões confluentes com comprometimento < 75% da luz esofágica e D) comprometimento > 75% da luz esofágica.

A utilização de endoscopia de alta resolução com magnificação demonstrou aumento da extensão das papilas e hiperplasia de células basais em 70% dos pacientes com doença do refluxo endoscopicamente negativa. Sua associação com ácido pode ser

ratificada já que, após quatro semanas de tratamento com IBP, em todos os pacientes essas lesões desapareceram(121), no entanto difere da esofagite erosiva por estar menos associada à hérnia hiatal e ao refluxo biliar (122).

Estudo radiológico baritado de esôfago, estômago e duodeno

O RxEE possibilita a avaliação da presença de hérnia hiatal, distúrbios motores como esôfago em quebra-nozes e acalásia, estase gástrica e estenose pilórica, e, combinando técnicas de compressão abdominal com duplo contraste, apresenta sensibilidade de 87% e acurácia de 81% no diagnóstico de DRGE (123). Campbel e cols. demonstraram que, pela redução ou ausência de peristaltismo associado a contrações não peristálticas do esôfago, pode-se inferir a ocorrência de DRGE(124). Ainda é possível dimensionar a porção de estômago intratorácico (125) como na Figura 3, e a irredutibilidade da hérnia de hiato por deslizamento está associada à esofagite de refluxo (126).



Adaptado de Kharilas e cols.(125)

Figura 3. Note-se que o Anel B está acima da impressão diafragmática mesmo após a deglutição.

Isso tem sugerido que, diante de refluxo severo ao estudo radiológico, o estudo do pH esofágico poderia ser dispensado (127). Em relação ao diagnóstico de hérnia de hiato, a endoscopia foi superior, com acurácia de 93% em comparação a 60% do RxEE. Nesse estudo não foi utilizada a técnica de duplo-contraste (128).

pH-metria de 24h

A presença de sintomas típicos da DRGE dispensa qualquer investigação adicional para se iniciar o tratamento da DRGE (40). Contudo, na ausência de esofagite em pacientes refratários aos tratamentos clínicos, ou naqueles com sintomas atípicos, existe a necessidade de se comprovar a indução dos sintomas pelo ácido. Os demais testes disponíveis inferem a presença de ácido, estando, portanto, sujeitos ao erro, ao passo que a pH-metria de 24h mede a quantidade de exposição ácida (129). A análise da pH- 24h considera os momentos em que o pH esofágico está abaixo de 4. Esse limite ficou assim definido porque em indivíduos normais o pH esofágico mantém-se acima de 4 durante 98,5% do tempo em monitoramento de 24h (130). Consequentemente, medindo a exposição ácida de esôfago, é possível quantificar o tempo de exposição ácida em 24h ou em períodos específicos, como após as refeições, durante o sono, em decúbito ortostático; medir o tempo decorrido para ocorrer o clareamento esofágico e correlacionar a ocorrência de sintomas com o período de exposição ácida (129).

Teste terapêutico

A proposição do Consenso de Montreal de que a ocorrência de sintomas típicos da DRGE dispensa investigação diagnóstica adicional faz do teste terapêutico a

ferramenta diagnóstica mais utilizada, já que, pela adequada resposta sintomática ao tratamento medicamentoso, é possível inferir a ocorrência de DRGE. Pacientes que não têm melhora da síndrome esofágica com o uso de IBP frequentemente apresentam outro diagnóstico como causa dos sintomas. O uso de Omeprazol demonstrou valor preditivo positivo de 68% (131) e uma sensibilidade de 75 a 80% (132, 133), quando o parâmetro é estabelecido por meio de pHmetria-24h. Essa abordagem tem sido amplamente utilizada em razão do baixo custo e da praticidade. Em avaliação de tosse de etiologia desconhecida, Ourse cols. demonstraram superioridade do teste terapêutico em relação à pH-metria de 24h (134).

OBESIDADE E DRGE

Obesidade é definida pelo IMC igual ou superior a 30 kg/m^2 e sua abrangência global caracteriza uma doença epidêmica cuja prevalência vem aumentando. Prova disso é que, em adultos, no período de 1980 a 2008, passou de 15 para 33% (135). Em crianças e adolescentes, a prevalência triplicou nesse mesmo período(136), e os custos disso aos sistemas de saúde são assustadores. Ainda em 1998, os gastos médicos com obesidade e sobrepeso nos EUA correspondiam a 9,1% do gasto total com saúde (137). A DRGE compromete 20% da população adulta dos EUA e sua incidência parece ter aumentado, sugerindo uma forte associação com obesidade, confirmada em uma análise de mais de 3.000 indivíduos com sintomas de DRGE, que foram comparados a 40.000 controles. Neste estudo a probabilidade de apresentar refluxo em mulheres e homens com IMC entre 25 e 30 Kg/m^2 duplica e, na obesidade (>30Kg/m^2), aumenta para três e quatro vezes, respectivamente (138). Vários estudos têm demonstrado a associação positiva entre IMC (136, 139-144), ou circunferência abdominal (48) (12) ,e DRGE.

Os indivíduos com obesidade frequentemente apresentam comorbidades graves e ameaçadoras à vida ou têm reduzida sua qualidade de vida. Diabetes tipo II, hipertensão arterial sistêmica, dislipidemias compõem a síndrome metabólica, que é a grande responsável pela mortalidade pela doença. Nesses indivíduos, além dos distúrbios metabólicos, as complicações articulares, a apneia do sono e a esteatose hepática melhoram significativamente com a perda de peso. Em virtude da baixa resposta aos tratamentos não cirúrgicos na obesidade severa, a cirurgia bariátrica é o tratamento de escolha. Recente estudo em 16.000 obesos demonstrou que aqueles submetidos à GYR apresentaram redução de 92% na mortalidade por diabetes tipo II, 56% por infarto agudo do miocárdio e 60% por câncer (145). A DRGE é uma das comorbidades associadas à obesidade e sintomas típicos da doença estão presentes em grande parte dos indivíduos obesos. Contudo, naqueles com IMC$\geq$ 35Kg/m^2, candidatos à cirurgia bariátrica, a aplicação do Consenso de Montreal apresenta valor preditivo negativo de 47%, com acurácia de 79% (16). Isso sugere menor sensibilidade visceral nesta população (17), de modo que investigação complementar deve ser considerada mesmo na ausência de sintomas.

A associação entre obesidade e DGRE tem motivado os clínicos a recomendar a perda de peso nos pacientes com DRGE, contudo essa resposta à perda ponderal é controversa (146, 147). Soma-se a isso o fato de que pacientes submetidos a procedimentos como banda gástrica ajustável laparoscópica, gastroplastia vertical com bandagem ou gastrectomia em manga laparoscópica frequentemente apresentam progressão da DRGE, a qual tem sido identificada novamente no pós-operatório em 12 a 22% (148-150). Contudo, recentes estudos têm demonstrado que a DRGE melhora substancialmente com a GYR e, pelo fato de oferecer benefícios em relação às demais comorbidades, tem sido preferida a opção cirúrgica em relação à

fundoplicatura de Nissen, mesmo em indivíduos com IMC de 30 Kg/m^2 (20, 22, 23).

FISIOPATOLOGIA DA DRGE NA OBESIDADE

A evidência de que o ganho de peso encontra-se associado ao aumento na prevalência e severidade da DRGE tem sido muito bem documentada, no entanto os mecanismos envolvidos permanecem obscuros. O aumento da ocorrência de hérnia hiatal em indivíduos obesos vem sendo demonstrado e, quando comparados a não obesos, a prevalência de hérnia hiatal aumenta em quatro vezes (151-153). A obesidade determina aumento da pressão abdominal e, obviamente, do gradiente de pressão abdômino-torácico (141, 154), o qual empurra o conteúdo gástrico em direção ao esôfago. Caberia, então, à competência do EIE e da crura diafragmática a contenção do refluxo. Esse aumento pressórico determina também estresse sobre a membrana frenoesofágica, que em razão da sua ruptura permite o deslocamento cranial da junção esofagogástrica, com o consequente afastamento do EIE da crura diafragmática. Pandolfino e cols. demonstraram correlação positiva entre IMC e afastamento do EIE da crura diafragmática mesmo após ajuste para idade, sexo e presença de DRGE (141). O gradiente gastroesofágico e IMC foram fatores preditivos da ocorrência de 69% de hérnia hiatal em pacientes consecutivos com sintomas típicos, sendo esta a única variável independente para DRGE (155). Já em uma série de pacientes obesos candidatos à cirurgia bariátrica, 52,6% deles apresentaram hérnia hiatal e 31%, esofagite (142). Obesidade também está relacionada a diversos distúrbios motores do esôfago. A ocorrência de hipotonia do EIE em candidatos à cirurgia bariátrica tem sido associada aos eventos de refluxo gastroesofágico. Entretanto, sua prevalência tem sido extremamente variável, de 3 a 69% (17, 142, 156, 157), e quando comparada em indivíduos com e sem obesidade,

não foi evidenciada diferença (158). A MEI prejudica o clareamento esofágico e prolonga a exposição do esôfago ao material gástrico refluído, sendo, no entanto, identificada em apenas 2% dos pacientes (156). Emerenziani e cols. demonstraram refluxo gastroesofágico no período pós-prandial imediato, no qual a distensão gástrica é máxima (159). Ainda, o relaxamento transitório do EIE está aumentado em indivíduos obesos, havendo correlação positiva tanto com IMC quanto com circunferência abdominal (154). Outro fator que dificulta o clareamento esofágico é a secreção salivar reduzida em indivíduos com IMC elevado (160). Características peculiares a indivíduos com obesidade também são relevantes na gênese da DRGE, que, assim como obesidade, está associada a apneia do sono (161), aumento de ingesta calórica e, especificamente, de gorduras (162) e aumento de secreção de bile e suco pancreático (144).

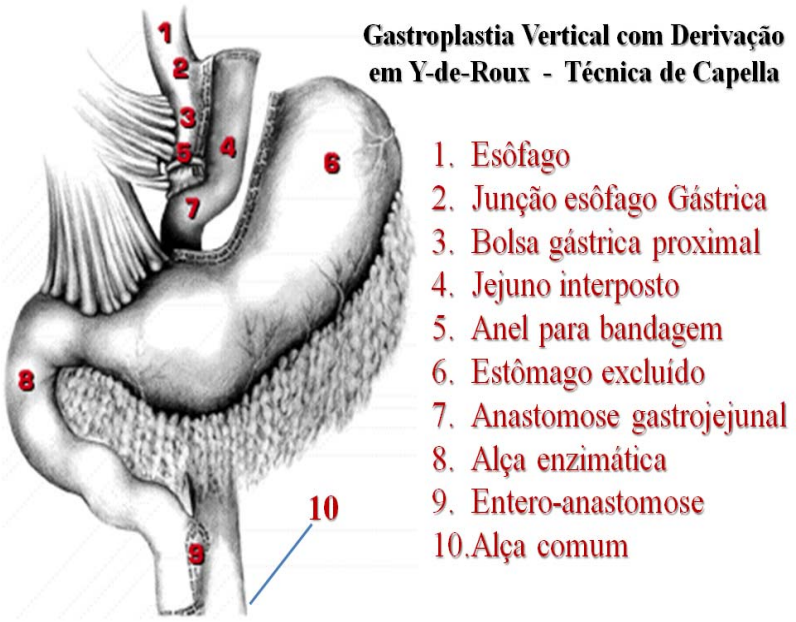
TRATAMENTO CIRÚRGICO DA DRGE NA OBESIDADE

DRGE e obesidade são doenças comuns e frequentemente coincidentes. Por conceito, o tratamento da DRGE implica redução de produção de ácido, melhora do esvaziamento gástrico, redução de refluxo duodenogástrico. Somam-se a essa medidas que aumentam a competência dos mecanismos antirrefluxo o reforço do tônus do EIE e a correção da hérnia de hiato. Embora tratamentos medicamentosos sejam eficientes, pela elevação do pH gástrico, o tratamento cirúrgico pode alcançar todas essas metas. A fundoplicatura é o padrão-ouro utilizado no tratamento cirúrgico da DRGE, entretanto recidivas na maioria das vezes se devem à migração da junção escamocolunar através do hiato, em razão da recidiva da hérnia (163). Fatores envolvidos na recorrência da hérnia de hiato são hérnias volumosas, vômitos alimentares no período pós-operatório imediato e início da experiência durante a

curva de aprendizado (164). É de se esperar que esses três aspectos sejam intensificados nos indivíduos obesos. Inicialmente, o aumento da pressão abdominal cria um ambiente favorável à ocorrência de hérnias e, no pós-operatório, favorece a ruptura da hiatoplastia. O aumento da pressão intra-abdominal também está associado a uma maior ocorrência de estase gástrica, favorecendo vômitos. Por fim, em razão da eficácia do tratamento clínico, existe uma tendência a se evitar cirurgia em indivíduos muito obesos, pois mesmo bons cirurgiões acabam enfrentando maior índice de complicações em obesos (165). Embora alguns autores tenham demonstrado que obesidade não afeta o resultado da cirurgia do refluxo (166, 167), em recente publicação houve recidiva 4,8 vezes maior em indivíduos com IMC $\geq$ 35 Kg/m^2, em comparação aos com sobrepeso e obesos (168). Perez e cols., sob o pretexto de reduzir as limitações técnicas determinadas pela obesidade visceral, compararam a abordagem torácica no tratamento da DRGE à técnica de Nissen por laparoscopia. Os autores identificaram que, independentemente da abordagem, a obesidade era o maior fator de risco para recidiva da DRGE. Nesse grupo a recidiva foi de 31% em obesos VS. 4,5% e 8% em indivíduos com peso ideal ou sobrepeso, respectivamente (18) .

CIRURGIA BARIÁTRICA E DRGE

Recentemente, a cirurgia bariátrica tornou-se popular no tratamento da obesidade e a melhora de suas comorbidades é amplamente verificada (169). Contudo, no que diz respeito ao tratamento da DRGE, tem sido demonstrado que procedimentos como banda gástrica laparoscópica e gastroplastia vertical com bandagem, além de não melhorarem, podem induzir sintomas de refluxo gastroesofágico (148-150). Capella e cols. propuseram uma técnica cirúrgica para tratamento de obesidade mórbida, que consistia na criação de um tubo gástrico ao longo da pequena curvatura com utilização de bandagem, como demonstrado na Figura 4 (170).



Adaptado de Capella, RF, Capella JF

Figura 4. Técnica da gastroplastia vertical com bandagem e derivação jejunal em Y-de-Roux

A observação de que GYR melhora sintomas de DRGE tem sido descrita em várias análises retrospectivas (23, 171). Em recente estudo, Mejía-Rivas e cols.

identificaram redução do percentual de tempo de pH esofágico, <4 de 10,7 para 1,6, e do escore de De-Meester, de 48,3 para 7,7 ($p<0.001$). Entretanto, este estudo não contemplou prevalência de esofagite nem se houve melhora endoscópica. Merrouche e cols., em estudo com 100 pacientes candidatos à banda gástrica laparoscópica ou GYR, avaliaram-nos no pré-operatório e no pós-operatório para DRGE. Hérnia de hiato foi identificada com a EDA em 39% e esofagite, em 6,4%. O escore de DeMeester foi patológico em 53,3% dos casos e em 69% dos casos houve hipotonia do EIE. Infelizmente, neste estudo houve perda de seguimento de 73%. Contudo, a análise dos pacientes remanescentes identificou significativa melhora à pH-metria de 24h nos pacientes submetidos à GYR e uma tendência de piora naqueles com banda gástrica laparoscópica(172).

Em recente consenso de cirurgiões americanos foi alcançado um elevado grau de entendimento, sugerindo que a cirurgia bariátrica pode ser destinada a pacientes com obesidade Grau I (IMC= 30-35 Kg/m^2), quando na presença de comorbidades relacionadas ao peso.A extensão da GYR a pacientes com DRGE tem sido reforçada (22, 173) com segurança e eficácia similar às da fundoplicatura(20).

CONCLUSÃO

DRGE e obesidade são doenças crônicas frequentes e, muitas vezes, coincidentes. Seu elevado impacto socioeconômico tem induzido clínicos e cirurgiões a buscar tratamentos que atuem no sentido de aliviar sintomas, promover resolução ou impedir progressão das comorbidades e/ou complicações. Igualmente necessário é aliviar os sistemas de saúde pela redução de custos dessas doenças de curso tão prolongado e melhorar a produtividade desses indivíduos. A melhor compreensão da fisiopatologia da DRGE e, particularmente, do papel da obesidade nesse cenário

indica a necessidade de serem reavaliados conceitos e métodos. Novos critérios endoscópicos, manométricos, ph-métricos e, sobretudo, clínicos devem ser definidos em pacientes com obesidade mórbida. Deve-se, ainda, considerar a GYR como alternativa terapêutica para pacientes obesos com DRGE.

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JUSTIFICATIVA

Obesidade mórbida e doença do refluxo estão associadas. O aumento da prevalência dessas duas doenças lança ao cirurgião desafios no tratamento cirúrgico. Os resultados da fundoplicatura no tratamento da cirúrgico da DRGE em obesos são controversos, já que aumento de recidiva dos sintomas, ou mesmo de lesão esofágica, tem sido mais prevalente nesses doentes. Esses critérios foram definidos pelo Consenso de Montreal, como sendo essenciais para a caracterização da doença.

A GYR, inicialmente descrita para promover perda de peso, tem sido recomendada como alternativa para tratamento de DRGE em pacientes obesos. . Embora resultados iniciais sejam favoráveis, poucos estudos prospectivos avaliam a GYR no controle da DRGE associada à obesidade.

Assim, é fundamental estabelecer a utilidade do Consenso de Montreal na detecção de DRGE em obesos mórbidos. Além disso, a avaliação da GYR em determinar alívio de sintomas e lesões de DRGE poderá reforçar esse tipo de técnica como escolha para esses pacientes. Ainda, a resposta em relação à hérnia hiatal e aos distúrbios de motilidade esofágica após esse procedimento é desconhecida. Em razão de todas essas questões em aberto, realizamos o presente estudo, prospectivo, procurando responder a algumas dessas questões e contribuir para o melhor entendimento dessas doenças.

OBJETIVOS

a. Principal:

- Avaliar a eficácia da gastroplastia vertical com bandagem e reconstrução em Y-de-Roux no tratamento da doença do refluxo gastroesofágico.

b. Secundários:

- Analisar a validade do consenso de Consenso de Montreal no diagnóstico de GERD em indivíduos com obesidade mórbida
- Verificar a prevalência de distúrbios motores do esôfago e hérnia hiatal em pacientes com obesidade e as alterações nessa prevalência após a realização de gastroplastia vertical com bandagem e reconstrução em Y-de-Roux

PRODUÇÃO CIENTÍFICA

ARTIGO 1 –Português submetido ao Annals of Surgery

Gastroplastia vertical com derivação em Y-de Roux melhora a doença do refluxo gastroesofágico em obesos mórbidos: um estudo prospectivo utilizando critérios do Consenso de Montreal

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Título abreviado: DRGE pré e pós Gastroplastia em Y-de-Roux

RESUMO

Objetivos: Avaliar o efeito da gastroplastia vertical com derivação em Y-de-Roux (GYR) na doença do refluxo gastroesofágico (DRGE) baseado no Consenso de Montreal. Métodos: oitenta e seis pacientes [25 homens; idade 38 ± 12 anos; IMC 45 (35-68 Kg/m2)] foram investigados para DRGE antes do GYR e seis meses após. Síndromes esofágicas e extraesofágicas foram avaliadas com base no Consenso de Montreal. Análises adicionais incluídas foram exposição ácida, acidez da bolsa gástrica, motilidade esofágica e hérnia hiatal deslizante. Resultados: Síndrome típica de refluxo (STR) foi evidenciada em 47 pacientes (55%) no pré-operatório e desapareceu em 39 (79%) após GYR. Dos 39 pacientes sem sintomas, 4 (10%) apresentaram STR no pós-operatório (P<0,0001). A mucosa esofágica melhorou em 17, permaneceu inalterada em 51 e piorou em 8 pacientes (P=0,001), relacionada à esofagite de refluxo. Síndromes extraesofágicas estavam presentes em 16 pacientes no período pré-operatório e em apenas um após GYR (P = 0,0003). Exposição ácida total foi reduzida de uma mediana de (IIQ25%-75%) de 5,1% (2-8,2) para 1,1%(0,2-4,8), (P=0,0002). A maioria dos pacientes (86%) apresentou uma bolsa gástrica ácida em jejum após GYR. Motilidade esofágica foi similar no sexto mês de pós-operatório, ao passo que hérnia hiatal foi relacionada à esofagite, mas não a sintomas no pós-operatório. Bem-estar relacionado à DRGE e uso de inibidores da bomba de prótons (IBP) melhoraram após GYR. Conclusões: GYR melhora sintomas de DRGE na maioria dos pacientes em seis meses após a cirurgia. Estudos a longo prazo são necessários para avaliar o comportamento da DRGE após GYR.

Palavras-chave: Obesidade mórbida, cirurgia bariátrica, doença do refluxo gastroesofágico, ph-metria de 24h, endoscopia, esofagograma.

INTRODUÇÃO

Obesidade mórbida e DRGE tornaram-se um problema de saúde pública. Essas entidades são globalmente prevalentes, determinando perda de qualidade de vida e elevados custos aos sistemas de saúde (1-7). Vários estudos têm sugerido uma associação causal da obesidade em relação à DRGE, baseada em fatores mecânicos, neuro-humorais e comportamentais visto que o excesso de peso atua favorecendo o refluxo (8-12).

Um consenso global sobre definições e classificação de DRGE foi proposto para orientar a abordagem do paciente na prática clínica e na pesquisa (13). Conforme esse consenso, DRGE foi definida pela presença de sintomas desconfortáveis e/ou complicações. A doença pode ainda ser classificada em síndromes esofágicas ou extraesofágicas, de acordo com as características dos sintomas. Recentemente descrevemos o desempenho desse consenso nos pacientes com obesidade mórbida. Foi demonstrada sensibilidade limitada na detecção de DRGE, já que pacientes que negavam sintomas apresentavam esofagite de refluxo (ER) ou aumento de exposição ácida (14).

A DRGE é peculiar em pacientes com obesidade mórbida. Sua prevalência mais elevada reforça a importância do estresse sobre a junção esofagogástrica, que ocorre pelo acentuado excesso de peso. Esse fenômeno pode ser manifestado pelo aumento do gradiente pressórico entre estômago e esôfago, bem como pelo aumento da frequência de hérnia hiatal deslizante (11;15). Como resultado, parâmetros objetivos de DRGE, incluindo ER e aumento de exposição ácida, têm sido frequentemente descritos em obesos (16-18). Apesar disso, uma percepção alterada de sintomas em

pacientes com achados objetivos de DRGE levou alguns autores a sugerir uma sensibilidade esofágica alterada em indivíduos com obesidade mórbida (18;19).

Obesidade mórbida tem sido convencionalmente tratada com cirurgia bariátrica. Dentre as técnicas disponíveis, GYR tem sido a mais utilizada (20-22), cujo efeito na DRGE parece ser favorável em estudos recentes realizados em populações oriental e ocidental (23-28). Entretanto, várias particularidades continuam desconhecidas sobre o efeito do GYR na DRGE, incluindo avaliação do desfecho clínico baseado no Consenso de Montreal, bem como exposição do esôfago ao ácido e à acidez da bolsa gástrica após GYR. Adicione-se a essas o efeito do GYR na motilidade esofágica e na hérnia hiatal. No sentido de prover essas respostas, conduzimos um estudo prospectivo avaliando DRGE antes e após a GYR.

MÉTODOS

Pacientes

Cento e vinte e seis pacientes obesos mórbidos [87 mulheres, idade 37 ± 11.6 anos, índice de massa corporal (IMC) 44.4 ± 7.5 Kg/m2], atendidos em clínica privada (Gastrobese) entre março e outubro de 2007, foram convidados a participar do estudo. Os critérios de inclusão foram: (1) idade entre 18 e 70 anos, (2) IMC≥40 Kg/m2 ou ≥ 35 Kg/m2 associado a comorbidades relacionadas ao excesso de peso, (3) ausência de cirurgia gastroesofágica, e (4) aceitar a submissão à GYR pela técnica laparotômica. Todos os pacientes foram recrutados independentemente da presença de sintomas de DRGE.

Os pacientes foram submetidos à avaliação antes e seis meses após a GYR seguindo-

se um protocolo padronizado, que consistiu em: (1) avaliação clínica com base no Consenso de Montreal, (2) endoscopia digestiva alta (EDA), (3) manometria esofágica e pHmetria esofágica de 24h e (4) estudo baritado de esôfago e estômago (RxEE).

O estudo foi conduzido em acordo com a declaração de Helsinki e foi aprovado pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre. Consentimento informado foi obtido para cada participante.

Avaliação clínica

Pacientes com sintomas de refluxo foram classificados como portadores de síndromes esofágicas ou extraesofágicas. Azia, regurgitação e disfagia foram graduadas pela aplicação de um questionário de sintomas validado (DRGE-QS) (29;30), com as respectivas perguntas: "Quanto lhe incomoda a azia", " Você percebe retorno de líquido azedo ou amargo do estômago para garganta?", e "Você tem dificuldade para engolir?". Cada resposta foi graduada como (0) sem sintomas, (1) sintomas presentes, mas não desconfortáveis, (2) sintomas desconfortáveis, mas não todos os dias, (3) sintomas desconfortáveis todos os dias, (4) sintomas que comprometem atividades diárias e (5) sintomas incapacitantes. Pirose, regurgitação e disfagia foram considerados incapacitantes se ≥ 2. Síndrome típica de refluxo (STR) foi definida na presença de pirose ou regurgitação desconfortáveis. Ainda foi graduado bem-estar relacionado à DRGE através da pergunta: "Como está sua satisfação com a sua atual condição?", sendo graduada de 1-6 : (1) incapacitado, (2) muito insatisfeito, (3) insatisfeito, (4) indiferente, (5) satisfeito, e (6) muito satisfeito. Sintomas laríngeos e respiratórios foram avaliados por tabela de dados. Ambos, DRGE-QS e revisão de sintomas, foram aplicados por enfermeira desconhecedora

dos exames complementares. Dados sobre o uso de medicações inibidoras de secreção ácida, como bloqueadores H2 e inibidores de bomba protônica (IBP), foram coletados. Peso e altura foram medidos com balança e estadiômetro Filizola, o IMC foi calculado pela razão do peso (kg) pelo quadrado da altura (m^2) (31).

Endoscopia digestiva alta

Endoscopia foi realizada após 8h de jejum, utilizando-se um videoendoscópio (Olympus GIF-130, Tokyo, Japan). ER foi descrita de acordo com a classificação de Los Angeles (32). Resumidamente, erosões (uma ou mais) sem extensão entre o topo de duas pregas mucosas foram classificadas como grau A (< 5 mm de extensão) ou B (> 5 mm de extensão), ao passo que erosões com extensão lateral foram classificadas como grau C (<75% da circunferência esofágica) ou D (> 75%). Os exames endoscópicos foram realizados por experientes endoscopistas, desconhecedores dos sintomas dos pacientes.

Esôfagomanometria

O estudo foi realizado por pacientes com jejum de 8 horas, utilizando-se cateter com um sensor de pressão circunferencial em estado sólido, posicionado distalmente, e dois sensores unidirecionais (Konigsberg Instruments, Pasadena, Ca, EUA), posicionados 5 e 10 cm proximais ao sensor distal. O cateter era introduzido por via transnasal até o esôfago com o sensor distal posicionado no lúmen gástrico, pelo menos, 3 cm distalmente ao esfíncter inferior do esôfago (EIE). Com o paciente em decúbito horizontal (cabeceira elevada 30^o), o cateter era tracionado cranialmente em

passos de 1 cm a cada 4-5 oscilação respiratória. Esse processo era mantido, ultrapassando-se zona de alta pressão correspondente ao EIE, até 3 cm acima do esfíncter. A pressão do EIE era medida distalmente ao ponto de inversão pressórica, ao nível expiratório médio. A motilidade do corpo esofágico era acessada após posicionar os sensores de pressão em 3, 8 e 13 cm acima do EIE. Em posição supina, os pacientes efetuavam dez deglutições líquidas (5 mL de água) com intervalos de 30 segundos. Os dados manométricos foram criados a partir de um programa de computador (Sandhill scientific inc, Highlands Ranch, CO, EUA). As dismotilidades esofágicas foram caracterizadas conforme os preconizados pela literatura.

pHmetria esofágica de 24

pH-metria de 24h foi realizada com um pHmetro portátil (Sandhill scientific inc, Highlands Ranch, CO, EUA) e um pH cateter contendo um sensor de antimônio. Após calibração em soluções de pH 4,0 e 7,0, o cateter era instalado via transnasal e posicionado no estômago pela observação de pH <4, sendo tracionado e posicionado 5 cm acima da borda proximal do EIE, determinado por manometria. Inibidores da secreção ácida, incluindo IBP e bloqueadores H2, foram suspensos pelo menos sete dias antes do estudo. Os pacientes foram instruídos a manter suas atividades diárias habituais e anotar em um diário o momento em que ocorriam sintomas, ingestão hídrica ou de alimentos, bem como mudanças posturais. No dia seguinte o cateter era removido e os dados, analisados (software GERDcheck, sanhill Scientific Inc.). Refluxo ácido era definido como uma rápida queda no pH esofágico abaixo de 4,0. Todos os períodos alimentares foram excluídos da análise.

Estudo baritado de esôfago e estômago

O exame radiológico foi realizado com pacientes em jejum de 12 horas, seguindo-se o protocolo padrão. Os pacientes foram estudados após ingesta de 200 mL de solução de bário diluído com radiografias efetuadas em decúbito ventral e ortostático. A determinação de hérnia hiatal baseou-se na avaliação da junção esofagogástrica na radiografia de esôfago durante o decúbito ventral. Um experiente radiologista, desconhecedor dos sintomas e exames do paciente, analisou os radiogramas. Hérnia hiatal foi caracterizada pela presença de anel B ou pregas gástricas localizadas, pelo menos, 2 cm acima da impressão diafragmática. Anel B foi definido como uma suave indentação anelar na junção esofagogástrica (35;36).

Gastroplastia vertical com derivação em Y-de-Roux

GYR foi realizada através de incisão mediana supraumbilical. Uma pequena bolsa gástrica foi criada pela septação gástrica com uso de grampeador linear cortante 100 mm (Ethicon), da pequena curvatura (7 cm verticalmente do cárdia), até 1 cm à esquerda do ângulo de Hiss. O volume estimado da bolsa gástrica é de 20 a 30mL. Na bolsa gástrica, em sua porção média, foi colocado um anel de silastic (6,5 cm em sua circunferência), em sua extremidade distal foi realizada uma anastomose jejunal com alça alimentar de 100 cm e uma alça biliopancreática variando de 60 a 80cm.

Análise estatística

Os dados são apresentados como média e desvio-padrão, para distribuições paramétricas, e mediana e intervalo interquartil, quando houver distribuição não-

paramétrica. Dados quantitativos foram analisados pelo teste t pareado quando normalmente distribuídos, ou por *wilcoxon rank test,* quando de distribuição não paramétrica para as comparações pré e pós-GYR. Teste de McNemar foi utilizado para testar diferenças em proporções pareadas, ao passo que proporções independentes foram analisadas utilizando-se teste de Fisher ou $\chi 2$. As análises estatísticas foram realizadas com GraphPad prism 4 (GraphPad Software,Inc., San Diego, Ca, EUA) and Win PEPI [Abramson JH (2004) WINPEPI computer programs for epidemiologists]. Os resultados foram considerados estatisticamente significantes quando $P < 0,05$.

RESULTADOS

Pacientes

Noventa e quatro pacientes foram incluídos no estudo. Desses oito pacientes foram excluídos por (1) opção pela técnica laparoscópica após avaliação inicial para DRGE (n = 4) e dois recusaram-se a fazer exames pós-operatórios para avaliar DRGE (n = 4).

A amostra final foi composta por 86 pacientes: 25 homens, com idade média de 38 anos (variando de 18 a 61 anos), 82 brancos e 4 mestiços. IMC foi reduzido de uma média (DP) de 43,7 (7,6) Kg/m2 no pré-operatório para 33,2 (5,9) Kg/m2 seis meses após a cirurgia ($P < 0,00001$). Uso de IBP foi reduzido de 17% pré para 5% pós-GYR ($P = 0,013$).

Consenso de Montreal

STR esteve presente em 47 pacientes (55%) no período pré-operatório: 21 com pirose desconfortável, 2 com regurgitação desconfortável e 24 pacientes com ambos. Desses 47 pacientes, 37 (79%) negaram sintomas desconfortáveis na avaliação pós-operatória e 10 continuaram com sintomas: quatro com pirose desconfortável, cinco com regurgitação desconfortável e um com ambos. Dos 39 pacientes que negavam STR no pré-operatório, quatro (10 %) referiram regurgitação desconfortável pós-operatória (P< 0,0001).

Disfagia desconfortável esteve presente em seis pacientes no pré-operatório. Esse sintoma foi resolvido em três após à cirurgia; ao passo que dois pacientes melhoraram, passando a desconfortáveis, e um persistiu com o sintoma. Disfagia não desconfortável foi identificada em cinco pacientes, dos quais dois persistiram com sintomas no período pós-operatório. Dos 75 pacientes que negavam disfagia pré-operatória, 7 (10%) apresentaram disfagia desconfortável e 14 (20 %) referiram disfagia não desconfortável (P=0,013).

Pré e pós-GYR escores de pirose, regurgitação e bem-estar relacionado à DRGE estão demonstrados na Figura 1. Uma melhora significativa foi observada [mediana (IIQ 25-75%)] para pirose [2 (0-2) vs. 0 (0-0); P < 0,0001], para regurgitação [0 (0-2) vs (0-1); P = 0,028] e para bem-estar [4 (3-4) vs 5 (4-5); P = 0,0001] no período pós-operatório, ao passo que em relação à disfagia houve uma discreta piora [0 (0-0) vs. 0 (0-1); P = 0,033].

Dor torácica foi referida por três pacientes no período pré-operatório, combinada à pirose como principal queixa. Esses pacientes negavam dor torácica após a GYR. Síndromes extraesofágicas caracterizadas por tosse crônica e sintomas laríngeos,

estiveram presentes em 17 pacientes (20 %) antes da cirurgia. Todos, com exceção de um paciente, negaram esses sintomas no período pós-operatório (P = 0,0003).

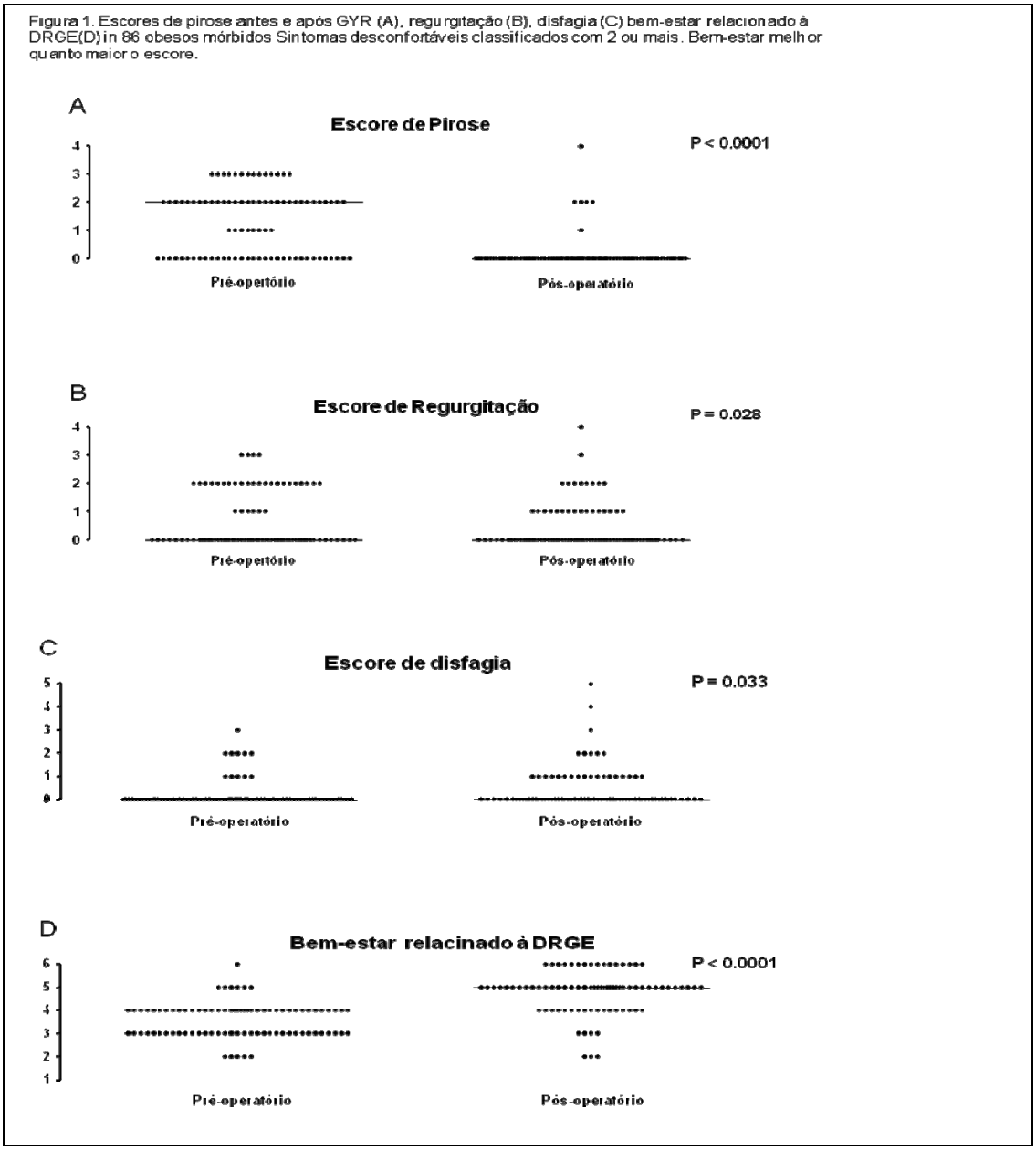


Figura 1. Escores de pirose antes e após GYR (A), regurgitação (B), disfagia (C) bem-estar relacionado à DRGE(D) in 86 obesos mórbidos Sintomas desconfortáveis classificados com 2 ou mais. Bem-estar melhor quanto maior o escore.

Síndromes com injúria esofágica estiveram representadas exclusivamente por ER, identificada em 36 pacientes (42%): 22 com grau A, 10 com grau B e 4 com grau C. Nesses pacientes ER desapareceu em 22, melhorou em cinco, não se modificou em seis e piorou em três após a cirurgia. Dos 50 pacientes sem lesão mucosa, cinco

apresentaram ER no pós-operatório: três com grau A e dois com grau B. Considerando-se os 86 pacientes, a mucosa esofágica melhorou em 27, permaneceu inalterada em 51 e piorou em oito pacientes (p = 0,001). Nem estenose péptica nem esôfago de Barrett eram identificados antes ou após a cirurgia.

Exposição esofágica ao ácido

Considerando todos os 86 pacientes, uma significativa redução da exposição ácida foi identificada [mediana (IIQ25-75%)] após a GYR em tempo total [5,1% (2-8,2) VS. 1,1 (0,2-4,8); P = 0,0002] e ortostático [5,4% (2,8-9,4) VS. 0,8% (0,1 – 2,7); P < 0,0001] (figura 2). Redução também foi evidenciada em posição supina [1,8% (0,1-6,3) VS. 0,3% (0-5,5); P = 0,223], porém sem atingir significância estatística. Dos 58 pacientes com exposição ácida anormal antes da GYR, 26 (45%) apresentaram sua exposição ácida normalizada após cirurgia. Dos 28 pacientes que não apresentaram exposição ácida anormal antes da cirurgia, cinco (18%) demonstraram exposição anormal no sexto mês de pós-operatório (p = 0,0002).

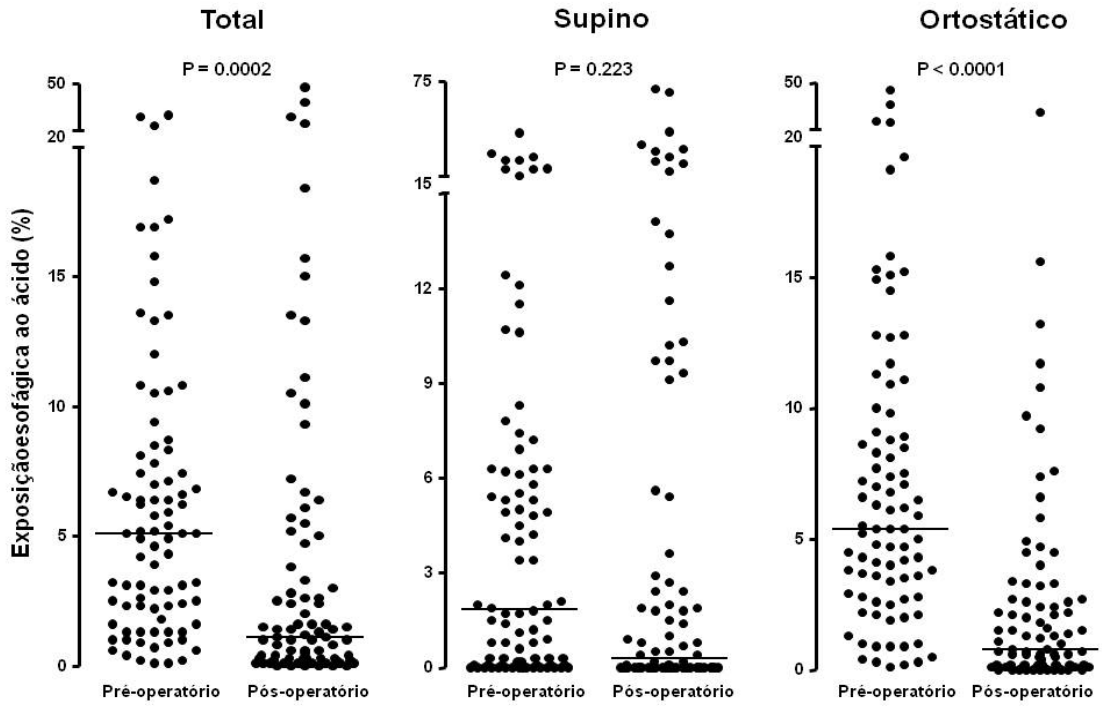
Na avaliação pré-operatória, pacientes com STR apresentaram uma exposição ácida total mais acentuada [mediana(IIQ25-75%)] que aqueles sem sintomas típicos [6,2% (3,2 – 10,5) VS. 2,5% (1,3 – 6,4); P = 0,007]. Na avaliação pós-operatória, pacientes com STR continuaram a apresentar maior exposição ácida total [8% (1 – 13,4) VS. 1% (0,2 – 2,6); P = 0,005].

Acidez da bolsa gástrica

Uma bolsa gástrica ácida (pH<4) foi observada em 74 pacientes (86%) pela pH-

metria pós-operatória. Estes pacientes demonstraram uma exposição ácida aumentada tanto em tempo total como ortostático ou supino, quando comparados aos que apresentaram uma bolsa gástrica não ácida (pH>4) (47% VS. 17%; P = 0,044). STR no período pós-operatório não foram diferentes nos pacientes com ou sem bolsa gástrica ácida (18% VS. 8%; P = 0,543). ER foi mais frequente em pacientes com bolsa gástrica ácida do que naqueles com uma bolsa gástrica não ácida (26% VS. 0%; P = 0,041).

Figura 2. Exposição esofágica ao ácido em período total, supino e ortostático em avaliação pré e pós-operatória(n = 86).



Achados manométricos

Houve uma significativa redução na pressão do EIE após GYR, porém sua extensão não se modificou (Tabela 1). Uma discreta, porém significativa, foi observada na amplitude esofágica distal pós-operatória. Classificações manométricas referentes à peristalse do corpo esofágico e ao tônus do EIE foram similares entre as avaliações pré e pós-operatórias.

Hérnia hiatal

84 pacientes realizaram RxEE antes e após a cirurgia. A hérnia hiatal deslizante foi identificada no pré-operatório em 27 pacientes (32%). Desses, 13 pacientes continuaram com hérnia hiatal deslizante no pós-operatório, ao passo que em 14 pacientes a hérnia hiatal desapareceu. Dos 57 pacientes sem hérnia hiatal radiológica no pré-operatório, 9 (16%) apresentaram-na após a cirurgia (P = 0,0404).

Tabela 1. Achados manométricos pre and post GYR (n = 86).

Achados manométricos	Pre GYR	Post GYR	P
Pressão do EIE [a], mediana (mín-máx)	21.3 (3.6 – 75)	18 (1 – 50.7)	0.004
Extensão do EIE (cm), média ± DP	4.9 ± 1.1	5.1 ± 1.4	0.485
Classificação EIE, n (%)	72 (84)	73 (85)	0.244
Normal	7 (8)	10 (11.5)	
Hipotônico	7 (8)	3 (3.5)	
Hipertônico			
AED (mm Hg), mediana (mín - máx)	106 (29 – 318)	96 (29 – 325)	0.001
CE[b] classification, n (%)	59 (68.5)	55 (64)	0.100[c]
Normal	11 (13)	19 (22)	
MEI	15 (17.5)	11 (13)	
EQN	1 (1)	1 (1)	
Outros[d]			

[a]Pressão do EIE in mm Hg; [b]Corpo esofágico; [c]Cálculado sem "outros"; [d]Espasmo difuso do esôfago (antes GYR) e distúrbio de motilidade inespecífico (após GYR); AED = amplitude esofágica distal; MEI = motilidade esofágica ineficaz; EQN = esôfago em quebra-nozes.

Na avaliação pré-operatória, mais pacientes com hérnia hiatal apresentavam mais frequentemente STR quando comparados àqueles sem hérnia hiatal (78% VS. 44%;

P = 0,003). Após a cirurgia, pacientes com hérnia hiatal apresentaram STR em proporção similar àqueles sem hérnia hiatal (27% VS. 13%; P = 0,140). EDA pré-operatória demonstrou esofagite de refluxo mais freqüentemente em pacientes com hérnia hiatal que aqueles sem hérnia hiatal (56% VS. 35%; P = 0,079), porém sem alcançar significância estatística. No período pós-operatório, a EDA demonstrou maior ocorrência de esofagite em pacientes com hérnia hiatal quando comparados àqueles sem hérnia hiatal (36% VS. 16%; P = 0,05).

DISCUSSÃO

O objetivo de nosso estudo foi avaliar o efeito da GYR na DRGE nos pacientes com obesidade mórbida, pela verificação de (1) avaliação da DRGE pelo Consenso de Montreal, (2) avaliação da exposição ácida do esôfago e (3) acidez da bolsa gástrica. Ainda foram avaliadas motilidade esofágica e hérnia hiatal deslizante antes e após a GYR. Para isso, pacientes não selecionados com obesidade mórbida foram investigados para DRGE antes e seis meses após a cirurgia, utilizando-se uma abordagem padronizada.

Nossos principais achados foram (1) GYR melhora as síndromes esofágicas e extra-esofágicas em pacientes com obesidade mórbida; (2) GYR reduz a exposição esofágica ao ácido particularmente em posição ortostática; (3) acidez da bolsa gástrica é observada na maior parte dos pacientes (86%), possivelmente relacionada à esofagite de refluxo após GYR. Achados secundários foram (1) similaridade no padrão de motilidade tanto do corpo esofágico quanto no tônus do EIE e (2) uma correlação positiva entre hérnia hiatal pós-operatória com esofagite, mas não com STR.

Nossos achados demonstram que GYR determina melhora nas síndromes esofágicas com obesidade mórbida avaliados seis meses após o procedimento. As síndromes esofágicas, incluindo STR e aquelas com injúria esofágica, ou seja, ER, desapareceram na maioria dos pacientes e surgiram em uma minoria daqueles que não as apresentavam no pré-operatório. Essa melhora foi seguida de melhora do bem-estar relacionada à DRGE. Reforçamos que sintomas de refluxo foram avaliados com a utilização de questionário validado (29), capaz de discriminar entre sintomas desconfortáveis daqueles que não incomodam. Esse método permitiu-nos classificar os pacientes pelas recomendações do Consenso de Montreal (13). Estudos têm demonstrado resultados conflitantes sobre o efeito da GYR na DRGE. A maioria dos autores sugere uma melhora na DRGE após a cirurgia (23-28), ao passo que outros demonstram ausência de efeito. No entanto, a perda de seguimento desses pacientes foi acentuada, chegando a 80% (28). Em nosso estudo, a perda de seguimento foi de apenas 9%. Ainda, a utilização do Consenso de Montreal como base de avaliação da DRGE, permitiu uma atualização na forma de relacionar a DRGE à obesidade mórbida.

Após GYR, disfagia apresentou-se em cerca de um terço dos pacientes que negavam esse sintoma anteriormente. Contudo, a maior parte deles graduou esse sintoma como não desconfortável. Em relação a esse achado, Ortega e cols. descreveram uma elevada frequência de disfagia três meses após a cirurgia, que diminuiu um ano após a cirurgia (26) sugerindo uma resposta adaptativa. Os mecanismos determinantes da disfagia após a cirurgia não estão claros. Acreditamos que a combinação de redução do reservatório gástrico e uso de uma banda ou anel gástrico pode explicar tal sintoma em detrimento da possibilidade de comprometimento do trânsito esofágico. Futuras pesquisas deverão esclarecer essa questão.

A GYR reduziu a média de exposição ácida em nossa amostra, efeito que foi limitado à exposição em períodos de ortostatismo. Como esperado, um aumento de exposição ácida foi encontrado em pacientes com STR tanto no pré como no pós-operatório, sugerindo que a exposição ácida da mucosa esofágica tem um papel importante na promoção dos sintomas de refluxo nessa população. Vários estudos suportam o efeito benéfico da GYR no controle da exposição ácida (23,24,26), entretanto os mecanismos envolvidos são desconhecidos. Pela redução do volume gástrico após a cirurgia (38), supõe-se que a quantidade de células parietais seja drasticamente reduzida, devendo ser acompanhada de uma redução da secreção de suco gástrico. Neste estudo demonstramos que a maioria dos pacientes apresentava uma bolsa gástrica ácida quando avaliados em jejum. Esse achado foi relacionado a um aumento na prevalência de esofagite de refluxo. Embora a técnica empregada seja incapaz de avaliar débito de secreção ácida, é capaz de evidenciar que a bolsa gástrica proximal produz ácido após a GYR na maioria dos pacientes. Em conformidade com esse achado, Hedberg e cols. identificaram que pacientes com úlcera de boca anastomótica apresentam aumento de produção ácida na bolsa gástrica proximal em comparação com pacientes assintomáticos (39). Se o débito de ácido da bolsa gástrica proximal difere entre os pacientes com DRGE após a GYR, outros estudos serão necessários.

O padrão da motilidade esofágica não foi significativamente modificado em seis meses após a GYR. Uma ligeira redução foi observada tanto no tônus do EIE quanto na amplitude esofágica distal. Embora o achado de motilidade esofágica ineficaz quase tivesse dobrado na avaliação pós-operatória, não alcançou significância estatística, provavelmente pelo pequeno número de pacientes ou pelo curto seguimento. Uma redução na amplitude esofágica distal pode ser explicada por uma

adaptação do corpo esofágico a um gradiente de pressão gastroesofágico (GPGE) consequente à perda de peso. Estudos têm demonstrado um paralelo entre IMC e GPGE, o que pode influenciar a performace da peristalse esofágica (11,40). Nossa amostra em estudo está em acompanhamento para determinar o comportamento da motilidade esofágica após dois anos da GYR.

Hérnia hiatal após a GYR foi tão frequente no pré quanto no pós-operatório, comprometendo cerca de 30% dos pacientes. Curiosamente, um terço do paciente com hérnia hiatal após a cirurgia não apresentava tal alteração no pré-operatório. Essa foi avaliada por RxEE, uma técnica adequada para esse propósito (36). Hérnia hiatal esteve relacionada à STR no pré e à ER no pós-operatório. Futuros estudos serão necessários para estabelecer a relevância clínica da ocorrência de hérnia hiatal após a GYR.

Em conclusão, avaliamos o efeito da GYR na DRGE em pacientes com obesidade mórbida. Com esse objetivo, os pacientes foram observados antes e seis meses após a cirurgia com a utilização do Consenso de Montreal para a caracterização de DRGE. Evidenciamos melhora das síndromes de DRGE com a GYR na maioria dos pacientes. Também observamos que a GYR reduz significativamente a exposição ácida do esôfago, apesar de haver produção de ácido pela bolsa gástrica proximal. Esses achados foram acompanhados de melhora do bem-estar relacionado à DRGE e redução do uso de IBP. Houve similaridade na avaliação de motilidade esofágica pré e pós-operatória, ao passo que hérnia hiatal não foi relacionada à STR no período pós-operatório. Estudos a longo prazo são necessários para verificar o efeito do comportamento de DRGE após a GYR.

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ARTICLE 1 –English version – submited to Annals of Surgery

Gastric bypass ameliorates gastroesophageal reflux disease in morbidly obese patients: a prospective study based on Montreal Consensus

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Short title: GERD pre and post gastric bypass

ABSTRACT

Objectives: To assess the effect of gastric bypass (GBP) on gastroesophageal reflux disease (GERD) based on Montreal Consensus. Methods: Eighty-six patients [25 men; aging 38 ± 12 years; BMI 45 (35-68 kg/m2)] were investigated for GERD preoperatively to GBP and 6 months later. Esophageal and extraesophageal syndromes were assessed based on Montreal Consensus. Further analysis included esophageal acid exposure, gastric pouch acidity, esophageal motility and sliding hiatal hernia. Results: Typical reflux syndrome (TRS) was present in 47 patients (55%) preoperatively and disappeared in 39 of them (79%) post GBP. Out of 39 patients with no symptoms, 4 (10%) developed TRS postoperatively ($P < 0.0001$). Esophageal mucosa improved in 27, was unchanged in 51 and worsened in 8 patients ($P = 0.001$) in regard of esophagitis. Extraesophageal syndromes were present in 16 patients preoperatively and in none but one post GBP ($P = 0.0003$). Total acid exposure decreased from a median (IQR25%-75%) of 5.1% (2-8.2) to 1.1% (0.2-4.8), ($P = 0.0002$). Most patients (86%) showed and acid gastric pouch in fasting conditions post GBP. Esophageal motility was similar 6 months after GBP, whereas sliding hiatal hernia was related with esophagitis rather than reflux symptoms postoperatively. GERD-related well being and use of proton pump inhibitors were both improved after GBP. Conclusions: GBP ameliorated GERD syndromes in most patients 6 months after the procedure. Long term studies are needed to assess the behavior of GERD post GBP.

Key words: morbid obesity; bariatric surgery; gastroesophageal reflux disease; esophageal pH monitoring; endoscopy, X-rays.

INTRODUCTION

Morbid obesity and gastroesophageal reflux disease (GERD) have become a public health problem. Both entities have been prevalent worldwide, deteriorating quality of life and demanding enormous costs for the health services (1-7) . Several studies have proposed a causative role for obesity on GERD, based on mechanical, neuro-humoral and behavioral factors that overweight exerts in favor of reflux (8-12).

A global consensus about definition and classification of GERD has been proposed to orientate patient's management in general practice and research (13). According to this consensus, GERD has been defined in the presence of troublesome symptoms and/or complications. The disease may be further classified in esophageal and extraesophageal syndromes, based on symptom's characteristics. We recently described the performance of this consensus in patients with morbid obesity. It showed limited sensitivity to detect GERD, as patients who denied reflux symptoms still had reflux esophagitis (RE) or increased acid exposure (14).

GERD has some peculiarities in patients with morbid obesity. Its higher prevalence highlights the importance of the stress over the gastroesophageal junction related with severe overweight. This phenomenon may be manifested by increased pressure gradients between stomach and esophagus, as well as higher frequency of sliding hiatal hernia (SHH) (11;15). As a result, objective GERD parameters, including RE and increased acid exposure have been frequently described in obese individuals (16-18). Despite of this, a reduced perception of symptoms in patients with objective findings of GERD has led some authors to suggest an altered sensitivity of the esophagus in morbidly obese individuals (18;19).

Morbid obesity has been conventionally treated with bariatric surgery. Among

available techniques, gastric bypass (GBP) has been the most employed worldwide (20-22). Its effect on GERD seems to be favorable in recent studies performed in oriental and occidental populations (23-28). However, several issues remain unclear between the effect of GBP on GERD, including the study of clinical outcomes based on Montreal Consensus, as well as esophageal acid exposure and gastric pouch acidity following GBP. Additional questions include the effect of GBP on esophageal motility and SHH. We conducted a prospective study evaluating GERD pre and post GBP to answer these questions.

METHODS

Patients

One hundred and twenty six morbidly obese patients [87 female, aging 37 ± 11.6 years, body mass index (BMI) 44.4 ± 7.5 Kg/m2] assisted in a private clinic (GASTROBESE) between March and October of 2007 were invited to participate in the study. Patients were considered eligible according to the following criteria: (1) age between 18 and 70 years, (2) BMI ≥ 40 Kg/m2 or ≥ 35 Kg/m2 combined with significant comorbidities, (3) absence of gastroesophageal surgery, and (4) acceptance to undergo open GBP. The recruitment of patients was performed irrespective of GERD symptoms.

Patients underwent evaluation of GERD before and 6 months after GBP following a standardized protocol. It consisted of: (1) Clinical assessment based on Montreal Consensus, (2) Upper gastrointestinal endoscopy, (3) Esophageal manometry and ambulatory pH monitoring, and (4) Barium swallow X-ray.

The study was carried out in accordance with Helsinki declaration and was approved by the Ethical Committee of the Hospital de Clinicas de Porto Alegre. Informed consent was obtained for every participant.

Clinical assessment

Patients with reflux symptoms were classified has having esophageal or extraesophageal syndromes. Heartburn, regurgitation and dysphagia were scored using a validated GERD symptoms questionnaire (GERD-SQ) (29;30), with the respective questions: “How bad is the heartburn?”, “Do you feel return of bitter material from the stomach to the throat?”, and “Do you have difficulty swallowing?”. Each question was scored as (0) no symptoms; (1) symptoms noticeable, but nontroublesome; (2) symptoms troublesome, but not every day; (3) symptoms troublesome every day; (4) symptoms affect daily activities; (5) symptoms are incapacitating. Heartburn, regurgitation and dysphagia were classified as troublesome if ≥ 2. Typical reflux syndrome (TRS) was defined in the presence of either troublesome heartburn or troublesome regurgitation. A question scored GERD related well being: “How satisfied are you with your present condition?”, ranging 1 to 6 as follows: (1) incapacitated; (2) very unsatisfied; (3) unsatisfied; (4) unaffected; (5) satisfied; (6) very satisfied. Respiratory and laryngeal symptoms possibly related to GERD were assessed using a chart review. Both GERD-SQ and chart review were applied by a nurse blinded to complementary tests. The use of acid suppressive medications including H2 blockers and proton pump inhibitors (PPI) was annotated. Body weight and height were measured using a Filizola scale and a stadiometer, and BMI was calculated by dividing the weight (kg) by the square of height (m2) (31).

Endoscopy

Endoscopy was performed after 8-hour fasting, using a videoendoscope (Olympus GIF-130, Tokyo, Japan). RE was described according with Los Angeles classification (32). Briefly, mucosal breaks (one or more) without extension between the tops of two mucosal folds were classified as grade A (<5mm length) or B (>5mm length), whereas mucosal breaks (one or more) showing lateral extension were classified as grade C (<75% of the esophageal circumference) or D (>75%). Endoscopy was performed by skilled endoscopists blinded to patients' symptoms.

Esophageal motility

The study was performed with patients fasting 8 hours, using a catheter with 1 circumferential solid-state pressure sensor positioned distally and 2 unidirectional sensors (Konigsberg Instruments, Pasadena, CA, USA) positioned 5 and 10 cm proximally to the distal sensor. The catheter was inserted transnasally into the esophagus with its distal pressure sensor placed into the gastric lumen, at least 3 cm below the lower esophageal sphincter (LES). With patients in horizontal position (head 30^{o}), the catheter was pulled out by 1 cm steps with intervals of 4-5 respiratory oscillations. Step pulled was performed crossing the high-pressure zone corresponding to LES up to 3 cm above the sphincter. LES pressure was measured distally to the pressure inversion point, at mid-expiratory level. Esophageal body motility was assessed after positioning the pressure sensors at 3, 8 and 13 cm above LES. In the supine position, patients received 10 liquid swallows (5ml of water), 30 seconds apart. Manometric recordings were generated and stored using a computer software package (Sandhill Scientific Inc, Highlands Ranch, CO, USA). Esophageal

motility disorders were characterized according with the literature (33).

24-h esophageal pH monitoring

Esophageal pH monitoring was performed with a portable pH data recorder (Sandhill Scientific, Inc.; Highlands Ranch, CO, USA) and a pH catheter containing an antimony sensor. After calibration in pH 4.0 and 7.0 solutions, the catheter was inserted transnasally and positioned into the stomach by observing a pH value < 4. The catheter was step pulled and placed at 5 cm above the proximal border of the LES, determined by manometry. Acid-suppressive medications, including PPI and H2 blockers, were stopped at least 7 days before the study. Patients were instructed to keep their habitual daily activities and record symptoms, food or fluid consumption and posture changes on a diary card. On the following day, the catheter was removed and the data downloaded and analyzed (software GERDcheck, Sandhill Scientific Inc.). Acid reflux was defined as a sudden drop in esophageal pH to below 4. All meal periods were excluded from pH analysis (34).

Barium swallow X-ray

X-ray was performed with patients fasting 12 hours, following a standardized protocol. Patients were studied after drinking 200 ml of diluted barium with radiographs took in prone horizontal and upright position. Determination of the presence of SHH was based on the appearance of the esophagogastric region on the prone horizontal radiographs of the lower esophagus. A skilled radiologist blinded to patient's symptoms and endoscopy results analyzed the studies. SHH was

characterized at the presence of either B ring or gastric folds located at least 2 cm above the diaphragmatic impression. B ring was defined as a smooth, symmetric ring-like indentation at esophagogastric junction (35;36).

GBP

Roux-en-Y GBP was performed through an upper midline incision. A gastric pouch was created by dividing the stomach with a 10-cm stapler from the lesser curvature (7 cm vertically from the cardia) to 1 cm to the left of the Hiss angle. The estimated volume of the gastric pouch was 20 to 30 ml. The gastric pouch was banded in its middle portion by using a silastic ring (6.5 cm long in circumference). A gastro-jejunal anastomosis was created distal to the ring, keeping an alimentary limb with 100 cm in length, and a biliopancreatic limb ranging 60 and 80 cm.

STUDY END POINTS

Primary end points were (1) assessment of GERD based on Montreal Consensus, (2) esophageal acid exposure, and (3) gastric pouch acidity after GBP. Secondary end points were (1) motility findings and (2) sliding hiatal hernia after GBP.

STATISTICAL ANALYSIS

Data are presented as mean ± standard deviation or when otherwise stated. Quantitative data were analyzed using paired t test when normally distributed or Wilcoxon rank test when otherwise, for comparisons of pre and post GPB data.

McNemar´s procedure was employed to test differences in paired proportions, whereas independent ones were analyzed using $\chi 2$ or Fisher´s exact test. The statistical analyses were carried out using GraphPad Prism 4 (GraphPad Software, Inc., San Diego, CA, USA) and WinPEPI [Abramson JH (2004) WINPEPI computer programs for epidemiologists]. Results were considered statistically significant if P-value < 0.05.

RESULTS

Patients

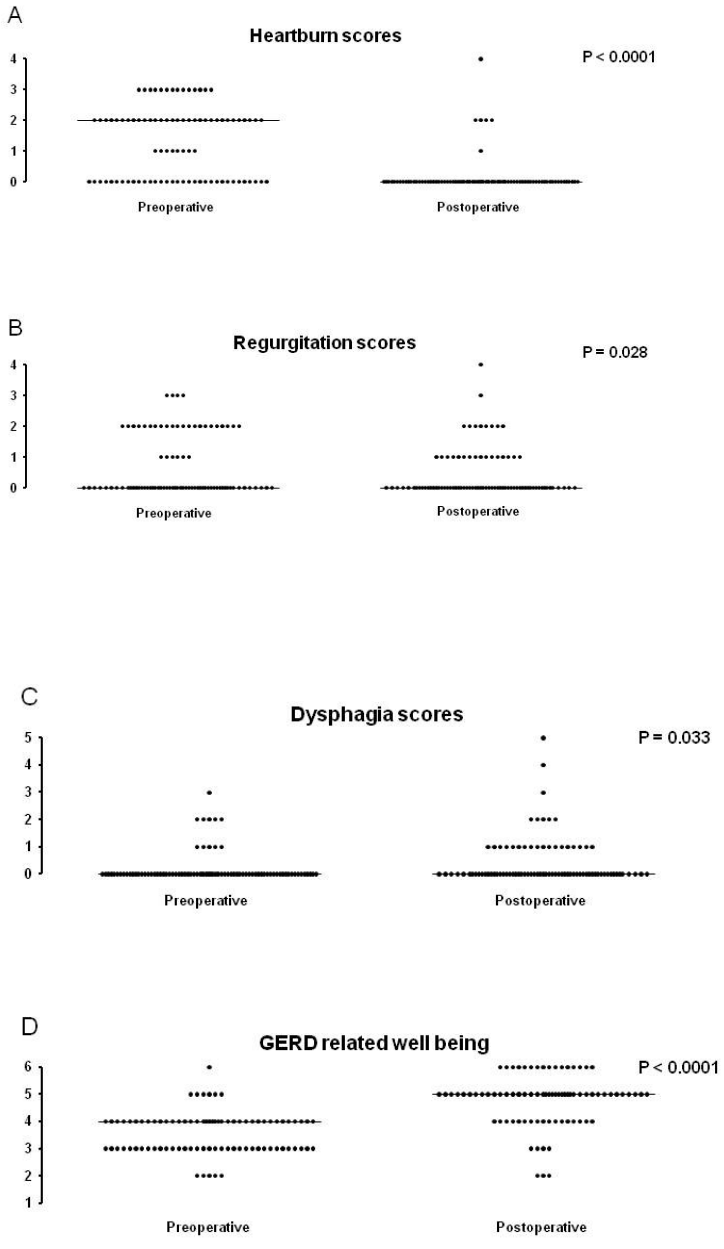
Ninety four patients were enrolled in the study. Of these, 8 patients were excluded due to (1) option for laparoscopic GBP after assessment of GERD (n = 4) and (2) refuse to undergo post-operative evaluation of GERD (n = 4). The final study sample was composed by 86 patients: 25 men; mean age 38 years (range 18 – 61), 82 white Brazilians and 4 multiracial Brazilians. BMI decreased from an average (SD) of 45.3 (7.6) Kg/m2 preoperatively to 33.2 (5.9) Kg/m2 6 months after the surgery (P < 0.0001). PPI usage decreased from 17% pre GBP to 5% postoperatively (P = 0.013).

Montreal Consensus

TRS was present in 47 patients (55%) preoperatively: 21 with troublesome heartburn, 2 with troublesome regurgitation and 24 patients with both symptoms. Of these 47 patients, 37 (79%) denied troublesome symptoms in the postoperative evaluation, while 10 patients continued with symptoms: 4 with troublesome heartburn, 5 with troublesome regurgitation and 1 with both symptoms. Out of 39

patients who denied TRS preoperatively, 4 patients (10%) reported troublesome regurgitation postoperatively (P < 0.0001).

Figure 1. Pre and post GBP scores of heartburn (A), regurgitation (B), dysphagia (C) and GERD-related well being (D) in 86 morbidly obese patients. Troublesome symptoms scored 2 or more. Well being was better as higher the score.



Troublesome dysphagia was present in 6 patients preoperatively. This symptom was solved in 3 patients postoperatively, whereas 2 patients improved to nontroublesome

dysphagia and one persisted with the symptom. Nontroublesome dysphagia was reported by 5 patients preoperatively, of which two persisted with the symptom postoperatively. Out of 75 patients who denied dysphagia preoperatively, 7 (10%) reported troublesome dysphagia and 14 (20%) had nontroublesome dysphagia postoperatively (P = 0.013).

Pre and post GBP scores of heartburn, regurgitation, dysphagia and GERD-related well being are shown in figure 1. A significant improvement was observed [median (IQR25-75%)] in heartburn [2 (0-2) vs. 0 (0-0); P < 0.0001], regurgitation [0 (0-2) vs. 0 (0-1); P = 0.028] and well being [4 (3-4) vs. 5 (4-5); P < 0.0001] in the postoperative evaluation, whereas dysphagia had a slight worsening [0 (0-0) vs. 0 (0-1); P = 0.033].

Chest pain was reported by 3 patients in the preoperative evaluation, combined with troublesome heartburn as the chief complaint. These patients denied chest pain postoperatively. Extraesophageal syndromes characterized by chronic cough and laryngeal symptoms were present in 16 patients (19%) preoperatively. All but one denied these symptoms post GBP (P = 0.0003).

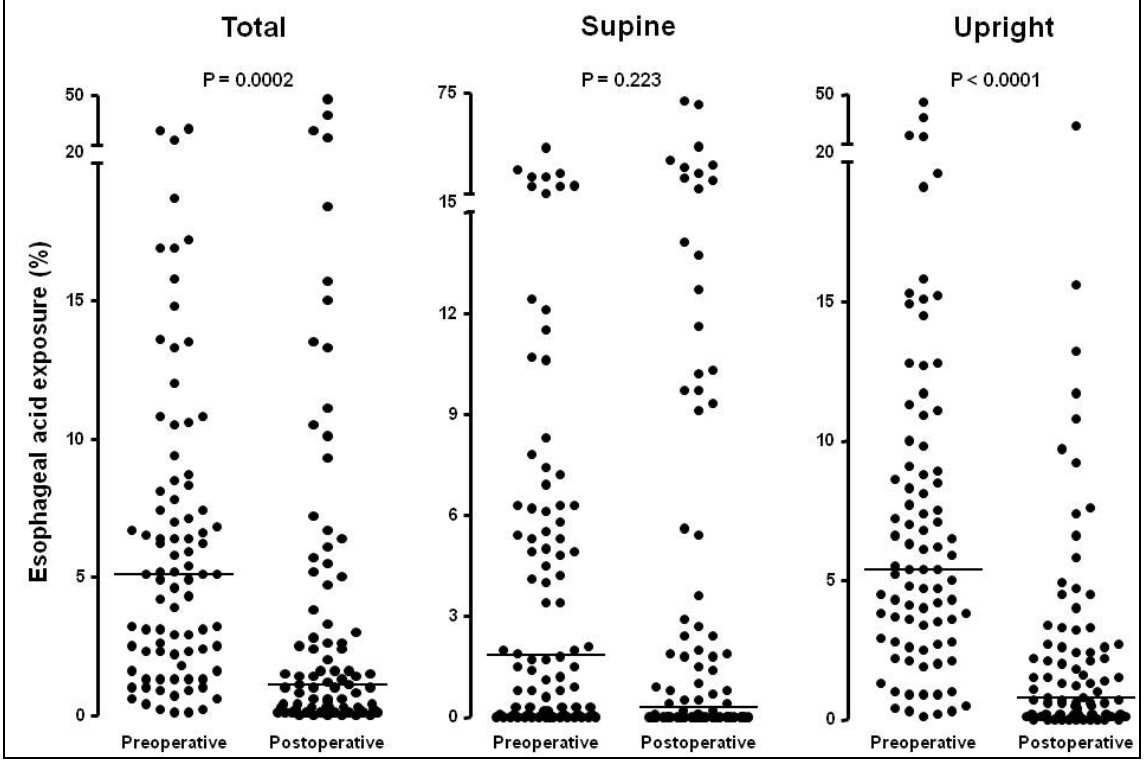
Syndromes with esophageal injury were represented exclusively by RE. It was identified in 36 patients (42%) preoperatively: 22 with grade A, 10 with grade B and 4 patients with grade C. In these patients, RE disappeared in 22, improved in 5, was unchanged in 6 and worsened in 3 patients post GBP. Out of 50 patients without RE before the surgery, 5 showed RE postoperatively: 3 with grade A and 2 with grade B. Taken all 86 patients, esophageal mucosa improved in 27, was unchanged in 51 and worsened in 8 patients (P = 0.001). Neither esophageal stricture nor Barrett

esophagus were found before and after the surgery.

Esophageal acid exposure

Taking all 86 patients, a significant decrease was observed in acid exposure [median (IQR25-75%)] after GBP in both total [5.1% (2-8.2) vs. 1.1% (0.2-4.8); P = 0.0002] and upright periods [5.4% (2.8-9.4) vs. 0.8% (0.1-2.7); P < 0.0001] (figure 2). A decrease was observed for supine acid exposure [1.8% (0.1-6.3) vs. 0.3% (0-5.5); P = 0.223] but without statistical significance. Out of 58 patients with abnormal acid exposure pre GBP, 26 (45%) had their acid exposure normalized post GBP. Out of 28 patients with normal acid exposure pre GBP, 5 (18%) showed abnormal pH-metry after the surgery (P = 0.0002).

Figure 2. Esophageal acid exposure in total, supine and upright periods at both pre and post GBP assessments (n = 86).



In the preoperative evaluation, patients with TRS showed higher total acid exposure [median (IQR25-75%)] than those without TRS [6.2% (3.2-10.5) vs. 2.5% (1.3-6.4); P = 0.007]. Postoperatively, patients with TRS continued to have higher total acid exposure than those with no TRS [8% (1-13.4) vs. 1% (0.2-2.6); P = 0.005].

Gastric pouch acidity

An acid gastric pouch (pH < 4) was observed in 74 patients (86%) in the postoperative pH-metry. These patients showed increased esophageal acid exposure either total, upright or supine more frequently than patients with a non-acid (pH > 4) gastric pouch (47% vs. 17%; P = 0.044). TRS in the postoperative evaluation did not differ between patients with and without an acid gastric pouch (18% vs. 8%; P = 0.543). Reflux esophagitis was more frequent in patients with an acid gastric pouch than those with a non-acid gastric pouch (26% vs. 0%; P = 0.041).

Manometry findings

There was a significant decrease in LES pressure after GBP, whereas LES length did not modify (table 1). A slight but significant decrease was observed for distal esophageal amplitude (DEA) following GBP. Manometric classifications regarding esophageal body peristalsis and LES tonicity were similar between pre and post GBP assessments.

Table 1. Manometry findings pre and post GBP (n = 86).

Manometry findings	Pre GBP	Post GBP	P
LES pressure[a], median (range)	21.3 (3.6 – 75)	18 (1 – 50.7)	0.004
LES length (cm), mean ± SD	4.9 ± 1.1	5.1 ± 1.4	0.485
LES classification, n (%)	72 (84)	73 (85)	0.244
	7 (8)	10 (11.5)	
Hypotonic	7 (8)	3 (3.5)	
Hypertonic			
DEA (mm Hg), median (range)	106 (29 – 318)	96 (29 – 325)	0.001
EB[b] classification, n (%)	59 (68.5)	55 (64)	0.100[c]
	11 (13)	19 (22)	
IEM	15 (17.5)	11 (13)	
NE	1 (1)	1 (1)	
Others[d]			

[a]LES pressure in mm Hg; [b]Esophageal body; [c]Calculation performed excluding "others"; [d]Diffuse esophageal spasm (pre GBP) and nonspecific motility disorder (post GBP); IEM = ineffective esophageal motility; NE = nutcracker esophagus.

Sliding hiatal hernia

Eighty four patients performed X-ray before and after the surgery. SHH was identified in 27 patients (32%) preoperatively. Of these, 13 patients still had SHH after the surgery, whereas in 14 patients SHH disappeared. Out of 57 patients without SHH preoperatively, 9 (16%) showed SHH after the surgery (P = 0.404).

In the preoperative evaluation, more patients with SHH had TRS than those without SHH (78% vs. 44%; P = 0.003). Postoperatively, those with SHH had TRS in a

similar rate compared to patients without SHH (27% vs. 13%; P = 0.140). Preoperative endoscopy showed reflux esophagitis more frequently in patients with SHH than those without SHH (56% vs. 35%; P = 0.079), but with a borderline significance. In the postoperative endoscopy, more patients with SHH had reflux esophagitis than patients without SHH (36% vs. 16%; P = 0.050).

DISCUSSION

The aim of our study was to assess the effect of GBP on GERD in patients with morbid obesity, assuming as end points (1) assessment of GERD based on Montreal Consensus, (2) esophageal acid exposure, and (3) gastric pouch acidity. We further assessed esophageal motility and sliding hiatal hernia before and after GBP. For these purposes, unselected patients with morbid obesity were investigated for GERD before and 6 months after the surgery, using a prospective and standardized approach.

Our main findings were (1) GBP ameliorated both esophageal and extraesophageal reflux syndromes in patients with morbid obesity; (2) GBP decreased esophageal acid exposure, particularly in upright periods; and (3) acidity in the gastric pouch was observed in most patients (86%), possibly related to reflux esophagitis post GBP. Secondary findings were (1) a similar pattern of esophageal motility in both esophageal body peristalsis and LES tonicity pre and post GBP; and (2) a positive relation between postoperative SHH and esophagitis but not with reflux symptoms.

We found that GBP ameliorates esophageal syndromes in patients with morbid obesity evaluated 6 months after the procedure. Esophageal syndromes including TRS and syndrome with esophageal injury i.e. reflux esophagitis disappeared in most

patients post GBP, and appeared in a minority of those with absence of GERD findings in the pre GBP assessment. The amelioration of reflux symptoms was accompanied by improvement in GERD-related well being. We emphasize that reflux symptoms were assessed using a validated questionnaire (29) able to discriminate between nontroublesome and troublesome symptoms. This method allowed us to classify patients according to the rules of the Montreal Consensus (13). Studies have shown conflicting results about the effect of GBP on GERD. Most of them have suggested an improvement of GERD parameters following GBP (23-28), while others have indicated no effect (37). However, the lost of patients in the follow-up was markedly high as 80% in these studies (28). In contrast, our study had a dropout of only 9%. Furthermore, the employment of the Montreal Consensus as the base for GERD assessment provided an update in the relation between morbid obesity and GERD.

In the post GBP, dysphagia appeared in nearly one third of patients who denied this symptom previously. Moreover, most patients graded dysphagia as nontroublesome. In accordance with this finding, Ortega and coworkers described a higher frequency of dysphagia 3 months after GBP, which decreased one year after the procedure (26). The mechanisms implicated with dysphagia post GBP are not clear. We believe that the combination of a small gastric pouch and a gastric band might underlie dysphagia rather than a compromising in esophageal transit. Further studies are needed to clarify this issue.

GBP decreased the averaged esophageal acid exposure in our study sample. This effect was limited to acid exposure in upright periods. As expected, an increased acid exposure was related with TRS either at pre or post GBP, suggesting that exposition of the esophageal mucosa to acid plays an important role on the generation of reflux

symptoms in this population. Several studies support a benefic effect of GPB on the control of acid exposure (23;24;26). However, the mechanisms underlying this finding are lacking. By the restriction of the gastric volume post GBP (38), the amount of parietal cell is expected to be drastically reduced and accompanied by a decrease in secretion of gastric juice. In the present study we found that most patients (86%) had an acidic gastric pouch when evaluated in fasting conditions. This finding was related with an increased prevalence of reflux esophagitis. Although the employed technique was unsuitable to evaluated acid gastric output, it provided evidence that the gastric pouch produces acid post GBP in most patients. In support of this finding, Hedberg et al. found that patients with stomal ulcers after GBP have increased acid production in their proximal pouch in comparison with asymptomatic patients (39). Whether the gastric acid output differs between patients with GERD post GBP deserves further studies.

The pattern of esophageal motility did not modify significantly 6 months after GBP. A slight decrease was observed in both LES resting pressure and DEA. Although the finding of ineffective esophageal motility nearly doubled at post GBP assessment, it did not reach significance probably due to a small study sample or a short follow-up. A lower DEA could be explained by an adaptation of the esophageal body to a lower gastroesophageal pressure gradient (GEPG) following weight lost. Studies have shown a parallel between BMI and GEPG, which can influence the performance of esophageal persitalsis (11;40). Our study sample is under follow-up to determine the behavior of esophageal motility after 2 years of GBP.

SHH post GBP was as common as in pre GBP assessment, affecting approximately 30% of patients. Curiously, one third of patients with SHH post GBP showed no hernia at pre GBP assessment. It was evaluated by swallow barium X-ray, a

technique accepted as suitable for this purpose (36). SHH was related with TRS at pre GBP and with reflux esophagitis postoperatively. Further studies are needed to clarify the clinical relevance of having a SHH post GBP.

In conclusion, we assessed the effect of GBP on GERD in patients with morbid obesity. For this purpose, patients were evaluated before and 6 months after the surgery, using the criteria of the Montreal Consensus to characterize GERD. We found that GBP ameliorates GERD syndromes in most patients. We also observed that GBP reduces significantly the esophageal acid exposure, despite the production of acid by the gastric pouch. These findings were accompanied by amelioration in GERD-related well being and a decrease in PPI usage. Esophageal motility was similar comparing pre and post GBP assessment, whereas SHH showed no relation with reflux symptoms postoperatively. Long term studies are needed to assess the behavior of GERD post GBP.

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RESEARCH ARTICLE

Performance of the Montreal Consensus in the Diagnosis of Gastroesophageal Reflux Disease in Morbidly Obese Patients

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Abstract
Background Gastroesophageal reflux disease (GERD) has been increasingly recognized in patients with morbid obesity. A recent global evidence-based consensus on GERD has been proposed, but its performance in patients with morbid obesity is unknown. The aim of this study was to assess the performance of the Montreal Consensus in the diagnosis of GERD in morbidly obese patients.
Methods Seventy-five consecutive morbidly obese patients underwent GERD symptoms assessment, upper gastrointestinal endoscopy, and ambulatory esophageal pH monitoring "off PPI". The performance of the Montreal Consensus was determined by comparing two diagnostic algorithms: 1. a gold standard approach in which any GERD symptom and findings from both endoscopy and pH monitoring were taken into account, and 2. the approach with the Montreal Consensus, in which troublesome GERD symptoms and endoscopic findings were considered.
Results GERD was found present in 57 patients by applying the gold standard approach. The Montreal Consensus identified 41 of these patients, whereas the remaining 34 patients were classified as "no GERD". Of these, 16 (47%) showed reflux esophagitis and/or abnormal pH-metry. The Montreal Consensus had an accuracy of 78.7%, sensitivity of 72% (95% CI 59–82%), specificity of 100% (95% CI 82–100%) and negative predictive value of 47% (95% CI 37–57%).
Conclusions In morbidly obese patients, the approach with the Montreal Consensus has high specificity and suboptimal sensitivity in the diagnosis of GERD. Its intermediate negative predictive value suggests that complementary investigation might be routine in these patients, particularly in those who do not present with troublesome GERD symptoms.

Keywords Morbid obesity · Gastroesophageal reflux disease · Endoscopy · Esophageal pH monitoring

Madalosso and Fornari contributed equally to the study.

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Introduction

Obesity and gastroesophageal reflux disease (GERD) have been increasingly recognized worldwide [1, 2]. Both diseases are associated with negative impact on quality of life and expressive burden in the public health systems [3, 4]. A link between obesity and GERD has been suggested, since studies have recognized obesity as an independent risk

factor for reflux symptoms, erosive esophagitis, Barrett's metaplasia, and esophageal adenocarcinoma [5–9].

Crescent rates of morbid obesity have emerged in the last decades, particularly in the western world [10, 11]. Among several comorbidities, GERD has been frequently found in patients with morbid obesity [12, 13]. Due to the extreme overweight, these patients are exposed to increased rates of transient lower esophageal sphincter relaxations (TLESRs) and gastroesophageal junction disruption, as well as augmented gastroesophageal pressure gradient, favoring the occurrence of reflux [14, 15]. Although crucial for both research and clinical practice, the diagnostic approach for GERD has not been made uniform in these patients.

A recent global consensus on the definition and classification of GERD (Montreal Consensus) has been suggested to standardize data collection in research and clinical practice [16]. Briefly, troublesome GERD symptoms and reflux esophagitis have been considered the "pounds" in the diagnosis of GERD. In spite of this, validated GERD specific questionnaires [17, 18] and traditional complementary techniques, such as a 24-h esophageal pH monitoring, remain as an alternative approach [19].

The increasing prevalence of both morbid obesity and GERD, and the recent description of decreased visceral sensitivity in morbidly obese patients [20, 21] raise the question whether the Montreal Consensus is able to properly recognize GERD in this population. Therefore, the aim of this study was to assess the performance of the Montreal Consensus in the diagnosis of GERD in morbidly obese patients.

Methods

Patients

Seventy-five unselected morbidly obese patients were prospectively studied before bariatric surgery between March and August of 2007. Morbid obesity was characterized by the presence of body mass index (BMI) ≥40 kg/m^2 or BMI between 35 and 40 kg/m^2 with significant comorbidity. After agreeing to participate in the study, patients underwent clinical evaluation, upper gastrointestinal endoscopy, esophageal manometry, and a 24-h esophageal pH monitoring.

Patients were excluded if they had any of the following conditions: achalasia, gastroesophageal surgery, or use of proton pump inhibitors (PPIs) prior (<7 days) to esophageal function tests. The study was approved by the ethical committee of the Hospital de Clínicas de Porto Alegre. Informed consent was obtained for every participant.

Clinical Evaluation

A standardized procedure was carried out to assess clinical data previously to esophageal function tests. Patients were asked to fill in a validated GERD symptom's questionnaire [17], in which troublesome heartburn and acid regurgitation were characterized. Briefly, this questionnaire consists of 11 questions about GERD symptoms, including six for heartburn and one for acid regurgitation. Each question grades the symptom in three levels of severity: 0—no symptoms; 1—symptoms noticeable but not troublesome; 2–5—symptoms noticeable and troublesome.

Subsequently, patients were asked about the presence of troublesome chest pain and extraesophageal symptoms possibly related to GERD, including chronic cough, asthma, and chronic laryngitis symptoms (hoarseness, sore throat, and throat clearing). In the presence of any GERD symptoms, patients were asked to elect their chief complaint. Prior gastroesophageal surgery and use of PPIs were also registered. Anthropometric measures (weight, height, and BMI) and demographic data, including race and school level, were taken by a trained nurse.

Upper Gastrointestinal Endoscopy

Endoscopy was carried out by two endoscopists following a standardized protocol, previously to esophageal function tests. Patients were examined after an 8-hour fasting, using a videoendoscope (Olympus GIF-130, Tokyo, Japan). Reflux esophagitis was described according to Los Angeles classification [22]. In case of esophagitis grade A, a consensus about the presence of mucosal breaks was reached after analysis of endoscopic pictures by a third endoscopist, blinded of the patient's symptoms and pH-metry results.

Ambulatory Esophageal pH Monitoring

Esophageal pH monitoring was performed with a portable pH data recorder (Sandhill Scientific, Inc.; Highlands Ranch, CO, USA) and a pH catheter containing an antimony sensor. After calibration in pH 4.0 and 7.0 solutions, the catheter was inserted transnasally and positioned 5 cm above the LES, as previously determined by manometry testing. The use of PPIs was discontinued at least 7 days before the study. Patients were instructed to keep their habitual daily activities and record symptoms, food or fluid consumption, and posture changes on a diary card. On the following day, the catheter was removed and the data downloaded and analyzed (software GERDcheck, Sandhill Scientific Inc.).

All meal periods were excluded from pH analysis [23]. Patients were considered to have increased esophageal acid

exposure if the fraction time with pH<4 was ≥4.4% during the total study period, ≥8.4% in the upright period or ≥3.5% in the supine period [24]. A composite score analysis (DeMeester) was performed, with a value ≥14.7 considered abnormal. Symptom index was calculated as the number of symptom episodes associated with acid reflux divided by the total number of symptom episodes, multiplied by 100%. It was assumed as positive (R^+S^+) if ≥50% [25]. Esophageal pH monitoring was considered abnormal in the presence of increased acid exposure, increased DeMeester composite score and/or R^+S^+.

Definition of GERD

The presence of GERD was assessed by two simulated approaches. The gold standard approach defined GERD in the presence of troublesome typical GERD symptoms, reflux esophagitis, and/or abnormal pH monitoring. Typical GERD symptoms included heartburn and acid regurgitation with intensity and frequency enough to be judged troublesome by the patient. Patients with non-troublesome typical GERD symptoms were also considered to have GERD if reflux esophagitis and/or abnormal pH monitoring were found at complementary investigation.

The approach with the Montreal Consensus defined GERD depending on symptom presentation and endoscopic findings [16]. The disease was recognized in the presence of troublesome GERD symptoms. Patients were further classified as having esophageal or extraesophageal syndromes according to the pattern of symptoms, i.e., troublesome heartburn, acid regurgitation, and chest pain, or troublesome cough, laryngitis, and asthma. According to the Montreal Consensus, the presence of GERD symptoms with frequency and intensity not sufficient to be troublesome does not characterize GERD and therefore these patients should not deserve further investigation. Complementary evaluation with endoscopy was carried out in patients with troublesome GERD symptoms to identify the presence of esophageal mucosa injury.

Statistical Analysis

Data are expressed as mean±SD. Quantitative variables were first tested for Gaussian distribution. Unpaired *t* test or Mann–Whitney test was employed when appropriate. Categorical variables were analyzed using chi-square test. The performance of the Montreal Consensus in the diagnosis of GERD was assessed by the calculation of test sensitivity, specificity, and predictive values, taking the gold standard approach as referential. The Consensus performance was determined assuming GERD prevalence values of the own study population and from reported data in morbidly obese patients [21]. Test performance was assessed using WinPEPI version 4.1 [26]. A *P* value of <0.05 was accepted as indicating statistical significance.

Results

Patients

All enrolled patients completed the study. There were 23 men and 52 women, with mean age of 37 years (range 18–61 years) and average BMI of 45.1 kg/m^2 (range 35.3–67.7 kg/m^2). Most patients (96%) were white Brazilians, while three patients were multiracial Brazilians. Out of the 75 patients, 64 (85%) had low education level, whereas 11 (15%) reported to have graduated from high school.

GERD According to the Gold Standard Approach

The diagnostic algorithm is presented in Fig. 1. Patients were first classified depending on the clinical presentation: 41 patients had troublesome GERD symptoms (Group 1), seven had non-troublesome GERD symptoms (Group 2), and 27 denied any reflux symptoms (Group 3).

Complementary investigation of Group 1 revealed objective GERD parameters in 33 patients (80%). Esophageal pH monitoring was abnormal in 29 patients: 27 had increased acid exposure (10.3±5.2%) and increased DeMeester score (36.4±17.5), of which 11 had R^+S^+ for heartburn, one patient had increased DeMeester score (19.4) with normal acid exposure, and one patient had R^+S^+ for heartburn with normal acid levels. Endoscopy revealed reflux esophagitis in 27 patients: grade A (n=14), grade B (n=9), and grade C (n=4). Eight patients showed no pathological findings at complementary investigation. These patients were considered to have GERD by the presence of troublesome GERD symptoms.

Group 2 had six patients (86%) with objective GERD parameters: five with increased acid exposure (17.1%±10.9%) and increased DeMeester score (57.6±32.9), of which one had R^+S^+ for heartburn, and one patient with R^+S^+ for heartburn and normal acid levels. Reflux esophagitis was found in five patients: grade A (n=3) and grade B (n=2). One patient with non-troublesome GERD symptoms was classified as "no GERD" by lack of pathological findings.

Complementary investigation of Group 3 showed objective GERD parameters in 10 patients (37%): nine had increased acid levels (6.7%±2.8%) at pH monitoring, of which seven showed increased DeMeester score (28.4±11.2). Reflux esophagitis was found in three patients (grade A). Seventeen patients had no findings compatible with GERD.

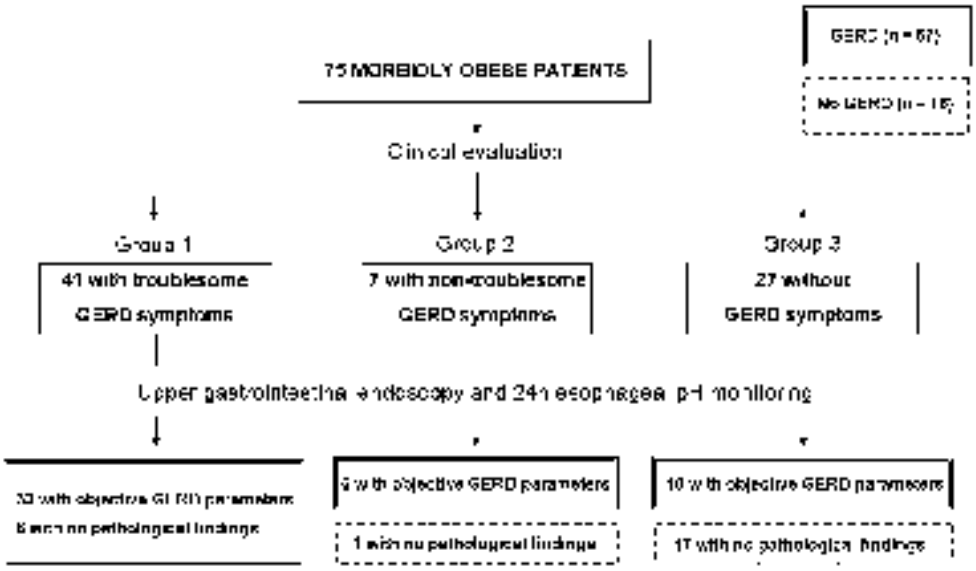

Fig. 1 GERD according with the gold standard approach. Patients were first classified depending on the clinical presentation. Those with troublesome GERD symptoms (group 1) were considered to have GERD independently of the complementary investigation. Patients with non-troublesome GERD symptoms (group 2) or without symptoms (group 3) were considered to have GERD in the presence of objective GERD parameters seen at endoscopy or pH-metry

In total, 18 out of 75 morbidly obese patients were considered as "no GERD" after clinical and complementary evaluation. The comparisons between patients with and without GERD showed no significant differences regarding age (38.7±9.6 vs. 33.9±13.3 years; P=0.097) and sex distribution (male, 35% vs. 17%; P=0.239). Regular use of PPI was reported by eight patients. Of these patients, seven had abnormal pH monitoring and six showed reflux esophagitis at endoscopy.

GERD According to the Montreal Consensus

The diagnostic algorithm is shown in Fig. 2. Out of the 75 patients, 41 had troublesome typical GERD symptoms by clinical evaluation. In these patients, upper endoscopy revealed normal esophageal mucosa in 14 (34%) and reflux esophagitis in 27 patients (66%).

The remaining 34 patients were classified as "no GERD" by the absence of troublesome reflux symptoms. The comparisons between patients with and without GERD revealed no significant differences regarding age (39.3±9.8 vs. 35.4± 11.4 years; P=0.118) and sex distribution (male, 27% vs. 35%; P=0.428).

Chest pain was reported by four patients in whom heartburn was the main symptom. Atypical GERD symptoms were reported by 14 patients: five with chronic cough, five with chronic laryngeal symptoms, and four patients with both chronic cough and laryngeal symptoms. These patients had heartburn or acid regurgitation as the chief complaint.

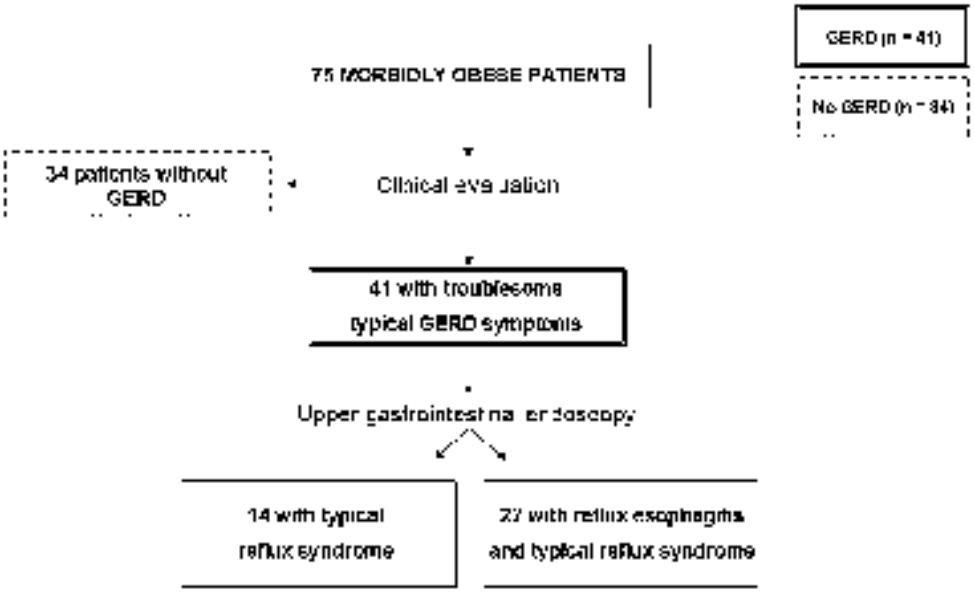

Fig. 2 GERD according to the Montreal Consensus. Patients were considered to have GERD in the presence of troublesome reflux symptoms. Those patients who denied troublesome GERD symptoms had not investigated further

Table 1 Performance of the Montreal Consensus in the diagnosis of GERD compared with the gold standard approach

Test performance	Montreal consensus [percentage (95% confidence interval)]
Specificity	100 (82–100)
Sensitivity	72 (59–82)
Positive predictive value	100 (36–100)
Negative predictive value	47 (37–57)

Performance of the Montreal Consensus in the Diagnosis of GERD

The Montreal Consensus showed high specificity, suboptimal sensitivity, high positive predictive value, and intermediate negative predictive value in the diagnosis of GERD after comparison with the gold standard approach (Table 1). Diagnostic accuracy of the Montreal Consensus was 78.7%. This performance was calculated applying the prevalence of GERD found in the study population (76%). By calculating test performance with a reported GERD prevalence of 60% [21], a deterioration was observed in its negative predictive value (70% [95% CI: 61–78%]), while test specificity and sensitivity remained unchanged.

Discussion

Gastroesophageal reflux disease and obesity have gained particular attention by its significant impact on global public health [2, 3, 11, 27]. Both diseases have been associated with lethal conditions, such as esophageal adenocarcinoma and morbid obesity [9, 28, 29]. This phenomenon claims for diagnostic tools of widespread application, able to standardize patient selection in both research and clinical practice. A global evidence-based consensus on GERD has been recently proposed to fulfill the above-mentioned gap [16]. Based on this, we assessed the performance of the Montreal Consensus in the diagnosis of GERD in morbidly obese patients. Test performance was determined after comparison with a gold standard approach for GERD.

The application of the Montreal Consensus had an accuracy of 78.7%, with high specificity and suboptimal sensitivity in the diagnosis of GERD. Posttest probability of the disease was high after a positive result, following its optimal specificity. However, posttest probability of GERD was relatively high (47%) after a negative result, since nearly half of patients labeled as "no GERD" actually showed objective GERD parameters at the gold standard approach.

The high specificity of the Montreal Consensus is linked to the fact that troublesome typical GERD symptoms are synonymous with the disease, irrespective of additional investigation [16]. By using a properly approach to characterize these symptoms, the specificity of the Montreal Consensus is expected to be high, independent of the study population. The key point of this phenomenon is the accuracy of the method applied to characterize symptoms. We believe that our approach was satisfactory based on the application of a structured GERD symptom's questionnaire, validated to our native language and able to differentiate between troublesome and non-troublesome typical reflux symptoms [17].

By comparing with the gold standard approach, the Montreal Consensus reached suboptimal sensitivity in the diagnosis of GERD. Missing patients were those who reported non-troublesome symptoms or denied reflux symptoms. Complementary investigation with endoscopy and pH monitoring revealed objective GERD parameters in approximately half of these patients. Consequently, the negative predictive value of the Montreal Consensus for GERD recognition was relatively high in our study population. The adoption of a lower GERD prevalence in the analytical model [21] did not change test sensitivity and specificity, but deteriorated its negative predictive value. This finding may be due to the effect of local disease prevalence and should be considered for clinical decisions in different populations investigated with the Montreal Consensus [30].

GERD was highly prevalent in our study population, raising methodological concerns. Participants were candidates for bariatric surgery who fulfilled the criteria for characterization of morbid obesity. After agreement to participate, patients were consecutively included in the study, independent of the presence of GERD symptoms. The high rate of objective GERD parameters found at both endoscopy and pH monitoring was obtained after careful analysis of complementary data, including revision of endoscopic images of patients with small (<5 mm) mucosal breaks, a condition potentially exposed to misinterpretation [31]. In addition, we adopted higher referential values [24] for classification of acid exposure than those routinely employed in our service [32].

Several studies have described an association between obesity and GERD, including crescent rates of reflux esophagitis [5, 6, 8, 33, 34], increased esophageal acid exposure [35], and abnormal visceral sensation [20, 21]. Racial influences and socioeconomic factors may also contribute to GERD in obese individuals. It has been recently shown that an increased obesity may disproportionately increase GERD symptoms in white populations [36]. In addition, a link has been suggested between low socioeconomic status and reflux symptoms [37]. Moreover, the mechanisms by which severe overweight provokes more reflux and consequent esophageal mucosa damage is

not clear, but the combination of gastroesophageal junction overstress and abnormal esophageal sensitivity is likely involved [14, 21].

In summary, we assessed the performance of the Montreal Consensus in the diagnosis of GERD in morbidly obese patients. The Consensus showed high specificity and suboptimal sensitivity in the diagnosis of GERD. A relatively high negative predictive value was demonstrated by the lack of recognition of objective GERD parameters in patients without troublesome reflux symptoms. These findings indicate that the Montreal consensus is not sufficient to diagnose all patients with GERD, and that further investigations should be performed routinely in patients who do not present with troublesome typical GERD symptoms. This is particularly important as bariatric surgery may interfere with the gastroesophageal barrier, and promote GERD, especially when surgical techniques such as gastric banding, sleeve gastrectomy, or vertical banded gastroplasty are employed.

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CONCLUSÃO

A progressão universal da DRGE pode ser, pelo menos em parte, atribuída ao aumento da obesidade. Essa associação, cada vez mais frequente na prática clínica, implica tratamento com o objetivo de perda ponderal e redução da exposição da mucosa esofágica ao ácido. O Consenso de Montreal foi cuidadosa e criteriosamente estabelecido no sentido de definir propedêutica clínica para DRGE baseada essencialmente em sintomas. Nosso primeiro estudo confirmou as limitações do Consenso de Montreal na avaliação das síndromes esofágicas em pacientes com OM, reforçando a necessidade de avaliação endoscópica complementar, independentemente da ocorrência de sintomas desconfortáveis de DRGE.

Nosso segundo estudo demonstrou que, embora o pH da bolsa gástrica se mantenha ácido e não seja realizada hiatoplastia mesmo em pacientes com hérnia hiatal, houve resposta favorável nos primeiros seis meses de pós-operatório em relação a sintomas e esofagite após a GYR. No entanto, resultados a longo prazo são necessários. Finalmente, pela avaliação de nossos estudos de revisão e pelos estudos originais, chegamos às seguintes conclusões:

1) a abordagem pelo Consenso de Montreal limita a identificação de DRGE em obesos mórbidos, sendo recomendada a investigação mesmo em pacientes sem sintomas desconfortáveis de GERD;

2) sintomas de DRGE, exposição ácida do esôfago e injúria mucosa do esôfago apresentam resposta favorável com a GYR;

3) melhora radiológica é observada em metade dos pacientes, a qual é

positivamente associada com alívio de sintomas;

4) não há melhora dos distúrbios motores do esôfago com a GYR:

5) resultados a longo prazo são necessários para confirmar essa operação como técnica de escolha para tratar DRGE mesmo em indivíduos com obesidade leve.

ANEXO 1. APROVAÇÃO DA COMISSÃO CIENTÍFICA E PESQUISA E ÉTICA EM SAÚDE

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 06-580 **Versão do Projeto:** 06/02/2007 **Versão do TCLE:** 20/03/2007

Pesquisadores:
RICHARD RICACHENEVSKY GURSKI
CARLOS AUGUSTO SCUSSEL MADALOSSO

Título: AVALIAÇÃO DA DOENÇA DO REFLUXO GASTRO-ESOFÁGICO EM PACIENTES COM OBESIDADE MÓRBIDA ANTES E APÓS GASTROPLASTIA VERTICAL COM ANEL E DERIVAÇÃO JEJUNAL EM Y DE ROUX.

Este projeto foi Aprovado em seus aspectos éticos e metodológicos, inclusive quanto ao seu Termo de Consentimento Livre e Esclarecido, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde. Os membros do CEP/HCPA não participaram do processo de avaliação dos projetos onde constam como pesquisadores. Toda e qualquer alteração do Projeto, assim como os eventos adversos graves, deverão ser comunicados imediatamente ao CEP/HCPA. Somente poderão ser utilizados os Termos de Consentimento onde conste a aprovação do GPPG/HCPA.

Porto Alegre, 20 de março de 2007.

Profª Nadine Clausell
Coordenadora do GPPG e CEP-HCPA

ANEXO 2 .TERMO DE CONSENTIMENTO APROVADO PELO GPPG

Ficha _____
Paciente _____

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você tem indicação de realizar uma cirurgia de redução gástrica com derivação jejunal para tratamento da obesidade mórbida. Para tanto, serão necessários alguns exames rotineiros tanto antes como depois da cirurgia.

Você está sendo convidado para participar de um estudo que tem por objetivo avaliar o efeito desta cirurgia no controle do refluxo gastroesofágico.

Se você aceitar participar do estudo, além dos exames já indicados para a realização da cirurgia, você responderá a um questionário para avaliar seus sintomas e deverá fazer mais alguns exames:

Os exames específicos para essa pesquisa são:

- Estudo radiológico de esôfago, estômago e duodeno (esofagograma baritado)
- Ph-metria de 24h
- Manometria de esôfago

Estes exames serão realizados antes e seis meses após à cirurgia. O esofagograma baritado é um estudo radiográfico em que o paciente deve engolir uma substância chamada contraste para estudo do interior do esôfago, estômago e duodeno. O uso de contraste pode causar algum desconforto. A manometria é realizada por meio da colocação de um catéter através do nariz, passando pela garganta e alcançando o esôfago, permanecendo por alguns minutos para medir as pressões do esôfago. A ph-metria esofágica de 24h é executada de modo similar sendo que ficará 24h conectado a um pequeno dispositivo com a finalidade de medir alterações do ph do esôfago.

Após seis meses da realização da cirurgia serão repetidos o questionário e os exames para comparar com os resultados daqueles que foram realizados antes da cirurgia.

As informações individuais coletadas na pesquisa são de caráter estritamente confidencial. Os dados coletados serão agrupados e expressos através de resultados numéricos, sem qualquer referência ao nome ou outros dados que possam identificar os participantes do grupo.

Todas as despesas relacionadas ao custo de exames serão cobertas por verbas próprias do Projeto de Pesquisa, sem custos para o paciente, que deverá providenciar apenas o seu transporte para o HCPA .

Eu, _____, fui informado dos objetivos e da justificativa desta pesquisa, de forma clara e detalhada, assim com declaro estar ciente das possíveis conseqüências, complicações e riscos do tratamento cirúrgico a mim proposto.

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Todas as minhas dúvidas foram respondidas com clareza, e sei que poderei solicitar novos esclarecimentos a qualquer momento. Além disso, terei liberdade de retirar o meu consentimento de participação na pesquisa ainda que durante o andamento da mesma.

O profissional _____ certificou-se de que as informações por mim fornecidas terão caráter confidencial.

Fui informado que todos os custos relacionados a exames diagnósticos e o tratamento cirúrgico serão cobertos por verbas próprias do Projeto de Pesquisa.

Porto Alegre, ___ de _____ de _____ .

_____

Assinatura do Paciente

_____

Assinatura do Responsável pelo Paciente

_____

Assinatura do Investigador

_____

Assinatura do Orientador do Projeto

PESQUISADOR RESPONSÁVEL
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ANEXO 3: PRODUÇÕES CIENTÍFICAS DECORRENTES DO PROJETO DE PESQUISA

Artigo A - Publicado no períódico Neurogastroenterology and Motiliy

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Heartburn during sleep: a clinical marker of gastro-oesophageal reflux disease in morbidly obese patients

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Abstract *Gastro-oesophageal reflux disease (GORD) and morbid obesity are entities with increasing prevalence. New clinical strategies are cornerstones for their management. The aim of this study was to assess the prevalence of heartburn during sleep (HDS) and whether this symptom predicts the presence of objective GORD parameters and increased heartburn perception in morbidly obese patients. Ninety-one consecutive morbidly obese patients underwent clinical evaluation, upper gastrointestinal endoscopy and oesophageal pH monitoring. HDS was characterized when patients replied positively to the question, 'Does heartburn wake you from sleep?'. A General Score for Heartburn (GSH) ranging between 0 and 5 was assessed with the question 'How bad is your heartburn?'. HDS was reported by 33 patients (36%). More patients with HDS had abnormal acid contact time or reflux oesophagitis than patients without HDS (94% vs 57%, P < 0.001). HDS had a positive predictive value of 94% (0.95 CI 82–98), sensitivity of 48% (0.95 CI 37–60%) and specificity of 93% (0.95 CI 77–98%) for detection of GORD. A higher proportion of patients with HDS perceived heartburn preceded by acid reflux in diurnal (39% vs 9%; P < 0.001) periods during pH-metry. HDS patients showed higher GSH (2.4 ± 0.5 vs 1.7 ± 0.4; P < 0.0001) compared with patients who denied HDS but reported diurnal heartburn. HDS occurs in a significant minority of patients with morbid obesity and has high positive predictive value for GORD. Symptomatic reflux during the sleep seems to be a marker of increased heartburn perception in this population.*

Keywords *gastro-oesophageal reflux disease, heartburn, morbid obesity, reflux oesophagitis, sleep.*

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INTRODUCTION

Gastro-oesophageal reflux disease (GORD) and obesity are increasing worldwide.[1–3] Both diseases are associated with negative impact on quality of life and substantial economic burden.[4–6] A link between obesity and GORD has been suggested, since studies have recognized obesity as an independent risk factor either for reflux symptoms, erosive oesophagitis, Barrett's metaplasia or oesophageal adenocarcinoma.[7–12]

Recent studies have shown that symptomatic nocturnal reflux is a frequent condition in patients with GORD and associates with sleep disturbance and decreased health-related quality of life.[13–16] In addition, nocturnal reflux is a well-known cause of respiratory complications and more severe oesophageal mucosa damage, including reflux oesophagitis with peptic stricture and Barrett's metaplasia.[17–20] Although sleep disturbance has been often described in patients with morbid obesity, most studies have focused on obstructive sleep apnea syndrome rather than on nocturnal

reflux as the source of sleep compromising.[21–24] Furthermore, there is evidence indicating a close interaction between obesity, nocturnal reflux and respiratory symptoms.[25,26]

Theoretically, patients with morbid obesity are at a greater risk of nocturnal reflux and its complications, mainly because of the combination of increased stress over the oesophagogastric junction and visceral hyposensitivity, the latter recently described in patients with morbid obesity.[27–30] However, the role of heartburn during sleep (HDS) as representative of nocturnal reflux and its potentially associated objective reflux parameters such as increased acid contact time (ACT) and reflux oesophagitis is lacking in morbidly obese patients.[21,31,32]

We hypothesized that nocturnal reflux, clinically detected by HDS, is prevalent in patients with morbid obesity and predicts the presence of objective GORD parameters. Additionally, HDS might be a clinical marker of increased heartburn perception in this population. Therefore, the aims of this study were to assess in morbidly obese patients: (i) the prevalence of HDS; (ii) whether HDS predicts the presence of objective GORD parameters; and (iii) If HDS associates with increased perception of heartburn.

METHODS

Patients

Ninety-one consecutive morbidly obese patients [body mass index (BMI) > 40 kg m^{-2}, or BMI > 35 kg m^{-2} in combination with relevant comorbidity] were prospectively studied before bariatric surgery between March and October 2007 at the ENDOPASSO, Passo Fundo, Brazil. After agreement to participate in the study, patients underwent assessment of GORD symptoms, upper gastrointestinal endoscopy and ambulatory oesophageal pH monitoring. Patients with HDS were compared with patients without HDS regarding objective reflux parameters and heartburn perception. The study was approved by the ethical committee of the Hospital de Clinicas de Porto Alegre. Informed consent was obtained from every participant.

Assessment of GORD symptoms

GORD symptoms were assessed by means of a GORD Symptom Questionnaire (GORD-SQ)[33] validated to the native language.[34] The questionnaire was systematically applied by a trained nurse before complementary investigation. Among six questions about heartburn, one question assessed HDS, one evaluated daytime heartburn and one provided a General Score for Heartburn (GSH). HDS was characterized when patients replied positively to the question, 'Does heartburn wake you from sleep?'. Daytime heartburn was evaluated with the question, 'Heartburn when standing up?', whereas GSH was assessed with the question, 'How had is your heartburn?', with all questions ranging between 0 and 5 as follows: 0 – no symptoms; 1 – symptoms noticeable but not troublesome; 2 – symptoms noticeable and troublesome, but not every day; 3 – symptoms troublesome every day; 4 – symptoms affect daily activities; and 5 – symptoms are incapacitating. Patients were considered to wake from sleep due to heartburn when replied 1 or more to the HDS question.

Upper gastrointestinal endoscopy

Endoscopy was carried out by two endoscopists following a standardized protocol, previously to oesophageal function tests. Patients were examined after 8-h fasting, using a videoendoscope (Olympus GIF-130, Tokyo, Japan). Patients stopped the use of acid-suppressive medications, including proton pump inhibitors and H2-blockers, at least 10 days before the procedure. Reflux oesophagitis was described according to Los Angeles classification.[35] Briefly, mucosal breaks (one or more) without extension between the tops of two mucosal folds were classified as A (<5 mm length) or B (>5 mm length), whereas mucosal breaks (one or more) showing lateral extensions were classified as C (<75% of the oesophageal circumference) or D (>75%). In case of oesophagitis grade A, a consensus about the presence of mucosal breaks was reached after analysis of endoscopic pictures by a third endoscopist, blinded by the patient's symptoms and pH-metry results.

Ambulatory oesophageal pH monitoring

Oesophageal pH monitoring was performed with a portable pH data recorder (Sandhill Scientific, Inc., Highlands Ranch, CO, USA) and a pH catheter containing an antimony sensor. Acid-suppressive medications were stopped at least 10 days before the study. After calibration in pH 4.0 and 7.0 solutions, the catheter was inserted transnasally and positioned at 5 cm above the proximal border of the lower oesophageal sphincter, as previously determined by manometry. Patients recorded the time of food or fluid consumption and posture changes on a diary card. Patients were asked not to eat between meals and to

preferably drink water during the recording. They were instructed to stay upright during the daytime. On the following day, the catheter was removed and the data downloaded and analysed (BioView pH; Sandhill Scientific Inc.).

Acid reflux was defined as a sudden drop in oesophageal pH to below 4. All meal periods were excluded from pH analysis.[36] Patients were considered to have abnormal ACT if the fraction time with pH < 4 was ≥4.2% during the total study period, ≥6.3% in the upright period or ≥1.2% in the supine period.[37] Symptom Index (SI) for heartburn was calculated as the number of symptom episodes preceded by acid reflux within 2 min, divided by the total number of symptom episodes, multiplied by 100. SI was considered positive if ≥50%.[38,39]

Definition of study outcomes

Objective reflux parameters were characterized in the presence of either reflux oesophagitis at endoscopy (grades A–D of Los Angeles) or abnormal ACT at pH monitoring (total, upright or supine periods). Increased heartburn perception was assessed subjectively by comparisons of GSH between patients with HDS and patients without HDS but with diurnal heartburn and objectively by the comparison of the SI for daytime heartburn during pH monitoring between groups.

Statistical analysis

Data are presented as mean ± SD or when otherwise stated. Parametric (Student's) or non-parametric (Mann–Whitney) *t*-tests were used to compare values between patients with and without HDS depending on the variable distribution by using GraphPad Prism 4 (GraphPad Software, Inc., San Diego, CA, USA). Differences in proportions were tested using chi-squared test or Fisher exact test. A multivariate logistic regression analysis was carried out to evaluate the relation between HDS, reflux oesophagitis and day- and nighttime ACT. For this purpose, both day- and nighttime ACT were dichotomized in normal/abnormal using the cut-offs of 6.2% and 1.2%, respectively. Logistic regression analysis was performed using SPSS version 13 (SPSS Inc., Chicago, ILL, USA). Statistical significance was considered if $P < 0.05$.

The yield of HDS as predictive of GORD with objective reflux parameters was estimated by the calculation of HDS accuracy, sensitivity, specificity and predictive values, taking the prevalence of GORD of the study population as reference. Test performance was calculated using WinPEPI version 4.8.

RESULTS

Patients

Ninety-one patients completed the study. HDS was reported by 33 patients (36%; 0.95 CI 27–47%), graded as follows: 5 patients (15%) with HDS noticeable but not troublesome; 23 patients (70%) with HDS noticeable and troublesome, but not every day; and 5 patients (15%) with HDS noticeable and troublesome every day. When the study population was stratified according to the report of daytime heartburn ($n = 54$), HDS was found in 61% (0.95 CI 48–73%) of the patients ($n = 33$). Demographic data and anthropometric measurements are presented in Table 1. There was a trend for patients with HDS to be older than patients without HDS, whereas sex distribution was similar between groups. No significant difference was observed comparing anthropometric measurements between patients with and without HDS. Out of 91 patients, 11 reported the use of protom pump inhibitors in the last month before stopping the medication for endoscopy and pH monitoring. Of these, 10 patients had HDS while 1 denied HDS (30% *vs* 2%, $P < 0.001$).

Objective GORD parameters

Out of 33 patients with HDS, 31 (94%) showed either abnormal ACT or reflux oesophagitis, whereas in those who denied HDS ($n = 58$), objective GORD parameters were found in 33 (57%) patients ($P < 0.001$).

Abnormal ACT was significantly more frequent in patients with HDS during both nocturnal (67% *vs* 36%, $P < 0.01$) and diurnal (64% *vs* 31%, $P < 0.01$) periods. As shown in Fig. 1, the percentage of time with pH < 4 was significantly higher in patients with HDS for both nocturnal [4.2% (0.1–7.6%) *vs* 0.3% (0–2.7%); $P < 0.05$] and diurnal periods [7.4%

Table 1 Demographic data and anthropometric measurements of patients with and without HDS ($n = 91$)

	HDS ($n = 33$)	No HDS ($n = 58$)	P
Demography			
Male, *n* (%)	11 (33)	17 (29)	0.689
Age, mean (range)	41.2 (18–59)	36.5 (18–61)	0.050
Anthropometry, mean (range)			
BMI	44.5 (35.3–64.5)	45.6 (36–67.7)	0.413
Waist circumference	126.1 (95–166)	129.5 (106–163)	0.375
Waist-hip ratio	0.95 (0.72–1.08)	0.97 (0.76–1.16)	0.480

HDS, heartburn during sleep; BMI, body mass index.

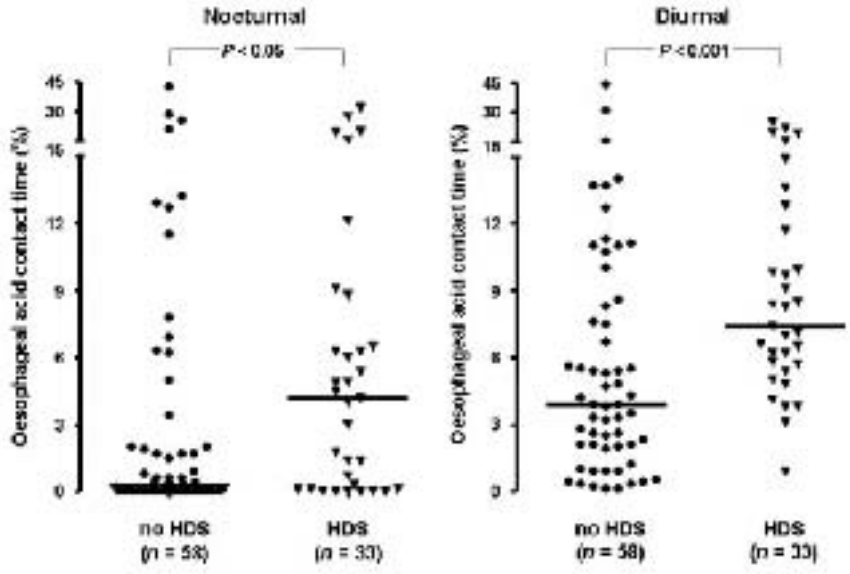

Figure 1 Oesophageal acid contact time during nocturnal and diurnal periods of patients who denied or reported heartburn during sleep. Horizontal bars express median.

(5.5–12.2%) *vs* 3.9% (1.9–8.4%); $P < 0.001$] when compared with patients who denied HDS.

Reflux oesophagitis was significantly more common in patients with HDS than in those without HDS (85% *vs* 24%, $P < 0.0001$), as presented in Fig. 2. In patients with HDS, oesophagitis was absent in 5 patients, grade A in 13, grade B in 11 and grade C in 4 patients. In patients without HDS, oesophagitis was absent in 44 patients, grade A in 11, grade B in 2 and grade C in 1 patient. The comparison of the proportion of patients with oesophagitis grade B or more between groups revealed a trend for patients with HDS to have more severe oesophagitis (54% *vs* 21%, $P = 0.057$).

Taking all patients with abnormal nighttime ACT (22 with HDS and 21 without HDS), the prevalence of reflux oesophagitis was significantly higher in HDS patients (91% *vs* 33%, $P < 0.001$).

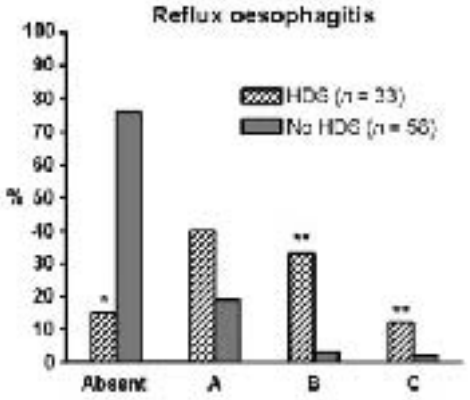

Figure 2 Presence and grade of reflux oesophagitis in patients with and without heartburn during sleep (HDS). Reflux oesophagitis was significantly more common in patients with HDS than in those who denied HDS (*$P < 0.0001$). A trend was observed for more severe mucosal damage (oesophagitis grade B or more) in patients with HDS (**$P = 0.057$).

Positive and negative predictive values of HDS

Test performance was calculated taking into account the GORD prevalence of the study population (70%). Diagnostic accuracy of the HDS for GORD with objective parameters was 61.5%. As shown in Table 2, HDS showed moderate sensitivity and high specificity for detection of GORD. Accordingly, HDS showed high positive and low negative predictive values for GORD. Controlling for day- and nighttime ACT, the report of HDS had an adjusted odds ratio (OR) of 13.3 (0.95 CI 4.2–42.3; $P < 0.001$) for reflux oesophagitis.

Increased heartburn perception

Data regarding GSH and reflux-associated heartburn during pH monitoring are presented in Table 3. Patients with HDS showed significantly higher GSH

Table 2 Performance of heartburn during sleep (HDS) as a test for detection of gastro-oesophageal reflux disease with objective reflux parameters in morbidly obese patients ($n = 91$)

Test performance	HDS % (0.95 CI)
Sensitivity	48 (37–60)
Specificity	93 (77–98)
Positive predictive value	94 (82–98)
Negative predictive value	44 (37–50)

Table 3 Heartburn perception assessed by means of general score for heartburn at Gastro-Oesophageal Reflux Disease-Symptom Questionnaire (GORD-SQ) and reflux-associated daytime heartburn at oesophageal pH monitoring

Heartburn perception	HDS (n = 33)	No HDS (n = 58)	P
General score (GORD-SQ)*	2.46 ± 0.6	1.71 ± 0.5	<0.0001
Reflux-associated daytime heartburn, n (%)	13 (39)	5 (9)	<0.001

*No heartburn during sleep (HDS) patients were those who reported heartburn other than the HDS patients (n = 24).

compared with patients who denied HDS but reported daytime heartburn. Compared with patients without HDS, a significantly higher proportion of patients with HDS had daytime heartburn preceded by acid reflux (SI+) during ambulatory oesophageal pH monitoring.

A logistic regression analysis was performed to assess the effect of daytime ACT on HDS controlling for nighttime ACT. The adjusted OR of abnormal daytime ACT was 3 (0.95 CI 1.2–7.8, P = 0.024), whereas the adjusted OR of abnormal nighttime ACT was 2.6 (0.95 CI 1.002–6.7, P = 0.049).

DISCUSSION

The development of new clinical strategies is cornerstone to help in the management of important diseases such as GORD and morbid obesity[1–3]. Taking this into account, we evaluated whether a simple question as "Does heartburn wake you from sleep?" is predictive of GORD in morbidly obese patients. In addition, we assessed how frequent is HDS in this population and if HDS might be a clinical marker of increased heartburn perception.

The main findings of this study were: (i) HDS is relatively frequent in morbidly obese patients, affecting approximately one-third of the patients; (ii) a positive report of HDS has high predictive value of GORD with objective reflux parameters; and (iii) HDS is associated with increased perception of heartburn in diurnal periods.

HDS was found in a significant minority (36%) of patients with morbid obesity evaluated before bariatric surgery. HDS was assessed by means of a validated questionnaire adapted to the native language of the study population and designed to approach GORD symptoms, including HDS, daytime heartburn and a general score for heartburn.[34] Our patients were consecutively included in the study, independent of the presence and severity of GORD symptoms. Therefore, the prevalence of HDS might be applicable to a general population of candidates to bariatric surgery rather than GORD patients with morbid obesity. Recent studies have reported significant rates of nocturnal heartburn in different populations, assessed by means of structured questionnaires. In a random-sample telephone survey conducted in the general US population, Farup *et al.*[14] found an overall prevalence of nocturnal GORD of 10%. In a large sample of adults with heartburn, Shaker *et al.*[16] found a prevalence of nocturnal symptoms of 79%. In the current study, when stratified according to the presence of daytime heartburn, HDS was reported by nearly two-thirds (61%) of the patients.

HDS showed high positive predictive value, moderate sensitivity and high specificity for detection of GORD with objective parameters in our study population. The high positive predictive value (94%) either for reflux oesophagitis at endoscopy or increased acid exposure at pH-metry suggests that HDS has good utility in the clinical practice. In contrast, its negative predictive value was low, as only 44% of the patients who denied HDS had absence of objective GORD parameters. Apart from the higher prevalence of reflux oesophagitis in HDS patients, a trend was observed for more severe oesophagitis in these patients. In agreement with this, several reports have suggested an association between nocturnal reflux and oesophageal mucosa damage, including peptic stricture and Barrett's oesophagus.[17,19,20] Lagergren *et al.*[12] described an increased risk of oesophageal adenocarcinoma in patients with nocturnal GORD symptoms. Noteworthy, approximately half of our patients with increased nocturnal acid exposure denied HDS, particularly those without reflux-associated mucosal breaks. Curiously, recent reports have suggested a phenomenon of visceral hyposensitivity in patients with morbid obesity, as either oesophageal motor disorders or pathological reflux have been frequently found in asymptomatic patients.[27–29]

The mechanisms involved in the relationship between morbid obesity and HDS are complex. HDS implies that the stimulus provoked by the reflux of gastric content on the oesophageal mucosa is either strong enough to wake the patient from a stable sleep or concurrent with periods of arousals, which in turn facilitates the perception of heartburn. The finding of higher nocturnal acid exposure in patients who reported HDS partially supports the first hypothesis. On the other hand, the association of decreased sleep quality frequently found in morbidly obese patients,[21,31,32] with higher rates of nocturnal GOR raises the chance of casual occurrence of reflux during

periods of arousals, favouring the latter hypotheses. Furthermore, the high prevalence of reflux-associated mucosal breaks found in patients with HDS likely contributes to sensitize the oesophageal mucosa during the sleep. In agreement with this, the finding of reflux oesophagitis in our study population was 13 times more likely in those who reported HDS.

To our knowledge, this is the first study indicating that HDS may be a clinical marker of oesophageal sensitization to reflux. We found that morbidly obese patients with HDS had increased heartburn perception, either by subjective or objective assessment. The subjective evidence comes from a higher general heartburn score in HDS patients compared with patients without HDS. For such comparisons, we had the caution to exclude from the group of patients without HDS those who denied heartburn. The objective evidence comes from the analysis of the SI obtained during oesophageal pH monitoring. More patients with HDS perceived daytime heartburn after episodes of acid reflux than patients without HDS. Interestingly, both day- and nighttime abnormal ACT were independently associated with HDS, as indicated by logistic regression analysis. The interaction between nocturnal reflux, sleep quality and perception of GORD symptoms has been the focus of recent studies. Dickman *et al.*[40] described that persons with worse GORD symptoms report poorer sleep quality, and greater acid exposure at night was related to a worse perception of sleep quality on the next day. Schey *et al.*[41] reported that sleep deprivation is hyperalgesic in patients with GORD. In combination with our findings, these evidences may have clinical implication, as an appropriate control of nocturnal reflux might decrease symptom perception during the day and improve daytime function.

We recognize some limitations of this study. The absence of sleep monitoring precluded either comparisons of sleep quality on the dependence of HDS, assessment of concurrent reflux and arousals as the mechanism for HDS or the interaction apnea/HDS.[42] The analysis of HDS with stratification by responses in order to compare more/less severe symptoms was not feasible due to a small number of patients with severe HDS. Additionally, the lack of a non-morbid obese population for comparisons of HDS frequency limited our findings specifically to patients with severe overweight. Nevertheless, the current study strengthens the importance of nocturnal reflux in morbidly obese patients and opens horizons for new research.

In conclusion, we assessed how frequent is HDS in morbidly obese patients who are candidates to bariatric surgery and whether this symptom predicts the presence of objective reflux parameters and increased perception of heartburn. We found that HDS affects a significant minority of morbidly obese patients and its report is highly predictive of GORD with objective reflux data. HDS accuracy and sensitivity were both moderate in these patients, possibly due to obesity-related visceral hyposensitivity. Nocturnal reflux strong enough to wake the patient seems to favour the perception of heartburn in periods of consciousness. This study suggests that questioning of HDS should be routine in the attendance of patients with morbid obesity, with a positive reply being practically synonymous of GORD.

COMPETING INTERESTS

The authors have no competing interests.

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The role of gastroesophageal pressure gradient and hiatal hernia on gastroesophageal reflux disease in morbidly obese patients

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Suggested running head: GEPG, hiatal hernia

ABSTRACT

Background and objectives: The relation between gastroesophageal pressure gradient (GEPG), sliding hiatal hernia (SHH) and gastroesophageal reflux disease (GERD) is under investigation. We assessed the role of GEPG and SHH on GERD in morbidly obese patients. **Methods:** Ninety-four consecutive patients were prospectively evaluated with esophageal manometry, 24-hs pH-metry, endoscopy and barium swallow x-ray. GEPG was measured at expiration and inspiration, whereas SHH was characterized by X-ray. Patients were classified as having physiological reflux or GERD depending on pH-metry results. Patients with esophagitis and normal pH-metry were excluded. **Results:** Eighty-nine patients composed the study sample (25 men, 38.3 ± 11.1 years; BMI 45 ± 6.9 kg/m^2). Sixty-two patients (70%) had GERD whereas 27 had physiological reflux. GEPG was higher in patients with GERD in both inspiration (19.0 ± 4.3 vs. 15.2 ± 4.1 mm Hg; P <0.001) and expiration (7.5 ± 3.2 vs. 4.7 ± 3.5 mm Hg; P <0.001). GERD was predicted either by inspiratory GEPG (prevalence ratio (PR) = 1.05; 95%CI: 1.03-1.08; P < 0.001) or expiratory GEPG (PR = 1.07; 95%CI: 1.03-1.11; P = 0.001), controlling for SHH, age and sex. SHH was more frequent (40% vs. 15%; P = 0.026) and larger (median: 4 vs. 2.25 cm; P = 0.036) in patients with GERD. SHH predicted GERD (PR: 1.54, 95%CI: 1.19-2.00; P = 0.001) controlling for sex and inspiratory GEPG. **Conclusions:** In morbidly obese patients both GEPGs and SHH are predictors of GERD. These findings give pathophysiological support to the higher prevalence of GERD in this population.

Key words: gastroesophageal reflux disease; morbid obesity; hiatal hernia; esophageal pH monitoring; reflux esophagitis

INTRODUCTION

Gastroesophageal reflux disease (GERD) and obesity are entities with increasing prevalence (1-4). Both diseases impair quality of life and demand frequent health-care utilization (5-8). Several reports have shown an association of obesity with reflux symptoms (9-12), erosive esophagitis (13;14) and Barrett's esophagus (15;16). Furthermore, studies suggest that an increased body mass index (BMI) is associated with prolonged esophageal exposure to reflux of gastric contents (7;17;18).

A hypothesis to explain how obesity promotes gastroesophageal reflux (GER) is an increased stress over the esophagogastric junction (EGJ) (19). Obesity increases the gastroesophageal pressure gradient (GEPG), a drive force that may be crucial in the occurrence of reflux (20-23). Apart from the GEPG, hiatal hernia (SHH) has been implicated in the relation between obesity and GERD (24-26). A recent study using high-resolution manometry suggested an association between obesity and both increased GEPG and SHH (27). However, studies assessing the effect of obesity-related disruption of the EGJ on quantitative reflux data such as esophageal acid exposure and reflux esophagitis are scarce (28).

Morbid obesity has been increasingly recognized worldwide with recent studies indicating a high rate of GERD in patients with this condition (29-32). It has been demonstrated that severely obese subjects have an increased GEPG compared to lean individuals (21). By the presence of remarkable overweight, morbid obesity might provide a suitable scenario to evaluate the relationship between obesity, stress over the EGJ and GERD. We hypothesized that increased GEPG and EGJ disruption associated with obesity contributes to pathological reflux in patients with severe overweight. Therefore, the aim of this study was to assess the role of gastroesophageal pressure

gradient and hiatal hernia on gastroesophageal reflux disease in morbidly obese patients.

METHODS

PATIENTS

Ninety-four morbidly obese patients (BMI > 40 kg/m^2, or BMI > 35 kg/m^2 in combination with relevant comorbidity) were consecutively studied between March and October 2007, before Roux-en-Y gastric bypass. After agreement to participate in the study, patients underwent clinical evaluation, esophageal manometry, 24h esophageal pH monitoring, upper gastrointestinal endoscopy, barium swallow x-ray and dosing of serum glycohemoglobin (HbA1c in %).

Patients were classified in two categories based on findings from pH monitoring and endoscopy: (1) “GERD patients” at the presence of increased acid exposure irrespective of endoscopy findings; and (2) “Physiological reflux patients” at the presence of both normal acid exposure and normal esophageal mucosa. Patients with reflux esophagitis and normal acid exposure were excluded.

The study was approved by the ethical committee of the Hospital de Clinicas de Porto Alegre. Informed consent was obtained for every participant.

Clinical Evaluation

Patients replied to a GERD symptom’s questionnaire (GERD-SQ) (33) validated to the native language (34), followed by acquisition of anthropometric measurements and annotation of acid-suppressive treatments. GERD-SQ scored heartburn (range 0 – 30)

with the sum of 6 questions (range 0 – 5 each), as worst as higher the score. A question assessed GERD-related well being, ranging 1 to 6 as follows: 1 – very satisfied; 2 – satisfied; 3 – unaffected; 4 – unsatisfied; 5 – very unsatisfied; 6 – incapacitated. Anthropometric measurements were obtained by a trained nurse. Body weight and height were measured using a Filizola scale and a stadiometer, and BMI was calculated by dividing the weight (kg) by the square of height (m^2). Body circumferences were taken in a standing position using a measuring tape. Waist circumference (WC, in cm) was measured at the greatest horizontal circumference between the ribs and the iliac crest. Hip circumference (HC, in cm) was measured at the largest horizontal circumference at the buttocks. Waist-hip ratio (WHR) was calculated by dividing WC by HC (35).

Measurement of GEPG

GEPG was measured during esophageal manometry. The study was performed with patients fasting 8 hours, using a catheter with 1 circumferential and 2 unidirectional solid-state pressure sensors (Konigsberg Instruments, Pasadena, CA, USA). The catheter was inserted transnasally into the esophagus with its distal pressure sensor (circumferential) placed into the gastric lumen, at least 3 cm below the lower esophageal sphincter (LES). With patients in horizontal position (head 30°), the catheter was pulled out by 1 cm steps with intervals of 4-5 respiratory oscillations. Step pulled was performed crossing the high-pressure zone up to 3 cm above the LES. GEPG was calculated as the difference between gastric and esophageal baseline pressures at expiration and inspiration. Manometric recordings were generated and stored using a computer software package (Sandhill Scientific Inc, Highlands Ranch, CO, USA).

Ambulatory esophageal pH monitoring

Esophageal pH monitoring was performed with a portable pH-metry (Sandhill Scientific, Inc.; Highlands Ranch, CO, USA). After calibration in pH 4.0 and 7.0 solutions, the catheter was inserted transnasally and positioned into the stomach by observing a pH value < 4. The catheter was step pulled and placed at 5 cm above the proximal border of the LES. Acid-suppressive medications, including proton pump inhibitors and H2 blockers, were stopped at least 7 days before the study. Patients were instructed to keep their habitual daily activities and record symptoms, food and fluid consumption and posture changes on a diary card. On the following day, the catheter was removed and the data downloaded and analyzed (BioView pH, Sandhill Scientific Inc.).

Acid reflux was defined as a sudden drop in esophageal pH to below 4. All meal periods were excluded from pH analysis (36). Patients were considered to have increased esophageal acid exposure if the fraction time with pH < 4 was ≥ 4.2% during the total study period, ≥ 6.3% in the upright period or ≥ 1.2% in the supine period (37).

Upper gastrointestinal endoscopy

Endoscopy was performed after 8-hour fasting, using a videoendoscope (Olympus GIF-130, Tokyo, Japan). Reflux esophagitis was described according to Los Angeles classification (38). Briefly, mucosal breaks (one or more) without extension between the tops of two mucosal folds were classified as A (< 5mm length) or B (> 5mm length), whereas mucosal breaks (one or more) showing lateral extension were classified as C (< 75% of the esophageal circumference) or D (> 75%).

Barium swallow x-ray

Barium swallow was performed with patients in fasting conditions. Determination of the presence of sliding hiatal hernia (SHH) was based on the appearance of the esophagogastric region on the prone horizontal radiographs of the lower esophagus, according to published criteria (39). SHH was characterized at the presence of one of the following criteria: i. B ring located above the diaphragmatic hiatal impression; ii. Gastric folds above the diaphragm. B ring was defined as a smooth, symmetric ring-like indentation at the esophagogastric junction. A skilled radiologist blinded to patient's symptoms and esophageal function tests analyzed the radiographs, defining presence/absence of SHH and its size in cm.

Statistical analysis

Data are presented as mean (± SD or range) or when otherwise stated. According to variable distribution, Student's *t* or nonparametric Wilcoxon-Mann-Whitney tests were used to compare groups in relation to quantitative data, whereas differences in proportions were tested by Fisher Exact test. Pearson´s product-moment or Spearman´s rank correlation coefficients were used to measure associations between quantitative variables. Due to skewed distribution, pH and GEGP measures were log transformed to satisfy the assumptions of the statistical tests.

Hiatal hernia, expiratory GEPG and inspiratory GEPG were tested as predictors of GERD, adjusting for sex, age, and anthropometric measures (BMI, WHR or WC). To accommodate known differences between sexes, WHR and WC were both reduced to a dichotomous variable with cut-points corresponding to the median value of the study

population (WHR-high > 1.038 for males and > 0.917 for females; WC-high > 136 cm for males and > 122 for females). Associations between variables and GERD were evaluated using multivariate Poisson regression analysis with robust variance.

Multiple linear regression analyses were carried out to assess the role of GEPGs and SHH on acid exposure during total, upright and supine periods. In order to compare the effects of different independent variables on pH measures, adjusted partial regression coefficients were standardized (multiplied by the ratio of the standard deviation - SD of the predictor to SD of the dependent variable) and named “beta”. In both Poisson and linear regression analyses the coefficients were adjusted for co-variables with P values lower than 0.20 in the multivariate model.

RESULTS

PATIENTS

Out of 94 patients, 5 were excluded due to the presence of reflux esophagitis combined with normal acid exposure at pH monitoring. The final study sample was composed by 89 patients. Of these, 62 (70%) had GERD and 27 patients (30%) had physiological reflux. Demographic data, anthropometric measurements, GERD-SQ scores and HbA1c levels are presented in table 1.

Male sex was significantly more frequent in the group of patients with GERD. This group also showed significantly worst scores for both heartburn and GERD-related well being. No significant differences were found in relation to age, anthropometry and HbA1c.

Out of 62 patients with GERD, there were 26 (42%) with nonerosive disease and 36

patients (58%) with reflux esophagitis: 21 with grade A, 11 with grade B and 4 with grade C of Los Angeles. Regular usage of PPI in the last 2 months was reported by 12 out of 62 GERD patients and by 1 out of 27 physiological reflux patients (19% vs. 4%; P = 0.098).

Table 1. Demographic data, anthropometric measurements and GERD-SQ scores of morbidly obese patients (n = 89).

	Physiological reflux (n = 27)	GERD (n = 62)	P
Demography			
Male, n (%)	3 (11)	22 (36)	0.021
Age, mean (range)	36.6 (18-61)	39.1 (18-59)	0.343
Anthropometry			
BMI, mean (range)	44.2 (36.0-53.7)	45.3 (35.3-64.5)	0.792
WC high[1], n (%)	14 (52)	35 (57)	0.817
WHR high[2], n (%)	11 (41)	34 (55)	0.221
GERD-SQ			
Heartburn, median (range)[3]	0 (0-12)	9 (0-18)	0.001
Well being[4], median (range)	3 (1-4)	4 (2-5)	0.003
Glycemic control[5]			
HbA1c (%), mean (range)	8.3 (4.3-12.3)	8 (4-12.7)	0.481

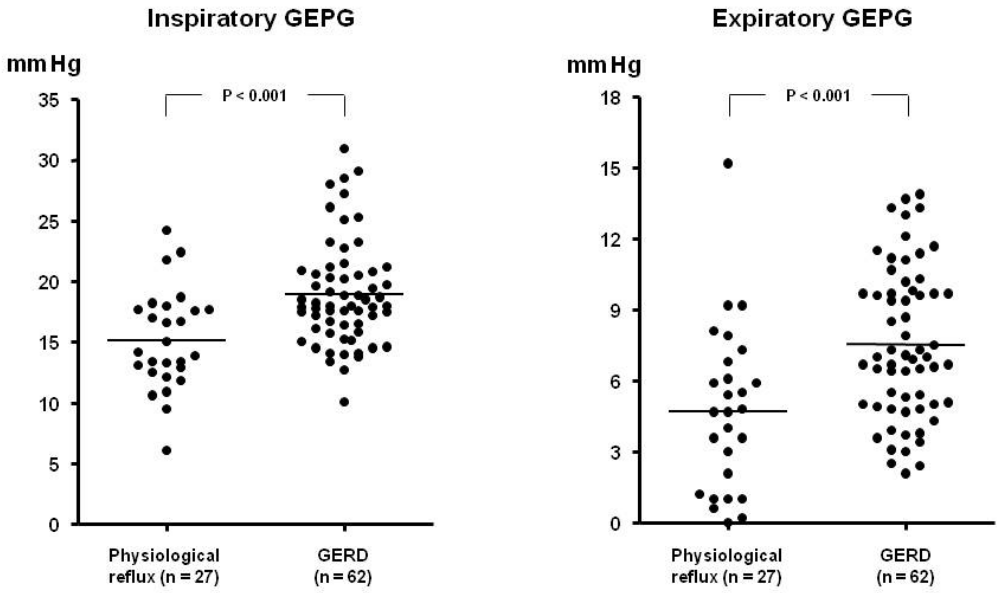
[1]Cut-point: 136 cm for males and 122 cm for females; [2]Cut-point: 1.038 for males and 0.917 for females; [3]Range 0 (worst) – 50 (best); [4]1 = Very satisfied; 2 = satisfied; 3 = unaffected; 4 = unsatisfied; 5 = very unsatisfied; [5]Available in 25 patients with physiological reflux and in 61 patients with GERD.

Gastroesophageal pressure gradient (GEPG)

GEPG was significantly higher in patients with GERD compared to those with physiological reflux in both inspiration (mean ± SD: 19.0 ± 4.3 vs. 15.2 ± 4.1 mm Hg;

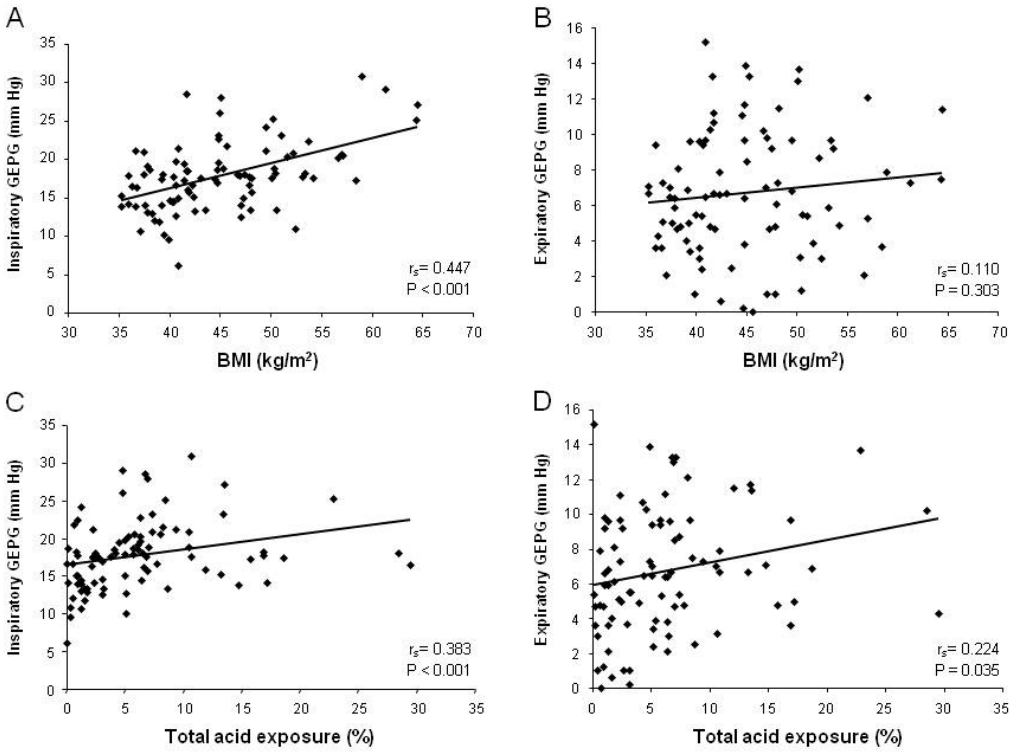
P <0.001) and expiration (7.5 ± 3.2 vs. 4.7 ± 3.5 mm Hg; P <0.001) – figure 1.

Figure 1. Inspiratory and expiratory GEPG in morbidly obese patients with physiological reflux and GERD.



As shown in figure 2, inspiratory GEPG showed a moderate correlation with both BMI (r_S = 0.447, P < 0.001) and total esophageal acid exposure (r_S = 0.383; P < 0.001). Patients with WC-high showed significantly higher inspiratory GEPG values (18.9 ± 4.7 vs. 16.3 ± 4.0 mm Hg; P = 0.005) than those with lower WC measures. No significant difference was observed between WHC-high/low (mean ± SD: 18.1 ± 4.0 mm Hg vs. 17.5 ± 5.1mm Hg; P = 0.239) in relation to inspiratory GEPG.

Figure 2. Correlations of inspiratory and expiratory GEPG with BMI (A and B respectively) and total esophageal acid exposure (C and D) in 89 patients.



A weaker correlation was observed between expiratory GEPG and total acid exposure (r_S = 0.224; P = 0.035). Expiratory GEPG presented no correlation either with BMI (r_S = 0.110; P = 0.303), WC-high (mean ± SD: 7.0 ± 3.7 and 6.4 ± 3.2 mm Hg in individuals with and without WC-high, respectively; P = 0.356) or WHC-high (7.1 ± 3.5 and 6.3 ± 3.5 mm Hg in patients with and without high WHR, respectively; P = 0.231). GEPG showed no correlation with HbA1c either for inspiratory (r_S = 0.056; P = 0.605) or expiratory gradients (r_S = - 0.032; P = 0.768).

Hiatal hernia

Out of 89 patients, 29 (33%) had hiatal hernia, with a median size of 4 cm (ranging 1.5

– 7 cm). SHH was significantly more frequent in patients with GERD than in those with physiological reflux (40% vs. 15%; P = 0.026). The former group also showed larger hernias than the latter (median and range): 4 (1.5-7 cm) vs. 2.25 (2-3 cm); P = 0.036. A negative correlation was observed between expiratory GEPG and SHH size, with borderline statistical significance ($r_S = – 0.33$, p = 0.077). No significant correlation was found between SHH size and inspiratory GEPG ($r_S = – 0.13$, p = 0.502).

Associations between GEPGs, SHH and GERD

Hiatal hernia, inspiratory GEPG and expiratory GEPG were tested as predictors of GERD. All three variables were significantly associated with GERD in univariate Poisson regression analyses. The unadjusted prevalence ratios (95% CI) were: SHH: 1.40 (1.09 - 1.79; P = 0.008); inspiratory GEPG: 1.05 (1.03-1.08; P < 0.001); expiratory GEPG: 1.07 (1.03 - 1.12; P = 0.001).

Both SHH and GEPGs showed significant associations with GERD (table 2) when considered together in a model adjusted for sex. The larger modification in the unadjusted prevalence ratio was observed for SHH (1.40), with an increase of 10% (PR = 1.54) after controlling for inspiratory GEPG and sex. Adjustments using a multivariate model containing sex, age and one anthropometric measure (one at a time) did not significantly modify the results (data not shown).

Table 2. Multivariate associations of GEPG and HH with GERD, adjusted for sex[1].

Model	Predictors	PR[2]	95% CI	P
1	Inspiratory GEPG	1.05	1.03-1.08	<0.001
	HH	1.54	1.19-2.00	0.001
2	Expiratory GEPG	1.07	1.03-1.11	0.001
	HH	1.48	1.16-1.90	0.002

[1]Co-variables were considered in the model only if the respective P values were < 0.20. Age and anthropometric measures presented P values > 0.20; [2]PR: prevalence ratio.

Table 3 presents standardized regression coefficients (beta) obtained in multivariate linear analyses carried out to assess the effect of GEPGs and SHH on total, upright and supine acid exposure, adjusting for co-variables with a P value < 0.20. Inspiratory GEPG showed significant effect either on total, upright or supine acid exposure, whereas the effect of expiratory GEPG was restricted on total and supine acid exposure. SHH showed a significant effect on total and upright acid exposure, and a borderline effect on supine pH values. No interactions were observed between GEPGs and SHH. In the comparison of two predictors, inspiratory GEPG had stronger effect (higher beta values) than SHH on total and upright acid exposure, while expiratory GEPG and SHH showed similar B values.

Table 3. Multivariable linear regression analysis of the effect of GEPG and HH on esophageal acid exposure: standardized adjusted regression coefficients (P values within parentheses).

		Esophageal acid exposure		
Model	Variable	Total[1]	Upright[1]	Supine[1]
1	Inspiratory GEPG[1]	0.428 (<0.001)	0.398 (<0.001)	0.247 (0.023)
	HH	0.272 (0.005)	0.258 (0.008)	0.207 (0.043)
	R^2	0.25 (<0.001)	0.22 (<0.001)	0.15 (0.003)
	(Adjusting for)[2]	-	-	Sex
2	Expiratory GEPG [1]	0.242 (0.016)	0.157 (0.132)	0.281 (0.006)
	HH	0.271 (0.007)	0.264 (0.013)	0.189 (0.061)
	R^2	0.19 (<0.001)	0.18 (0.006)	0.17(0.001)
	(Adjusting for)[2]	Sex	Sex, age, BMI	Sex

[1]Log transformed; [2]Adjustments were made only for variables with P-value lower than 0.20 in the multivariate regression model.

DISCUSSION

Obesity is an independent and modifiable risk factor for GERD (6;40;41). Although several reports have recently assessed the mechanisms linking obesity and GERD (27;28;42;43), many points remain unclear (19;44). We tested the hypothesis that in patients with morbid obesity, increased stress over the gastroesophageal junction due to severe overweight participates in the physiopathology of GERD, explaining at last in part the high prevalence of GERD in this population (29;30). For this purpose, we assessed the role of gastroesophageal pressure gradient (GEPG) and hiatal hernia (SHH) on GER in morbidly obese patients candidates for bariatric surgery.

The main findings of our study were: 1. Inspiratory and expiratory GEPGs were both predictors of GERD, which was defined as abnormal esophageal acid exposure at 24-h pH-metry; 2. Hiatal hernia predicted GERD, independently of the effects of GEPGs. All these associations were observed after controlling for potential cofounders, including age, sex and anthropometric measures. Secondary findings were: 1. GERD was highly prevalent in this young population with morbid obesity; 2. Inspiratory GEPG was significantly higher in patients with WC-high than in those with lower WC; 3. Glycemic control estimated by HbA1c had no relation with GEPGs and GERD.

In morbidly obese patients, both inspiratory and expiratory GEPGs predicted the presence of GERD, independently of SHH, sex, age and anthropometric measures. The effect of inspiratory GEPG was significantly different for both upright and supine esophageal acid exposure. However, a more pronounced effect on acid exposure was observed in upright periods. Differently, expiratory GEPG predicted acid exposure only in supine periods. The lack of studies showing associations between GEPGs and esophageal acid exposure preclude comparisons with our results. In a recent study de Vries et al found no association between GEPGs and acid exposure in non-obese and obese GERD patients (28). In the present study, the association between GEPGs and acid exposure might reflect peculiarities inherent to morbid obesity. In our patients, inspiratory GEPG was at least 50% higher than that observed in patients of the referred study. Similar differences are valid for expiratory GEPG as well. We believe in a dose-response phenomenon, i.e. the higher the gradients the stronger the effect on reflux of gastric contents. Thus, our study confirms what stated by Pandolfino et al concerning the role of GEPG as a “driving force for reflux to occur” (27).

SHH was a predictor of GERD in our patients with morbid obesity. Adjusting for sex, the effect of SHH on GERD was stronger than that observed with GEPGs. When

controlling for inspiratory GEPG, SHH predicted acid exposure in both upright and supine periods. In contrast, this association was weaker when SHH was controlled for expiratory GEPG. These findings could be explained by the mechanisms underlying SHH and supine reflux, which occurs during periods of increased stress over the EGJ region, such as inspiration (45).

GERD was highly prevalent in our study population, affecting two thirds of patients. In agreement with this, high rates of GERD have been described in studies involving patients with morbid obesity (30;32). It must be mentioned that our patients were candidate to bariatric surgery and were selected irrespective of GERD symptoms. To the best of our knowledge, a 70% prevalence of GERD with objective parameters is the highest rate ever published in a non-selected population. This finding highlights the importance of the link between obesity and GERD. Apart from the mechanical effect of obesity on the promotion of GER, as supported in this and other studies (17;20-23;27;28), additional mechanisms have been proposed, although with scarce evidence (19). An elegant study recently described an association of metabolic syndrome and visceral obesity with reflux esophagitis (42). In the present study, inspiratory GEPG was significantly higher in patients with WC-high than in those with lower WC. In contrast, glycemic control was similar between patients with GERD and those with physiological reflux, suggesting that in morbidly obese patients visceral fat is linked to GERD due to mechanical factors rather than neuro-humoral influences.

We emphasize some methodological characteristics of our study: 1. The study was prospective, minimizing bias of selection and assessment; 2. Endoscopy and 24-h pH-metry were both employed to define GERD and physiological reflux; 3. GEPGs were measured using solid-state catheter, attenuating technical shortcomings related with the use of water-perfused assemblies; 4. Hiatal hernia was characterized by X-ray, a

technique considered superior to endoscopy; and 5. The relation among GEPGs, SHH and acid exposure were calculated taking into account anthropometric measures, including BMI, WHR and WC.

In conclusion, we assessed the role of GEPGs and SHH on GERD in patients with morbid obesity. We found that inspiratory GEPG, expiratory GEPG and SHH were independent predictors of GERD, controlling for potential confounders. These findings support the involvement of mechanical factors related with severe overweight in the complex pathophysiology of GERD. Future studies should analyze if weight loss induced by diets and bariatric procedures affect the relationship between GEPGs and GERD.

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Artigo C Submetido ao periódico Obesity Surgery

Diagnosing sliding hiatal hernia in patients with morbid obesity before and after gastric bypass: Barium swallow X-ray or endoscopy?

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Short title: Diagnosing sliding hiatal hernia in morbid obesity

ABSTRACT

Background: Endoscopy and barium swallow X-ray are largely used to diagnose sliding hiatal hernia (SHH). The utility of these techniques in patients with morbid obesity is unknown. **Aims:** To assess the performance of endoscopy and X-ray in diagnosing SHH before and after gastric bypass (GBP) in morbidly obese patients. **Methods:** Ninety-one patients underwent reflux symptoms assessment, endoscopy, X-ray and 24-h pH-metry before and 6 months after GBP. Patients were classified in Endo SHH when hernia was diagnosed by endoscopy, X-ray SHH when hernia was diagnosed exclusively by X-ray, and No SHH. **Results:** Preoperatively, the comparisons between groups Endo SHH (n = 13), X-ray SHH (n = 18) and No SHH (n = 60) revealed that the first had higher frequency either of heartburn (100% vs. 61% vs. 42%; P < 0.001), regurgitation (69% vs. 28% vs. 22%; P = 0.003) or reflux esophagitis (85% vs. 39% vs. 38%; P = 0.008). Total esophageal acid exposure [median (IQR)] was higher in Endo SHH compared to No SHH [7.8% (4.5 – 14) vs. 3.8% (1.4 – 6.9); P < 0.05]. Postoperatively, reflux symptoms either heartburn or regurgitation had similar frequency between Endo SHH, X-ray SHH and No SHH (40% vs. 25% vs. 12%; P = 0.135), while esophagitis was more frequent in X-ray SHH compared to Endo SHH and No SHH (40% vs. 20% vs. 15%; P = 0.028). **Conclusions:** In morbidly obese patients, endoscopy had higher clinical utility in diagnosing SHH pre GBP, while X-ray was slightly superior in the post GBP assessment.

Kew words: Morbid obesity; gastroesophageal reflux disease; hiatal hernia; endoscopy; X-rays.

INTRODUCTION

Sliding hiatal hernia (SHH) refers to a condition in which the proximal stomach herniates through the esophageal hiatus of the diaphragm into the mediastinum. Its clinical relevance is based on the association with increased gastroesophageal reflux (GER) and its consequences, including troublesome symptoms and tissue damage (1-3). The pathophysiological basis of this phenomenon is the failure of the antireflux barrier and the compromising of the esophageal clearance, both resulting from the separation of the lower esophageal sphincter and the diaphragmatic crura (4-7). Among several pathophysiological factors implicated with GERD, SHH size seems to be the strongest predictor of severity of both reflux esophagitis and esophageal acid exposure (8-10).

Diagnostic techniques widely employed to identify SHH include upper gastrointestinal endoscopy and barium swallow X-ray (11). SHH has been characterized at endoscopy in the presence of partial migration of the stomach into the thorax, represented by dislocation of the gastric folds greater than 2 cm above the diaphragmatic pinch, combined or not with hiatus enlargement at gastric retroview (12-15). Radiological criteria for SHH rely on the demonstration of gastric folds inside the thorax, combined or not with diaphragmatic hiatus enlargement and inferior oesophageal ring (16-18). Among these techniques, no consensus has been reached about the best in diagnosing SHH (11). In addition, most studies have focused on identification of SHH rather than the clinical relevance of finding a SHH.

Obesity has been described as a risk factor for gastroesophageal reflux disease (19;20). Several factors may pay a role on this association, being increased incidence of SHH one of them (21;22). Among obese individuals, those with morbid obesity seem to carry a particular risk of GERD (23;24). In this population, the clinical utility of endoscopy and X-ray in diagnosing SHH is unknown. In addition, the diagnosis of SHH after

gastric bypass (GBP), a procedure increasingly employed to treat patients with morbid obesity, is lacking. Therefore, the aim of this study was to assess the performance of endoscopy and X-ray in diagnosing SHH before and after GBP in morbidly obese patients.

METHODS

Patients

Ninety-two patients with morbid obesity (64 female, aging 38 ± 11.5 years, BMI 45.5 ± 7.6 kg/m^2) were consecutively investigated between March and October of 2007, before bariatric surgery. The recruitment was performed irrespective of GERD symptoms. Patients were considered to be eligible for the study by the following criteria: (1) age between 18 and 70 years; (2) BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 in the presence of significant comorbidities; (3) absence of gastroesophageal surgery; (4) agreement to participate in the study.

Patients underwent GERD symptoms evaluation, upper gastrointestinal endoscopy, barium swallow X-ray and 24-h esophageal pH-metry before and 6 months after GBP. All procedures were prospectively performed following a standardized protocol. Patients were categorized in 3 groups: (1) “Endo SHH” i.e. hernia diagnosed by endoscopy irrespective of X-ray findings; (2) “X-ray SHH” i.e. hernia diagnosed exclusively by X-ray; and (3) “No SHH” i.e. absence of hernia at any test. Comparisons between groups were performed in regard of symptoms, esophagitis and pH-metry results.

The study was approved by the Ethical Committee of the Hospital de Clinicas de Porto Alegre. Informed consent was obtained for every participant.

Clinical assessment

Reflux symptoms were assessed by a GERD symptom's questionnaire (GERD-SQ) (25) validated to the native language (26). GERD-SQ scored heartburn with the question "How bad is the heartburn", whereas regurgitation was scored with the question "Do you feel returning of bitter material from the stomach to the throat?". Symptoms were graded as follows: (0) no symptoms; (1) symptoms noticeable but no troublesome; (2) symptoms troublesome, but not every day; (3) symptoms troublesome every day; (4) symptoms affect daily life; (5) symptoms are incapacitating. The questionnaire was applied by a nurse blinded to complementary tests. Body weight and height were measured using a Filizola scale and a stadiometer, and BMI was calculated by dividing the weight (kg) by the square of height (m^2).

ENDOSCOPY

Endoscopy was performed after 8-hour fasting, using a videoendoscope (Olympus GIF-130, Tokyo, Japan). Reflux esophagitis was described according with Los Angeles (LA) classification (27). Briefly, mucosal breaks (one or more) without extension between the tops of two mucosal folds were classified as A (< 5mm length) or B (> 5mm length), whereas mucosal breaks (one or more) showing lateral extension were classified as C (< 75% of the esophageal circumference) or D (> 75%).

SHH was searched at the end of the procedure after aspiration of the gastric lumen. SHH was characterized when gastric folds were located at least 2 cm above the diaphragmatic pinch on inspiration (12;28;29). Endoscopy was performed with examiners blinded to both patient's symptoms and X-ray findings.

24-H PH-METRY

Esophageal pH-metry was performed with a portable pH data recorder (Sandhill Scientific, Inc.; Highlands Ranch, CO, USA) and a pH catheter containing an antimony sensor. After calibration in pH 4.0 and 7.0 solutions, the catheter was inserted transnasally and positioned into the stomach by observing a pH value < 4. The catheter was step pulled and placed at 5 cm above the proximal border of the LES, previously studied by manometry. Acid-suppressive medications, including proton pump inhibitors and H2 blockers, were stopped at least 7 days before the study. Patients were instructed to keep their habitual daily activities and record symptoms, food or fluid consumption and posture changes on a diary card. On the following day, the catheter was removed and the data downloaded and analyzed (software GERDcheck, Sandhill Scientific Inc.).

Acid reflux was defined as a sudden drop in esophageal pH to below 4. All meal periods were excluded from pH analysis (30). Esophageal acid exposure was described as the percentage of study time with pH < 4. Symptom index for heartburn was calculated as the number of symptom episodes preceded by acid reflux within 2 min, divided by the total number of symptom episodes, multiplied by 100. It was considered positive if ≥ 50% (31;32).

BARIUM SWALLOW X-RAY

X-ray was performed with patients in fasting conditions, following a standardized protocol in both pre and post GBP. Patients were studied after drinking 200 ml of diluted barium. Determination of the presence of sliding hiatal hernia (SHH) was based on the appearance of the esophagogastric region on the prone horizontal radiographs of the lower esophagus, according to published criteria (10). A skilled radiologist blinded

to patient's symptoms and endoscopy findings analyzed the radiographs. SHH was characterized at the presence of either B ring or gastric folds located at least 2 cm above the diaphragmatic pinch. B ring was defined as a smooth, symmetric ring-like indentation at the esophagogastric junction. Hiatus enlargement and SHH size in cm were also described.

GBP

Roux-en-Y GBP was performed through an upper midline incision. A gastric pouch was created by dividing the stomach with a 10-cm stapler from the lesser curvature (7 cm vertically from the cardia) to 1 cm to the left of the Hiss angle. The estimated volume of the gastric pouch was 20 to 30 ml. The gastric pouch was banded in its middle portion by using a silastic ring (6.5 cm long in circumference). A gastro-jejunal anastomosis was created distal to the ring, keeping an alimentary limb with 100 cm in length, and a biliopancreatic limb ranging 60 and 80 cm.

STATISTICAL ANALYSIS

Data are presented as median (IQR 25%-75%) or when otherwise stated. Parametric (ANOVA and Tukey's test) or nonparametric tests (Kruskal-Wallis and Dunn's test) were used to compare values between groups depending on the variable distribution by using GraphPad Prism 4 (GraphPad Software, Inc., San Diego, CA, USA). Differences in proportions were tested using χ^2 test or Fisher test. Statistical significance was considered if $P < 0.05$.

Grade of reflux esophagitis was compared between groups after coding Los Angeles

classification as follows: no esophagitis = 0, LA grade A = 1, grade B = 2, grade C = 3 and grade D = 4. The performances of endoscopy and X-ray in predicting SHH with GERD symptoms were assessed using presence/absence of troublesome heartburn and troublesome regurgitation as referential. Tests accuracy, sensitivity, specificity and predictive values were calculated by using WinPEPI version 4.8. Tests characteristics were considered as follows: optimal (100%), very high (99-80%), high (79-60%), intermediate (59-40%) and low (< 40%).

RESULTS

Patients

One patient was excluded due to technical problems on pH-metry pre GBP. The final study sample was composed by 91 patients. Of these, 13 (14%) had SHH at endoscopy (of which 11 showed SHH also by X-ray), 18 (20%) had SHH exclusively at X-ray, and 60 patients (66%) showed no SHH. Characteristics of patients are shown in table 1. Endo SHH patients were significantly older than patients with no SHH. Sex and BMI did not differ significantly between groups.

GERD symptoms pre GBP

Troublesome heartburn was significantly more frequent in patients with Endo SHH. All patients of this group graded heartburn as troublesome (≥ grade 2), in comparison with 61% of patients of the X-ray SHH group and 42% of patients of the No SHH group (P < 0.001). In these respective groups (figure 1A), the median (IQR) scores for heartburn

Table 1. Characteristics of patients in the pre GBP assessment (n = 91).
*Endo SHH vs. No SHH

	Endo SHH (n = 13)	X-ray SHH (n = 18)	No SHH (n = 60)	P
Age, mean (range)	44 (28-59)	40 (22-51)	36 (18-61)	0.049*
Male, n (%)	4 (31)	3 (17)	21 (35)	0.335
BMI, mean ± SD	43 ± 7.3	43.1 ± 5	46.7 ± 8	0.096

were 2 (2-3) vs. 2 (0-2) vs. 1 (1-2) (P < 0.01 Endo SHH vs. No SHH).

Troublesome regurgitation was significantly more frequent in Endo SHH patients compared to X-ray SHH and No SHH patients (69% vs. 28% vs. 22%; P = 0.003). In these groups (figure 1B), the median (IQR) scores for regurgitation were 2 (0-2) vs. 0 (0-2) vs. 0 (0-1) (P < 0.05 Endo SHH vs. No SHH).

Reflux esophagitis pre GBP

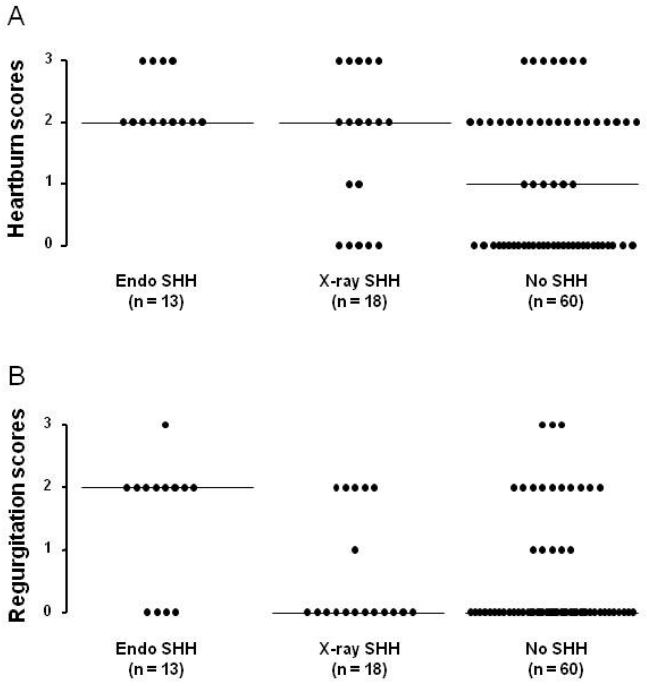
Esophagitis was significantly more frequent in patients with Endo SHH compared to X-ray SHH and No SHH patients (85% vs. 39% vs. 38%; P = 0.008). Grade of reflux esophagitis [median (IQR)] was significantly more severe in patients with Endo SHH compared to X-ray SHH [1 (1-2.5) vs. 0 (0-1.5); P < 0.05] and No SHH patients [1 (1-

2.5) vs. 0 (0-1); P < 0.001].

Esophageal acid exposure and symptom index pre GBP

Total esophageal acid exposure [median (IQR)] was significantly higher in patients with Endo SHH compared to No SHH [7.8% (4.5 – 14) vs. 3.8% (1.4 – 6.9); P < 0.05]. No significant difference was found comparing X-ray SHH with other groups (data not shown). A positive symptom index for heartburn was more frequent in patients with Endo SHH than in those with either X-ray SHH or No SHH (62% vs. 17% vs. 10%; P < 0.0001).

Figure 1. Scores of heartburn (A) and regurgitation (B) in patients with Endo SHH, X-ray SHH and No SHH. Scores ≥ 2 correspond to troublesome symptoms.



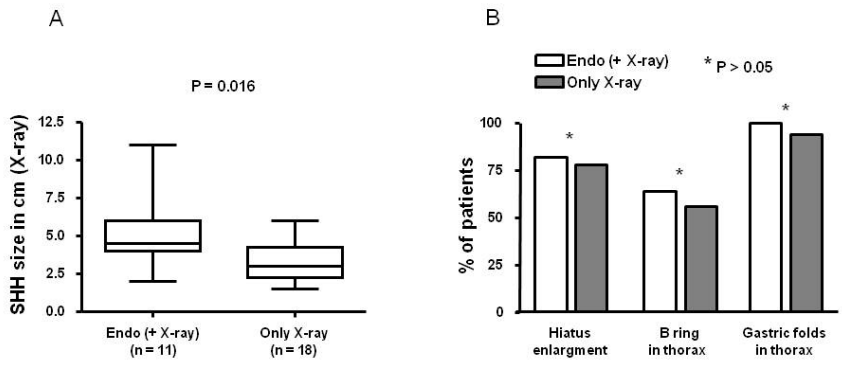
Radiological markers of SHH as predictors of GERD

In the pre GBP assessment, radiological markers of SHH other than gastric folds in the thorax, present in all but one patient, where B ring and hiatus enlargement. Median

(IQR25-75%) scores for heartburn were similar comparing SHH patients with and without hiatus enlargement [2 (1-3) vs. 2.5 (1.5-2.5); P = 0.791]. SHH patients with and without B ring also showed similar scores for heartburn [2 (1.5-3) vs. 2.5 (1.5-2.5); P = 0.663]. Comparisons between patients with and without these markers showed no significant differences in regard of regurgitation scores and esophagitis grades (data not shown).

When radiologically measured, SHH characterized by endoscopy (n = 11) was significantly larger [median (IQR)] than SHH characterized solely at X-ray (n = 18): 4.5 cm (4 – 6) vs. 3 cm (2.25 – 4.25); P = 0.016, as shown in figure 2A. There was no significant difference between these groups regarding frequency of either hiatus enlargement (82% vs. 78%; P = 0.999) or B ring (64% vs. 56%; P = 0.716).

Figure 2. Radiological markers of SHH and their relation with presence of SHH at endoscopy. A, hernia size in cm; B, hiatus enlargement, inferior esophageal ring (B ring) and gastric folds in thorax.



Performance of endoscopy and X-ray in predicting SHH with GERD symptoms

Performances of endoscopy and X-ray at pre GBP assessment are shown in table 2. Endoscopy showed low sensitivity and optimal specificity in predicting SHH with troublesome heartburn. Positive and negative predictive values were optimal and

intermediate respectively. X-ray showed intermediate sensitivity and very high specificity in predicting SHH with troublesome heartburn, while positive and negative predictive values were high and intermediate respectively. Accuracies of endoscopy and X-ray were 60% and 62% respectively.

Endoscopy showed low sensitivity and very high specificity in predicting SHH with troublesome regurgitation. Positive and negative predictive values were both high. X-ray showed intermediated sensitivity, high specificity, intermediated positive predictive value and high negative predicate value for SHH with troublesome regurgitation. The accuracies of X-ray and endoscopy were 67% and 76% respectively.

Table 2. Performance of endoscopy and X-ray in predicting SHH with GERD symptoms in the pre GBP assessment.

Test characteristics	Troublesome heartburn		Troublesome regurgitation	
	Endoscopy	X-ray	Endoscopy	X-Ray
	Percentage (95%CI)			
Sensitivity	27 (16-40)	45 (32-59)	33 (19-52)	48 (31-66)
Specificity	100 (92-100)	83 (69-92)	94 (85-98)	75 (63-84)
+ ve predictive value	100 (54-100)	76 (60-87)	69 (44-86)	45 (31-59)
- ve predictive value	54 (50-58)	56 (49-63)	77 (72-81)	77 (70-83)

ve: positive; -ve: negative

Diagnosing SHH 6 months after GBP

Out of 91 patients, 84 (92%) underwent endoscopy and X-ray 6 months after GBP. Of these, 5 (6%) had SHH at endoscopy (of which 2 showed SHH also by X-ray), 20 (24%) had SHH exclusively at X-ray, and 59 patients (70%) showed no SHH. Out of 25

patients with SHH post GBP, 15 had SHH pre GBP either at endoscopy or X-ray.

The report of GERD symptoms either troublesome heartburn or troublesome regurgitation did not differ between Endo SHH, X-ray SHH and No SHH groups (40% vs. 25% vs. 12%; P = 0.135). The finding of reflux esophagitis differed between groups (χ^2 = 7.09; P = 0.028). It was significantly more frequent in patients with X-ray SHH compared to those with Endo SHH and No SHH (40% vs. 20% vs. 15%). The comparison of total acid exposure between these group did not reveal significant differences [3.1% (0.3-7.8) vs. 0.3% (0.2-8.9) vs. 1% (0.2-2.6); P = 0.252]. The analysis of radiological markers of SHH as predictors of GERD was precluded by the technical impossibility to evaluate the presence of either hiatus enlargement or B ring. Tests performances were not calculated due to a small sample size in Endo SHH (n = 5).

DISCUSSION

Obesity has been linked with GERD (19,20). A major hypothesis to explain this association is an increasing incidence of SHH in patients with overweight (21;22;33;34). Given the crescent relevance of morbid obesity, diagnostic techniques most employed to identify SHH such as endoscopy and X-ray need to be tested in terms of performance. Additionally, the diagnosis of SHH post GBP deserves clarification. In the light of this, we aimed to assess the performance of endoscopy and X-ray in diagnosing SHH before and after GBP.

In our study, endoscopy was superior to X-ray in diagnosing SHH pre GBP. All patients in which SHH was identified by endoscopy complained of troublesome heartburn, while only 60% of patients with SHH diagnosed exclusively by X-ray reported this symptom. Troublesome regurgitation was present in more than double of patients with Endo SHH compared to patients with SHH exclusively at X-ray. Noteworthy, the latter group had a rate of regurgitation comparable to patients with no SHH. We have to mention that the

comparative groups were classified considering the higher sensitivity of X-ray to detect SHH (table 2, 45% vs. 27%). Thus, we decided to assess the clinical relevance of having a SHH at X-ray but not at endoscopy. In addition, endoscopists and radiologists were both blinded to clinical data, avoiding information bias (28).

Reflux esophagitis was more common and severe in Endo SHH compared to other groups preoperatively. While most patients with Endo SHH (85%) had esophagitis, in X-ray SHH group only 39% of patients showed esophagitis, similar with found in those with no SHH (38%). Several studies have shown that SHH increases the risk of esophageal mucosa injury in patients with GERD, secondary to antireflux barrier compromising and delaying of esophageal clearance (4;5;8-10). However, it is known that SHH is not a synonymous of GERD. The reasons for having a SHH without clinical relevance may be explained either by (1) protective mechanisms precluding the generation of symptoms and mucosal injury or (2) a false diagnosis of SHH. A recent global consensus on GERD has proposed that reflux disease conceptually characterizes by the presence of troublesome symptoms and or complications, including reflux esophagitis (35). Based on this Consensus, our study suggests that endoscopy had higher clinical utility in diagnosing SHH in morbidly obese patients evaluated before GBP.

The prevalence of SHH in our study sample (14%) was similar with described in reports in which the endoscopy was the employed technique. Munoz and coworkers reported 10.7% of prevalence of SHH in a large group of morbidly obese patients (36). The authors concluded that endoscopy should be performed to all patients prior bariatric surgery. In support of our findings showing superiority of endoscopy over X-ray, a recent study performed in GERD patients treated with antireflux surgery showed that a correct classification of hiatal hernia was confirmed in 80% by endoscopy and in only

50% by barium swallow (37).

Apart from a closer relation of Endo SHH with reflux symptoms and esophagitis, patients of this group also showed higher values of total acid exposure compared to No SHH group. Furthermore, a positive symptom index for heartburn was found in most patients with Endo SHH. Keeping a proportion between heartburn patients and those who had heartburn preceded by acid reflux at pH-metry, a double of patients with Endo SHH showed a positive symptom index compared to X-ray SHH group, reinforcing the superiority of endoscopy.

Radiological markers of SHH were analyzed as predictors of reflux symptoms and SHH at endoscopy. To our surprise, neither hiatus enlargement nor B ring showed relation with either heartburn or regurgitation. This could be explained by a true lack of effect or an insufficient sample of patients to confirm a negative result. In contrast, a relation was found between SHH size at X-ray and the presence of SHH at endoscopy. Patients with SHH seen at both endoscopy and X-ray had larger hernias than those with SHH seen exclusively by X-ray. Experts in this field have stated that a 2 cm error of size estimation may occur due to deglutitive related esophageal shortening during a barium swallow X-ray (11).

The analysis of tests performances to predict SHH with reflux symptoms revealed that endoscopy had higher specificity whereas X-ray showed higher sensitivity. Predictive values were favorable to endoscopy compared to X-ray. Considering that SHH can motivate the realization of a surgical procedure, a specific test might have higher clinical utility than a sensitive test, reducing the risk of indicating a surgery for a patient in whom the symptoms are not related with hernia.

To our knowledge, this is the first study assessing the diagnosis of SHH at post gastric bypass. Six months after GBP, endoscopy showed less SHH than X-ray in comparison

with pre GBP evaluation. The prevalence of SHH at endoscopy reduced from 14% to 6% post GBP, while at X-ray it was from 32% to 26%. However, no technique showed advantage in terms of prediction of reflux symptoms. A slight superiority was observed for X-ray to predict the presence of SHH in combination with esophagitis. Total acid exposure was also higher in X-ray SHH group, although with no statistical significance. We have to mention that a small sample size particularly in the Endo SHH group (n = 5) may had favor a type II error.

In conclusion, we assessed the performance of endoscopy and X-ray in diagnosing SHH in morbidly obese patients before and after GBP. Endoscopy had higher clinical utility in diagnosing SHH preoperatively. Endoscopy was superior to X-ray in predicting either GERD symptoms, reflux esophagitis or abnormal pH-metry. At post GBP assessment, X-ray showed a slight superiority in predicting SHH combined with reflux esophagitis. Further studies are needed to clarify the diagnosis of SHH at post GBP and the utility of other techniques, particularly high resolution manometry.

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THE EFFECT OF GASTRIC BYPASS ON GASTROESOPHAGEAL REFLUX DISEASE IN MORBIDLY OBESE PATIENTS

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Background: Gastric bypass (GBP) has been increasingly employed to treat patients with morbid obesity. Its effect on gastroesophageal reflux disease (GERD) is not well understood. The **aim** of this study was to assess the effect of gastric bypass on GERD in morbidly obese patients. **Methods:** Seventy-one morbidly obese patients [30% male; 38 ± 11.6 years; BMI 45.2 (35.3-64.5 kg/m^2)] were investigated for GERD preoperatively to GBP and six months later. GERD was assessed by a validated symptom's questionnaire and 24h esophageal pH monitoring off acid suppressive medications. Heartburn was scored between 0 (no symptom) and 5 (worst) with the question "How bad is your heartburn?", whereas objective GERD was established at the presence of increased acid contact time (ACT) at pH monitoring. **Results:** All patients completed

the study. There was a significant decreased in both BMI (45.2 ± 7.2 vs. 33 ± 6.2; P < 0.0001) and heartburn score [2 (0-4) vs. 0 (0 – 0); P < 0.0001] six month after GBP. A significant decrease was also observed for total ACT [5.2% (2.3-9.4%) vs. 1.1% (0.2-5%); P = 0.001). Out of 29 patients with normal ACT pre GBP, 4 (14%) showed increased ACT six months later. Out of 42 patients with increased ACT pre GBP, 27 (64%) had their ACT normalized. **Conclusions:** In morbidly obese patients, the net effect of gastric by-pass was beneficial for both subjective and objective GERD parameters six months after the procedure.

TEMA-LIVRE A : IX CONGRESSO BRASILEIRO DA SBCB, Dez 2007 - Curitiba, PR

PERFORMANCE OF THE MONTREAL CONSENSUS IN THE DIAGNOSIS OF GASTROESOPHAGEAL REFLUX DISEASE IN MORBIDLY OBESE PATIENTS

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Objectives: Gastroesophageal reflux disease (GERD) has been increasingly recognized in patients with morbid obesity. A recent global evidence-based consensus on GERD has been proposed, but its performance in patients with morbid obesity is unknown. The aim of this study was to assess the performance of the Montreal Consensus in the diagnosis of GERD in morbidly obese patients. **Methods:** Seventy-five consecutive morbidly obese patients underwent GERD symptoms assessment, upper gastrointestinal endoscopy and ambulatory esophageal pH monitoring "off PPI". The performance of the Montreal Consensus was determined by comparing two diagnostic algorithms: 1. a gold standard approach, in which any GERD symptom and findings from both endoscopy and pH monitoring were taking into account and 2. the approach with the Montreal Consensus, in which troublesome GERD symptoms and endoscopic findings were considered. **Results:** GERD was present in 58 patients by applying the gold standard approach. The Montreal Consensus identified 41 of these patients, whereas the remaining 34 patients were classified as "no GERD". Of these, 17 (50%) showed reflux esophagitis and/or abnormal pH-metry. The Montreal Consensus had a sensitivity of

71% (95%CI 58-81%), specificity of 100% (95%CI 82-100%) and negative predictive value of 50% (95%CI 41-60%). **Conclusions:** In morbidly obese patients the approach with the Montreal Consensus has high specificity and suboptimal sensitivity in the diagnosis of GERD. Its intermediate negative predictive value suggests that complementary investigation for GERD might be routine in these patients.

TEMA-LIVRE B: IX CONGRESSO BRASILEIRO DA SBCB, Dez 2007 -Curitiba, PR

PIROSE NOTURNA É UM BOM INDICADOR DE ESOFAGITE DE REFLUXO E PERCEPÇÃO DIURNA DE PIROSE EM PACIENTES COM OBESIDADE MÓRBIDA

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Introdução: A doença do refluxo gastroesofágico é prevalente em obesos mórbidos. Refluxo noturno pode ser frequente nessa população, o que poderia contribuir para a ocorrência de esofagite de refluxo e a percepção diurna de pirose. **Objetivos:** Avaliar se pirose noturna (PN) é preditiva de esofagite de refluxo e pirose diurna em obesos mórbidos. **Métodos:** Oitenta pacientes obesos mórbidos candidatos à cirurgia bariátrica (30% do sexo masculino, 38 ± 11anos, 45 ± 7 Kg/m^2) foram consecutivamente avaliados quanto a sintomas de refluxo e submetidos à endoscopia digestiva alta e pH-metria de 24h, sem o uso de medicamentos antissecretores gástricos. PN foi definida como aquela que desperta o paciente durante o sono. **Resultados**: PN foi relatada por 29 pacientes (36%). Aumento de exposição ácida esofágica noturna foi significativamente mais prevalente em pacientes com PN (66% vs. 35%; $P < 0.01$), bem como naqueles com esofagite de refluxo (83% VS. 25%; $p < 0,0001$) quando comparados aos que negaram PN. Uma proporção significativamente maior de pacientes com PN referiu

pirose diurna associada a refluxo ácido à pH-metria de 24h (34% VS. 8%; $p < 0,01$). **Conclusões:** Pirose que desperta do sono é frequente em pacientes com obesidade mórbida. Este sintoma parece ser um bom indicador da presença de esofagite de refluxo e da percepção diurna de pirose.