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MASTÓCITOS DUODENAIS: potencial associação com a infecção pelo *Helicobacter pylori* e com os sintomas da dispepsia funcional

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SUMÁRIO

RESUMO

A infecção pelo *Helicobacter pylori* é uma das mais prevalentes, acometendo aproximadamente metade da humanidade. Ela causa um processo inflamatório gástrico (gastrite), e é o principal fator etiológico das úlceras pépticas e do câncer gástrico. A sua relação com os sintomas de alguns pacientes dispépticos funcionais também tem sido evidenciada. Sabe-se que a infecção pela bactéria aumenta de 2 a 3 vezes o número de mastócitos na mucosa gástrica e que esses podem estar relacionados com formação de edema e de liberação de fatores quimiotáticos locais. Entretanto, não está definida a associação do *H. pylori* com a população de mastócitos duodenais. Alterações histológicas duodenais, secundárias à infecção gástrica pelo *H. pylori* são pouco conhecidas e poucos trabalhos foram publicados até o presente momento. Além disso, estudos recentes têm sugerido que a presença de eosinófilos e de mastócitos na mucosa duodenal podem estar associados com os sintomas da dispepsia funcional. O objetivo foi avaliar a associação da infecção gástrica pelo *H. pylori* com a presença de mastócitos na mucosa duodenal e dos mastócitos duodenais com a intensidade dos sintomas da dispepsia funcional. Esse estudo está aninhado ao *Heroes Trial*, do Hospital de Clínicas de Porto Alegre (HCPA). A população é constituída por pacientes de ambos os sexos com mais de 18 anos de idade, e com diagnóstico de dispepsia funcional segundo os critérios do Consenso de Roma III. As biópsias duodenais foram revisadas através de imuno-histoquímica pelo anticorpo CD117 (c-kit), comparando a população de mastócitos duodenais entre os pacientes dispépticos funcionais *H. pylori* positivos e *H. pylori* negativos. Foi também avaliada a correlação entre a intensidade do infiltrado de mastócitos da mucosa duodenal com a intensidade dos sintomas dispépticos, através do questionário PADYQ (Porto Alegre *Dyspeptic Symptoms Questionnaire*). A quantidade de mastócitos duodenais foi semelhante entre populações com e sem infecção do *H. pylori*. A intensidade dos sintomas dispépticos não mostrou correlação com a quantidade de

mastócitos duodenais. Entretanto, houve diferença estatisticamente significativa entre a contagem de mastócitos duodenais no subtipo de dispepsia funcional tipo dor epigástrica comparativamente com a subtipo desconforto pós-prandial. Os mastócitos na mucosa duodenal não mostraram relação significativa com infecção pelo *H. pylori*, embora tenham sido mais numerosos na dispepsia funcional tipo dor epigástrica.

Palavras-chave: Dispepsia. H. Pylori. Inflamação duodenal.

ABSTRACT

Helicobacter pylori infection is one of the most prevalent, affecting approximately half of humanity. It causes a gastric inflammatory process (gastritis), and is the main etiological factor of peptic ulcers and gastric cancer. It's relationship with the symptoms of some functional dyspeptic patients has also been evidenced. It is known that infection by the bacterium increases the number of mast cells in the gastric mucosa by 2 to 3 times and that these may be related to the formation of edema and the release of local chemotactic factors. However, the association of *H. pylori* with the population of duodenal mast cells has not been defined. Duodenal histological changes secondary to gastric infection by *H. pylori* are little known and few studies have been published so far. Furthermore, recent studies have suggested that the presence of eosinophils and mast cells in the duodenal mucosa may be associated with the symptoms of functional dyspepsia. The objective was to evaluate the potential association between *H. pylori* gastric infection and the presence of mast cells in the duodenal mucosa and the association of duodenal mast cells with the intensity of functional dyspepsia symptoms. Population and Methods: This study is nested within the Heroes Trial, at Hospital de Clínicas de Porto Alegre (HCPA). The population consists of patients of both sexes over 18 years of age, diagnosed with functional dyspepsia according to the criteria of the Rome III Consensus. Duodenal biopsies were reviewed by immunohistochemistry using the CD117 antibody (c-kit), comparing the population of duodenal mast cells between H. pylori positive and H. pylori negative functional dyspeptic patients. The relationship between the intensity of mast cell infiltration of the duodenal mucosa and the intensity of dyspeptic symptoms was also assessed using the PADYQ questionnaire (Porto Alegre Dyspeptic Symptoms Questionnaire). The number of duodenal mast cells was similar between populations with and without *H. pylori* infection. The intensity of dyspeptic symptoms was not correlated to the amount of duodenal mast cells. However, there

was a higher count with statistically significant difference between the duodenal mast cell count in the subtype of functional dyspepsia type epigastric pain compared to the subtype postprandial discomfort. Mast cells in the duodenal mucosa did not show a significant relationship with H. pylori infection, although they were more numerous in functional dyspepsia like postprandial discomfort.

Keywords: Dyspepsia. H. pylori. Duodenal inflammation.

APRESENTAÇÃO

Esta dissertação é constituída por uma introdução com os principais tópicos sobre mastócitos duodenais, *Helicobacter pylori*, dispepsia, assim como à relação da contagem de mastócitos no duodeno com a presença do *Helicobacter pylori* e intensidade dos sintomas dispépticos. Após serão descritos os Objetivos (gerais e específicos), um capítulo na forma de artigo científico contendo os Materiais e Métodos utilizados, os Resultados encontrados, a Discussão, Conclusão e Referências. No final do texto serão apresentadas as conclusões, perspectivas e referências bibliográficas utilizadas para a elaboração dessa dissertação.

LISTA DE ABREVIATURAS

CNS - Conselho Nacional de Saúde

DRGE -Doença do Refluxo Gastroesofágico

GPPG - Grupo de Pesquisa e Pós-Graduação

HCPA - Hospital de Clínicas de Porto Alegre

H. pylori - *Helicobacter pylori*

Heroes Trial -*Helicobacter* Eradication Relief of Dyspeptic Symptoms Trial

PADYQ - Porto Alegre Dyspeptic Symptoms Questionnaire

SPSS - *Statistical Package for Social Sciences*

TCLE - Termo de Consentimento Livre e Esclarecido

TNF - Fator de Necrose Tumoral

LISTA DE ILUSTRAÇÕES

1 INTRODUÇÃO

O *Helicobacter pylori* é uma bactéria que infecta o estômago de seus hospedeiros sendo a principal causa de úlceras gástricas e duodenais, além de ser considerada o principal fator de risco para o desenvolvimento de câncer gástrico. No entanto, a erradicação da bactéria pode mudar o curso natural dessas doenças.(1)

Segundo os critérios de Roma III, a dispepsia é definida pela presença de um ou mais dos seguintes sintomas: dor ou queimação epigástrica, plenitude pós-prandial e saciedade precoce. A dispepsia é dita funcional na presença desses sintomas, mas na ausência de doenças orgânicas, metabólicas ou sistêmicas que justifiquem.(2) A dispepsia funcional é subdividida nos tipos dor epigástrica (sintomas de dor epigástrica ao menos uma vez por semana) e síndrome do desconforto pós prandial (saciedade precoce e plenitude pós prandial ao menos três vezes por semana). Dispepsia funcional é uma situação frequente, que acarreta grandes custos e perda de qualidade de vida nos pacientes acometidos.(3) Sua etiologia ainda não está bem definida, embora a literatura tenha demonstrado que o *H. pylori* possa ser a causa dos sintomas num pequeno número desses pacientes.(4) Em 2016 houve o consenso de Roma IV, que manteve praticamente inalterados os critérios diagnósticos.(5)

Mastócitos são células que podem estar presentes em todo o trato gastrointestinal normal, variando de 2-5% das células mononucleares, dependendo do local no trato digestivo.(6) Estão presentes em grande número no estômago de indivíduos infectados pelo *H. pylori*. Entretanto, pouco se sabe sobre a presença destas células na mucosa duodenal.

2 REVISÃO BIBLIOGRÁFICA

2.1 HELICOBACTER PYLORI

O *H. pylori* causa uma das mais prevalentes infecções da humanidade, acometendo aproximadamente 50% da população mundial.(4) Foi descoberta em 1982 pelos pesquisadores Robin Warren e Barry Marshall e chamou muita a atenção do mundo científico.(7)

Trata-se de um bacilo em forma de espiral, gram-negativo, multiflagelado e com fácil adaptação ao meio ácido gástrico. Isso ocorre devido a produção de urease, que converte a ureia local em óxido carbônico e amônia, levando a neutralização parcial da acidez do estômago. O formato em hélice espiralada permite que o *Helicobacter pylori* atravesse a camada de muco que protege o epitélio gástrico.(8)

É um patógeno que infecta essencialmente os humanos e que causa processo inflamatório gástrico (gastrite) em todos os indivíduos contaminados.(1) Essa reação inflamatória é caracterizada por processo agudo e crônico com infiltração celular característica.(9) O epitélio foveolar é infiltrado diretamente pelos neutrófilos, mastócitos, eosinófilos e células dendríticas, enquanto que a lâmina própria é permeada pelas células mononucleares, como linfócitos, macrófagos e plasmócitos.(10)

Mastócitos são encontrados em estados inflamatórios gástricos, como nas gastrites crônicas causadas pelo *H. pylori*.(9) Sua infiltração no tecido se dá de forma intraepitelial na mucosa gástrica, e o número de mastócitos é diretamente proporcional à intensidade do processo inflamatório.(11)

Os efeitos da infecção gástrica pelo *H. pylori* sobre a mucosa duodenal não estão bem definidos. Indivíduos com infecção isolada no antro gástrico pelo *H. pylori* (gastrite antral)

podem apresentar hipergastrinemia, com aumento da produção de secreção ácida. Essa secreção ácida excessiva pode provocar inflamação duodenal crônica e desenvolvimento de áreas de metaplasia de mucosa tipo gástrica no duodeno, com risco aumentado de formação de úlceras duodenais.(12)

Em um estudo prévio de Caselli *et al.* foi descrita a metaplasia gástrica no duodeno como um fator imprescindível à colonização duodenal pelo *H. pylori.* Além disso, foi observado intenso infiltrado de plasmócitos e linfócitos na lâmina própria duodenal em um grupo de pacientes com duodenite, caracterizada por metaplasia gástrica duodenal e pela colonização do *H. pylori*.(13)

2.2 MASTÓCITOS

Mastócitos são células globosas, grandes e com o citoplasma carregado de grânulos basófilos. São provenientes da medula óssea e estão presentes não somente no tecido inflamado, mas também em tecido sadio, prontos para serem acionados. São consideradas células pró inflamatórias, pois liberam citocinas e mediadores químicos no início de processos inflamatórios.

De maneira geral, os mastócitos têm papel importante nos processos inflamatórios agudos, alérgicos, remodelamento de tecidos, cicatrização e na angiogênese. Por estarem envolvidos na produção de citocinas, interleucina-10, fatores de crescimento e histamina, também influenciam na mudança da imunidade nativa para imunidade adaptativa.(14) Os mastócitos estão relacionados com a formação de edema (através da degranulação, secreção de mediadores e fatores quimiotáticos) e vasodilatação (através da liberação de histamina). Portanto, essas células estão ativamente envolvidas na patogênese da gastrite pelo *H. pylori* e são responsáveis pela sua manutenção, assim como pela reparação do tecido lesado pela bactéria.(11,15) Estudos

têm demonstrado que quanto maior a densidade de mastócitos na mucosa gástrica, maior é a atividade inflamatória da gastrite causada pelo *H. pylori*.(11) Após a erradicação do *H. pylori* ocorre redução no número de mastócitos na mucosa gástrica e consequentemente melhora da atividade inflamatória tecidual.(15)

Os mastócitos recrutam outras células conforme as necessidades inflamatórias. Através de proteases, são capazes de recrutar neutrófilos e eosinófilos. São liberadores precoces do Fator de Necrose Tumoral (TNF) - importante no processo inflamatório e no combate aos patógenos – além de participarem nas mudanças fisiológicas de defesa inata precoce como bronco constrição, aumento da motilidade intestinal e desprendimento epitelial.(16)

O número de mastócitos pode variar conforme o sítio gastrointestinal. Suas funções no trato digestivo incluem o controle da permeabilidade, secreção, peristalse, nocicepção, imunidade adaptativa e inata, angiogênese. Por apresentarem todas essas funções, podem estar envolvidos em doenças funcionais e orgânicas do trato gastrointestinal.(17) Os mastócitos estão localizados preferencialmente próximos aos nervos terminais na lâmina própria. Em decorrência dessa localização eles têm um importante papel na sensibilidade visceral mediada pela histamina e pela protease. Existe forte associação deles com os nervos entéricos que podem ser facilmente influenciados também pelo estresse e por alguns alimentos.(6,17) Os mastócitos são efetores importantes do eixo cérebro-intestino que traduzem os sinais de estresse na liberação de uma ampla gama de neurotransmissores e citocinas pró-inflamatórias, o que pode afetar profundamente a fisiologia gastrointestinal.(18)

2.3 DISPEPSIA E DISPEPSIA FUNCIONAL

Dispepsia é uma das queixas mais comuns no consultório dos clínicos e gastroenterologistas. Caracteriza-se por pelo menos um dos seguintes sintomas: dor ou

queimação epigástrica, plenitude pós-prandial e saciedade precoce. Existem algumas causas para à dispepsia, como doença ulcerosa péptica, malignidade do trato gastrointestinal alto, medicações como os AINE e dispepsia funcional.(2) O Consenso de Roma III, que aborda os distúrbios funcionais gastrointestinais, conceituou dispepsia funcional como: dor ou queimação centrada no andar superior do abdômen, plenitude pós-prandial e saciedade precoce na ausência de doenças orgânicas, metabólicas ou sistêmicas que justifiquem esses sintomas, presentes nos últimos três meses e há pelo menos 6 meses.(19) No ano de 2016 foi publicado o consenso de Roma IV que apresentou apenas pequenas alterações. Os mesmos sintomas continuam definindo o diagnóstico de dispepsia funcional e foi acrescentado no Roma IV, que os sintomas devem interferir na atividade diária e ter periodicidade mínima semanal. Passou, a incluir-se nos critérios de suporte, a existência frequente de sobreposição de sintomas entre os dois grupos de dispepsia funcional, assim como a possibilidade de estes doentes poderem ter sintomas ou distúrbios funcionais de outras partes do tubo digestivo, favorecendo a ideia de distúrbio funcional generalizado do tubo digestivo.(20)

A dispepsia, conforme os consensos de Roma III e IV, se subdividem em dois subtipos. A dispepsia funcional tipo dor epigástrica, a qual se caracteriza por epigastralgia pelo menos uma vez por semana; e a tipo desconforto pós-prandial, o qual se caracteriza por saciedade precoce e/ou plenitude pós-prandial pelo menos três vezes por semana.(5)

A dispepsia funcional é uma doença de etiologia ainda indefinida e de manejo clínico muito complicado. Muitas teorias têm sido lançadas para tentar explicar a sua causa. Fatores psicológicos, especialmente ansiedade, estão particularmente associados a pacientes dispépticos funcionais.(21) Alguns pacientes acabam apresentando sintomas intestinais, como cólicas, dor abdominal e diarreia antes dos sintomas dispépticos. Características genéticas podem estar associadas com dispepsia funcional e acredita-se que os sintomas possam estar relacionados com a acomodação gástrica inadequada.(22) Outro potencial causador da

dispepsia funcional é o *H. pylori*, e sua erradicação está associado com a melhora dos sintomas em uma parcela desses pacientes.(4) Um estudo sugeriu que dispepsia funcional é multifatorial e os autores consideraram que acomodação inadequada, esvaziamento gástrico inadequado, hipersensibilidade visceral e inflamação gástrica de baixo grau estão envolvidos.(23) Talley *et al.* observaram que 40% dos pacientes apresentam inflamação duodenal, especialmente com eosinófilos e mastócitos no local.(24)

2.4 INFECÇÃO GÁSTRICA PELO *H. PYLORI* E MASTÓCITOS DUODENAIS

Existem poucos estudos e com resultados conflitantes associando a infecção pelo *H. pylori* com aumento dos mastócitos duodenais. Um estudo polonês de Maciorkowska e*t al.*, publicado em 2000, observou aumento significativo do número de mastócitos no duodeno em crianças infectadas pelo *H. pylori*, (25) revelando a importância dessas células na infecção. Em 2019, Taki *et al.*, no entanto, não mostraram diferença na contagem de mastócitos duodenais entre os pacientes *H. pylori* positivos e negativos.(26) Alguns estudos mais recentes sugerem forte associação entre a presença do *H.pylori* e inflamação gástrica com maior contagem de mastócitos no estômago nestes pacientes. (27, 28)

2.5 MASTÓCITOS DUODENAIS E SINTOMAS DISPÉPTICOS

Binesh *et al.*, em um estudo caso-controle, não evidenciou diferença estatística na contagem de mastócitos no duodeno de pacientes com dispepsia funcional comparados aos indivíduos não dispépticos.(29)

Entretanto, Liebregts *et al.* mostrou uma tendência de associação entre os sintomas de dor epigástrica, cólicas, plenitude pós-prandial, saciedade precoce, náuseas e vômitos, com alguns

dos mediadores inflamatórios liberados pelos mastócitos (citocinas, TNF e interleucina 10).(30) Outros estudos associaram estado inflamatório duodenal com dispepsia funcional, pelo aumento do número de mastócitos e eosinófilos nessa região.(22,24,26,31,32) Portanto, persistem controvérsias na literatura a respeito do papel de mastócitos duodenais na etiologia dos sintomas da dispepsia funcional.

3 JUSTIFICATIVA

As metanálises e estudos recentes têm demonstrado que a infecção pelo *H. pylori* pode ser uma das causas da dispepsia.(4,33). E, o papel dos mastócitos duodenais na etiologia dos sintomas da dispepsia funcional, ainda não é bem estabelecido. Em uma metanálise publicada em 2022, os pacientes com dispepsia funcional apresentavam um aumento significativo no número de mastócitos quando comparados aos controles, porém houve significativa heterogeneidade entre os estudos.(34)

Não existem informações conclusivas na literatura, do papel da infecção gástrica pelo *H. pylori* sobre a população de mastócitos duodenais. Poucos estudos avaliaram essa relação e os dados são insuficientes para uma conclusão mais definitiva.(25)

Diante disso, buscamos avaliar se a infecção pelo *H. pylori* causa aumento da população de mastócitos no duodeno, o que poderia explicar a origem ou a intensidade dos sintomas em pacientes com dispepsia funcional.

Também procuramos avaliar se o número de mastócitos duodenais tem alguma relação com os sintomas da dispepsia funcional, independentemente da presença de infecção gástrica pelo *H. pylori*.

4 QUESTÃO DA PESQUISA

Existe diferença na população de mastócitos duodenais entre pacientes dispépticos funcionais *H. pylori* positivos em relação aos *H. pylori* negativos? A população de mastócitos duodenais tem alguma influência na intensidade dos sintomas da dispepsia funcional?

5 HIPÓTESE DA PESQUISA

O *H. pylori* aumenta a população de mastócitos duodenais e essa alteração provoca aumento na intensidade dos sintomas da dispepsia funcional.

6 OBJETIVOS

6.1 GERAL

Avaliar o papel da infecção gástrica pelo *H. pylori* sobre a população de mastócitos na mucosa duodenal. Também avaliar se a intensidade dos sintomas da dispepsia funcional está relacionada com o número de mastócitos duodenais.

6.2 ESPECÍFICOS

- Avaliar se fatores demográficos e ambientais podem ter influência na população de mastócitos da mucosa duodenal.
- Avaliar se anti-inflamatórios não esteroides influenciam na população de mastócitos duodenais.
- Relacionar os achados endoscópicos do duodeno com a população de mastócitos duodenais.
- Correlacionar o número de mastócitos duodenais com os subtipos da dispepsia.

7 ARTIGO CIENTÍFICO

Artigo em preparação.

Duodenal Mast Cells: Potential association between *Helicobacter pylori* infections and Functional Dyspepsia symptoms

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ABSTRACT

Introduction: *Helicobacter pylori* infections are one of the most prevalent, affecting approximately half of humanity. They cause a gastric inflammatory process (gastritis) and are the main etiological factor of peptic ulcers and gastric cancer. Their relationship with the symptoms of some functional dyspeptic patients has also been evidenced. It is known that infection by the bacterium increases by 2 to 3 times the number of mast cells in the gastric mucosa and that these can be related to the formation of edema and the release of local chemotactic factors. However, the association of *H. pylori* with the population of duodenal mast cells has not been defined. Duodenal histological changes secondary to gastric infection by *H. pylori* are little known and few studies have been published to the present day. Furthermore, recent studies have suggested that the presence of eosinophils and mast cells in the duodenal mucosa can be associated with the functional dyspepsia symptoms.

Objective: To evaluate the potential association between *H. pylori* gastric infections and presence of mast cells in the duodenal mucosa, as well as the association of duodenal mast cells with the intensity and characteristics of functional dyspepsia symptoms.

Population and Methods: This study is nested to the *Heroes Trial* (Helicobacter Eradication Relief of Dyspeptic Symptoms), at the Porto Alegre Clinical Complex Hospital (*Hospital de Clínicas de Porto Alegre*, HCPA). The population consists of patients of both genders over 18 years of age, diagnosed with functional dyspepsia according to the Rome III Consensus criteria. Duodenal biopsies were reviewed by immunohistochemistry using the CD117 antibody (c-kit), comparing the population of duodenal mast cells between *H. pylori* positive and *H. pylori* negative functional dyspeptic patients. The association between the intensity of mast cell infiltration of the duodenal mucosa and the intensity and characteristics of dyspeptic symptoms was also assessed using PADYQ (Porto Alegre Dyspeptic Symptoms Questionnaire).

Results: The number of duodenal mast cells was similar between populations with and without *H. pylori* infections. The intensity of dyspeptic symptoms was not correlated to the number of duodenal mast cells. However, there was a higher count with a statistically significant difference between the duodenal mast cell count in the functional dyspepsia of the epigastric pain subtype when compared to the postprandial discomfort subtype.

Conclusion: Our study did not show any significant association between gastric *H. pylori* infections and duodenal mast cells, nor with the intensity of functional dyspepsia symptoms. However, an association between duodenal mast cells and the functional dyspepsia of the epigastric pain subtype was observed.

Keywords: *H. pylori*, dyspepsia, mast cells, dyspeptic symptoms.

INTRODUCTION

Helicobacter pylori is a bacterium discovered in 1982 by researchers Robin Warren and Barry Marshall and which drew a lot of attention from the scientific world.(1) It affects approximately 50% of the world's population.(2) *H. pylori* infects the stomach of its hosts and is the main cause of gastric and duodenal ulcers, in addition to being considered the main risk factor for the development of gastric cancer. It is known that eradicating the bacterium changes the natural course of these diseases.(3)

It is a pathogen that essentially infects humans and causes a gastric inflammatory process (gastritis) in all infected individuals.(3) This inflammatory reaction is characterized by an acute and chronic process, with infiltration of neutrophils, lymphocytes, mast cells and plasma cells.(4)

The effects of gastric *H. pylori* infections on the duodenal mucosa are not well defined. It is known that individuals with isolated *H. pylori* infections in the gastric antrum (antral gastritis) can present hypergastrinemia, with increased production of acid secretion. This excessive acid secretion can cause chronic duodenal inflammation and development of gastric-type mucosal metaplasia areas in the duodenum, with an increased risk of duodenal ulcers.(5)

Mast cells play an important role in acute inflammatory and allergic processes, tissue remodeling, permeability control, peristalsis, healing and angiogenesis. As they are involved in the production of cytokines, interleukin-10, growth factors and histamine, they also influence the change from innate to adaptive immunity.(6) They are cells that actively participate in the pathogenesis of gastritis, being responsible for maintaining inflammation, as well as repairing tissue damaged by the bacterium.(7,8) Therefore, they are involved in functional and organic diseases of the gastrointestinal tract.(9,10)

The number of mast cells can vary depending on the gastrointestinal site. Previous studies have shown that the higher the density of mast cells in the gastric mucosa, the greater the inflammatory activity of gastritis caused by *H. pylori*.(7,11) After *H. pylori* eradication, there is a reduction in the number of mast cells in the gastric mucosa.(8)

Mast cells are preferentially located close to terminal nerves in the *lamina propria*. As a result of this location, they play an important role in visceral sensitivity mediated by histamine and protease. There is a strong association between them and the enteric nerves, which can also be easily influenced by stress and some food products.(9,12) Mast cells are important effectors of the brain-gut axis that translate stress signals into the release of a wide range of neurotransmitters and pro-inflammatory cytokines, which can profoundly affect gastrointestinal physiology.(13)

Functional dyspepsia is a disease of still undefined etiology and very complicated clinical management. Many theories have been launched to try to explain its cause. Psychological factors, especially anxiety, are particularly associated with functional dyspeptic patients.(14) Other hypotheses include motor dysfunction (a previous study found that gastric emptying was slow in some patients),(15) as well as visceral hypersensitivity, impaired mucosal integrity, low-grade immune activation and dysregulation of the brain-gut axis.(16) Visceral hypersensitivity appears to play an important role in pathophysiology, although not fully proven. The presence of gastroduodenal micro-inflammation, oftentimes post-infectious, has a strong association with development of visceral hypersensitivity.(17) In this context, mast cells can play a role in dyspepsia, as their functions in the digestive tract include control of permeability, secretion, peristalsis, nociception, angiogenesis, adaptive and innate immunity. For having all these functions, they may be involved in functional and organic diseases of the gastrointestinal tract.(9)

There is no conclusive information in the literature regarding the role of gastric infections by *H. pylori* on the population of duodenal mast cells. Few studies have evaluated this relationship and the data are insufficient to draw a more definitive conclusion.(18) The role of duodenal mast cells in the characteristics and intensity of functional dyspepsia symptoms has also not been defined.(19)

Therefore, we aimed at evaluating whether *H. pylori* infections cause an increase in the population of mast cells in the duodenum, which might influence the type and intensity of symptoms in patients with functional dyspepsia.

METHODS

Study design

A cross-sectional study carried out at the Clinical Research Center, the Gastroenterology Service and the Pathology Service of the Porto Alegre Clinical Complex Hospital (*Hospital de Clínicas de Porto Alegre*, HCPA).

Population

A total of 100 adult functional dyspeptic patients were included (50 *H. pylori* positive and 50 *H. pylori* negative), over 18 years old, of both genders, and with an established diagnosis of functional dyspepsia according to the criteria set forth by the Rome III Consensus. These patients participated in the Heroes Trial study – *Helicobacter* Eradication Relief of Dyspeptic Symptoms (clinicaltrials.gov number NCT 00404534)(2) and the first 100 in the study were selected.

Patients who did not sign the free and informed consent form were excluded, as well as those with reduced intellectual levels that were not able to understand the study objective,

pregnant women and/or women of childbearing age who did not use safe contraceptive methods, individuals with previous diagnosis of systemic diseases or in use of medications that might interfere with sensitivity or motility of the upper gastrointestinal tract, presence of serious comorbidities (hepatic, renal, cardiological and neurological), history of upper gastrointestinal surgery, previous treatment for *H. pylori*, previous investigation with upper digestive endoscopy showing relevant organic changes, clinical condition suggestive of symptomatic cholelithiasis, weight loss greater than 10% of body weight within 12 months and changes in physical examination suggestive of organic diseases, warning signs (dysphagia, digestive bleeding, anorexia, incoercible vomiting, anemia), previous history of peptic ulcer disease, symptoms exclusive to irritable bowel syndrome or Gastroesophageal Reflux Disease (GERD).

Study procedures

The patients were recruited into the "*Helicobacter* Eradication Relief of Dyspeptic Symptoms - (HEROES)"[2] study between October 2006 and June 2008. Initially, a selection consultation was carried out with anamnesis, demographic data collection and physical examination. The patients that met the inclusion criteria and did not present any exclusion criteria were referred for collection of laboratory tests and endoscopic examination. Intensity of the dyspeptic symptoms was assessed using the PADYQ questionnaire (Porto Alegre Dyspeptic Symptoms Questionnaire).(20) This is a unidimensional instrument that has shown high levels of internal consistency, reproducibility, responsiveness, apparent validity, discriminant validity and concurrent validity. This 11-question instrument assesses the frequency, duration and intensity of dyspeptic symptoms during the previous 30 days. The score varies from 0 to 44, with symptoms considered mild up to 22, moderate from 23 to 29 and severe when above 30 points.

The endoscopies were performed at HCPA. All endoscopies were in charge of two experienced endoscopists and, in case of disagreement, a third endoscopist performed the tiebreaker. Endoscopic gastritis was classified according to the Sydney Endoscopic Classification(21) and gastric biopsies were classified according to the Sydney Histological Classification.(22)

H. pylori positivity was assessed using the Urease test and anatomopathological examination (Hematoxylin–eosin and Giemsa), and should be positive by both methods, or negative by both. In case of discrepancies between the results of these tests, another pathologist analyzed the material to define the diagnosis.

In the current study, biopsies from the second duodenal portion were used, which were sent for immunohistochemical (IH) evaluation using the CD117 antibody (c-kit).(23,24)

The slides were stained on an automated IH platform, VENTANA BenchMark Systems®, model ULTRA, using the CD117 antibody from manufacturer Cell Marque, clone YR145, at a 1:250 dilution.

Two pathologists separately analyzed the mast cells present in the duodenal biopsy samples (mucosa and submucosa). The mast cells were counted at the three points with the highest concentration (Hot Spots) of duodenal mast cells in these locations, in a 10X field; the mean of this count was taken and then a final mean value was calculated with the count from each pathologist. This result was compared between *H. pylori* positive and *H. pylori* negative patients.

The final mean number of mast cells in the "Hot Spots" was also compared to the PADYQ questionnaire results to evaluate the correlation between intensity of the dyspeptic symptoms and the dyspepsia subtype, with the number of mast cells found on the slides. PADYQ was initially analyzed quantitatively and later on dichotomized into those below and above 22 points

(half the score). It was also categorized into tertiles, which were defined as mild (up to 22 points), moderate (23 to 29 points) and severe (>30 points) dyspepsia.

The dyspepsia subtype was self-defined by the patients in the first study visit, only taking into account the main symptom. Therefore, epigastric pain syndrome was defined if the main symptom was epigastric pain, and postprandial distress syndrome when postprandial fullness or early satiety were the patients' most important symptoms.

Other demographic characteristics and consumption of NSAIDs, *chimarrão,* coffee, alcohol and tobacco were also evaluated.

Statistical analysis:

The sample size calculation was for convenience (100 first patients of the *Heroes* Trial study. The data were entered into Excel and subsequently exported to the SPSS program, v. 20.0, for statistical analysis. The categorical variables were described by means of frequencies and percentages. Normality of the quantitative variables was verified using the Kolmogorov-Smirnov test. The quantitative variables with normal distribution were described by mean and standard deviation.

The quantitative variables were compared using Student's t test for independent samples in case of comparisons of two categories, or with Analysis of Variance (ANOVA) in case of three categories or more.

To evaluate the correlation between quantitative variables, Pearson's correlation test was used.

A total of 3 measurements of mast cell Hot Spots established were made by each evaluator, and the mean of all 3 measurements was calculated. Agreement between the evaluators was calculated and represented by the intraclass correlation coefficient.

Ethical considerations:

The study was developed in accordance with Resolution 466/2012 of the National Health Council and approved by the Research Ethics Committee of the Porto Alegre Clinical Complex Hospital (HCPA) under code GPPG 2018-0394, as well as the *Heroes* Trial study (GPPG 05-422). Written informed consent was obtained from all patients before enrollment. None of the authors of this study had any conflicts of interest.

RESULTS

The intraclass correlation coefficient of the mean of the measures obtained by both evaluators was 0.78, indicating good interobserver agreement (>0.75) for obtaining the study results.

The baseline characteristics of *H. pylori*-positive and *H. pylori*-negative individuals are expressed in Table 1.

Table 1. Patients' characteristics according to H. Pylori status.

Variables	Total n=100	*H. Pylori* positive n=50	*H. Pylori* negative n=50	*p*
Age (years old), mean±SD	41.8±13.8	39.7±13.4	43.8±13.9	0.137[a]
Gender, n (%)				0.758[b]
Male	12 (12.0)	5 (10.0)	7 (14.0)	
Female	88 (88.0)	45 (90.0)	43 (86.0)	
Skin color, n (%)				0.435[b]
White	82 (82.0)	39 (78.0)	43 (86.0)	
Not white	18 (18.0)	11 (22.0)	7 (14.0)	
BMI (n=97)*, MD [P25–75]	24.96 [22.72–28.89]	24.77 [22.72–28.89]	25.59 [22.64–28.96]	0.608[e]
Years of study (n=98)*, n (%)				0.840[c]
<10	46 (47.0)	24 (49.0)	22 (45.0)	
≥10	52 (53.0)	25 (51.0)	27 (55.0)	
Marital status, n (%)				0.840[c]
Without a partner	56 (56.0)	27 (54.0)	29 (58.0)	
With a partner	44 (44.0)	23 (46.0)	21 (42.0)	
Income (R$) years 2006/2008, MD [P25–75]	1,200 [700–2,000]	1,200 [800–2,000]	1,150 [600–2,000]	0.380[e]
Smoking status, n (%)				0.675[c]
Never smoked	65 (65.0)	34 (68.0)	31 (62.0)	
Currently smokes	35 (35.0)	16 (32.0)	19 (38.0)	

Alcohol consumption, n (%)					0.594[b]
	No	83 (83.0)	43 (86.0)	40 (80.0)	
	Yes	17 (17.0)	7 (14.0)	10 (20.0)	
Chimarrão consumption, n (%)					0.837[c]
	No	62 (62.0)	30 (60.0)	32 (64.0)	
	Yes	38 (38.0)	20 (40.0)	18 (36.0)	
Coffee consumption, n (%)					>0.999[c]
	No	31 (31.0)	16 (32.0)	15 (30.0)	
	Yes	69 (69.0)	34 (68.0)	35 (70.0)	
PADYQ (n=92)*, MD [P25–75]		26.00 [20.00–30.5]	26.00 [18.00–31.00]	25,50 [20.50–30.00]	0.888[e]
Type of dyspepsia, n (%)					0.228[c]
	Epigastric pain syndrome	55 (55.0)	24 (48.0)	31 (62.0)	
	Postprandial distress syndrome	45 (45.0)	26 (52.0)	19 (38.0)	
Gastroscopy findings (n=96)*, n (%)					0.224[d]
	Normal	28 (29.2)	17 (35.4)	11 (22.9)	
	Enanthematous	28 (29.2)	15 (31.3)	13 (27.1)	
	Erosive	38 (39.6)	16 (33.3)	22 (45.8)	
	Atrophic	2 (2.0)	-	2 (4.2)	

SD: Standard Deviation. MD: Median. P25–75: 25th and 75th percentiles. BMI: Body Mass Index. PADYQ: Porto Alegre Dyspeptic Symptoms Questionnaire. *n reduced due to lost data. [a]Student's t-test. [b]Chi-square with Yates continuity correction. [c]Fisher's Exact Test. [d]Pearson's chi-square. [e]Mann-Whitney's U test.

Presence of gastric *H. pylori* infections was not associated with presence or concentration of duodenal mast cells (p=0.778), as shown in Table 2. The mean number of duodenal mast cells did not show any statistically significant relationship with gastric or duodenal endoscopic findings (site, type or intensity of the changes) (Table 3).

Table 2. Comparison between the mean duodenal mast cells and H. pylori infections.

	n assessed	Mean mast cells	p
H. pylori			0.778
Positive	50	19.91±7.02	
Negative	50	19.53±6.40	

Data presented as mean ± standard deviation and compared using Student's t test for independent samples.

Table 3. Comparison between the mean duodenal mast cells to gastric and duodenal endoscopic findings.

	n assessed	Mean duodenal mast cells	p
Stomach			
Endoscopic findings			0.323
Normal	28	17.61±4.55	
Enanthematous gastritis	24	21.03±7.17	
Erosive gastritis	37	19.94±7.16	

Gastric nodosity	4	19.63±4.40	
Atrophic gastritis	2	15.67±2.36	
Local gastritis			0.258
Antro	55	20.84±6.95	
Body	3	20.78±7.10	
Diffuse	7	16.36±4.11	
Gastritis intensity			0.368
Mild	48	20.84±7.21	
Moderate	10	20.15±5.80	
Accentuated	5	16.23±4.90	
Duodenum			
Endoscopic findings			0.165
Normal	91	19.91±6.52	
Enanthematous duodenitis	5	21.23±10.08	
Erosive duodenitis	4	13.67±3.05	
Duodenitis intensity			0.673
Mild	4	15.63±5.23	
Moderate	3	16.11±1.00	
Accentuated	1	11.83±0	

Data presented as mean±standard deviation and compared by means of Analysis of Variance (ANOVA).

There was a loss in the number evaluated from the PADYQ questionnaire in 8 patients due to data lost during collection.

Assessed with the PADYQ questionnaire, intensity of the dyspeptic symptoms did not show any statistically significant relationship with the mean duodenal mast cells (p=0.344). Table 4 shows that there was no significant difference in the number of duodenal mast cells when the patients were divided into those with less severe symptoms (<22 PADYQ points) and those with more intense symptoms (p=0.451). There were also no differences (p=0.519) between duodenal mast cells in the tertiles of symptom severity (mild up to 22 points, moderate from 23 to 29 and severe with more than 30 PADYQ points).

However, there was a significant difference in mean duodenal mast cells between the functional dyspepsia subgroups. As shown in Table 5 and Graph 1, the subgroup of patients with dyspepsia of the epigastric pain type presented a higher mean number of duodenal mast cells (p=0.016).

Table 4. Comparison between the mean duodenal mast cells and intensity of the dyspeptic symptoms.

	n assessed	Mean mast cell	p
PADYQ Score	92*		0.451[a]
≤22	31	18.78±7.37	
>22	61	19.90±6.41	
PADYQ Score tertiles			0.519[b]
Mild	31	18.78±7.37	
Moderate	30	20.66±7.03	
Severe	31	19.17±5.78	

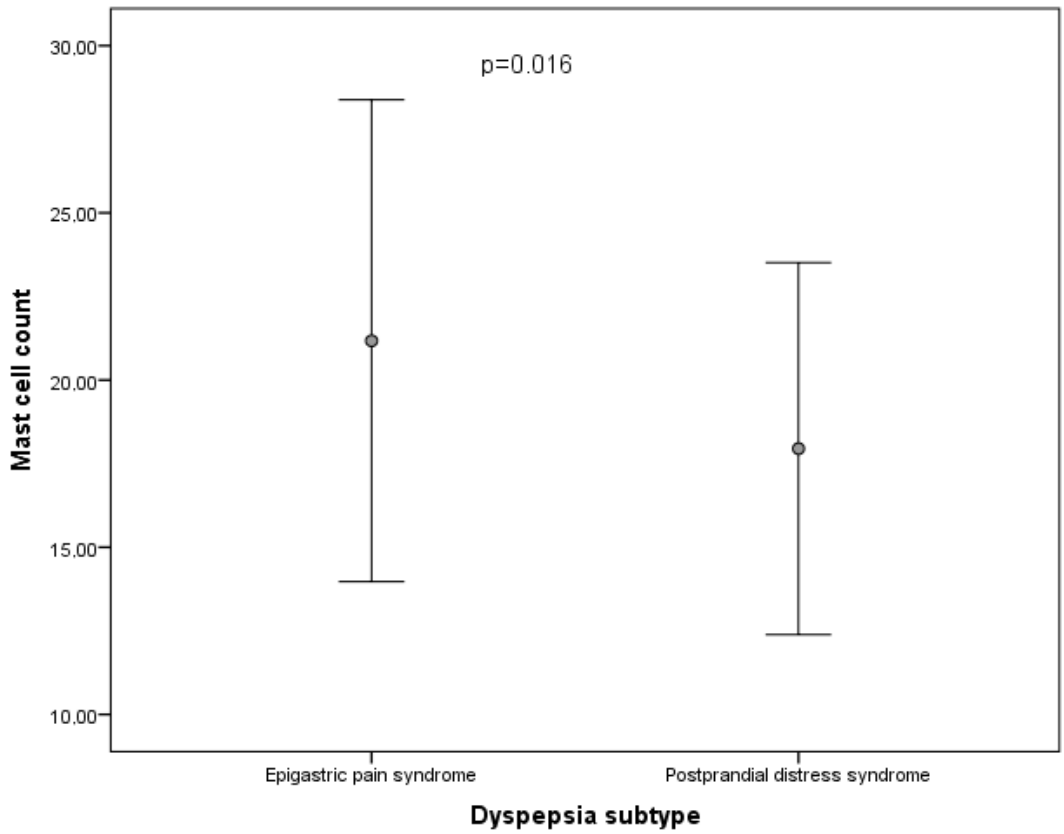
Data presented as mean±standard deviation and compared using: [a]Student's t test for independent samples, [b]Analysis of Variance (ANOVA)*; there was data loss from 8 patients during collection.

Table 5. Comparison between the mean duodenal mast cells and type of dyspepsia.

Type of dyspepsia	n assessed	Mean mast cells	p
			0.016
Epigastric pain syndrome	55	21.17±7.20	
Postprandial distress syndrome	45	17.95±5.56	

Data presented as mean±standard deviation and compared by means of Student's t test for independent samples.

Graph 1. Comparative representation of the mast cell means values to the functional dyspepsia subtypes.



The exposure factors of the study patients, such as tobacco, alcohol, coffee and *chimarrão* consumption, and use of non-steroidal anti-inflammatory drugs (NSAIDs) were also analyzed and compared to the mean number of duodenal mast cells and showed no statistical difference (Table 6).

Table 6 . Comparison between the mean duodenal mast cells and exposure factors.

Exposure factors		n assessed	Mean mast cells	p
Smoking				0.225
	No	65	20.27±6.83	
	Yes	21	17.48±6.24	
	Former smoker	14	20.52±6.35	
Alcohol				0.994

	No	83	19.69±6.57	
	Yes	6	19.72±7.09	
	Former drinker	11	19.94±7.95	
Coffee				0.264
	No	31	20.99±8.13	
	Yes	69	19.15±5.90	
Chimarrão				0.145
	No	62	20.49±6.73	
	Yes	38	18.48±6.50	
NSAIDs				0.903
	Yes	13	19.94±7.72	
	No	87	19.69±6.56	

Data presented as mean±standard deviation and compared by means of Student's t test for independent samples (2 categories) or Analysis of Variance (ANOVA) (3 or more categories).

The mean number of duodenal mast cells did not show significant differences in the demographic variables analyzed: gender (p=0.497), schooling (p=0.481), family income (p=0.069), skin color (p=0.993), marital status (p=0.918) and BMI (p=0.813).

DISCUSSION

This study showed that *H. pylori* infections did not significantly correlate with the mean number of mast cells in the duodenum. In addition, the number of duodenal mast cells was not correlated to intensity of the dyspeptic symptoms. However, a higher duodenal mast cell count was found in the functional dyspepsia of the epigastric pain type when compared to the postprandial distress syndrome subtype.

Mast cells recruit other cells according to inflammatory needs, are early releasers of Tumor Necrosis Factor (TNF) and participate in physiological changes such as intestinal motility. Their functions in the digestive tract include control of permeability, secretion, peristalsis,

nociception, angiogenesis, adaptive and innate immunity. Mast cells are preferentially located close to terminal nerves in the *lamina propria*, which plays an important role in visceral sensitivity mediated by histamine and protease. These cells are also important effectors of the brain-gut axis, which translate stress signals into release of a wide range of neurotransmitters and pro-inflammatory cytokines, which can affect gastrointestinal physiology with the potential to be involved in the pathophysiology of functional dyspepsia.

Previous studies have shown that *H. pylori* positive patients had more mast cells in the stomach.(5,7,8,25) However, the analysis of duodenal mast cells in patients infected with *H. pylori* is rare in the literature, with only one study in children, which, unlike our study, found more duodenal mast cells in patients infected with *H. pylori*.(18)

Recent studies have evaluated the potential association of duodenal mast cell infiltration with the dyspepsia diagnosis.(19,26) Nevertheless, none have evaluated the relationship between intensity of the dyspeptic symptoms and duodenal infiltration of these cells. A recent meta-analysis based on case-control studies showed an increased number of mast cells and eosinophils in the duodenum in dyspeptic patients, when compared to control groups.(19) This type of positive association was also found in other literature citations,(26-28) which used similar methodologies to our study, although they only compared the number of mast cells in functional dyspeptics vs non-dyspeptics, without evaluating intensity of the symptoms or "Hot Spots". Binesh *et al.*(29) found no differences in duodenal mast cell counts between dyspeptic patients and nondyspeptic controls, although this study only evaluated 52 patients. Our study did not observe any association between number of duodenal mast cells and intensity of the dyspeptic symptoms, although it did find differences in relation to the type of clinical presentation of functional dyspepsia.

An interesting finding of our study was the difference in mast cell counts in the dyspepsia subtypes, which was higher in the epigastric pain subtype. We only found one publication in the literature that compared the functional dyspepsia subtypes to the number of duodenal mast cells. This study was carried out in South Korea in 2022 and showed no difference between the duodenal mast cell count and the dyspepsia subtypes, although they described a slight higher count of duodenal mast cells in patients with "overlapping" of both subtypes of the disease, a fact that the researchers associated with characteristics of patients with Irritable Bowel Syndrome.(30) Patients with dyspepsia of the epigastric pain subtype respond better to proton pump inhibitors when compared to those with postprandial discomfort. A potential explanation for this might be related to greater duodenal mast cell infiltration in dyspepsia of the epigastric pain type, which makes this study an interesting basis for future studies to evaluate this possibility and understand the potential role of proton pump inhibitors in this profile of patients.

The strengths of our study were the evaluation of a homogeneous population with functional dyspepsia, with reliable exclusion of organic diseases such as neoplasms and ulcers. Demographic, clinical, endoscopic and histological data were evaluated with controlled methods, and the *H. pylori* research was screened by histopathological analysis and rapid urease test. The intensity and subtype of functional dyspepsia were assessed with a validated questionnaire, which allowed quantifying the dyspeptic symptoms and defining the functional dyspepsia subtypes. The assessment of duodenal mast cells used to count at three points of highest concentration (Hot Spots), in accordance with what has been used in recent studies,(27,31,32) and there was good interobserver agreement between the pathologists that evaluated the histological samples.

Our study has some limitations. It was carried out in a single center and this may limit its external validity. As this study was carried out only with dyspeptic patients, the presence of duodenal mast cells between functional dyspeptics and asymptomatic controls was not

compared; we only compared the difference in intensity and type of the dyspeptic symptoms. In addition to that, the number of mast cells considered normal in the duodenum has not yet been defined, which can lead to differences in the study results. Another limitation of our study is that we cannot define a cause and effect relationship in our results, although they generate hypotheses about infiltration of mast cells in the duodenum as a potential cause of dyspepsia of the epigastric pain subtype.

CONCLUSIONS

Our study did not show any significant association between gastric *H. pylori* infections and duodenal mast cells, nor with intensity of the functional dyspepsia symptoms. However, a higher duodenal mast cell count was observed with the functional dyspepsia of the epigastric pain type. More studies are required to better define the relationship between duodenal mast cells and functional dyspepsia.

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8 CONCLUSÃO

Nosso estudo não mostrou diferença na contagem de mastócitos duodenais em pacientes infectados ou não pelo *H. pylori,* assim como na correlação dessa contagem com a intensidade dos sintomas dispépticos. No entanto, foi possível identificar uma maior contagem de mastócitos duodenais nos pacientes do subgrupo dor epigástrica, comparativamente com o subgrupo desconforto pós-prandial.

9 PERSPECTIVAS

Por se tratar de uma área de interesse recente, a associação de microinflamação duodenal com a dispepsia funcional vem despertando diversos estudos muito interessantes. O nosso achado do subtipo dor epigástrica apresentar maior contagem de mastócitos, se torna interessante não só pelo fato de haver poucos estudos na literatura, mas também por conseguirmos focar em um tratamento mais específico para este subtipo. Sabemos que este perfil de paciente responde melhor ao IBP do que o do desconforto pós-prandial. A justificativa para isso pode estar relacionada a essa questão da infiltração mastocitária duodenal. Mais estudos são necessários para elucidar essa questão.

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APÊNDICE A - Questionário de Sintomas Dispépticos

Com relação aos últimos 30 dias:

DOR

Qual a intensidade da dor abdominal (superior) na maioria dos dias neste período? ( )

0. Ausente
1. Muito leve
2. Leve
3. Moderada
4. Forte
5. Muito forte

Qual a duração da dor na maioria dos dias neste período? ( )

0. Não se aplica
1. Alguns minutos (menos que 30 minutos)
2. Menor que 2 horas
3. Maior que 2 horas

Com que frequência os Sr./Sra. apresentou dor abdominal nos últimos 30 dias? ( )

0. Não se aplica
1. Raramente
2. 1 a 2 dias/semana
3. Quase diariamente
4. Diariamente

ESCORE TOTAL DOR _____ (máximo 12 pontos)

NÁUSEAS/VÔMITOS

Qual a intensidade das náuseas na maioria dos dias deste período? ( )

0. Ausente
1. Muito leve
2. Leve
3. Moderada
4. Forte
5. Muito forte

Qual a duração aproximada da maioria dos episódios de náuseas? ( )

0. Não se aplica
1. Alguns minutos (menos que 30 minutos)
2. Menor que 2 horas
3. Maior que 2 horas

Com que frequência o Sr./Sra. apresentou náuseas nos últimos 30 dias? ( )

0. Não se aplica
1. Raramente
2. 1 a 2 dias/semana
3. Quase diariamente
4. Diariamente

Com que frequência o Sr./Sra. apresentou vômitos nos últimos 30 dias? ( )

0. Não se aplica
1. Raramente
2. 1 a 2 dias/semana
3. Quase diariamente
4. Diariamente

ESCORE TOTAL NÁUSEAS/VÔMITOS: _____ (máximo 16 pontos)

DISTENSÃO/SACIEDADE

Qual a intensidade da sensação de distensão ("estufamento"/inchaço) nos últimos 30 dias? ( )

0. Ausente
1. Muito leve
2. Leve
3. Moderada
4. Forte
5. Muito forte

Qual a duração destes episódios nestes períodos? ( )

0. Não se aplica
1. Alguns minutos (menos que 30 minutos)
2. Menor que 2 horas
3. Maior que 2 horas

Com que frequência os Sr./Sra. apresentou esses episódios de distensão/inchaço no abdômen superior nos últimos 30 dias? ( )

0. Não se aplica
1. Raramente
2. 1 a 2 dias/semana
3. Quase diariamente
4. Diariamente

Com que frequência o Sr./Sra. apresentou sensação de estar com o estômago cheio logo após começar a comer, nos últimos 30 dias? ( )

0. Sem saciedade precoce
1. Raramente
2. 1 a 2 dias/semana
3. Quase diariamente
4. Diariamente

ESCORE TOTAL DISTENSÃO/SACIEDADE _____ (máximo 16 pontos)

PONTUAÇÃO TOTAL DOS SINTOMAS DISPÉPTICOS:_____ (máximo 44 pontos)