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RELACIÓN ENTRE DIETA, FUNCIÓN Y SÍNTOMAS DIGESTIVOS

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Fernando Azpiroz Vidaur

A mis padres y hermanos.
Papá esta tesis te la dedico a ti.

A mi esposa Carla y a mis hijos,
por su paciencia y apoyo incondicional.

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ABREVIATURAS

DF: Dispepsia funcional.

ECA: Ensayos clínicos controlados.

EF: Estreñimiento funcional.

FODMAP: Carbohidratos de cadena corta (monosacáridos, disacáridos y oligosacáridos

fermentables) y polioles.

FOS: Fructooligosacáridos.

GOS: Galactooligosacáridos.

ISAPP: Asociación Científica Internacional de Probióticos y Prebióticos.

OMS: Organización mundial de la salud.

SCFA: Ácidos grasos de cadena corta.

SDE: Síndrome de dolor epigástrico.

SDP: Síndrome de distress postprandial

SII: Síndrome de intestino irritable.

SII-PI: Síndrome de intestino irritable postinfeccioso.

TC: Tomografía computarizada.

TFD: Trastornos funcionales digestivos.

RNM: Resonancia nuclear magnética.

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SUMMARY

Functional gastrointestinal disorders are the most common diagnoses in gastroenterology disorders. It is a group of disorders of the gut-brain interaction and are classified according to the predominant symptoms. The best known are functional dyspepsia, irritable bowel syndrome, constipation and defecation disorders. It is known that there is a relationship between diet, function and digestive symptoms. However, the pathophysiology of functional gastrointestinal disorders is not entirely clear. In this doctoral thesis we propose the following general hypothesis: intestinal content is a key factor in triggering symptoms in patients with different types of functional gastrointestinal syndromes. The main aim was to determine if the factors that determine the intestinal content, both the diet and depositional habit, influence functional gastrointestinal symptoms.

Firstly, we performed a randomized, parallel and double-blind study of patients with functional gastrointestinal disorders, and compared the effect of a prebiotic supplement (2.8 g/d Bimuno containing 1.37 g B-GOS) plus a placebo (Mediterranean-type diet) versus a placebo supplement (2.8 g xylose) plus a diet low in FODMAP. The arm of this study was to determine the specific influence of different types of fermentable residues from the diet (prebiotics and FODMAP) on gas-related symptoms in patient, with functional gastrointestinal disorders. The results were that both treatments improved the symptoms to a similar extent. However, both strategies had different consequences after treatment discontinuation; while the improvement of symptoms persisted 2 weeks after prebiotic administration was discontinued, the symptoms relapsed after the termination of the low FODMAP diet. Also, both treatments induced different effects on microbiota, particularly in relation to the *Bifidobacterium* (increased with prebiotic and decreased with low FODMAP diet).

Next, we performed a randomized, parallel study of patients with functional dyspepsia with postprandial distress syndrome and functional constipation with dyssynergic defecation and compared correction of dyssynergic defecation by biofeedback techniques vs fiber supplementation (3.5 g plantago ovata per day) for 4 weeks. The arm of this study was to determine the pathophysiologic role of constipation in functional dyspepsia, that is, if the associated constipation influences dyspeptic symptoms. The results were that the correction of dyssynergic defecation was associated with a significant improvement of dyspeptic symptoms and this subjective improvement was associated with an objective reduction in

the number of anal gas evacuations. None of these effects were observed in the group that received fiber supplements.

The conclusions of this doctoral thesis were that the factors that determine the intestinal content, both the diet and the depositional habit, influence the functional gastrointestinal symptoms and that the different functional gastrointestinal syndromes share a common pathophysiological basis that involves the intestinal content.

Key words: Microbiota, irritable bowel syndrome, functional dyspepsia, biofeedback techniques, constipation, abdominal distension, abdominal pain.

RESUMEN

Los trastornos funcionales digestivos son los trastornos más frecuentes en gastroenterología. Se trata de un grupo de trastornos de la interacción cerebro-intestino, que se clasifican de acuerdo con los síntomas predominantes, los más conocidos son la dispepsia funcional, el síndrome de intestino irritable, el estreñimiento y los trastornos de la defecación. Se sabe que hay una relación entre la dieta, función y los síntomas digestivos. Sin embargo, la fisiopatología de los trastornos funcionales digestivos no está del todo aclarada. En esta tesis doctoral planteamos la siguiente hipótesis general: el contenido intestinal es un factor clave en el desencadenamiento de síntomas en pacientes con distintos tipos de síndromes digestivos funcionales. El objetivo principal fue determinar si los factores que determinar el contenido intestinal, tanto la dieta como el hábito deposicional, influyen sobre los síntomas digestivos funcionales.

En primer lugar, realizamos un estudio randomizado, doble ciego, en pacientes con trastornos funcionales digestivos, donde se comparó el efecto de un suplemento (2.8 g/día Bimuno que contiene 1.37 g B-GOS) más un placebo (dieta mediterránea típica) vs un suplemento de placebo (2.8 g de xilosa) más una dieta baja en FODMAPs. El objetivo de este estudio fue determinar la influencia específica de distintos tipos de residuos fermentables de la dieta (prebióticos y FODMAPs) sobre los síntomas relacionados con el gas intestinal en paciente con síndromes funcionales digestivos. Los resultados fueron que ambos tratamientos presentaron mejoría en los scores de síntomas. Sin embargo, ambas estrategias tuvieron consecuencias después de descontinuar el tratamiento. Aunque la mejoría de los síntomas persistió 2 semanas después de la administración del prebiótico, los síntomas empeoraron después de descontinuar la dieta baja en FODMAPs. Además, los tratamientos inducen efectos diferentes en la microbiota, en relación a las *Bifidobacterias* (incremento con prebióticos y disminución con la dieta baja en FODMAP).

A continuación, realizamos un estudio randomizado, paralelo, en pacientes con dispepsia funcional con síndrome de distress postprandial y con estreñimiento funcional con disinergia defecatoria, donde se comparó la corrección de la disinergia defecatoria mediante biofeedback anorectal vs un suplemento de fibra (3.5 g de plantago de ovata por día) durante 4 semanas. El objetivo de este estudio fue determinar el papel fisiopatológico del estreñimiento en la dispepsia funcional, es decir si el estreñimiento asociado influye sobre los síntomas dispépticos. Los resultados fueron que la corrección de la disinergia defecatoria estuvo asociado con una mejora en los síntomas dispépticos y esta mejoría subjetiva estuvo

asociada con una reducción objetiva en el número de evacuaciones de gas anal, ninguno de estos efectos se observó en el grupo que recibió suplementos de fibra.

Las conclusiones de esta tesis doctoral fueron que los factores que determinan el contenido intestinal, tanto la dieta como el hábito deposicional, influyen sobre los síntomas digestivos funcionales y que los distintos síndromes funcionales digestivos comparten una base fisiopatológica común que involucra el contenido intestinal.

Palabras clave: Microbiota, síndrome de intestino irritable, dispepsia funcional, estreñimiento, biofeedback anorrectal, distensión abdominal, gas intestinal, dolor abdominal.

1. INTRODUCCIÓN

1.1 TRASTORNOS FUNCIONALES DIGESTIVOS (síntomas y función digestiva)

Los trastornos funcionales digestivos (TFD), son unos de los trastornos más frecuentes en gastroenterología. Se trata de un grupo de trastornos de la interacción cerebro-intestino, que se clasifican de acuerdo con los síntomas predominantes. La última clasificación de estos trastornos se basa en los criterios Roma IV (2016), que han pretendido tener un enfoque más clínico y práctico con respecto a ediciones anteriores(1) .

1.1.1 DISPEPSIA FUNCIONAL

Al menos el 20% de la población tiene síntomas crónicos que puede ser atribuidos a trastornos de la función gastroduodenal, y sin evidencia de causa orgánica(2). Los criterios Roma, subdividió a los pacientes que presentaban síntomas de trastornos funcionales gastroduodenales en entidades basadas en el patrón de los síntomas(3). La dispepsia funcional (DF) es uno de los más comunes y se refiere a trastornos funcionales con síntomas que se consideran originados en la región gastroduodenal(4). Los síntomas principales de la DF son: plenitud postprandial, saciedad precoz, dolor epigástrico y ardor epigástrico. Los criterios de Roma III y IV consideraron la DF como una entidad heterogénea y propusieron dividirla en dos subgrupos: El *síndrome de distrés postprandial* (SDP), con síntomas desencadenados con las comidas como la plenitud postprandial y la saciedad precoz, y el *síndrome de dolor epigástrico* (SDE), caracterizado por síntomas no relacionados con las comidas como el dolor y ardor epigástrico(2,4).

1.1.1.1 Epidemiología

La epidemiología de la DF de acuerdo con los criterios Roma IV se evaluó mediante una encuesta en tres países en 5931 pacientes. La prevalencia de DF estuvo en el rango entre el 8% y el 12%, con 61% para SPD, 18% para SDE y un 21% para un solapamiento entre ambos síndromes(5). Estos hallazgos que identificaron al SDP como el mayor subgrupo de DF a nivel poblacional, se confirmaron en otro estudio poblacional(6). En un único estudio realizado en España, utilizando una definición más amplia (síntomas digestivos focalizados

en la parte superior del abdomen), se estimó que el 39% de la población había presentado síntomas dispépticos alguna vez en su vida y el 24% en los últimos 6 meses(7).

La prevalencia de la DF es mayor en las mujeres que en los hombres(8). La DF se asocia con un gran impacto en la calidad de vida, en el gasto sanitario y en el deterioro de las actividades de la vida diaria incluido el trabajo(9,10).

1.1.1.2 Diagnóstico

El diagnóstico de la DF se basa en la definición de los síntomas clínicos, reformulados según los criterios de Roma IV(11).

Criterios* de Roma IV para el diagnóstico de Dispepsia Funcional

Uno o más de los siguientes:
    Plenitud postprandial molesta
    Saciedad precoz molesta
    Dolor epigástrico molesto
    Ardor epigástrico molesto
No hay evidencia de enfermedad estructural (habitualmente se realiza una endoscopia oral) que podría explicar los síntomas.

*Los criterios deben cumplirse durante los últimos 3 meses y los síntomas deben haber comenzado al menos 6 meses antes del diagnóstico.

Se divide en dos subgrupos: el *síndrome de distrés postprandial*, que se presenta con uno o ambos de los siguientes síntomas al menos 3 días por semana: plenitud postprandial molesta y/o saciedad precoz molesta y el *síndrome de dolor en epigastrio*, que incluye al menos uno de los siguientes síntomas por lo menos un día a la semana: dolor epigastrio molesto y/o ardor epigástrico molesto. En ambos subtipos no hay evidencia de enfermedad orgánica, sistémica o metabólica que podrían explicar los síntomas.

En estos pacientes es importante determinar si existen síntomas o signos de alarma indicativos de que puedan tener una enfermedad orgánica de base: inicio a los 55 años, hemorragia gastrointestinal, disfagia, vómitos persistentes, pérdida de peso involuntaria, antecedentes familiares de cáncer gástrico o esofágico, evidencia de anemia por déficit de hierro(12).

1.1.1.3 Fisiopatología

La fisiopatología de la DF es compleja y multifactorial y no está completamente aclarada.

Motilidad gastroduodenal

La función motora del estómago cumple dos funciones principales, primero, proporcionar un reservorio para almacenar una comida heterogénea ingerida rápidamente, y segundo, luego proporcionar al intestino delgado un quimo homogeneizado a una velocidad que coincida con la capacidad de procesamiento intestinal(13). Durante la ingesta de la comida, el estómago proximal se relaja para acomodarse a la comida, pero sigue ejerciendo un tono residual para impulsar el vaciamiento gástrico. Durante el periodo postprandial, el tono en el estómago proximal aumenta progresivamente, esta contracción tónica fuerza suavemente el quimo intragástrico distalmente(14). Este proceso esta regulado por mecanismos complejos de retroalimentación(15).

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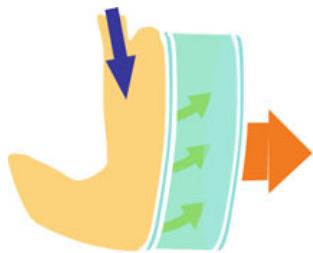
Relajación parcial

VACIAMIENTO

Contracción gradual

Tomada de Azpiroz et al (13)

La alteración de la acomodación gástrica está presente en el 40% de pacientes con DF, pero existe controversias en su relación con el patrón de los síntomas(16–18). Un estudio muestra que la saciedad precoz se reportaba en el 90% de los pacientes con alteración de la acomodación comparada con sólo el 40% de pacientes con acomodación normal(16). Sin embargo, otros estudios no encuentran asociación entre acomodación y síntomas(17,18).

El vaciamiento gástrico enlentecido está presente en cerca del 30% de pacientes con DF y se ha asociado con síntomas de distrés postprandial, síntoma principal del SDP, pero también con náusea y vómitos síntomas que son más sugestivos de gastroparesia(19–21). En un pequeño subgrupo de pacientes con DF, el vaciamiento gástrico es más rápido de los normal(22). No está claro si el vaciado gástrico rápido constituye un mecanismo distinto, tal vez a través de retroalimentación duodenal defectuosa, o si representa otra manifestación de acomodación deficiente(23).

Sensibilidad gastroduodenal

Se ha demostrado que los estímulos aplicados en el aparato digestivo activan receptores en la pared conectados con vías sensitivas y producen percepción de sensaciones(24). La percepción de estímulos digestivos depende del número de receptores activados por un

fenómeno de sumación espacial, es decir de la extensión del tubo digestivo en la que se aplican estímulos(25) .

La hipersensibilidad visceral, tradicionalmente evaluada como percepción a estimulos de distensión, es uno de los mecanismos principales implicados en la generación de síntomas en la DF(26–29). Los pacientes con DF muestran una mayor percepción a la distensión antral y fúndica y refieren molestias a los estímulos que son bien tolerados en los sujetos sanos(30–34).
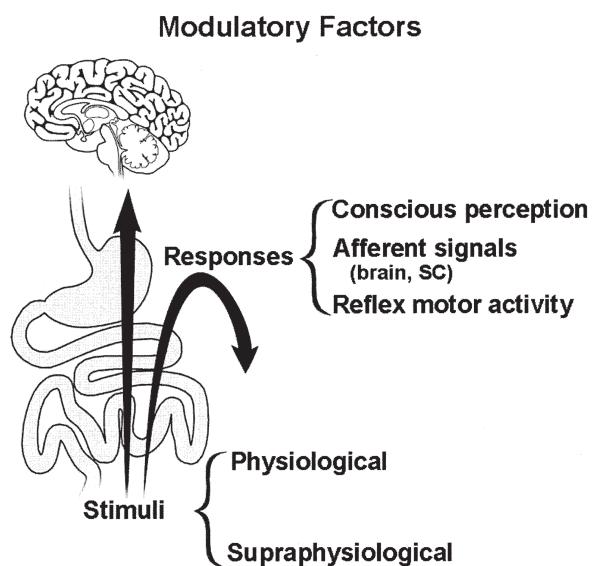
Tomada de Kellow et al (35)

Procesamiento cerebral alterado

La ingesta de una comida normalmente induce saciedad y plenitud y estas sensaciones estan involucradas en el control homeostático del consumo de alimentos(36,37). Estas sensaciones homeostáticas tienen una dimensión hedónica que influye en el bienestar digestivo y en el estado de ánimo(38). De hecho, dependiendo de varios factores, la sensación de saciedad y plenitud pueden tener una dimensión placentera asociada a la satisfacción o una dimensión aversiva con un deterioro del bienestar digestivo y el estado de ánimo(38,39). Se ha demostrado que la palatabilidad de las comidas con una composición idéntica influye en las

sensaciones postprandiales, es decir, las comidas más sabrosas tienen un valor de recompensa más fuerte e inducen una mayor satisfacción posterior(40). Sin embargo, la palatabilidad no es la única característica de la comida que determina la respuesta, ya que se ha demostrado que las comidas igualmente agradables inducen un grado de satisfacción diferente, particularmente se ha demostrado que la grasa es el componente clave en la comida en relación a la satisfacción(41–43).

Los pacientes con DF tienen niveles más elevados de ansiedad, depresión y somatización y esto potenciaría su asociación con la hipersensibilidad visceral(44,45). Un estudio sobre la respuesta de la actividad regional cerebral con RNM, antes y después de un test de sobrecarga de agua en estómago, encontró diferentes actividades regionales cerebrales en reposo y durante el test de sobrecarga entre voluntarios sanos y pacientes con DF, pero las mayores diferencias fueron observadas en pacientes con SDE, lo que sugiere que estas alteraciones se correlacionarían con el dolor(46).

Alteraciones de la mucosa

Las investigaciones en los últimos años se han centrado en la presencia de una alteración en la integridad de la mucosa duodenal, con una inflamación de la mucosa de bajo grado caracterizado por un incremento de eosinófilos y mastocitos en la mucosa(47,48). Estos hallazgos están más asociados con síntomas de saciedad precoz, lo que sugiere que esto es principalmente una característica del SDP(48).

Microbiota

Poco se sabe sobre el papel de la microbiota gástrica en la fisiopatología de DF. Un estudio reciente que estudió la microbiota en el líquido gástrico aspirado de 24 pacientes con DF y 21 controles, encontró niveles elevados de ácidos biliares, Bacteroides y ausencia de Acidobacterias en pacientes con DF(49). Un estudio preliminar sugiere que los pacientes con DF pueden tener alterado la composición de la microbiota duodenal(50). No está claro si algunos cambios del microbiota son específicos del SDP.

1.1.1.4 Características clínicas

Los pacientes con DF con frecuencia refieren exceso de gases en el intestino, que se puede manifestar como eructos, sensación de presión abdominal excesiva (hinchazón), incremento de la circunferencia abdominal (distensión), ruidos intestinales aumentados y flatulencias excesivas(51). No esta claro si estos síntomas pertenecen al espectro de síntomas de DF o reflejan un solapamiento con el SII.

Un ensayo experimental de provocación con gas (infusión de gas exógeno de alta velocidad directamente en el yeyuno) ha demostrado que los pacientes con DF que refieren distensión abdominal tienen un aclaramiento deficiente del gas intestinal, es decir retención del gas, síntomas abdominales o ambos(33). Sin embargo, los estudios que utilizaron TC Y RM abdominal en condiciones clínicas reales, no pudieron correlacionar los síntomas abdominales con el exceso de gas en estos pacientes, ya que en la mayoría de estos pacientes el volumen y la distribución del gas estaba dentro de los rangos normales(52,53). Por lo tanto, la percepción de la hinchazón abdominal podría estar relacionado con una baja tolerancia al contenido intestinal normal.

Una gran proporción de pacientes con DF refieren distensión abdominal después de las comidas y atribuyen la distensión abdominal a la producción de gas en respuesta a algunos alimentos (54). Esta distensión anormal se produce por una contracción paradójica del diafragma, que se asocia con una relajación de los músculos de la pared abdominal anterior(54,55). En pacientes con DF esta respuesta paradójica del diafragma y de los músculos de la pared abdominal se puede inducir experimentalmente mediante la ingesta de una comida de prueba (líquido con nutrientes mixtos a 50 ml por minuto) (55).

1.1.2 SINDROME DE INTESTINO IRRITABLE

El síndrome de intestino irritable (SII) es un trastorno funcional del intestino delgado, tradicionalmente se ha etiquetado como diagnóstico de funcional, cuando no se han encontrado anomalías estructurales o bioquímicas claras, pero la evidencia reciente sugiere que distintas alteraciones fisiopatológicas pueden ser responsables de los síntomas y que es poco probable que el SII sea sólo un trastorno somatosensorial(56,57). El SII se define como

la presencia de dolor abdominal recidivante asociado a alteraciones del ritmo deposicional, sea en forma de estreñimiento, de diarrea o de ambos; la hinchazón y la distensión abdominal son muy frecuentes en el SII(58).

1.1.2.1 Epidemiología

La prevalencia mundial del SII es del 11,2% basado en un metaanálisis de 80 estudios con 260,960 personas(59). La incidencia del SII se ha estimado entre 1,35% a 1,5%, basado en dos estudios poblacionales longitudinales con una duración de 10 a 12 años(60,61). Sin embargo, esta varía según los criterios diagnósticos empleados. En un estudio epidemiológico reciente que comparan los nuevos criterios diagnósticos Roma IV con los anteriores Roma III, donde se obtuvieron datos sobre población general en Estados Unidos, Reino Unido y Canadá, se observó que en los tres países la prevalencia era menor con los criterios Roma IV. Además, el SII es mayor en mujeres que en hombres y se observó una disminución progresiva según se incrementaba la edad de la población estudiada(62).

Las molestias del SII tienen una importante repercusión sobre las actividades personales y sociales de los pacientes, en los estudios que las han valorado se ha demostrado que las personas con SII tienen un empeoramiento de su calidad de vida relacionada con la salud, así como la productividad laboral en comparación la población general(63,64).

1.1.2.2 Diagnóstico

En mayo del 2016 se publicaron los criterios de Roma IV(65), que son los que están vigentes en la actualidad. El SII se diagnostica por la presencia de dolor abdominal recidivante que ha de estar presente al menos 1 día a la semana y con dos o más de las siguientes características:

1. Se asocia a la defecación.
2. Está relacionado con un cambio en la frecuencia de las deposiciones.
3. Se asocia con un cambio en la consistencia de las deposiciones.

En cuanto a los requerimientos temporales, hay que tener en cuenta que los criterios deben cumplirse durante los últimos 3 meses y los síntomas haber comenzado un mínimo de 6 meses antes del diagnóstico.

Roma IV aconseja establecer los subtipos del SII de acuerdo con la consistencia de las deposiciones evaluada según la escala de Bristol que clasifica la consistencia de las heces en base a su forma entre 1 (heces caprinas) y 7 (heces liquidas). De esta forma, si más del 25% de las deposiciones corresponden a los tipos 1 o 2, se considera que el paciente tiene SII-E; cuando más del 25% de las deposiciones son del tipo 6 o 7, padece de SII-D; si existe más del 25% de ambas (tanto 1 o 2 como 6 o 7), se establece el diagnóstico de SII con hábito deposicional mixto, y cuando hay menos del 25% de ambas se habla de hábito deposicional no clasificable. Para establecer el subtipo debe tenerse en cuenta sólo los días en los que las deposiciones no tienen una consistencia normal y realizarse cuando el paciente no está tomando medicación que alteren la consistencia de las heces(65).

Escala de heces de Bristol

Tipo 1		pedazos duros separados, como nueces (difícil de excretar)
Tipo 2		Con forma de salchicha, pero llena de bultos
Tipo 3		Como una salchicha pero con rajaduras en la superficie
Tipo 4		Como una viborita, suave y blanda
Tipo 5		Pedazos blandos con bordes claros (se excretan fácilmente)
Tipo 6		Pedazos blandos con bordes deshechos
Tipo 7		Aguado, sin trozos sólidos. **Enteramente líquido**

1.1.2.3 Fisiopatología

El SII se considera como una desorganización del eje cerebro-intestino que incluye una función anormal del sistema nervioso, alteraciones de la motilidad gastrointestinal, procesamiento distorsionado de las señales periféricas de la sensibilidad visceral y factores psicológicos y sociales agregados(57,66). Además, la reciente evidencia sugiere que, la barrera epitelial, la microbiota intestinal, los antígenos alimentarios y los ácido biliares provocan respuestas anormales en los reguladores de la función sensoriomotora, incluido el eje hipotálamo-pituitaria-suprarrenal, el sistema inmunitario, el eje cerebro-intestino y el sistema nervioso entérico(56,67,68). Muchos factores juegan un papel importante para la generación de los síntomas del SII, pero algunos pueden ser más predominantes en ciertos individuos que en otros.

Motilidad intestinal

Varios estudios han demostrado que los pacientes con SII tienen aumentado la motilidad intestinal especialmente después de las comidas o de una situación de stress(69,70). En el SII se observan con más frecuencia varias alteraciones de la motilidad, como contracciones propagadas prolongadas y contracciones propagadas de gran amplitud, en comparación con sujetos sanos(71,72). Sin embargo, no se ha definido una alteración de la motilidad consistente que pudiera explicar todos los síntomas en los pacientes con SII(73). En términos de patrones de motilidad, los pacientes con SII con predominio diarrea (SII-D) muestran tiempos de tránsito gastrointestinal más rápidos que los sujetos normales, mientras que los pacientes con SII con predominio estreñimiento (SII-E) tienen un tránsito gastrointestinal normal o más lento que lo normal(74–76).

La dismotilidad gastrointestinal puede desarrollarse a través de varios mecanismos que involucran el eje cerebro-intestino. En primer lugar, varios procesos inflamatorios, inmunes, infiltrativos o degenerativos pueden afectar directamente al músculo o a otros elementos del sistema efector del sistema nervioso entérico. La dismotilidad también se puede desencadenar indirectamente en respuesta al exceso de estimulación por las fibras viscerales aferentes (sensoriales) que influyen en la función motora gastrointestinal local a través de la modulación de las neuronas motoras en los ganglios prevertebrales(77,78).

Hipersensibilidad visceral

La hipersensibilidad visceral es un hallazgo frecuente en pacientes con SII (50 a 90% de pacientes en diferentes series) y probablemente desempeña un papel en los síntomas de estos pacientes(79,80). Sin embargo, la hipersensibilidad visceral en el SII sigue siendo una condición heterogénea, puede estar presente o ausente, puede ser específica de un órgano o distribuirse por todo el tracto digestivo, puede ser resistente a fármacos o responder a estos, puede ser exclusiva del tracto gastrointestinal o ir acompañada de hipersensibilidad somática(81–85). La caracterización individual de los pacientes por síntomas, características fisiológicas y genotípicas deben ser necesarios para superar los efectos de la heterogeneidad.

Los pacientes con SII tienen mayor sensibilidad a la distensión con un balón en el tracto digestivo superior e inferior y son sensibles a las contracciones intestinales en comparación a los sujetos normales(79,86). De acuerdo con estos datos, se muestra que los pacientes con SII tienen hipersensibilidad rectal además de hipersensibilidad somática a estímulos térmicos(87). Dos mecanismos se han postulado como explicación de la hipersensibilidad visceral en los pacientes con SII; la hipervigilancia hacia eventos adversos esperados y la hiperalgesia inducida por una estimulación visceral (88).

Modulación nerviosa central

La señalización desde el cerebro hasta el tracto gastrointestinal es importante para garantizar las funciones digestivas óptimas, lo que influye en estado de ánimo. Con el incremento de técnicas funcionales de neuroimagen, ha surgido evidencia de la modulación nerviosa central del eje cerebro-intestino(89–91). En el SII, las imágenes cerebrales funcionales muestran que las respuestas sensoriales viscerales, afectivas y motoras alteradas están asociadas con diferencias en el flujo sanguíneo regional cerebral(90).

El dolor en muchos pacientes con SII se debe a una mayor percepción viscero-somática, que se cree se debe a una sensibilización central y periférica(120). La sensibilización central se refiere al aumento de la transmisión de las señales del dolor a través de los nervios sensoriales aferentes a la médula espinal y al cerebro y a la disminución de la modulación inhibitoria descendente del dolor. La sensibilización periférica se produce al aumentar la

activación de los nervios sensoriales periféricos que además contribuyen a la sensibilización central(121).

La distensión con balón en el colon distal demuestra diferencias en la activación regional cerebral en pacientes con SII en comparación con controles sanos. La región dorsal de la corteza cingulada anterior está constantemente más activada en pacientes con SII en comparación con los controles, esta región es responsable del procesamiento cognitivo de la información sensorial(92). Estos hallazgos apoyan una contribución clínicamente importante de una modulación nerviosa central del dolor visceral en el SII. En apoyo de esto, el tratamiento del SII puede afectar significativamente la activación cerebral en regiones clave para las sensaciones de dolor visceral y correlacionarse con la mejora de los síntomas(93).

Sistema nervioso autónomo

El sistema nervioso autónomo con sus ramas simpáticas y parasimpáticas media la comunicación entre el aparato digestivo y el cerebro. De esta manera, la motilidad gastrointestinal, la secreción y la función inmune se coordinan y modulan. Por otra parte el sistema nervioso autónomo participa en la respuesta digestiva al estress. De hecho, el estress y los eventos estresantes de la vida pueden jugar un papel en los síntomas del SII(94,95).

Sistema inmunológico de la mucosa intestinal

Los estudios reportan que entre el 7 al 30% de los pacientes con antecedentes recientes de gastroenteritis bacteriana comprobada desarrollan síntomas similares al SII, lo que se denomina "SII postinfeccioso" (SII-PI)(96,97). Observaciones adicionales corroboran anomalías de la mucosa del colon de pacientes con SII-PI(98). En pacientes con historia de infección previa por Campylobacter y SII-PI se encontró que tenían un aumento del número de linfocitos intraepiteliales y células enterocromafines con incremento de la permeabilidad intestinal incluso después de un año en comparación con los controles(99).

La mucosa intestinal de pacientes con SII presenta un aumento del número de mastocitos y/o sus mediadores, principalmente triptasa e histamina, a lo largo de todo el tracto gastrointestinal, desde le duodeno hasta el recto(100–103). Este aumento de mastocitos se ha observado en todos los subtipos de SII, pero de manera predominante en pacientes con SII-D y con SII-PI. La activación mastocitaria se correlaciona con el aumento del número y de la consistencia de las deposiciones en el SII-D(104–106).

Factores genéticos

Los factores genéticos pueden conferir una predisposición a la inflamación, la síntesis de ácido biliares, la expresión de nueropéptidos bioactivos y la secreción intestinal a través de la mutación en la vía secretora del guanilato ciclasa(107,108).

Microbiota intestinal

La microbiota intestinal juega un papel fundamental en el desarrollo del sistema inmune, en el mantenimiento de las uniones estrechas y en la secreción de moco y de IgA en la mucosa intestinal (109–111). Muchos de estos efectos fisiológicos descritos en la microbiota intestinal se atribuyen a los productos que las distintas especies generan en el proceso de metabolización de residuos fermentables de la dieta. Numerosos estudios dan soporte a la existencia de alteraciones en la microbiota intestinal en pacientes con SII(112,113). Datos recientes sugieren que estos presentarían menor diversidad de especies, con mayor abundancia de enterotipos proinflamatorios comparados con la población sana y que estas alteraciones se correlacionarían con la gravedad del SII(114). Sin embargo, el efecto no es del todo previsible ya que el problema del SII es que es multifactorial. Se han hecho intentos para delinear la microbiota típica del SII, donde la Prevotella y Clostridium estarían representados en exceso, este último asociada a la flora metanogénica, relacionado con el subtipo de SII-E(115). En este contexto puede ser importante la composición de la microbiota, tanto dentro de la luz intestinal como en el revestimiento de la capa mucosa interna y en el borde el epitelio(116).

Mecanismos en la hinchazón y distensión abdominal funcional
Incremento de la tensión en la pared intestinal
Expansión gástrica e intestinal por el aire deglutido(117)
Tolerancia alterada a las cargas de gases intestinales, por moléculas osmóticamente activas(118–120)
Acumulación de heces en el colon debido a inercia colónica y/o obstrucción de la salida funcional(121,122)
Aumento del gas endógeno en el colon debido a:
Retención de los sustratos fermentables(123)
Microbiota productora de gas(124,125)
Reducción del consumo de gas por la microbiota(126,127)
Deterioro de la difusión de los gases intestinales(128–131)
Percepción consciente aumentada de la tensión de la pared
Inflamación de la pared intestinal(132,133)
Neurosensibilización: circuitos del dolor local, espinal y cerebral(134).
Emocional: estrés, ansiedad, somatización e hipervigilancia(135).
Otros: ritmo circadiano, comidas grasas, tejido adiposo intraabdominal y perimestrual(136–138)
Remodelación de la cavidad abdominal por respuestas viscero-somáticas anormales
Maniobras conductuales alteradas en respuesta a estímulos intestinales(139–142)
Expansión torácica
Descenso del diafragma
Relajación de los músculos de la pared abdominal

1.1.2.4 Características clínicas

Como consta en la definición las manifestaciones clínicas fundamentales del SII son: dolor abdominal, hinchazón, distensión abdominal y alteración del ritmo deposicional, sea en forma de diarrea, estreñimiento o de ambas(143,144).

Las alteraciones en las vías neuronales centrales y periféricas pueden llevar a alteraciones en el tránsito intestinal, lo que produce diarrea o estreñimiento. El dolor abdominal es un síntoma exigido, sin el no puede establecerse el diagnóstico de SII: puede ser cólico o constante, aparecer de manera impredecible, ser de localización variable y tener una intensidad que se modifica con la defecación o las flatulencias.

Los factores psicológicos desempeñan un papel en el desarrollo o la exacerbación de los síntomas en el SII al alterar el procesamiento central de la información sensorial, lo que a menudo produce hipervigilancia y una mayor percepción(145).

La distensión se ha definido como una sensación de aumento de la presión abdominal que puede o no estar acompañada de distensión abdominal objetiva, es decir aumento visible del perímetro abdominal. Por el contrario, esto último puede ocurrir sin sensación de hinchazón asociada. Por lo tanto, la hinchazón es una sensación y la distensión es un signo, pero cualquiera de los dos puede producir disconfort significativo(146,147).

La distensión abdominal y la hinchazón pueden producirse por diferentes mecanismos, que a veces coinciden en el mismo individuo (tabla). La distensión abdominal se produce por una contractura diafragmática y una relajación de la musculatura de la pared abdominal anterior, que se puede corregir con biofeedback. De hecho, se ha demostrado que la actividad de la electromiografía de los intercostales y el diafragma disminuyó significativamente después del biofeedback, mientras que la actividad de los músculos abdominal, especialmente el oblicuo interno aumentó significativamente(148,149).

1.1.3 Estreñimiento y trastornos de la defecación

El estreñimiento se caracteriza por la presencia de heces duras y/o esfuerzo o dificultad en la defecación. El estreñimiento funcional (EF) comparte con el SII-E la ausencia en la mayoría de los casos de alteraciones morfológicas, metabólicas o neurológicas que los expliquen mediante métodos convencionales y se diferencia en que este último el dolor abdominal es su principal característica.

El estreñimiento funcional se define según los criterios de Roma IV como:

Presencia de dos o más de los siguientes criterios
En más de 25% de las ocasiones:
Esfuerzo defecatorio
Heces duras
Sensación de evacuación incompleta
Sensación de obstrucción o bloqueo anorrectal
Maniobras manuales para facilitar la defecación
Menos de tres deposiciones espontáneas completas por semana
La presencia de heces líquidas es rara sin el uso de laxantes
No debe existir criterios suficientes para el diagnóstico de síndrome de intestino irritable

Los criterios deben cumplirse al menos durante los últimos tres meses y los síntomas deben haber iniciado como mínimo seis meses antes del diagnóstico.

1.1.3.1 Epidemiología

La prevalencia global del estreñimiento crónico varía entre 11% al 18%(150). La prevalencia real está subestimada porque muchos de los pacientes que lo presentan no consultan al médico por este motivo(151). Por lo general, la prevalencia es más amplia cuando el estreñimiento es referido por la propia persona y más baja cuando se aplican los criterios de Roma. El estreñimiento crónico tiene un gran impacto en la utilización de recursos sanitarios, afecta de forma negativa la calidad de vida de las personas y provoca ausentismo laboral y escolar(152,153).

1.1.3.2 Fisiopatología

Estreñimiento con tránsito colónico normal

En el estreñimiento de tránsito normal, las heces se desplazan a lo largo del colon a una velocidad normal. Algunos de estos pacientes tienen anomalías de función sensitiva y motora anorrectal indistinguibles de las presentes con estreñimiento con tránsito lento(154,155). No está claro si una mayor capacidad de distensión rectal y menor sensación del recto son consecuencia del estreñimiento crónico o contribuyen a la ausencia de percepción de la necesidad de defecar, pero la mayoría de los pacientes tienen pruebas fisiológicas normales(156,157).

Inercia colónica

El estreñimiento de tránsito lento es más frecuente en las mujeres jóvenes y se caracteriza por deposiciones infrecuentes y se debe a un trastorno de la función motora de colon(158). Los pacientes que tienen retrasos leves del tránsito colónico presentan síntomas similares a los observado en pacientes con SII(159). En los pacientes con síntomas más graves (inercia colónica), la fisiopatología incluye retraso del vaciamiento del colon proximal y no aumento de la actividad motora del colon después de una comida. Estos hallazgos sugieren una disfunción del plexo nervios mientérico(160). Se ha demostrado una disminución del número de células intersticiales de Cajal en el plexo mientérico en muestras de colon resecados de algunos de estos pacientes, se cree que estas células desempeñan un papel importante en el control de la motilidad en el colon(161,162).

Disinergia defecatoria

La defecación normalmente implica una relajación coordinada del músculo puborectal y del esfínter anal externo junto con un incremento de la presión intraabdominal(163–166). Un estudio prospectivo mostró que la mayoría de los pacientes con disinergia de la defecación presentaban una incapacidad para coordinar los músculos abdominales, rectoanal y pélvicos para facilitar la defecación(167). Este fallo de la coordinación rectoanal consiste en una fuerza propulsora inadecuada o una relajación anal inadecuada. Adicionalmente, un 50% a 60% de los pacientes también presentan un empeoramiento de la sensibilidad rectal(168).

La definición de Roma IV para trastornos de la defecación (169) se describe a continuación:

El paciente debe cumplir los criterios diagnósticos de estreñimiento funcional y/o de síndrome de intestino irritable tipo estreñimiento; además

Durante intentos repetidos para defecar, debe haber elementos de evacuación inadecuada, demostrada por, al menos, dos de las siguientes pruebas:

Test de expulsión del balón patológica

Patrón de evacuación anorrectal anormal demostrado por manometría o por electromiografía anal de superficie.

Evacuación rectal alterada demostrada por técnica de imagen.

Estos criterios deben cumplirse al menos durante los últimos tres meses y los síntomas deben haberse iniciado como mínimo seis meses antes del diagnóstico.

1.1.3.4 Test de expulsión del balón

El test de expulsión del balón es muy útil y sencillo de realizar, se coloca en la ampolla rectal una sonda que lleva un balón hinchado en su extremo con la intención de simular la presencia de heces. Normalmente se rellena con 50ml de agua templada. Se realiza en posición sentada para asemejarse lo máximo posible a una defecación normal(170). Para valorar la utilidad como método capaz de excluir la disinergia defecatoria en paciente con estreñimiento crónico funcional, se realizó un estudio prospectivo que incluyó 359 con estreñimiento crónico funcional y se obtuvo una especificidad del 89% y un valor predictivo negativo del 97% cuando se comparó con la manometría rectal(171). Sin embargo, un estudio más reciente muestra una gran discordancia entre el test de expulsión del balón, la manometria anorrectal y la defecografía(172).

1.1.3.5 Manometría anorrectal

La manometría anorrectal valora la actividad presiva de la región anorrectal, la sensibilidad rectal, los reflejos rectoanales y la función del esfínter anal tanto en reposo como durante la defecación(169,170). Normalmente, la compresión abdominal durante el esfuerzo (incremento de la presión intrarrectal) se asocia con a relajación anal (caída de la presión

anal). Se mide la compresión abdominal, así como el cambio en la presión anal durante el esfuerzo. *Disinergia defecatoria* se define como una relajación anal defectuosa (< 20%) durante el esfuerzo.
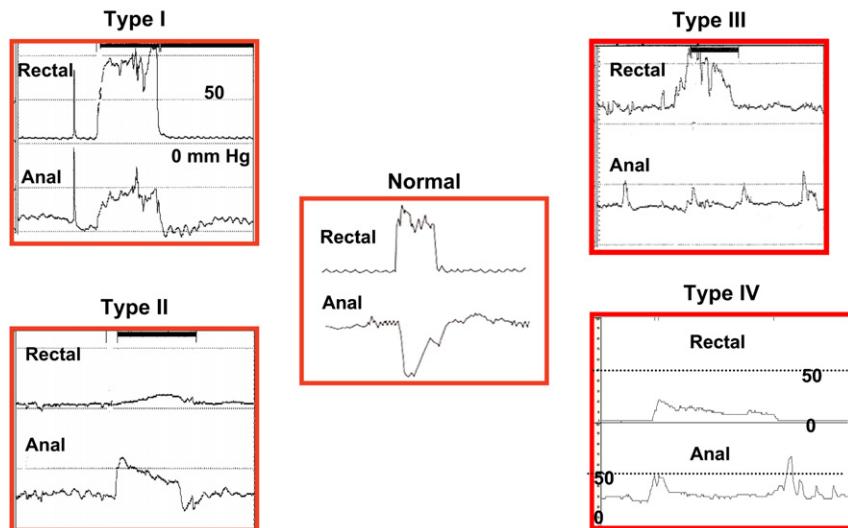
Tomada de Rao et al (173)

1.1.3.6 Biofeedback anorrectal

Los objetivos de la terapia con *Biofeedback* son corregir la incoordinación de la musculatura abdominal-pelviana y mejorar la hiposensibilidad rectal reeducando la percepción del llenado rectal(174,175). Es fundamental realizar un aprendizaje y entrenamiento para relajar la musculatura del suelo pélvico durante la defecación. Para ello se siguen cuatro pasos, educar al paciente (enseñarle, apoyándonos en los medios audiovisuales, su error al realizar de forma inadvertida una contracción o no relajación del esfínter), mejorar el esfuerzo de empuje (utilizando el sensor rectal para aprender la forma adecuada de realizar el esfuerzo de empuje abdominal y diafragmático), entrenar la relajación de los músculos del suelo pélvico (con apoyo visual que nos enseña las presiones que mantenemos en el canal anal) y practicar de forma repetida defecaciones simuladas (con el balón inflado en el recto)(176,177).

La eficacia observada del Biofeedback para la disinergia defecatoria es del 70% al 80%, tanto en estudios a corto como a largo plazo(177–179).

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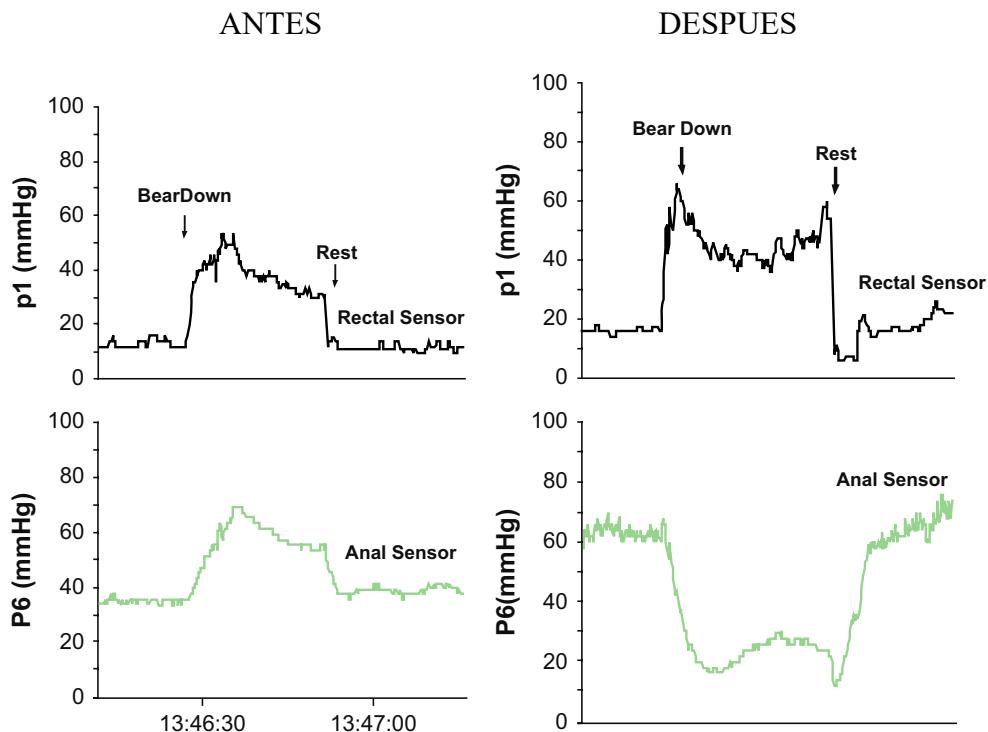
Tomada de Rao et al (175)

1.2 DIETA Y SÍNTOMAS DIGESTIVOS

Muchos pacientes con trastornos funcionales digestivos refieren que sus síntomas están relacionados con una mayor sensibilidad a los alimentos(180). Existe una creciente evidencia que lo factores dietéticos pueden desempeñar un papel importante en la etiología y fisiopatología de los síntomas tanto en pacientes con dispepsia funcional como síndrome de intestino irritable. Este impacto podría estar mediado a través de interacciones directas entre los componentes de la dieta y los receptores de la mucosa que pueden estar sensibilizados a estos estímulos, o por medio de eventos derivados de componentes de la dieta, como la liberación de hormonas intestinales, cambios en la morfología epitelial, generación de respuestas inmunes o una alteración en la señalización cerebro-intestino(181). Se ha sugerido que la restricción de determinados alimentos como la fibra, gluten,

carbohidratos de cadena corta, entre otros, podrían producir beneficio en estos pacientes(182).

1.2.1 Fibra

La fibra se ha usado durante mucho tiempo para el tratamiento de diversas afecciones enfermedades gastrointestinales como el estreñimiento(183) y la diarrea(184). El Instituto de Medicina de la Academia Nacional de Ciencias recomienda un consumo de 25 a 30 g de fibra por día, pero el promedio de ingesta diaria de fibra de los estadounidenses es de 12g a 18g de fibra por día(185). Aunque no existe una definición de fibra aceptada universalmente, se acepta que este término incluya a hidratos de carbono que no se hidrolizan ni se absorben en el tracto digestivo superior. La fibra dietética se puede separar en fibra soluble (pectina, gomas y mucilagos) y fibra insoluble (celulosa y ligninas), o caracterizarse en función de la longitud de los carbohidratos (cadena larga o corta) y en su capacidad de fermentación(186).

Los mecanismos propuestos por los cuales la fibra dietética beneficia a aquellos pacientes con trastornos funcionales digestivos son: Aumento del volumen de las heces a través de la fermentación de los productos (fibra soluble) o el tránsito colónico acelerado mediante estimulación mecánica (fibra insoluble). Influencia en la microbiota: producción de ácidos grasos de cadena corta y disminución del pH colónico favorecen el crecimiento como lactobacilos y bifidobacterias. Influencias en el sistema neuroendocrino del tracto gastrointestinal a través de la liberación de hormonas como la serótina que afecta la sensibilidad visceral y el péptido YY que aumenta la absorción de agua y electrolitos en el colon(187).
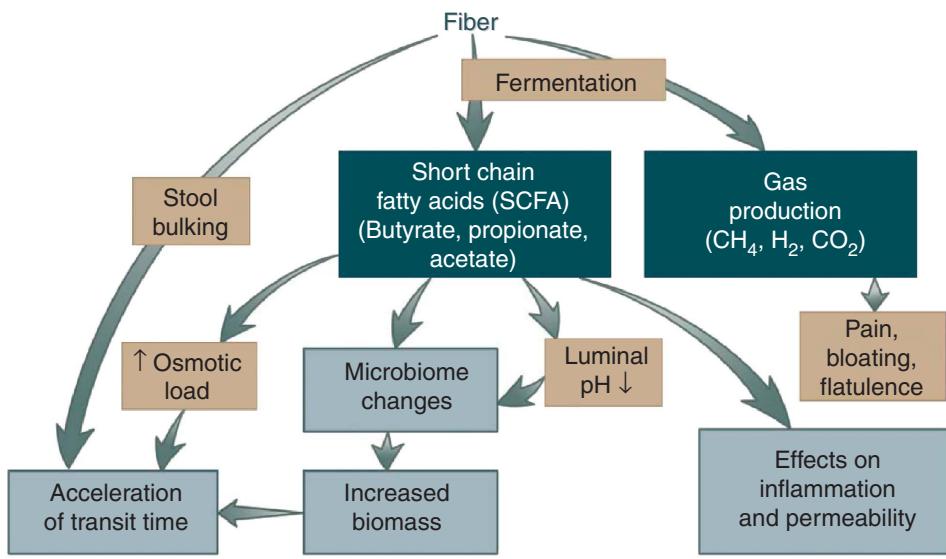
Tomada de Eswaran et al (186).

Las guías clínicas para el manejo del estreñimiento crónico, además de recomendar una ingesta adecuada de líquidos y ejercicio, una dieta alta en fibra suele ser su primera recomendación, ya se que se cree que la falta de fibra contribuye al estreñimiento(188). Si bien en varios estudios se ha visto como la fibra o suplementos de fibra mejoran el estreñimiento(189), la respuesta de los síntomas abdominales (distensión y dolor abdominal) es muy variable, empeorándolos en muchos casos(125,126,190) . Por lo que actualmente no hay evidencias científicas claras para la recomendación de aumentar la fibra en pacientes con síndrome de intestino irritable, y si se hace debe ser a base de fibra soluble, comenzando con dosis bajas y aumentando de forma progresiva(191).

1.2.2 Dieta baja en FODMAP

El acrónimo FODMAP incluye a un grupo de carbohidratos de cadena corta (monosacáridos, disacáridos y oligosacáridos fermentables) y polioles. Estudios recientes han demostrado que los carbohidratos de cadena corta fermentables aumentan el volumen de agua del intestino delgado distal y la producción de gas en el colon, y en personas con hipersensibilidad visceral producirían síntomas funcionales gastrointestinales(192–194).
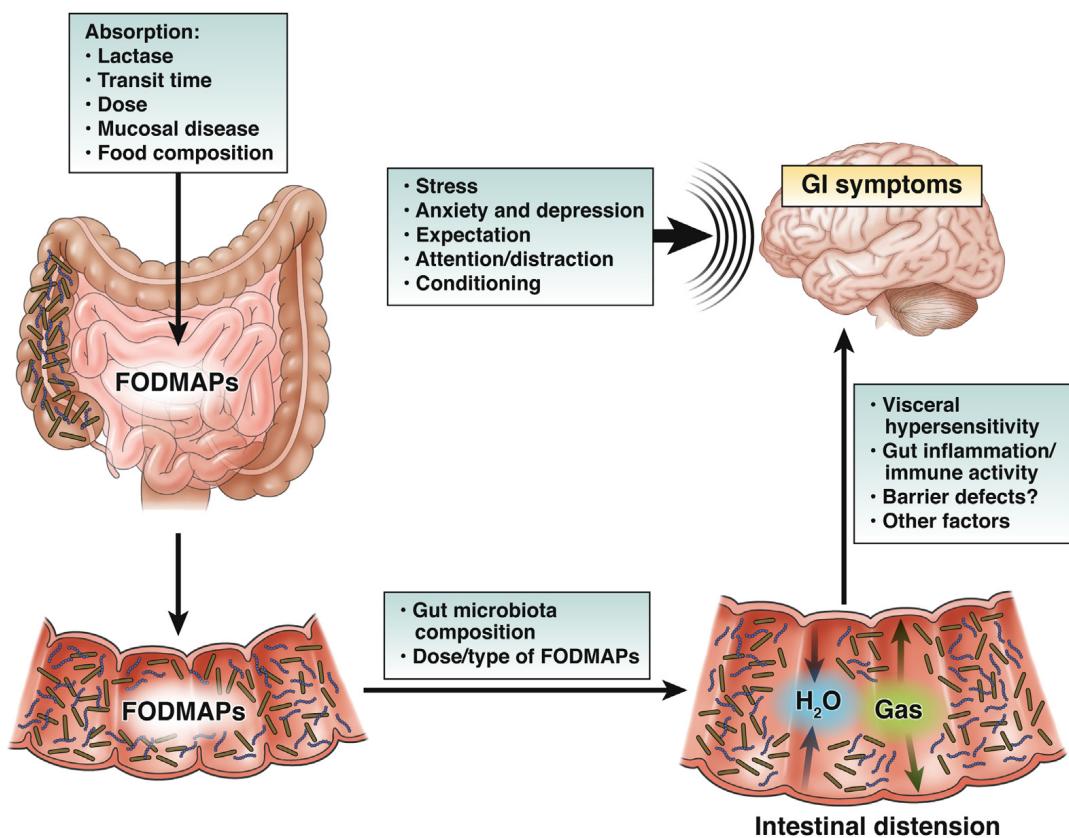
Tomada de Simrén M (195)

Actualmente hay numerosos ensayos clínicos, que muestran que la dieta baja en FODMAP conduce a respuesta clínica en el 50 % al 80% de los pacientes con síndrome de intestino irritable, especialmente en la hinchazón, flatulencias, diarrea y síntomas globales(196–200). Sin embargo, junto con el impacto clínico beneficioso, estudios recientes han demostrado que esta dieta produce cambios profundos en la microbiota(201–204) y en la metabolómica(205), cuya duración y relevancia clínica son aún desconocidos. Por lo que actualmente, a falta de estudios que evalúen estos potenciales efectos perjudiciales a largo plazo, no se puede recomendar la dieta baja en FODMAP a todos los pacientes.

1.2.3 PREBIÓTICOS

La Asociación Científica Internacional de Probióticos y Prebióticos (ISAPP), en su último consenso en el 2017, define a los prebióticos como un sustrato que es utilizado

selectivamente por los microorganismos del hospedador confiriendo un beneficio para la salud(206). La siguiente figura muestra los prebióticos aceptados con la evidencia actual. Siendo los fructooligosacáridos (FOS) y los galactooligosacáridos (GOS) los prebióticos más investigados.
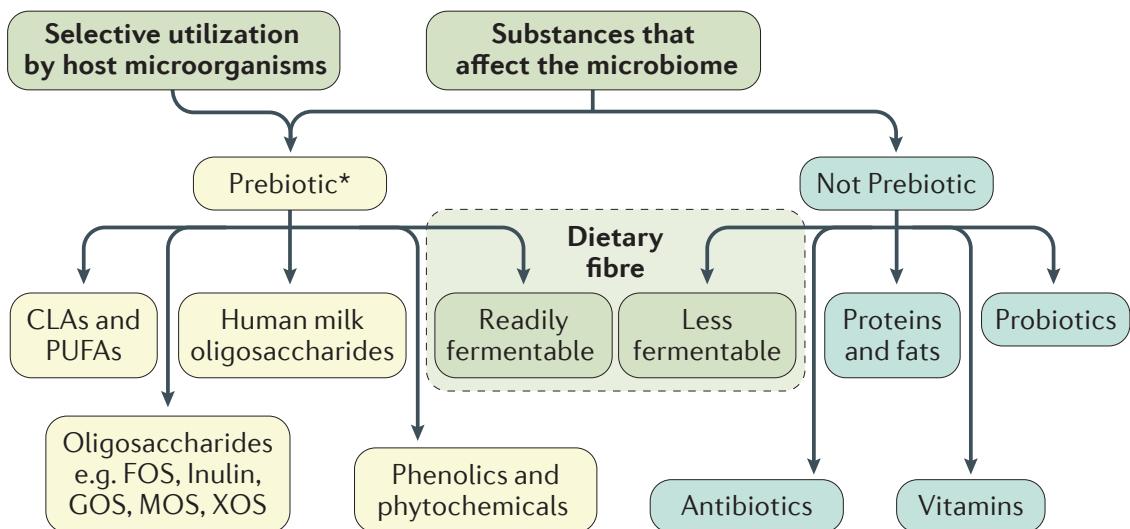
Tomada de Gibson et al (206)

Aunque la mayoría de los prebióticos actuales se administran por vía oral, también pueden administrase directamente a otros sitios del cuerpo colonizados por microbios, como el tracto vaginal y la piel.

Los efectos en la salud de los prebióticos están evolucionando, pero actualmente incluyen beneficios(206):

- Tracto gastrointestinal (inhibición de patógenos, estimulación inmune)
- Cardiometabolismo (reducción en los niveles de lípidos en la sangre, efectos sobre la resistencia ala insulina).
- Salud mental (metabolitos) que influyan en la función cerebral, la energía y la cognición.
- Los huesos (la biodisponibilidad de los minerales), entre otros.

Los prebióticos establecidos actualmente están basados en carbohidratos, pero otras sustancias como los polifenoles y los ácidos grasos poliinsaturados convertidos en los respectivos ácidos grasos conjugados podrían ajustarse a la definición actualizada asumiendo un peso convincente de evidencia en el huésped objetivo(207).

Entre los efectos producidos en el colon, cabe mencionar, que los prebióticos estimulan el crecimiento de bacterias fermentativas (bifidobacterias y lactobacilos) con efectos beneficiosos; generan ácidos grasos de cadena corta (SCFA) que producen un descenso del pH, controlando el desarrollo de ciertas comunidades que pueden generar efectos perjudiciales (por ejemplo, algunas especies de Bacteroides, Fusobacterium y Clostridium spp). Las bifidobacterias no producen butirato, pero estimulan el crecimiento de bacterias productoras de este SCFA en el colon, como son las eubacterias. Además, los prebióticos actúan sobre determinadas funciones intestinales reduciendo el tiempo de tránsito intestinal, al producir un aumento del volumen del bolo fecal y del número de deposiciones(208–213).

A pesar de los numerosos efectos beneficiosos que pueden ejercer los prebióticos, hay que consideran la importancia que tiene el establecimiento de la ingesta adecuada para evitar efectos adversos, porque si esta ingesta de prebióticos es excesiva podría provocar síntomas digestivos como: hinchazón abdominal, flatulencias y diarrea.

1.2.4 PROBIÓTICOS

La Organización Mundial de la Salud (OMS) define probióticos como microorganismos vivos que cuando se administran en cantidades adecuadas, confieren un beneficio para la salud en el huésped(214,215). Los probióticos afectan el ecosistema intestinal al afectar los mecanismos inmunitarios, al interactuar con los microbios comensales o patógenos potenciales, al generar productos metabólicos finales como los ácidos grasos de cadena corta y mediante la comunicación con las células huésped a través de señalización química. En la siguiente tabla se enumeran los principales mecanismos de acción de los probióticos(215,216):

| Beneficios inmunológicos | - Activar los macrófagos locales para aumentar la presentación de antígenos a los linfocitos B y aumentar la producción de inmunoglobulina A secretora local y sistémica. |
| | - Modular los perfiles de citoquinas |

	-	Inducir tolerancia a los antígenos alimentarios
Beneficios no inmunológicos	-	Digerir los alimentos y competir por los nutrientes con los patógenos.
	-	Alterar el pH local para crear un entorno local desfavorable para los patógenos.
	-	Eliminar los radicales superóxidos.
	-	Estimular la producción de mucina epitelial.
	-	Mejorar la función de la barrera epitelial intestinal.
	-	Competir por la adhesión con los patógenos.
	-	Modificar las toxinas derivadas de los patógenos.

En la siguiente figura se explica como los probióticos pueden variar los ecosistemas bacterianos intestinales y suprimir el crecimiento de patógenos al inducir la producción en el huésped de B-defensina e Ig A. Además, muestra como los probióticos pueden fortalecer la barrera epitelial intestinal al mantener las uniones estrechas (tight junctions) e inducir la producción de mucina(217).
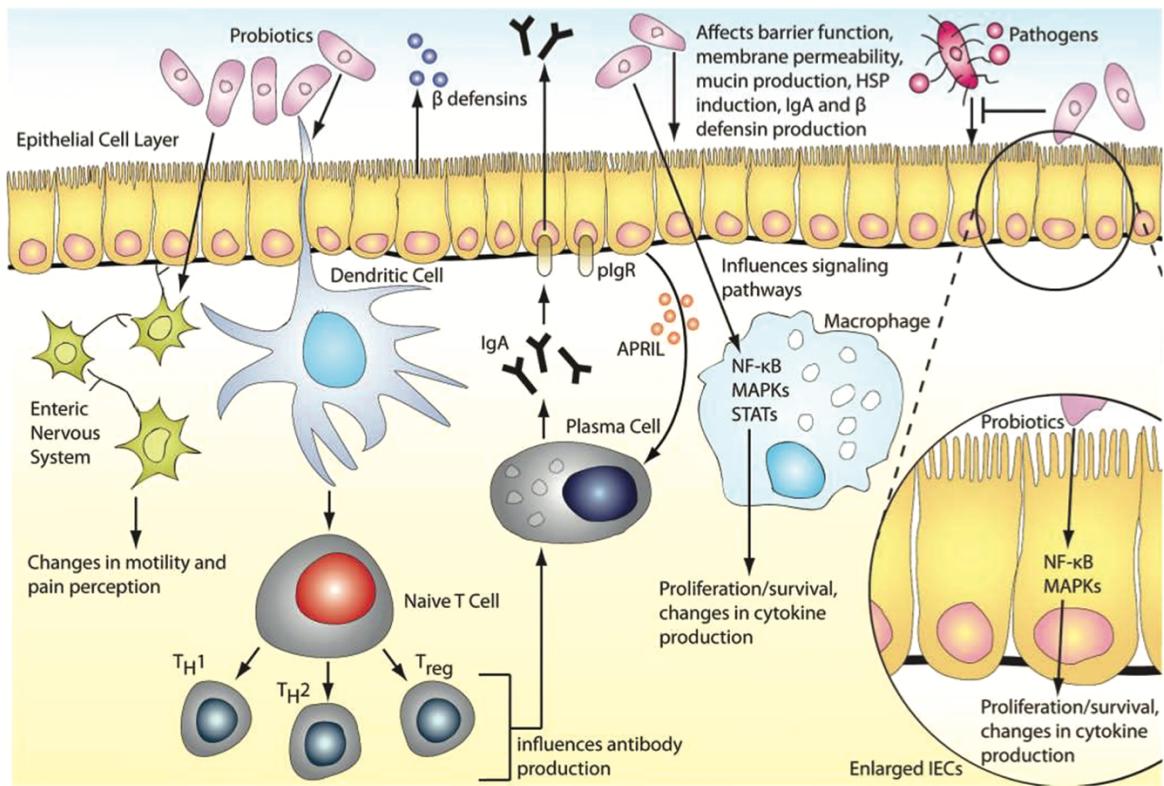
Tomada de Hemarajata et al (217)

En esta revisión y metaanálisis se encontró que los probióticos son mejores que el placebo para reducir la persistencia de los síntomas en el SII y tuvieron efectos beneficiosos a nivel global en el SII y en los scores de dolor abdominal, hinchazón y flatulencias según los resultados de 35 ensayos clínicos controlados y aleatorizados (ECA). Se usó una amplia gama de probióticos con cepas únicas y múltiples, y no estaba claro que cepas individuales eran las más beneficiosas(218). Los mismos autores actualizaron su metaanálisis en el 2018, incluyendo 53 ECA, encontrando que el uso de combinaciones específicas de probióticos o especies y cepas específicas si sugería una mejoría significativa en los sores de los síntomas del SII, sin embargo, los autores tuvieron reserva sobre sacra conclusiones definitivas sobre su eficacia(210).

2. HIPÓTESIS Y OBJETIVOS

2.1 HIPÓTESIS GENERAL Y MARCO DE TRABAJO

Como se ha descrito en los apartados anteriores, hay una relación entre la dieta, función y los síntomas digestivos. Sin embargo, la fisiopatología de los trastornos funcionales digestivos no está del todo aclarada. El aumento de la sensibilidad visceral es un mecanismo común en todos los trastornos funcionales digestivo de forma que estímulos intraluminales determinados por el contenido intestinal podrían desencadenar los síntomas y este fenómeno parece aplicable a distintos tipos de síndromes digestivos funcionales.

En esta tesis doctoral planteamos la siguiente hipótesis general: el contenido intestinal es un factor clave en el desencadenamiento de síntomas en pacientes con distintos tipos de síndromes digestivos funcionales.

2.2 OBJETIVOS

Objetivo primario:

Determinar si los factores que determinan el contenido intestinal, tanto la dieta como el hábito deposicional, influyen sobre los síntomas digestivos funcionales.

Objetivos secundarios:

1. Determinar la influencia específica de distintos tipos de residuos fermentables en la dieta (prebióticos y FODMAPS) sobre los síntomas relacionados con el gas intestinal en pacientes con síndromes funcionales digestivos.
2. Determinar el papel fisiopatológico del estreñimiento en la dispepsia funcional, es decir si el estreñimiento asociado influye sobre los síntomas dispépticos.

3. PUBLICACIONES

3.1. Primera publicación

Título:

Effects of Prebiotics vs a Diet Low in FODMAPs in Patients With Functional Gut Disorders.

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Jose-Walter Huaman, Marianela Mego, Chaysavanh Manichanh, Nicolau Cañellas, Daniel Cañueto, Hegoi Segurola, Marta Jansana, Carolina Malagelada, Anna Accarino, Jelena Vulevic, George Tzortzis, Glenn Gibson, Esteban Saperas, Francisco Guarner, and Fernando Azpiroz.

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EFFECTS OF PREBIOTICS VS A DIET LOW IN FODMAPS IN PATIENTS WITH FUNCTIONAL GUT DISORDER

Short title: Prebiotics versus FODMAP diet

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Disclosures: None

Authorship Statement: Guarantor of the article: Fernando Azpiroz

Author contributions: JWH: randomization of participants (generation of allocation sequence and assignation of participants to interventions), study management, conduction of experiments and data analysis; MM: study management, conduction of experiments and data analysis; C Manichanh: microbiota analysis; DC: metabolomic analysis; NC: metabolomic analysis; HS, nutritionist: dietary guidance; MJ, nutritionist: dietary guidance; C Malagelada: metabolomic analysis; AA: supervision of studies; JV: study design, interpretation of results, manuscript revision; GT: study design, interpretation of results; GG: study design, interpretation of results, manuscript revision; ES: study design, manuscript revision; FG: study design, data interpretation manuscript revision; FA: study design, and manuscript preparation.
All authors approved the final draft of the manuscript.

ABSTRACT

Prebiotics and diets low in fermentable residues (low-FODMAP diet) might reduce symptoms in patients with functional gastrointestinal disorders, despite reports that some non-absorbable, fermentable meal products (prebiotics) provide substrates for colonic bacteria and thereby increase gas production. We performed a randomized, parallel, double-blind study of patients with functional gastrointestinal disorders with flatulence. We compared the effects of a prebiotic supplement (2.8 g/day Bimuno containing 1.37g B-GOS) plus a placebo (Mediterranean-type diet; prebiotic group, n=19) vs a placebo supplement (2.8 g xylose) plus a diet low in fermentable oligo-, di-, mono-saccharides and polyols (low-FODMAP group, n=21) for 4 weeks; patients were then followed for 2 weeks. The primary outcome was effects on composition of the fecal microbiota, analyzed by 16S sequencing. Secondary outcomes were intestinal gas production and digestive sensations. After 4 weeks, we observed opposite effects on microbiota in each group—particularly in relation to the abundance of Bifidobacterium sequences (increase in the prebiotic group and decrease in the low-FODMAP group; P=.042), and *Bilophila wadsworthia* (decrease in the prebiotic group and increase in the low-FODMAP group; P=.050). After 4 weeks, both groups had statistically significant reductions in all symptom scores, except reductions in flatulence and borborygmi were not significant in the prebiotic group. Although the decrease in symptoms persisted for 2 weeks after patients discontinued prebiotic supplementation, symptoms reappeared immediately after patients discontinued the low-FODMAP diet. Intermittent prebiotic administration might therefore be an alternative to dietary restrictions for patients with functional gut symptoms.

ClinicalTrials.gov no: NCT02210572.

By 4 weeks administration, both treatments had opposite effects on intestinal microbiota but a similar clinical benefit in patients with functional gut disorders.

After treatment discontinuation the decrease in symptoms persisted in the prebiotic group, but reappeared immediately in the low-FODMAP group.

Intermittent prebiotic administration might be an alternative to continuous dietary restrictions for patients with functional gut symptoms.
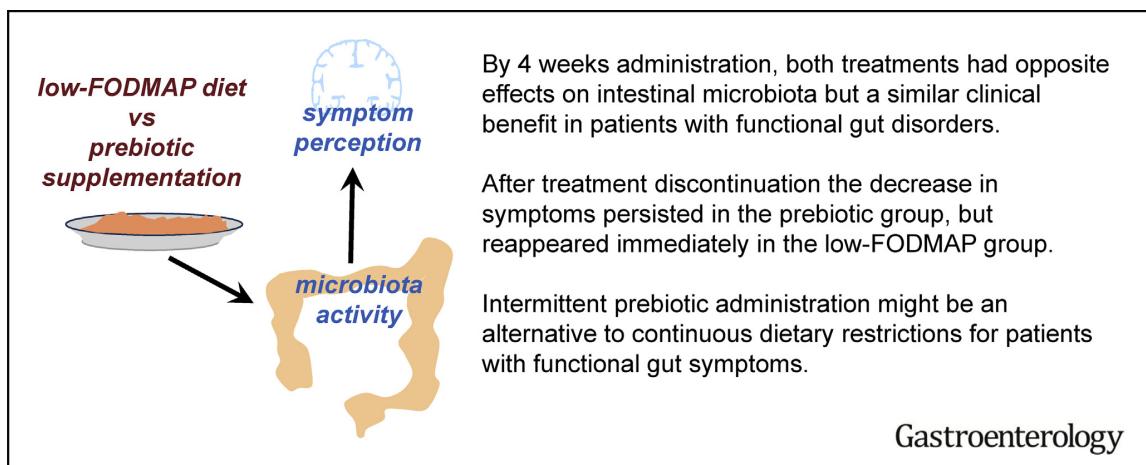
It has been shown that patients complaining of gas-related symptoms significantly improve on various types of diets low in fermentable residues [1-4]. However, other studies have suggested that some non-absorbable, fermentable meal products (prebiotics) that serve as substrates for colonic bacteria produce a similar effect on gas-related symptoms [5]. To address these apparent inconsistencies, we performed a randomized, two-center, parallel double-blind study in patients with functional gut disorders who complained of flatulence (Supplemental Document 1). We compared the effect of a prebiotic supplement (2.8 g per day Bimuno containing 1.37 g B-GOS, Clasado Biosciences, Jersey, Channel Islands) plus a placebo (Mediterranean-type) diet (prebiotic group) versus a placebo supplement (2.8 g xylose) plus a low FODMAP diet (LFD group). The primary outcome was the effect of the treatments on gut microbiota composition, specifically the relative abundance of bifidobacteria analyzed by 16S sequencing. Secondary outcomes were intestinal gas production, as an index of microbiota activity, and digestive symptoms. Samples size was calculated based on the effect of the prebiotic BGOs on fecal bifidobacteria in previous studies [6].

Forty-four patients (31 with irritable bowel syndrome and 13 with functional abdominal distension) were randomized (21 in the prebiotic and 23 in the LFD group) and 40 of them completed the study (19 and 21 patients, respectively); no demographic or clinical differences between groups were found. Adherence to dietary instructions was good (≥5 on a 1-7 scale) [7]. A per intention-to-treat analysis was performed.

Both treatments induced different effects on microbiota, particularly with relation to the abundance of *Bifidobacterium* genus sequences (increased with prebiotic and decreased with LFD; p=0.042), and *Bilophila wadsworthia* (decreased

with prebiotic and increased with LFD; p=0.050) (Figure 1; Supplemental Document 2).

Before treatment, the patients exhibited mild to moderate symptoms on their habitual diets, recording 15±1 evacuations of gas during the daytime without significant differences between the study groups (Figure 2). By 4 weeks, both treatments reduced the symptom scores on the daily questionnaires (Figure 2); the reductions were statistically significant for all symptoms except for flatulence and borborygmi in the prebiotic group, but no differences in the effect of treatment (treatment values minus pretreatment values) were detected between the study groups (p=0.293 by MANOVA). However, both strategies had different consequences after treatment discontinuation. While the improvement of symptoms persisted 2 weeks after prebiotic administration, symptoms tended to relapse after discontinuing the LFD (still lower than pretreatment), although the change (from treatment values to post-treatment values) was not significantly different between groups (p=0.093 by MANOVA). Both treatments reduced the number of daytime anal gas evacuations; the effect was more prominent (and statistically significant; p<0.001) in the LFD group, but without differences between groups (p=0.091). After prebiotic treatment, the number of gas evacuations was maintained, but it increased (not significantly) after discontinuation of the LFD, (p=0.073 vs change in prebiotic group) (Figure 2).

The clinical outcome associated with the LFD in our study was similar to that previously reported [2-4]. The LFD reduced gas production; this effect was similar to that produced by low flatulogenic diet and conceivably contributed to the improvement of gas-related symptoms [1]. The improvement of gas-related symptoms due to supplementation with the B-GOS prebiotic in our study was

consistent with previous observations [5]. B-GOS serves as a substrate for colonic microbiota and initially increases intestinal gas production. However, continuous B-GOS administration elicited an adaptation of gut microbiota and progressive decrease in gas production back to pre-administration levels by 7-10 days of treatment [6] [8]. It is not known whether the effects of B-GOS administration on symptoms and microbiota are product-specific or are common to other prebiotics. The tendency to symptom relapse after LFD discontinuation may be related to its effect on intestinal microbiota [9] [10].

The main limitation of this study relates to the relatively small sample size. As anticipated, the sample size demonstrated that despite the treatments having significantly different effects on gut microbiota, as the primary outcome, their effects on clinical symptoms, as secondary endpoints, were similar. Furthermore, the study was short and did not allow estimating the long-term efficacy of the treatments, and in the prebiotic group the potential contribution of the Mediterranean diet cannot be ascertained.

From a practical perspective, our study indicated that, in the short run, daily administration of B-GOS prebiotic was equally effective as an LFD. Since dietary restrictions, particularly the LFD, are cumbersome to follow, these results present an alternative patient management strategy. Furthermore, given the sustained effect of B-GOS compared to the reversible effects of LFD, intermittent treatment with B-GOS might represent an additional advantage over the continuous treatment required with LFD. Recent data indicate that simultaneous administration of a probiotic may prevent the potentially deleterious influences of LFD on microbiota [4]. Possibly, the combination of various therapies may have synergistic effects. Gas-related symptoms may benefit from individualized treatment with diet, prebiotics

and/or probiotics in single or combined therapy. Ideally, individual treatment strategies would be based on biological markers, including microbiota metabolic activity and composition.

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FIGURE LEGENDS

Figure 1. Effect of treatment on relative abundance in *Bifidobacterium* and *Bilophila wadsworthia* measured by 16S rRNA sequencing. Overall differences were tested by non-parametric Kruskal-Wallis analysis of variance on ranks, and the Mann-Whitney test was used for post hoc comparisons (LFD n=21; prebiotic group n=19). Data are median and interquartile range of the difference in abundance of bacterial sequences in fecal samples from pretreatment to treatment (see Supplemental Document 2).
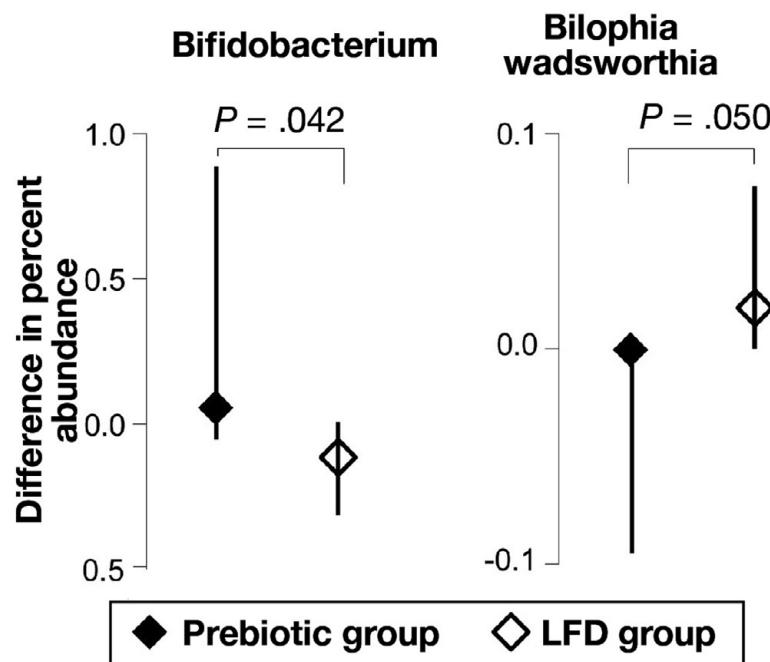
Figure 2. Symptoms and number of anal gas evacuations measured pretreatment (white), in the 4th week treatment (black) and in the 2nd week posttreatment phase (gray). Per intention-to-treat analysis in 44 patients (21 prebiotic, 23 LFD group); differences between groups were not statistically significant. Data are the mean±SE.
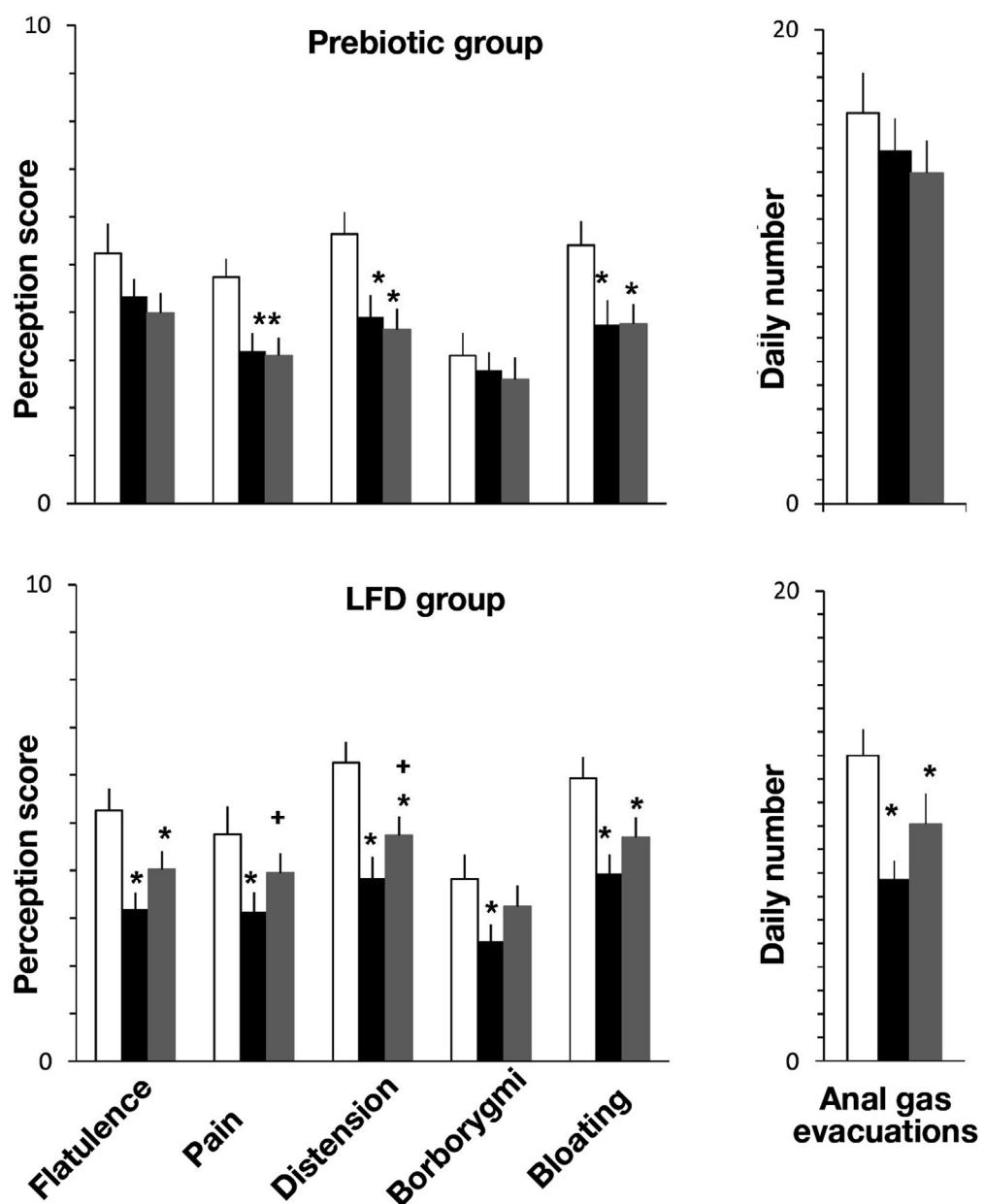
*$P < .05$ vs pre-treatment phase; $+ P < .05$ vs treatment phase

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Non-absorbable residues of the diet are fermented by intestinal microbiota, releasing gas. Thus, diets low in fermentable residues, such as low FODMAP diets, improve gas-related complaints; paradoxically, some products that are selectively fermented by colonic microbiota (prebiotics) produce a similar benefit.

NEW FINDINGS

The decrease in symptoms produced by a low FODMAP diet in patients with functional gut disorders disappeared soon after discontinuation of the diet. In contrast, prebiotic administration enriched the microbiota and the decrease in symptoms persisted for 2 weeks.

LIMITATIONS

The study is small, did not estimate long-term efficacy and did not determine whether the prebiotic effect is product-specific or generic.

IMPACT

Intermittent treatment with prebiotics might represent an advantage over dietary restrictions for patients with functional gut symptoms.

Supplementary Material:

SUPPLEMENTAL DOCUMENT 1: MATERIALS AND METHODS

Study design

This study was a randomized, two-centre, parallel and double-blind study performed between August 2014 and July 2015 in 2 tertiary care referral centers. The study protocol was registered with ClinicalTrials.gov (NCT02210572). All co-authors had access to the study data and reviewed and approved the final manuscript. The study compared the effect of a prebiotic supplement plus a placebo diet (prebiotic group) versus a placebo supplement plus a low FODMAP diet (LFD group; see sections on supplement products and treatment diets below). The study lasted 7 weeks (49 days) with 3 phases: a 1-wk pretreatment phase (days 1-7), a 4-wk treatment phase (days 8-35) and 2-wk post-treatment phase (days 36-49) (Figure panel A).

The primary outcome was the effect of the treatments on gut microbiota composition, specifically the relative abundance of bifidobacteria. Secondary outcomes were intestinal gas production, as an index of microbiota activity, and digestive sensations.

Endpoints and rationale

Planned endpoints

a) Effect of treatments on relative abundance of bifidobacteria. Prebiotics and LFD have been shown to induce opposite effects on bifidobacteria abundance.

b) Effect of treatment on symptoms. Based on previous data, we anticipated that despite their different effects on microbiota both treatments might have similar effects on symptoms.

c) Gas evacuation. Prebiotics have been blamed for increasing gas production and symptoms, some data indicated that after a period of adaptation these effects subside and symptoms improve.

Exploratory endpoints

a) Post-treatment effects, i.e. effects on symptoms and number of gas evacuations after treatment discontinuation, anticipating that the specific effects of the treatments on microbiota may influence the evolution of symptoms after treatment discontinuation.

b) Effect of treatments on the relative abundance of other microorganisms in fecal samples. Supplemental Document 2.

c) Effects of treatments on the tolerance of a challenge diet; patients with functional gut disorders have a poor tolerance to diets rich in fermentable residues and we anticipated that treatments with different effects on intestinal microbiota might influence the patients susceptibility to a dietary challenge. Supplemental Document 3.

d) Effects of treatment on the response to a probe meal. A probe meal was primarily administered to measure the volume of gas produced and evacuated per anus in the postprandial period on standard conditions. We anticipated that the influence of treatments on microbiota would be also reflected by its metabolic activity, and intestinal gas production was used as an index of microbiota activity. Supplemental Document 4.

e) Urine metabolomics were expected to be differently influenced by the treatments and was intended to serve as an indirect index of adherence to diets. Supplemental Document 5.

Randomization and masking

Participants were randomized using a block design (n=10 per block) by a computer-generated randomization list. Participants did not know which treatment they were assigned, and all patients received dietary instructions following the same schema of intervention visits; the dietary supplement was delivered in numbered containers. The investigators performing the tests, the clinical follow-up and the data analysis were blinded to the intervention (supplement and diet). To allow reliable blinding, the patients were informed that specific dietary instructions and a dietary supplement were going to be tested, without specifying the two possible types of diets.

Participants

Patients fulfilling the criteria of having a functional gastrointestinal disorder and complaining (not necessarily as the primary complaint) of excessive anal gas evacuation (i.e., flatulence) (35 women, 5 men; age range 24 - 73 years) participated in the study (Figure panel B); these would be patients in whom a LFD might be indicated. Antibiotic consumption during the previous 2 months was an exclusion criterion. Participants were instructed to fill out a clinical questionnaire to evaluate bowel habits and gastrointestinal symptoms. Subjects gave written informed consent to participate in the study. The protocol for the study had previously been approved by the Institutional Review Board of University Hospital Vall d´Hebron.

Supplement product

During the treatment phase (days 8-35) participants consumed 1 sachet per day of either prebiotic (2.8 g per day Bimuno containing 1.37g B-GOS, Clasado Biosciences , Jersey, Channel Islands) or placebo (2.8 g xylose).

Dietary instructions

The treatment diet, either a low FODMAP or a placebo diet, was administered during the first 23 days of the treatment phase (days 8-31). To determine the effects of the treatments on the tolerance of a dietary challenge, participants were put on a standard, highly flatulogenic diet during 3-day periods at the end of the pretreatment phase (days 5-7) and the treatment phase (days 33-35). During the first 4 days of the pretreatment phase (days 1-4) and the post-treatment phase (days 36-49), the participants consumed their habitual diet. For the duration of the study, including the 1-wk pretreatment phase, patients were not allowed to consume any fermented dairy products or any tablets, pills or food supplements containing pre- or probiotics other than those provided. A dietician provided menus with the food items to consume for breakfast lunch and dinner, and indications of the food items to avoid. Using a structured consumption questionnaire (1) adherence to dietary instructions rated 6.5±1.1 in the prebiotic group and 6.5±1.3 in the LFD group on a 1-7 scale.

<u>Treatment diets</u>

Low FODMAP diet. The food list for the diet was based on published information adapted to local eating habits (2-5). The diet included (and specifically excluded) food items in the following categories: a) meat, fowl, fish, eggs; b) spinach, pepper, tomato, zucchini, eggplant, chard, green beans (excluding Brussels sprouts, broccoli, cabbage, garlic, leeks, onions, peas, lettuce, and

cauliflower). c) rice, oat, corn, potatoes, tapioca, and quinoa (excluding wheat, rye, barley, chickpeas, beans, lentils and soya beans); d) tangerine, orange, kiwi, pineapple, strawberries, pomelo (excluding apples, pears, peaches, apricots, cherries, mangoes, watermelon, melon and prunes); and e) lactose-free milk (excluding lactose-containing dairy products).

Placebo diet. The diet was balanced and Mediterranean-type (6), including the following every day: a) meat, fowl, fish, or eggs, b) vegetables, salad or legumes, c) bread, rice, pasta, potatoes or cereals, d) dairy products, and e) fruits.

Challenge diet

The challenge diet consisted of: a) *breakfast* of wholemeal cookies (39 g) plus coffee, tea and/or milk, b) *lunch* of white beans (200 g), mixed vegetables (250 g) or chickpeas (200 g) and wholemeal bread (50 g), plus meat, fowl or fish and fruit (banana, figs peaches or prunes), and c) *dinner* of vegetable soup (200 mL), wholemeal bread (50 g) and fruit (banana, figs, peaches or prunes).

Outcomes

The outcomes were measured during 3-day periods at 5 time points throughout the study: in the pretreatment phase just before and during the challenge diet (days 2-4 and 5-7, respectively), in the treatment phase just before and during the challenge diet (days 30-32 and 33-35, respectively), and at the end of the post-treatment phase (days 47-49) (Figure panel A).

Daily symptom questionnaire

During the 3 days of each evaluation period, the participants were instructed to fill out daily questionnaires that included the following parameters: (a) subjective sensations of flatulence (defined as anal gas evacuation), abdominal bloating (pressure/fullness), abdominal distension (sensation of girth increase), borborygmi and abdominal discomfort/pain using 0–10 analogue scales, (b) digestive well-being using a 10-point scale graded from +5 (extremely pleasant sensation/satisfaction) to −5 (extremely unpleasant sensation/dissatisfaction), and (c) mood on similar scale graded from +5 (very positive) to −5 (very negative). For each symptom, the scores for each 3-day period were averaged. This questionnaire has been previously used and has been shown to be sensitive enough to detect the effects of dietary interventions in different populations (6-9).

Number of anal gas evacuations

The number of anal gas evacuations during the last 2 days of each evaluation period were measured and averaged. Participants were instructed to carry an event marker (Hand Tally Counter No 101, Digi Sport Instruments, Shanggiu, China) during the day and to use it to register each passage of anal gas. This method has been previously used with reproducible and consistent results (6, 7, 10, 11); furthermore, studies measuring the number of gas evacuations by an event marker and continuously recording anal gas evacuations have shown a very good correlation between the results of the two methods (R>0.95; p<0.05) (12-15).

Response to a probe meal

The test was performed the day after the pretreatment and treatment phases. Participants reported to the laboratory after an overnight fast and consumed a probe

meal. The probe meal consisted of a ham omelet (1 egg, 30 g sliced ham cooked with 5 g oil), 46 g of white bread, 10 g of butter, 25 g of jam and 200 mL of fruit juice (400 Kcal, 350 mL total volume, 1.5 g of fibre).

The volume of gas evacuated by anus was measured for 4 h after the probe meal, as previously described (7, 16, 17). Briefly, gas was collected using a rectal balloon catheter (20 F Foley catheter, Bard, Barcelona, Spain) connected via a gas-tight line to a barostat, and the volume was continuously recorded. The intrarectal balloon was inflated with 5 mL of water to prevent anal gas leaks.

Patients' perceptions of abdominal sensations were measured every 30 min during the 4-h gas collection period using the same scales as described above: 0 to 10 scales for scoring abdominal bloating (pressure/fullness), abdominal distension (sensation of girth increase), borborygmi and abdominal discomfort/pain and − 5 to + 5 scales for scoring digestive well-being and mood.

Metabolomic analysis

Urine was collected for 24 h during the last day of the pretreatment and treatment periods (days 7 and 35, respectively). For each sample, a one-dimensional 1H NMR spectrum was acquired according to the standard recommendations (18, 19). Analyses of the histamine levels and P-cresol level in the urine samples were performed by mass spectroscopy.

Microbiota composition

Fecal samples were collected from 40 patients during the pretreatment, treatment and post-treatment phases (days 5, 32 and 49, respectively) (Figure panel A). After collection and homogenization, the samples were immediately frozen by the

participants in their home freezers at -20 ºC and later brought to the laboratory in a freezer pack, where they were stored at -80°C. Microbiota analysis was performed as previously described. Changes in abundance of bifidobacteria were initially assessed by genus-specific qPCR. A definitive analysis of microbiota composition was performed by 16 S sequencing (see Supplemental document 2).

Statistical analysis

Sample size calculation. Sample size calculation was performed based on the effect of the prebiotic B-GOS on fecal bifidobacteria. In previous studies (10), B-GOS cosumption increased relative abundande of bifidobateria in 13 out 20 subjects (65%); by contrast, low FODMAP diet did not induce this effect (20). Assuming a bifidobacteria increase in 65% of patients on B-GOS and in less than 15% of patients on low FODMAP diet, it was estimated that a sample size of 18 individuals per group would provide a 90% power to detect statistical differences between groups*.*

Metabolomic analysis. Differences from pre- and post-treatment spectra were used for comparisons between groups.

Microbiota analysis. The Shapiro-Wilk test was used to assess the normality of the data, and pairwise comparisons were made between the study groups with the non-parametric Kruskal-Wallis one-way analysis of variance test, which compares means between groups. The non-parametric repeated measures Friedman test was used for intragroup comparisons over time, and the Mann-Whitney *U* test was used for between group comparisons. The association of quantitative parameters was analyzed using linear regression. Between group differences in qualitative variables (i.e. response rate) were tested by means of the Fisher's exact test. A false

discovery rate (FDR) of corrected p-values was taken into account when considering the significance of the results.

Overall comparisons. In each group, data were analyzed by calculating the differences: a) for treatment period minus pretreatment, b) for post-treatment period minus pretreatment, and c) for post-treatment period minus treatment period. Comparisons between groups were performed using these differences by an intention to treat analysis. The Kolmogorov-Smirnov test was used to check the normality of the data distribution. The means (±SE) or medians and interquartile values of the measured variables were calculated as corresponded. Parametric normally distributed data were compared by Student's *t*-test for paired or unpaired data; otherwise, the Wilcoxon signed-rank test was used for paired data, and the Mann-Whitney *U* test was used for unpaired data. Differences in the clinical responses between treatments were tested by multivariate analysis of variance (MANOVA). The association of parameters was analyzed using linear regression.

Figure

A. Design

LF diet + placebo supplement

Placebo diet + prebiotic supplement

diet — habitual — challenge — treatment

symptom questionnaire

daytime gas evacuations

gas collection test

24-h urine collection

stool sampling

study days

1   7   8   35   36   49

pre-   treatment   post-

STUDY PHASE

B. Flow Chart

Asessed for elegibility (n=50)

Randomized (n=44)

Prebiotic (n=21)   Low FODMAPs (n=23)

Discontinued intervention: travel (n=1), antibiòtics (n=1)

Discontinued intervention: no adherence to diet (n=1) or to visits (n=1)

Analysed (n=19)   Analysed (n=21)

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SUPPLEMENTAL DOCUMENT 2. EFFECT OF TREATMENT ON FECAL MICROBIOTA

Analytical procedure

Genomic DNA extraction. A frozen aliquot (250 mg) of each sample was suspended in 250 μL of guanidine thiocyanate, 0.1 M Tris (pH 7.5), 40 μL of 10% N-lauroyl sarcosine and 500 μL of 5% N-lauroyl sarcosine. DNA was extracted by mechanical disruption of microbial cells with beads, and the recovery of nucleic acids from the clear lysates was achieved by alcohol precipitation, as previously described (1). An equivalent of 1 mg of each sample was used for DNA quantification using a NanoDrop ND-1000 spectrophotometer (Nucliber, Madrid, Spain).

High-throughput DNA sequencing. To profile the microbiome composition, the hyper-variable region (V4) of the bacterial and archaeal 16S rRNA gene was amplified by PCR. On the basis of our analysis performed using PrimerProspector software (2), the V4 primer pairs used in this study were expected to amplify almost 100% of the bacterial and archaeal domains. The 5' ends of the forward (V4F_515_19: 5'- GTGCCAGCAMGCCGCGGTAA -3') and reverse (V4R_806_20: 5'- GGACTACCAGGGTATCTAAT -3') primers targeting the 16S gene were tagged with specific sequences as follows: 5'-{AATGATACGGCGACCACCGAGATCTACACTATGGTAATTGT} {GTGCCAGCMGCCGCGGTAA}-3' and 5'-{CAAGCAGAAGACGGCATACGAGAT} {Golay barcode} {AGTCAGTCAGCC} {GGACTACHVGGGTWTCTAAT}-3'. Multiplex identifiers, known as Golay codes, had 12 bases and were specified downstream of the reverse primer sequence (V4R_806_20) (3). Standard PCR (0.75 units of Taq polymerase (Roche, Barcelona, Spain) and 20 pmol/μL forward

and reverse primers) was run in a Mastercycler gradient (Eppendorf, Madrid, Spain) at 94°C for 3 min, followed by 35 cycles at 94°C for 45 sec, 56°C for 60 sec, 72°C for 90 sec, and a final cycle of 72°C for 10 min. Amplicons were purified using a QIAquick PCR Purification Kit (Qiagen, Barcelona, Spain), quantified using a NanoDrop ND-1000 spectrophotometer (Nucliber, Madrid, Spain), and then pooled in equal concentrations. Pooled amplicons (2 nM) were then subjected to sequencing using Illumina MiSeq technology in the technical support unit of the Autonomous University of Barcelona (UAB, Spain) following standard Illumina platform protocols.

Sequence analysis. Sequences obtained from the 60 faecal samples after the sequencing step were analysed with QIIME (Quantitative Insights into Microbial Ecology)

1.9.1 (4) using an in-house script that performs upstream and downstream analyses. Low-quality raw sequences with a Phred score of less than 20 were removed from the analysis. Each read was assigned back to its corresponding sample during a demultiplexing step, and the barcodes were removed from the sequences. After filtering, we obtained a total of 2,460,589 high-quality sequences. The USEARCH (ultra-fast sequence analysis) (5) tool was used to cluster similar sequences into operational taxonomic units (OTUs) or taxa based on a 97% similarity level, and the UCHIME (ultra-fast chimeric search) algorithm was used to remove chimeric sequences. From each of the OTUs, one representative sequence was selected and then aligned using PyNAST (Python Nearest Alignment Space Termination tool) against a Greengenes template alignment from the most recent version of the database (gg_13_8). Then, a taxonomical assignment step was performed using the basic local alignment search tool (BLAST) to map each

representative sequence against a combined database encompassing the Greengenes and PATRIC (Pathosystems Resource Integration Center) databases. A phylogenetic tree was constructed using the FastTree programme and an OTU table. To avoid false positive OTUs, we eliminated those that did not represent at least 0.2% of the sequences in at least two samples. The final OTU table was rarefied at 15396 sequence reads per sample. Rarefaction is used to overcome cases in which read counts were not similar between samples.

Quantification of Bifidobacterium. Changes in *Bifidobacterium spp.* abundance were additionally tested by quantitative real-time PCR (qPCR). Aliquots of the extracted genomic DNA were amplified using the following specific primers: Bifgenus_F (5'-TGG CTC AGG ATG AAC GCT G-3'), Bifgenus_R (5'-TGA TAG GAC GCG ACC CCA T-3') and the TaqMan MGB probe (FAM[TM] dye-labelled; 5'-CAT CCG GCA TTA CCA-3'). To calibrate the qPCR reactions, we used calculated amounts of extracted DNA from three isolated *Bifidobacterium* species (*B. breve, B. longum and B. infantis*). Serial dilutions of the pooled DNA were amplified (copy number ranging from 25 to 2.5×10^6) to extrapolate the bifidobacterial number in each sample. The qPCR was performed with the 7500 Fast Real-Time PCR system (Applied Biosystems, Barcelona, Spain) using optical-grade 96-well plates. The PCR reaction was performed in a total volume of 25 µL using the TaqMan Universal PCR Master Mix (Applied Biosystems), containing 300 nM of each primer and 100 nM of the MGB probe. The reaction conditions for the amplification of DNA were 50ºC for 2 min, 95ºC for 10 min, 40 cycles of 95ºC for 15 sec and 60ºC for 1 min. All reactions were performed in triplicate, and the mean values were calculated. The data were analysed using Sequence Detection Software version 1.4, supplied by Applied Biosystems.

Results

Changes in abundance of bifidobacteria were initially assessed by genus-specific qPCR. When comparing treatment to pretreatment, it was found an increase in bifidobacteria in 75% of patients in prebiotic group and 35% of patients in LFD (p=0.022). The mean abundance of bifidobacteria significantly increased during prebiotic administration (from 4.2e8±1.7e8 copies per gram of feces to 9.5e8±3.0e8; p=0.026), while no significant effect of treatment was detected in the LFD group (5.6e8±1.3e8 copies/g pretreatment and 5.7e8±2.1e8 treatment); the change from pretreatment in the prebiotic group was significantly different than the change in the LFD group (p=0.029).

Assessment of bifidobacteria by 16 S sequencing in a definitive analysis confirmed these initial results, showing an increase in bifidobacterium genus sequences in 67% of prebiotic treated patients and in 28% of LFD patients (p=0.038). Median abundance of bifidobacterium genus sequences increased in the prebiotic group from 0.11% [0.00-0.38] to 0.21% [0.02-1.66] but did not reach statistical significance probably due to the large dispersion (p=0.070). The median abundance of bifidobacteria in the LFD group decreased significantly (p=0.047) from 0.15 [0.08-0.53] to 0.04 [0.03-0.09]. The change in the prebiotic group (increase) was significantly different than in the LFD group (decrease; p=0.042) (Figure 1 in main text).

In the LFD group, treatment was associated with a decrease in the relative abundance of unknown Clostridiales and *Bacteroides* species and an increase in the abundance of species belonging to *Ruminococcaceae* (mucin degraders), *Desulphovibronaceae* (sulphate-reducing bacteria) and *Enterobacteriaceae* families (Table panel A). In the post-treatment phase, changes in several bacterial

taxa were detected, including an increase in the abundance of members of the *Bifidobacterium* genus (Table panel A), which were reduced (not significantly) during treatment (Figure 1 in main text). Interestingly, in the LFD group, the increase in gas frequency in the post-treatment phase correlated with the increase in *Bilophila wadsworthia* abundance (r=0.48, p=0.050), and this correlation was absent in the prebiotic group (r=0.07, p=0.796).

In the prebiotic group, the abundance of two *Lachnospiraceae* species, which produce butyrate and other short chain fatty acids, increased during treatment, while the abundance of *Parabacteroides, Oscillospira, Barnesiellaceae, Christensenellaceae* and *Bilophila wadsworthia*, decreased (Table panel B). The decrease in *Bilophila wadsworthia* persisted in the post-treatment phase. Potentially beneficial effects of B-GOS on microbiota include the increase in *Lachnospiraceae* and the decrease in *Bilophila wadsworthia*, a sulphate-reducing bacterium that has been found to play a role in individuals complaining of excess flatus (6) and has been associated with intestinal inflammation in experimental models (7).

Table. Changes in bacterial taxa during and after intervention

Changes during treatment from pre-treatment phase

TAXA	p^1	Trend
Clostridiales; unknown genus; species 324	<0.01	↓
Lachnospiraceae; unknown genus; species 40	<0.02	↑
Ruminococcaceae; unknown genus; species 53	<0.03	↑
Bacteroidales; unknown genus; species 39	<0.03	↑
Ruminococcaceae; unknown genus; species 486	<0.03	↑
Bacteroides; species 293	<0.03	↓
Desulfovibrionaceae; unknown genus; species 508	<0.05	↑
Enterobacteriaceae; unknown genus ;species 217	<0.05	↑

A. LOW FODMAP GROUP

Changes post-treatment from treatment phase

TAXA	p^1	Trend
Streptococcus; species 72	<0.01	↑
Holdemania; species 509	<0.01	↓
Erysipelotrichaceae; genus unknown ;species 27	<0.03	↑
Clostridiales; genus unknown; species 122	<0.03	↓
Barnesiellaceae; genus unknown ;species 314	<0.03	↓
Clostridiales; genus unknown;species 292	<0.03	↓
Clostridiales; genus unknown; species 251	<0.05	↓
Lachnospiraceae; genus unknown;species 558	<0.05	↓
Enterobacteriaceae; genus unknown; species 449	<0.05	↑
Bifidobacterium genus	<0.05	↑

B. PREBIOTIC GROUP

Changes during treatment from pre-treatment phase

TAXA	p^1	Trend
Parabacteroides distasonis	<0.01	↓
Clostridiaceae; genus unknown; species 319	<0.02	↓
Ruminococcaceae ;genus unknown; species 118	<0.02	↑
Lachnospiraceae; genus unknown; species 40	<0.02	↑
Oscillospira; species 52	<0.02	↓
Oscillospira; species 409	<0.03	↓
Lachnospiraceae ;genus unknown; species 783	<0.03	↑
Barnesiellaceae; genus unknown; species 542	<0.05	↓
Christensenellaceae ;genus unknown; species 497	<0.05	↓
Ruminococcus; species 584	<0.05	↓
Bilophila wadsworthia	<0.05	↓

Changes post-treatment from treatment phase

TAXA	p^1	Trend
Lachnospiraceae; genus unknown; species 19	<0.01	↓
Bacteroides; species 119	<0.02	↑
Clostridiales; genus unknown; species 171	<0.02	↓
Peptococcaceae; genus unknown; species 373	<0.03	↓
Veillonellaceae; genus unknown; species 284	<0.03	↑
Lachnospiraceae; genus unknown; species 206	<0.03	↑
Bacteroides; species 124	<0.05	↑
Clostridiales; genus unknown; species 410	<0.05	↓
Ruminococcaceae; genus unknown; species 130	<0.05	↑
Ruminococcaceae; genus unknown; species 592	<0.05	↑
Alphaproteobacteria; genus unknown; species 223	<0.05	↓

[1] Non-parametric repeated measures Friedman test.

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SUPPLEMENTAL DOCUMENT 3. EFFECT OF TREATMENT ON RESPONSES TO CHALLENGE DIET

As in previous studies in patients with functional gut disorders (1), the challenge diet substantially increased anal gas evacuations and symptom scores. In the pretreatment phase, the intensity of symptoms increased similarly in both groups (Figure). The number of daytime gas evacuations increased in the prebiotic and the LFD groups (by 12±4 evacuations and 6±2 evacuations, respectively; p=0.160 between groups; p≤0.005 vs habitual diet for both).

In the treatment phase, the increase in daily symptoms scores produced by the challenge diet was similar to that observed before treatment; hence, since the patients felt better with the treatments, the challenge was better tolerated in terms of absolute symptom scores. The effect was not different between treatments (p=0.148 by MANOVA) (Figure). The increase in the number of gas evacuations in response to the challenge diet was similar to the increase observed during the pretreatment phase in both groups (increase of 12±3 evacuations in the prebiotic group and 7±2 evacuations in the LFD group; p=0.117 between groups; p≤0.002 vs habitual diet for both). In contrast to what we anticipated, the response to the challenge diet was similar with both treatments; conceivably, the challenge was too strong and overcame the potential influences of the treatments, and this was a potential limitation of the study.

Figure
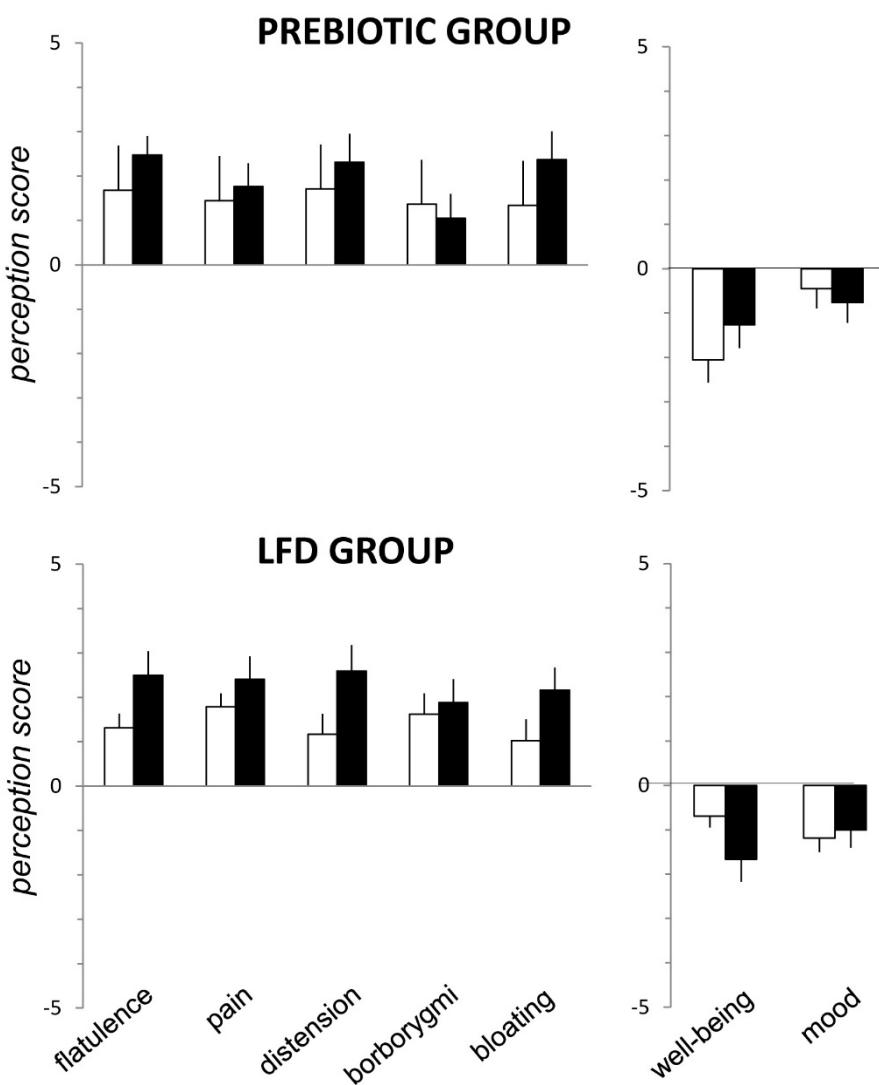
Figure legend

Effect or treatment on the tolerance of the challenge diet. Figure shows changes in symptom scores from before to during challenge diet administered in the pretreatment phase (average score over days 5-7 minus average over days 2-4; white) and in the treatment phase (average score over days 33-35 minus average days 32-34; black); no differences were detected between groups (prebiotic n=19; LFD group n=21; p=0.148 by MANOVA).

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SUPPLEMENTAL DOCUMENT 4. EFFECT OF TREATMENT ON THE VOLUME OF GAS EVACUATED AFTER THE PROBE MEAL

After the probe meal, the total volume of gas evacuated by anus in the 4-hour postprandial period was similar in both groups (149±20 mL in the prebiotic group and 173±22 mL in the LFD group). Participants reported symptoms after the probe meal and the symptoms scores were similar in both groups (Figure).

In both groups, the probe meal produced the same volume of gas in the treatment phase (140±17 mL in prebiotic and 160±29 mL in LFD group) and in the pretreatment phase; hence, the treatments did not affect the volume of gas produced after the probe meal. The tolerance of the probe meal was somewhat better during the treatment phase (Figure) without differences between groups (p=0.570 by MANOVA). This unexpected lack of differences could be related to the study design, because the probe meal was administered after 3 days on the challenge diet, which provided a heavy colonic load and conceivably blurred the effect of treatment. Indeed, intestinal gas production depends on previous fermentable residue loads (1).

Figure

PREBIOTIC GROUP
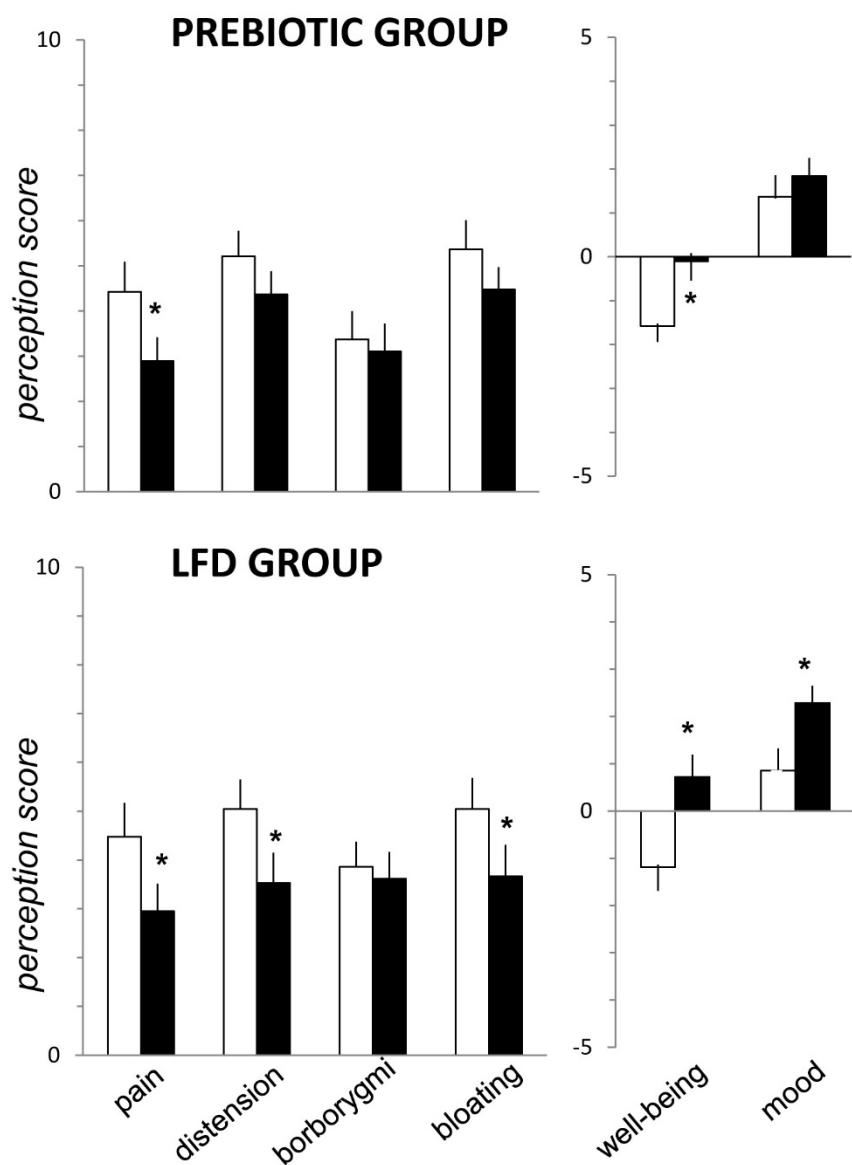
LFD GROUP

* p<0.05 vs pre-treatment phase

Figure legend

Symptoms in response to probe meal in the pre-treatment phase (day 5, white)

and in the treatment phase (day 33, black); no differences were detected between

groups (prebiotic n=19; LFD group n=21; p=0.570 by MANOVA).

Reference

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SUPPLEMENTAL DOCUMENT 5. METABOLOMIC ANALYSIS

Urine samples from 22 patients, 11 from each treatment group, were available for metabolomic analysis. The initial analysis was performed using a fingerprinting approach. Significant differences between both treatments were detected in five integrated regions of the spectrum. These regions were located at 7.911-7.898 ppm, 4.165-4.148 ppm, 2.789-2.786 ppm, 2.003-1.956 ppm, and 1.677-1.662 ppm. Using the Human Metabolome Database (HMDB) (1) and STOCSY (2), only two of these regions were identified as previously described metabolites, xanthine and an unsaturated fatty acid. A partial least squares discriminant analysis (PLS-DA) classification using the five integrated regions that were different between groups showed good discrimination between treatments: All patients were correctly classified according to their treatment (Figure). In addition to the integrated regions, the metabolite 4-deoxythreonic acid, a metabolite previously found to decrease in urine incubated with *E. coli*, was found to have significant weight in the model (3).

Previous studies have shown that a low FODMAP diet modulates histamine levels in urine (4) and that P-cresol, a bacterial protein fermentation metabolite, reflects the influence of diet on amino acid fermentation in the colon (5); however, no significant differences in the concentrations of histamine or P-cresol in urine samples according to treatment or group were detected in our study.

Urine metabolomics was included as an indirect proof of adherence to the dietary instructions; many samples were missing for analysis, but in the subset analyzed, a good discrimination between treatments was observed. These data indicate that the treatments produced different changes in urine metabolites, although the significance of the changes is difficult to ascertain.

Figure
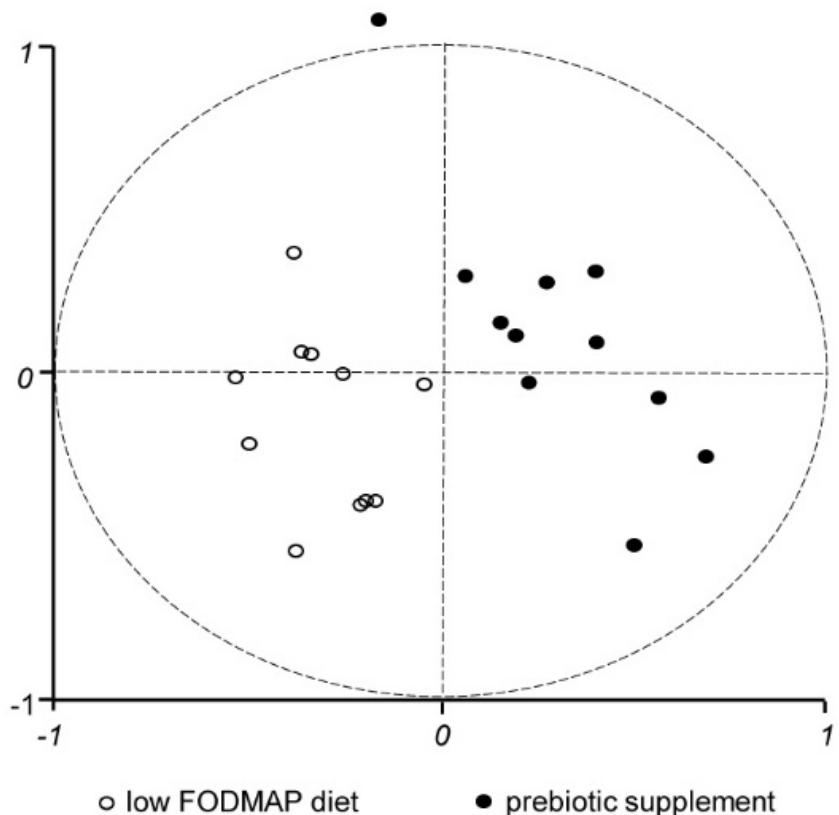
Figure legend

Differential metabolomic response to treatments. Fingerprinting approach detected significant differences between treatments in five regions of the metabolomic spectra. A partial least squares discriminant analysis (PLS-DA) classifier using the five regions showed good discrimination between treatments.

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3.2. Segunda publicación

Título:

Correction of Dyssynergic Defecation, but not Fiber Supplementation, Reduces Symptoms of Functional Dyspepsia in Patients With Constipation in a Randomized Trial.

Autores:

Jose-Walter Huamán, Marianela Mego, Alvaro Bendezú, Hugo Monrroy, Maria-Jose Perez, Sara Samino, Anna Accarino, Esteban Saperas, Fernando Azpiroz.

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Correction of Dyssynergic Defecation, but not Fiber Supplementation, Reduces Symptoms of Functional Dyspepsia in Patients With Constipation in a Randomized Trial

Short title: Dyssynergic defecation in functional dyspepsia

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Conflict of interest: none to declare

Authorship Statement:
Guarantor of the article: Fernando Azpiroz

ABSTRACT

Background & Aims: Patients with functional dyspepsia are believed to have increased sensitivity of the gastrointestinal tract, and some also have functional constipation. We investigated whether in patients with functional dyspepsia, correction of dyssynergic defecation can reduce postprandial fullness.

Methods: We performed a parallel trial at 2 referral centers in Spain, from June 2016 through January 2018 of 50 patients who fulfilled the Rome IV criteria for functional dyspepsia with postprandial distress syndrome and functional constipation and dyssynergic defecation. After a 2-week pretreatment phase, the patients were randomly assigned to groups that learned to correct dyssynergic defecation (2–3 sessions of biofeedback combined with instructions for daily exercise; n=25) or received dietary fiber supplementation (3.5 g plantago ovata per day; n=25) for 4 weeks. The primary outcome was change in postprandial abdominal fullness, measured daily on a scale of 0–10, during the last 7 days treatment phase vs the last 7 days of the pretreatment phase. Anal gas evacuations were measured (by an event marker) during the last 2 days of the pretreatment vs treatment phases.

Results: Biofeedback treatment corrected dyssynergic defecation in 19/25 patients; corrected dyssynergic defection reduced postprandial fullness by 22%±1% in these patients (*P*<.001), and reduced the number of anal evacuations by 21%±8% (*P*=.009). Fiber supplementation did not reduce postprandial fullness or anal evacuations (*P*≤.023 between groups for both parameters in the intent to treat analysis).

Conclusions: Diagnosis and correction of dyssynergic defecation reduces dyspeptic symptoms by more than 20% in patients with functional dyspepsia and

associated constipation. Dietary fiber supplementation does not reduce symptoms in these patients. ClinicalTrials.gov no: NCT02956187

INTRODUCTION

Functional dyspepsia is characterized by symptoms apparently originating from the stomach without detectable cause by conventional diagnostic tests. To define functional dyspepsia, a series of clinical criteria were developed by consensus. In the Rome IV classification, two syndromes of dyspepsia were defined: epigastric pain syndrome and postprandial fullness [1]. The pathophysiology of dyspepsia is largely unknown, but data indicate that dyspeptic patients have increased digestive system sensitivity, so that normally unperceived physiological stimuli induce their symptoms, e.g., bothersome postprandial fullness after meal ingestion. Given the lack of information related to the cause and the mechanisms that produce dyspeptic symptoms, the treatment is largely empirical and of limited efficacy.

A proportion of patients with functional dyspepsia also have functional constipation [2]. In normal conditions, defecation is produced by a coordinated maneuver involving abdominal compression and anal relaxation. Patients with impaired evacuation, specifically those with dyssynergic defecation, have defective anal relaxation during straining. Constipation due to dyssynergic defecation is effectively treated by biofeedback techniques, teaching the patient to correct the defecatory maneuver [3, 4]. On the other hand, fiber supplementation is a conventional treatment of constipation.

We hypothesized that in patients with functional dyspepsia, constipation due to dyssynergic defecation facilitates or triggers dyspeptic symptoms, which, conversely, are alleviated by the correction of dyssynergic defecation. In previous studies, we demonstrated that stimuli applied in the digestive system activate wall receptors linked to sensory pathways that produce conscious sensations [5].

Perception of digestive stimuli depends on the number of receptors activated by a phenomenon of spatial summation, i.e., the extent of the digestive tract to which the stimulus is applied [6]. A stimulus in the gastrointestinal tract sensitizes other segments of the gut and affects the reflex and sensory responses to a second stimulus [7]. It has been previously shown that voluntary suppression of defecation in healthy subjects delays gastric emptying [8], and conceivably could also affect gastric sensitivity. Hence, in patients with functional dyspepsia, the symptoms triggered by meal ingestion may be aggravated by concomitant conditions, such as constipation, affecting other areas of the digestive tract. Our aim was to demonstrate that in these patients, normalizing defecation improves dyspeptic symptoms.

Functional dyspepsia, defined by purely clinical criteria, brings together a diverse group of conditions with different pathophysiologies [1]. As a result, the treatment is empirical and globally inefficient. The purpose of this study was to identify a subset of patients with a common pathophysiological mechanism of dyspeptic symptoms (dyssynergic defecation) who may respond to a targeted mechanistic treatment (correction of defecation).

MATERIAL AND METHODS

Study design

This study was a randomized, parallel and double blind study performed between June 2016 and January 2018 in 2 tertiary care referral centers. The study protocol was registered with ClinicalTrials.gov (NCT02956187). All authors had access to the study data and reviewed and approved the final manuscript. The study compared correction of dyssynergic defecation versus fiber supplementation for the treatment of dyspeptic symptoms in patients with constipation due to impaired

evacuation. The study lasted 6 weeks, with a 2-wk pretreatment phase and a 4-wk treatment phase (Figure 1). The primary outcome was the change in postprandial abdominal fullness in response to treatment measured daily by 0-10 score scales for 7 consecutive days before and during the last week of the treatment phase. Postprandial abdominal fullness, the cardinal symptom in the postprandial distress syndrome, was selected as the primary endpoint, but the effect of treatment on other dyspeptic symptoms was also measured (see below).

Participants

Consecutive patients complaining of symptoms of functional dyspepsia and constipation with impaired evacuation were recruited, as follows. Patients with symptoms of functional dyspepsia after meals (postprandial distress syndrome) and associated constipation underwent anorectal functional testing, and those presenting dyssynergic defecation were offered the opportunity to participate in the study. The following Rome IV criteria were all required for inclusion: a) functional dyspepsia, type postprandial distress syndrome [1]; b) functional constipation [9]; and c) dyssynergic defecation [10], defined as abnormal anorectal evacuation pattern with manometry (less than 20% reduction in the anal pressure during the defecatory maneuver) plus abnormal balloon expulsion test (see Supplemental Material). Anorectal testing was repeated after biofeedback treatment to identify the patients in whom the dyssynergic defecation was corrected (>20% reduction in anal pressure during the defecatory maneuver and normal balloon expulsion test).

Patients gave written informed consent to participate in the study. The protocol for the study had previously been approved by the Institutional Review Board of the University Hospital Vall d´Hebron.

Randomization and masking

Participants were randomized using a block design (n=10 per block) by a computer-generated randomization list. Participants did not know which intervention they were assigned (correction of defecation or fiber supplementation). To allow reliable blinding, the patients were informed that a specific treatment for their overall symptoms was going to be tested, without specifying the two possible types of interventions. Patients were not informed about the results of the manometry performed after biofeedback treatment (whether they had responded or not) until the end of the study.

Dietary instructions

Participants were put on standard high-residue diet during 7-day periods at the end of the pretreatment phase (days 8-14) and the treatment phase (days 36-42). The high-residue diet (28 g fiber daily intake) consisted of: a) *breakfast* of wholemeal cookies (55 g) plus coffee, tea and/or milk, b) *lunch* of white beans (200 g), mixed vegetables (250 g) or chickpeas (200 g) and wholemeal bread (50 g), plus meat, fowl or fish and fruit (pear, apple, orange or cherry), and c) *dinner* of vegetable soup (200 mL) and wholemeal bread (50 g).

During the rest of the study, the participants consumed their habitual diet. For the duration of the study, patients were not allowed to consume any fermented dairy products or any tablets, pills or food supplements containing pre- or probiotics other than those provided.

Interventions

Patients were assigned to correction of defecation and fiber supplementation arms.

Correction of defecation was undertaken by means of the standard biofeedback technique in our laboratory [4]: 2-3 sessions of biofeedback combined with instructions for daily exercising were performed during the treatment phase. Using a manometric technique (see Supplemental Material), intrarectal and anal pressures were recorded and displayed on a monitor within view of the patients. Patients were asked to attempt evacuation and were instructed to try to correct their defective anal relaxation (incomplete relaxation or paradoxical contraction) during straining. The sessions lasted 30-45 min and were performed within the first 3 weeks of the intervention phase.

Fiber supplementation: 3.5 g plantago ovata per day (Plantago ovata, Meda Pharma, Madrid, Spain) was administered during the treatment phase. A follow-up interview to remind and check adherence to study instructions, was performed by the second week of treatment.

Outcomes

The outcomes were measured during 7-day periods at 3 time points throughout the study: a) in the pretreatment phase on the habitual diet (days 1-7), b) in the pretreatment phase during the challenge diet (days 8-14), and c) in the treatment phase during the challenge diet (days 36-42) (Figure 1).

<u>Daily symptom questionnaire</u>

During the 7 days of each evaluation period, the participants were instructed to fill out daily questionnaires (Figure 1) that included 0–10 analogue scales for scoring: a) postprandial abdominal fullness, b) postprandial abdominal distension (sensation of girth increase), c) postprandial abdominal discomfort/pain, d) straining, e) sensation of incomplete evacuation, and f) subjective sensation of flatulence (defined as anal gas evacuation); two additional scales graded from +5 to −5 were used for scoring: g) digestive well-being (from extremely pleasant sensation/satisfaction to extremely unpleasant sensation/dissatisfaction) and h) mood (from very positive to very negative); the questionnaire also recorded; i) the number of bowel movements, and j) stool form using the Bristol scale. For each item, the values for each 7-day period were averaged. This questionnaire has been previously used and has been shown to be sensitive enough to detect the effects of dietary interventions in different populations [11].

<u>Number of anal gas evacuations</u>

The number of anal gas evacuations during the last 2 days of each evaluation period were measured and averaged (Figure 1). Participants were instructed to carry an event marker (Hand Tally Counter No 101, Digi Sport Instruments, Shanggiu, China) during the day and to use it to register each passage of anal gas. Anal gas evacuation was used as an objective marker of the effectivity of the challenge diet in the pretreatment phase and of the potential effect treatment under these conditions. This method has been previously used with reproducible and consistent results [11, 12]; furthermore, studies measuring the number of gas evacuations by an event marker and continuously recording anal gas evacuations

have shown a very good correlation between the results of the two methods (R>0.95; p<0.05) [13].

Colonic content

Colonic content was measured by abdominal magnetic resonance imaging in the pretreatment and treatment phases both on the challenge diet to check the potential effect of the interventions on colonic biomass (see Supplemental Material).

Statistical analysis

Sample size calculation. Based on previous data on the variability of abdominal fullness/bloating sensation in patients with functional gut disorders [12], it was calculated that a sample size of 15 subjects per group would allow the detection of a 40% difference in the effect of treatment between groups (correction of dyssynergic defecation versus fiber supplementation) with 80% power and 5% significant thresholds. Estimating that biofeedback would correct dyssynergic defecation in 66% of the patients [4, 14], 50 patients were included in the study.

Statistical analysis was performed using the Stata Software for Windows, (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

The means or grand means (±SE) of the variables measured during each evaluation period were calculated for each group. The Kolmogorov-Smirnov test was used to check the normality of the data distribution. Parametric normally distributed data were compared by Student's *t*-test for paired or unpaired data; otherwise, the Wilcoxon signed-rank test was used for paired data, and the Mann-Whitney *U* test was used for unpaired data. The association of parameters was

analyzed using linear regression. The effects of treatment (treatment minus pretreatment values) were compared between groups by intention to treat (ITT) analysis.

Differences were considered significant at a p value <0.05.

RESULTS

Demographics and clinical presentation

Fifty patients were included in the study (Figure 2 and Table 1). No differences in the demographic data and anorectal function were found between groups (Table 1). During the first evaluation period, i.e., before treatment on their habitual diet, patients reported: a) postprandial abdominal fullness, b) postprandial abdominal distension, c) postprandial abdominal discomfort/pain, d) straining, e) sensation of incomplete evacuation and f) flatulence. All exhibited abnormal evacuation patterns with manometry (dyssynergic defecation) and impaired balloon expulsion test. No differences between study groups were detected in these parameters, the number of bowel movements or stool form (Table 1).

Effect of the standard high-residue diet during the pretreatment phase

As compared to the evaluation of the patients on their habitual diet, the high-residue diet increased the number of anal gas evacuations (from 13±1 to 17±1 daytime evacuations; p<0.001). This objective effect was associated with an increase in the subjective sensation of flatulence (from 4.0±0.2 score to 4.7±0.3 score; p=0.006). No changes in the rest of the measured parameters were detected, except for a trend towards an increase in the number of bowel movements (from

4.9±0.3 to 5.4±0.3 bowel movements per week; p=0.072). No differences between groups were detected.

Correction of dyssynergic defecation by biofeedback

Anorectal testing after biofeedback treatment showed that dyssynergic defecation was effectively corrected in 19 patients and it was not corrected in 4 patients; 2 patients discontinued their participation in the study (Figure 2). The 19 patients who responded exhibited improved anal relaxation (from 56±7% pressure increase, i.e., paradoxical contraction, before treatment to 51±4% decrease, i.e., relaxation, after treatment; p<0.001) and a reduction of straining (from 71±7 mmHg before to 50±6 mmHg after treatment; p=0.028). In the 4 patients who did not respond, no changes were observed in either anal relaxation (21±7% paradoxical contraction before and 13±8% contraction after treatment; p=0.443) or straining (73±9 mmHg before and 78±8 mmHg after treatment; p=0.182).

Effect of treatment

Effect on symptoms

In the patients who responded to biofeedback treatment and corrected dyssynergic defecation, the sensation of straining, incomplete evacuation and stool frequency improved, whereas fiber supplementation had no effects, and the differences between groups were statistically significant for straining (p=0.025) and for incomplete evacuation (p=0.004) by ITT analysis (Figure 3). No differences in stool consistency were detected within or between groups.

The correction of dyssynergic defecation was associated with a significant improvement of dyspeptic symptoms (postprandial fullness, postprandial distension

and postprandial discomfort/pain), flatulence, digestive well-being and mood, whereas fiber supplementation had no effect. The effects of treatment were significantly different between groups for postprandial fullness (p=0.003), distension (p=0.003), discomfort/pain (p=0.015), flatulence (p=0.004) and mood (p=0.036), and borderline for well-being (p=0.058) by ITT analysis (Figures 3 and 4).

Anal gas evacuation

Correction of dyssynergic defecation decreased the number of anal gas evacuations (p=0.009 vs before correction; i.e., prevented the increase produced by the challenge diet), whereas fiber supplementation did not, and the difference between treatments was statistically significant by ITT analysis (p=0.023; Figure 3).

Colonic content

No consistent effects of treatment on colonic content were detected within or between groups (see Supplemental Material). However, after correction of dyssynergic defecation, some correlations between colonic content and symptoms were detected: less volume of colonic content was associated with lower scores of postprandial fullness (R=0.58; p=0.014), straining (R=0.69; p=0.002) and incomplete evacuation (R=0.53; p=0.028), and with higher scores of digestive well-being (R=-0.48; p=0.049). No correlations were found during fiber administration.

DISCUSSION

Our study shows that in patients with functional dyspepsia and dyssynergic defecation, correction of defecation produces a significant relief of dyspepsia. These

data support our hypothesis and indicate that meal-related symptoms of functional dyspepsia are aggravated by concomitant constipation.

Several considerations have to be addressed in relation to this association. We recruited patients whose predominant complaints were related to functional dyspepsia, specifically, symptoms associated with meal ingestion, referred to the upper abdomen and not alleviated by defecation; the cardinal symptom was bothersome postprandial fullness associated with or without postprandial distension and postprandial discomfort/pain. Patients were also required to fulfil criteria of constipation; however, constipation was not the predominant complaint and was not severe. Indeed, it was manifested by a sensation of straining and incomplete evacuation, without derangement of bowel habit. All patients were required to exhibit a dyssynergic defecation; in fact, they exhibited a paradoxical anal contraction during attempted defecation, excessive straining and impaired balloon expulsion test. Hence, our patients had a florid syndrome of functional dyspepsia associated with objective dyssynergic defecation, manifested by symptoms of defecatory dysfunction fulfilling criteria of functional constipation, but with minor impact on bowel habit.

In this proof-of-concept-study, we focused on a pathophysiological mechanism, i.e., dyssynergic defecation, and to test our hypothesis we compared dyspeptic symptoms in the same patients before and after effective correction of defecation. We acknowledge that biofeedback may involve a "health care attention" bias, and after having proved the concept, this would justify a trial to compare the efficacy of different treatment modalities, e.g., biofeedback versus a more effective treatment option as comparator. Indeed, the amount of fiber in the control group was relatively small and in fact did not produce an overload worsening the symptoms.

The effectivity of biofeedback techniques for the treatment of dyssynergic defecation was similar to that previously reported [14]. Furthermore, it has been shown that biofeedback improves constipation, as in our study, and may also improve concomitant symptoms of IBS [15]. The benefit of correction of dyssynergic defecation on both IBS and functional dyspepsia may be explained by the commonality of pathophysiological mechanisms, such as visceral hypersensitivity and reduced tolerance of intraluminal stimuli. Dyssynergic defecation may also coexist with delayed gastric emptying [16], but the effect of biofeedback on this condition has not been investigated. We acknowledge that the study period was short and precluded long-term observations, but previous studies indicate that the benefits of biofeedback both on anal function and symptoms are durable [14, 17], and this could also apply to the improvement of dyspeptic symptoms.

Obviously, the benefits observed in our study are confined to the subgroup of dyspeptic patients with dyssynergic defecation, and hence, the relevance of our findings depend on how common this association is. A large study using Rome IV diagnostic questionnaires found that 39% of patients with diagnosis of functional dyspepsia also fulfilled criteria of functional constipation [2], and this would suggest that a substantial proportion of patients with functional dyspepsia have dyssynergic defecation and symptom of impaired defecation. A stated in the Introduction, the underlying hypothesis of this study is that the heterogeneity of functional dyspepsia makes empirical treatments globally ineffective, and following-up our results, it could be speculated that uncorrected dyssynergia may be an obstacle to effective treatment of dyspepsia.

Our data may have relevant practical implications, particularly considering the putative frequency of this clinical condition [2]. A key issue not resolved yet is how

to identify among patients with functional dyspepsia those who also have dyssynergic defecation. A plausible option seems to enquire about symptoms of impaired defecation, even if not spontaneously volunteered because patients may ignore these complaints when consulting for dyspepsia. If defecatory symptoms are present, anorectal testing may be performed; however, the predictive value, both in terms of sensitivity and specificity, of these symptoms with regard of anorectal dyssynergia is uncertain, which implies that patients with asymptomatic dyssynergia will be missed, while some dispensable testing will be performed. Our proof-of-concept study shows that correcting dyssynergia improves dyspeptic symptoms, but the intention to treat analysis further shows a significant benefit of referring patients with functional dyspepsia and dyssynergic defecation to anorectal biofeedback.

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Table 1. Demographics and clinical data before treatment

	STUDY GROUPS		
	Correction of defecation (n=25)	Fiber supplement (n=25)	p value
Demographic data			
- age (range), years	39 (20-73)	42 (19-69)	0.494
- sex, M/F	3/22	4/21	0.291
- symptom duration, years	2.3±0.2	2.1±0.2	0.441
- bowel habit, No./wk	4.5±0.4	5.3±0.5	0.237
- stool form, Bristol score	2.9±0.2	3.3±0.2	0.214
Symptoms, score*			
- postprandial bloating	5.2±0.4	5.5±0.3	0.500
- postprandial distension	5.4±0.3	5.4±0.4	0.963
- discomfort/pain	4.3±0.4	4.3±0.4	0.944
- flatulence	4.3±0.3	3.7±0.4	0.264
- straining	4.9±0.5	5.3±0.4	0.575
- incomplete evacuation	5.9±0.4	4.9±0.4	0.118
Defecation by manometry			
- abdominal compression, mmHg	71±5	69±8	0.844
- anal pressure change, %	49±6[+]	59±12[+]	0.432

* daily measurements on 0-10 scales averaged over 7 days in the pretreatment phase on their habitual diet; [+] paradoxical contraction

FIGURE LEGENDS

Figure 1.   Experimental design.
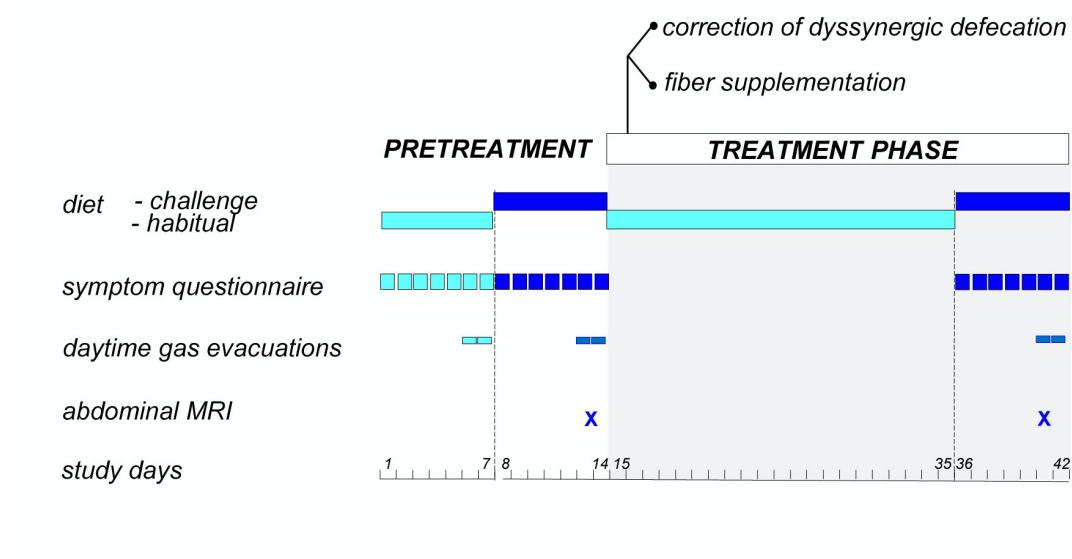
Figure 2.   Flow chart.
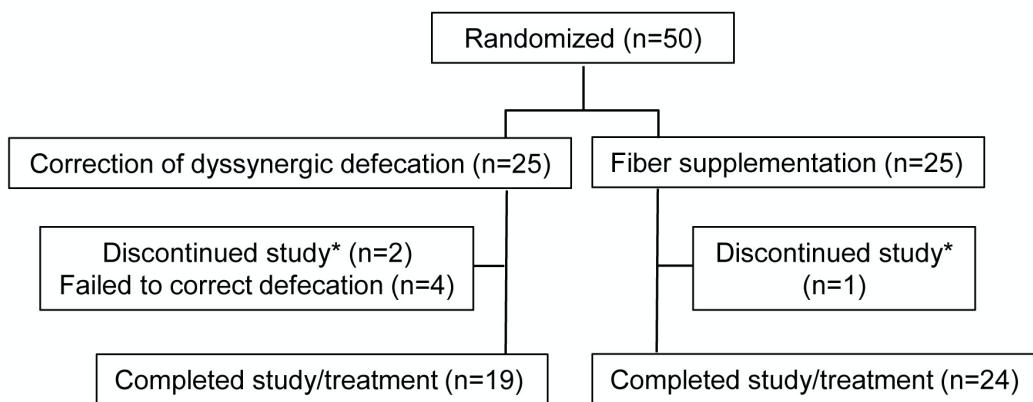
Figure 3. Effect of treatment on symptoms of constipation and gas evacuation. Correction of dyssynergic defecation (n=19) was associated with improved sensation of straining, incomplete evacuation and flatulence with reduced number of anal gas evacuations and increased stool frequency, whereas fiber supplementation (n=24) had no effects. By intention to treat analysis the effects of treatment were significantly different between groups for straining (p=0.025), incomplete evacuation (p=0.004) and flatulence (p=0.004). Figure shows data by intention to treat analysis.

BIOFEEDBACK TREATMENT
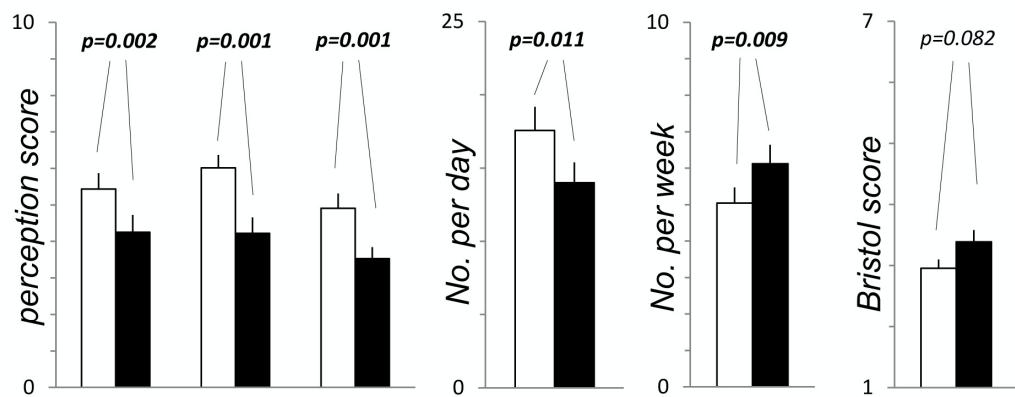
FIBER SUPLEMENTATION
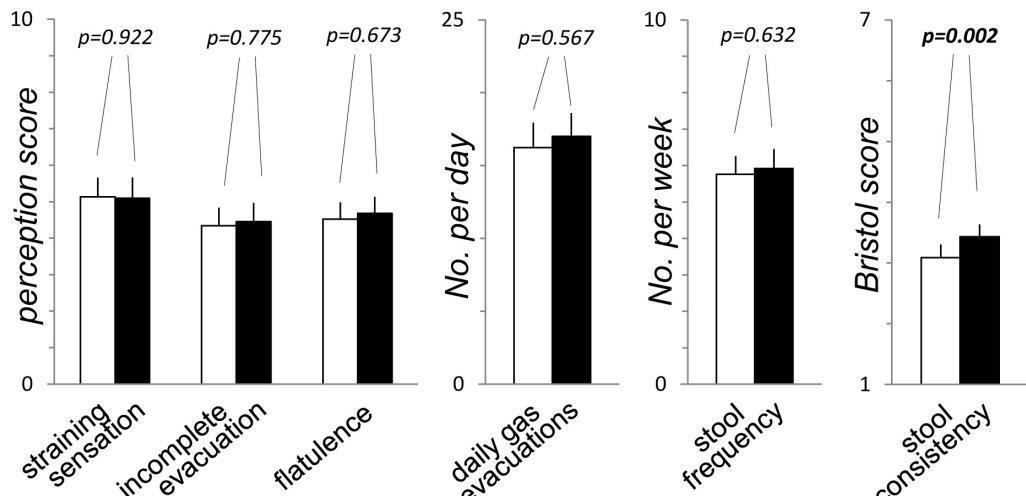
☐ pretreatment   ■ treatment phase

Figure 4. Effect of treatment on symptoms of dyspepsia and hedonic domain. Correction of dyssynergic defecation (n=19) was associated with a significant improvement of dyspeptic symptoms (postprandial fullness, postprandial distension and postprandial discomfort/pain), digestive well-being and mood, whereas fiber supplementation (n=24) had no effects. By intention to treat analysis the effects of treatment were significantly different between groups for postprandial fullness (p=0.003), distension (p=0.003), discomfort/pain (p=0.015) and mood (p=0.036), and borderline for well-being (p=0.058). Figure shows data by intention to treat analysis.

SUPPLEMENTAL MATERIAL

1. Evaluation of defecation

The pattern of defecation was measured with a manometric technique using a 5 lumen polyvinyl catheter (4.8 mm outside diameter, ARM[®,] Arndorfer, Wisconsin, USA) with 4 manometric ports 1 cm apart and a distal tip latex balloon located 5 mm from the distal port [1, 2]. With the manometric ports located in the anal canal and the balloon inflated with 25 mL air in the rectum, patients were asked to attempt defecation; normally, the abdominal compression during straining (intrarectal pressure increment) is associated with anal relaxation (anal pressure drop). Both the abdominal compression and the change in anal pressure during straining were measured. Following the inclusion criteria, all patients required an impaired (<20%) anal relaxation during straining and abnormal balloon expulsion test. Expulsion capacity was measured by a balloon expulsion test following the standard procedure in our laboratory; abnormal evacuation was defined as inability to evacuate a 10 mL water-filled rectal balloon in 3 attempts.

2. Colonic content measurement

MR imaging examinations of the colon were performed in the pretreatment and treatment phases (both on the challenge diet) using a 1.5-T MR imaging system (Aera; Siemens Healthcare, Erlangen, Germany) with two six-channel phased-array abdominal coils to cover the whole abdomen. The abdomen was imaged obtaining a T2-weighted HASTE sequence in the coronal plane (1400 ms repetition time, 90 ms echo time, 3.5 mm slice thickness, 180º flip angle, and 256x256 matrix resolution) during two apneas of 20 s each and a T1-weighted VIBE Fat-Sat sequence in the coronal plane (3.71 ms repetition time, 1.66 ms echo time, 1.5 mm

slice thickness, 10º flip angle and 320x189 matrix resolution) in one apnea of 12 s. No drugs or contrast were used.

Analysis of the images was made using an original software developed for this purpose [3]. The program allows semiautomatic segmentation of the colon on the images using a region-growing-based algorithm. First, an anisotropic contrast enhancement filter is applied to enhance the boundary of the colon without loss of inside detail. Then, seed points are placed that expand depending on the gray-level mapping defined by the window-level setting of the images. To facilitate colonic segmentation, a toolkit was developed that permits enlarging or reducing the segmentation obtained by the region-growing algorithm. Colonic segmentation was correlated in T2 and T1 images. Nongaseous colonic content was measured in T1 colonic images, and gaseous colonic content was measured by subtracting T1 from T2 colonic volumes. A three-dimensional reconstruction program with 360º rotation over the three dimensions was used to facilitate measurement of volumes in selected regions of the colon [4].

No consistent effects of treatment on colonic content were detected within or between groups (corrected defecation n=18, fiber supplementation n=22), and this could be related to the residue overload in the challenge diet that blurred the potential influence of the treatments.

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4. RESUMEN GLOBAL DE LOS RESULTADOS

En el primer estudio titulado **"Effects of Prebiotics vs a Diet Low in FODMAP in Patients With Functional Gut Disorders",** donde comparamos el efecto de un suplemento prebiótico (2.8 g por día de Bimuno, que contiene 1.37 g de beta-galactooligosacárido [B-GOS] más una dieta placebo (tipo mediterránea) **(grupo prebiótico)** versus suplemento placebo (2.8 g de xilosa) más una dieta baja en FODMAP **(grupo dieta baja en FODMAP)**, tuvo el siguiente diseño:
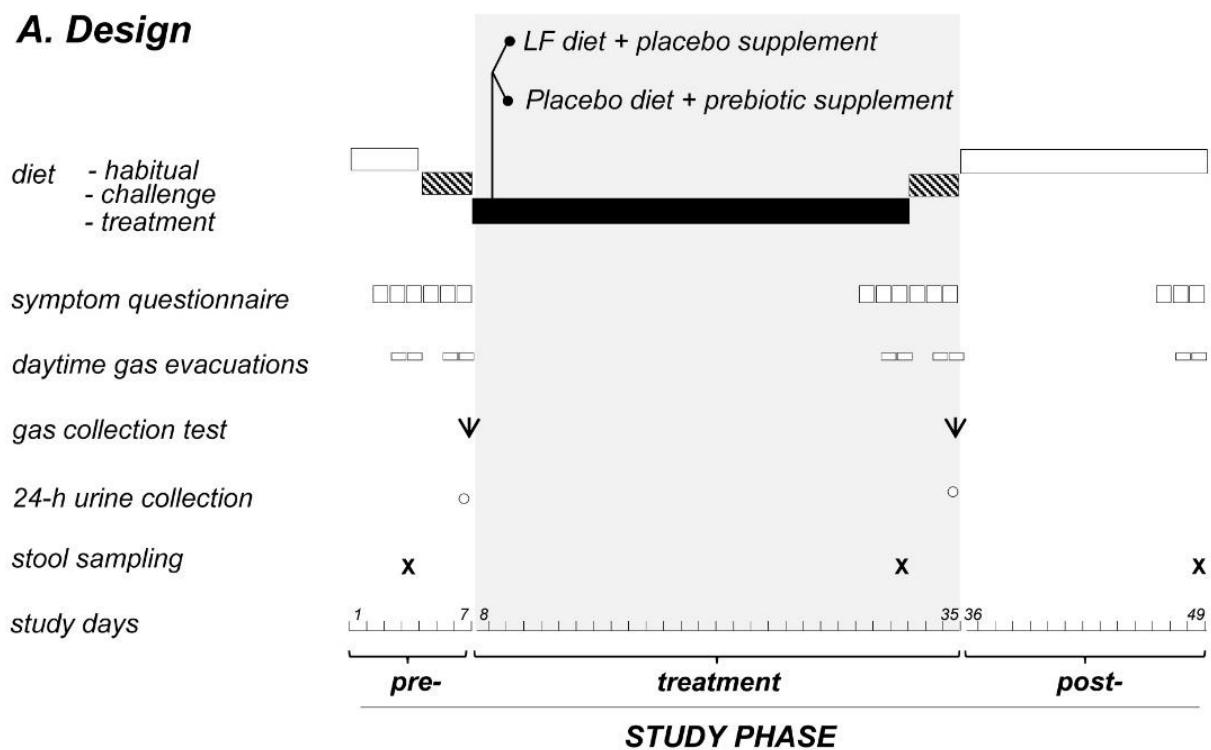
Fueron seleccionados e incluidos 44 pacientes que tenían diagnóstico de trastornos funcionales intestinales según criterios de Roma III. No hubo diferencias clínicas ni demográficas entre ambos grupos.

Table 1. Demographics and clinical data

	STUDY GROUPS		
	Prebiotic (n=24)	Low FODMAPs (n=21)	p value
- Age (range), years	43 (24-73)	48 (26-69)	0.309
- Sex, M/F	2/17	3/18	1
- Diagnosis, IBS-a/IBS-d/FAP	9/5/5	9/5/7	0.889
- Bowel habit, No./wk	6.1±0.8	5.9±0.7	0.679
- Stool form, Bristol score	4.9±1.0	4.8±1.0	0.797
- Symptom duration, years	4.7±1.8	4.4±1.5	0.694
- Flatulence, score*	5.2±3.0	5.3±2.3	0.976
- Abdominal bloating*	5.4±2.4	5.9±2.2	0.474
- Abdominal distension*	5.7±2.2	6.3±2.2	0.374
- Borborigmi*	3.1±2.3	3.8±2.5	0.348
- Discomfort/pain, score*	4.7±1.8	4.8±2.9	0.975

FAP, functional abdominal pain; * average of daily measurements over 3-day pre-treatment evaluation period

Los resultados fueron que ambos tratamientos inducen efectos diferentes en la microbiota con la relación a la abundancia de secuencia de genes de *Bifidobacterium* (incrementa con prebióticos y disminuye con la dieta baja en FODMAP; P = .042), y *Bilophila wadsworthia* (disminuye con prebiótico e incrementa con dieta baja en FODMAP; P = .50).
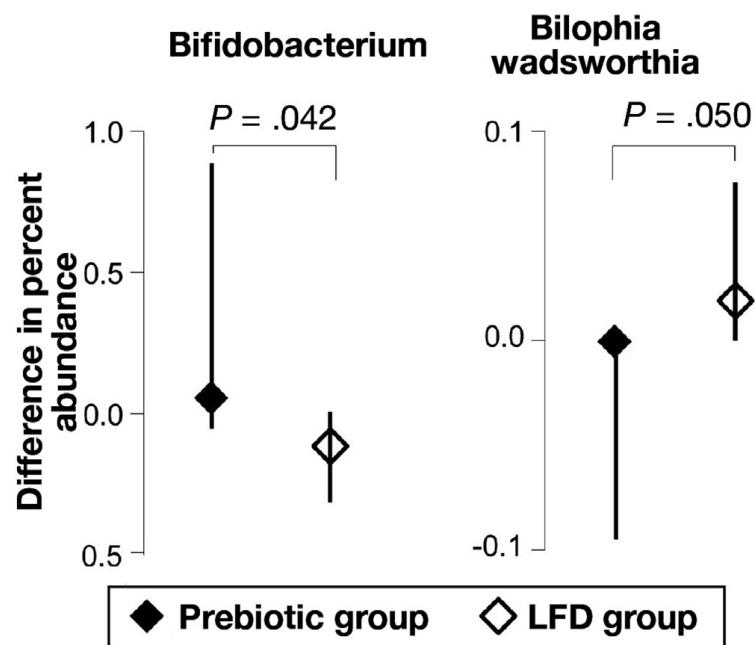
En ambos tratamientos, por 4 semanas, los pacientes presentaron una mejoría en los score de síntomas, esta reducción fue estadísticamente significativa para todos los síntomas excepto para la flatulencias y borborigmos en le grupo prebiótico. Sin embargo, ambas estrategias tuvieron consecuencias después de descontinuar el tratamiento. Aunque la mejoría de los síntomas persistió 2 semanas después de la administración del prebiótico, los síntomas empeoraron después de descontinuar la dieta baja en FODMAP.

Síntomas digestivos
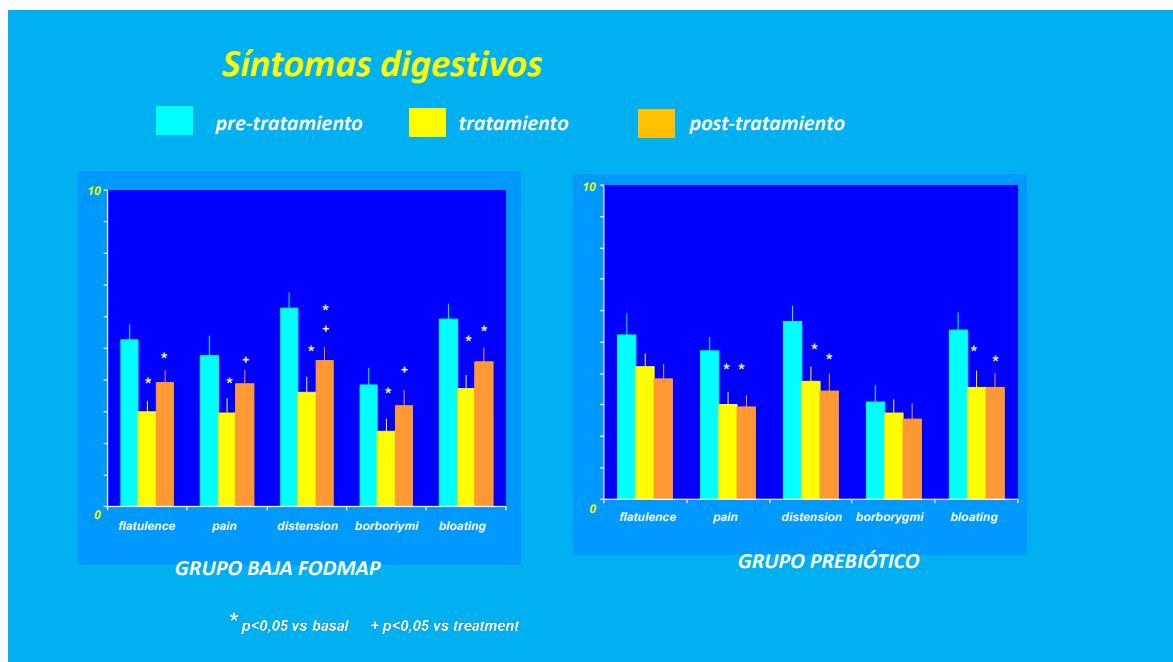
Ambos tratamientos redujeron el número de evacuaciones de gas anal, el efecto fue más pronunciado (y estadísticamente significativo; P < .001) en le grupo de dieta baja en FODMAP, pero sin diferencia entre grupos (P= .991). Después del tratamiento del grupo prebiótico, el número de evacuaciones de gas anal fue mantenido, mientras que hubo un incremento (no significativo) después de descontinuar la dieta baja en FODMAP.

Número de evacuaciones de gas anal

GRUPO BAJA FODMAP · GRUPO PREBIÓTICO
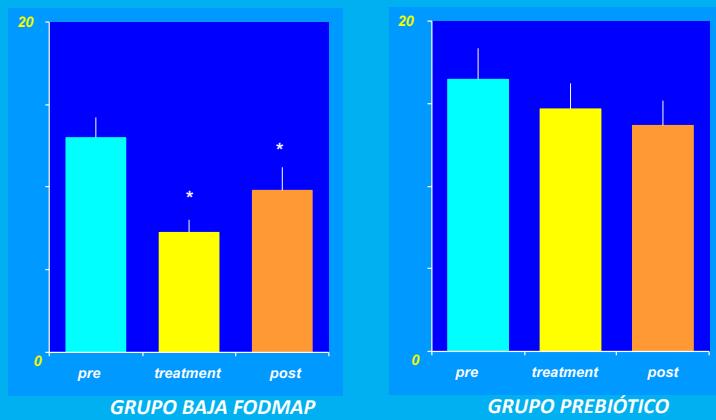
* p<0.05 vs pre-treatment

En el segundo estudio titulado: **Correction of Dyssynergic Defecation Reduces Symptoms of Functional Dyspepsia in Patients With Constipation in a Randomized Trial**, donde comparamos el efecto de corregir la disinergia defecatoria (biofeedback anorrectal) versus un suplemento de fibra (3.5 g de plantago de ovata por día) en pacientes que cumplan criterios de Roma IV para: a) dispepsia funcional tipo distrés postpradial, b) estreñimiento funcional y c) disinergia defecatoria, tuvo el siguiente diseño:
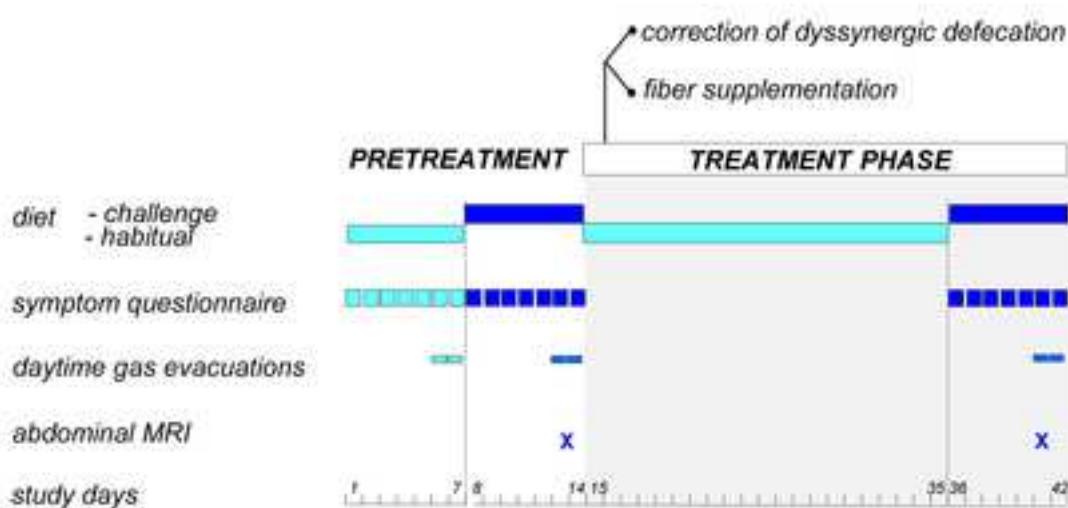
Fueron incluidos 50 pacientes en el estudio, no se encontraron diferencias en los datos demográfico ni en la función anorrectal entre ambos grupos. Durante el periodo de evaluación antes del tratamiento y con su dieta habitual los pacientes reportaron síntomas como: distensión abdominal postprandial, plenitud postprandial, dolor abdominal postprandial, esfuerzo defecatorio, sensación de evacuación incompleta y flatulencias, no se encontraron diferencias entre ambos grupos en los parámetros anteriores.

Table 1. Demographics and clinical data before treatment

	STUDY GROUPS		
	Correction of defecation (n=25)	Fiber supplement (n=25)	p value
Demographic data			
- age (range), years	39 (20-73)	42 (19-69)	0.494
- sex, M/F	3/22	4/21	0.291
- symptom duration, years	2.3±0.2	2.1±0.2	0.441
- bowel habit, No./wk	4.5±0.4	5.3±0.5	0.237
- stool form, Bristol score	2.9±0.2	3.3±0.2	0.214
Symptoms, score*			
- postprandial bloating	5.2±0.4	5.5±0.3	0.500
- postprandial distension	5.4±0.3	5.4±0.4	0.963
- discomfort/pain	4.3±0.4	4.3±0.4	0.944
- flatulence	4.3±0.3	3.7±0.4	0.264
- straining	4.9±0.5	5.3±0.4	0.575
- incomplete evacuation	5.9±0.4	4.9±0.4	0.118
Defecation by manometry			
- abdominal compression, mmHg	71±5	69±8	0.844
- anal pressure change, %	49±6[+]	59±12[+]	0.432

* daily measurements on 0-10 scales averaged over 7 days in the pretreatment phase on their habitual diet; [+] paradoxical contraction

Los resultados fueron que la corrección de la disinergia defecatoria estuvo asociado con una mejora en los síntomas dispépticos (22%; P < .001) y esta mejora subjetiva estuvo asociado con una reducción objetiva en le número de evacuaciones de gas anal (21%; P = .009); ninguno de estos efectos se observó en el grupo que recibió suplementos de fibra.

En esta figura se muestra el efecto del tratamiento sobre los síntomas de estreñimiento y evacuación de gases. La *corrección de la disinergia defecatoria* (n = 19) se asoció con una mejoría del esfuerzo defecatorio, evacuación incompleta y flatulencia con una reducción en el número evacuaciones de gases por el ano y un incremento en el número de deposiciones por semana, mientras que en el *suplemento con fibra* (n = 24) no tuvo efectos. El análisis por intención de tratar, los efectos del tratamiento fueron significativamente diferentes entre los grupos en el esfuerzo defecatorio (p = 0.025), evacuación incompleta (p = 0.004) y flatulencia (p = 0.004). La figura muestra el análisis de los datos por intención de tratar.
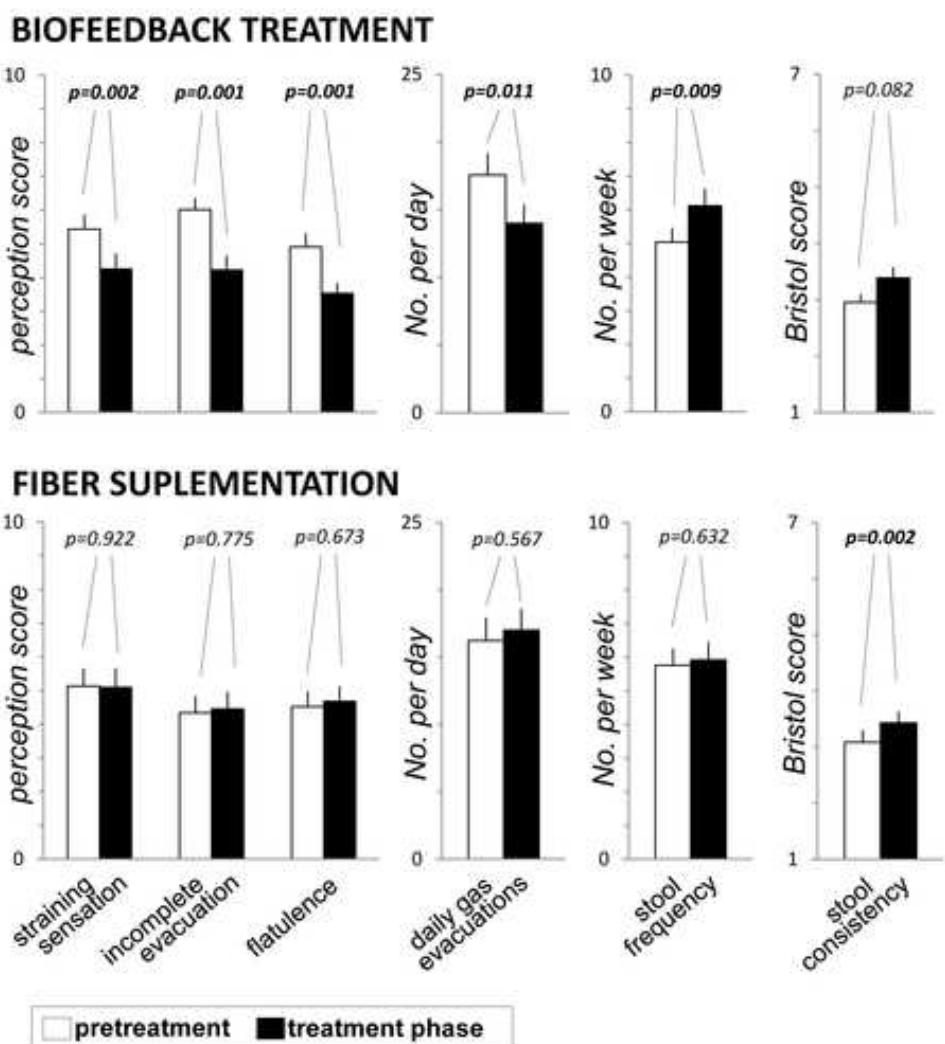
En esta figura se muestra el efecto del tratamiento sobre los síntomas de dispépticos. La *corrección de la disinergia defecatoria* (n = 19) se asoció con una mejora significativa de los síntomas dispépticos (plenitud posprandial, distensión posprandial y malestar / dolor posprandial), bienestar digestivo y estado de ánimo, mientras que *el suplemento con fibra* (n = 24) no tuvo efectos. El análisis por intención de tratar, los efectos del tratamiento fueron significativamente diferentes entre los grupos para la plenitud posprandial (p = 0.003), distensión (p = 0.003), malestar / dolor (p = 0.015) y estado de ánimo (p = 0.036), y límite para el bienestar digestivo (p = 0.058). La figura muestra el análisis de los datos por intención de tratar.
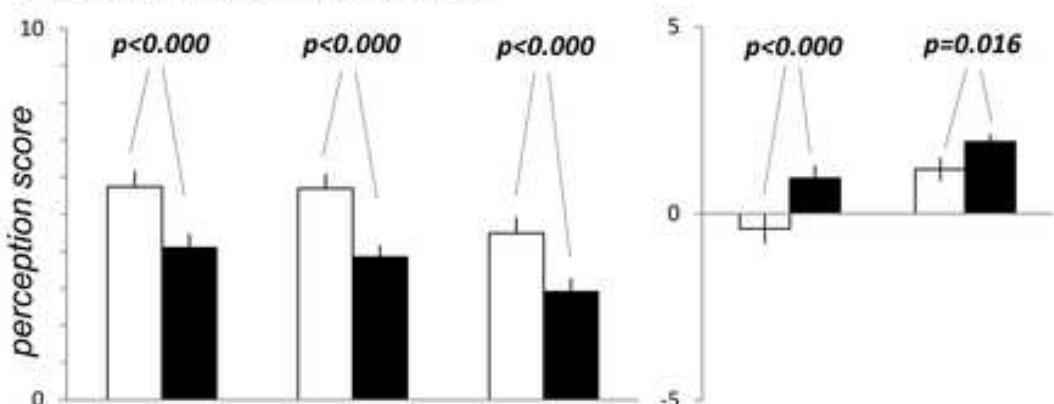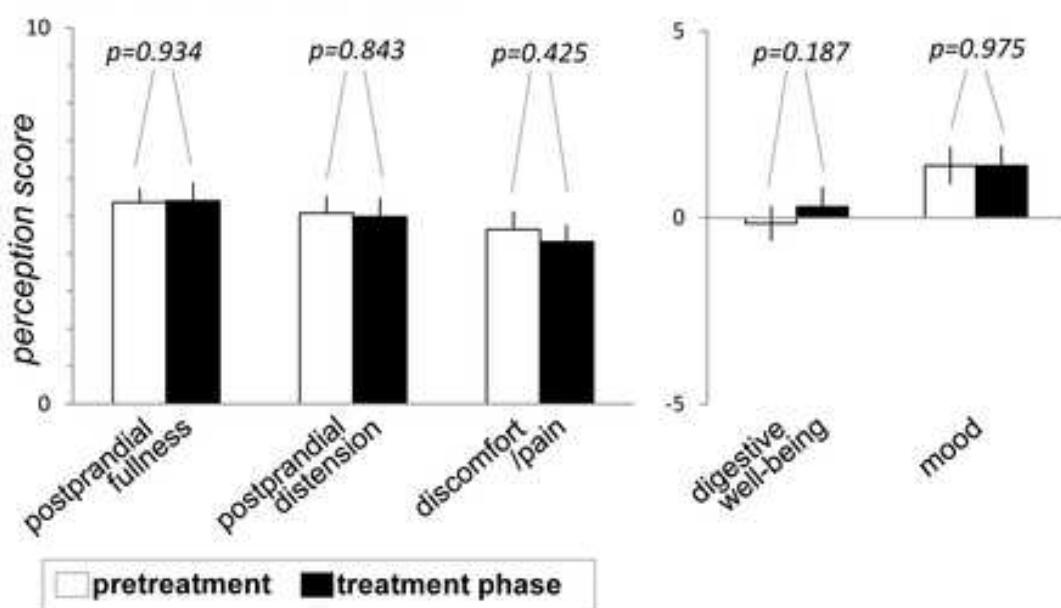
5. RESUMEN GLOBAL DE LA DISCUSIÓN

Los trabajos que componen esta tesis doctoral están enfocados al estudio de la relación entre la dieta, función y síntomas digestivos.

En nuestro primer trabajo, mostramos que ambos tratamientos: la dieta baja en FODMAP y el prebiótico B-GOS (2,8 g al día de Bimuno, Clasado Biosciences, Jersey, Channel Islands) tuvieron una efectividad similar en el tratamiento de los síntomas relacionados con el gas en pacientes con trastornos intestinales funcionales (síndrome de intestino irritable y distensión abdominal funcional). Sin embargo, ambas estrategias tuvieron diferentes consecuencias después de descontinuar el tratamiento. Mientras que la mejora de los síntomas persistió 2 semanas después de terminar la administración del prebiótico, los síntomas empeoraran después de descontinuar la dieta baja en FODMAP.

Efecto de la dieta baja en FODMAP en los síntomas - mecanismos

La respuesta clínica asociada con la dieta baja en FODMAP en nuestro estudio es similar a estudios previos reportados(196,200,219). La dieta baja en FODMAP reduce la producción de gas, y posiblemente este efecto contribuyó a la mejora de los síntomas relacionados con el gas. Las dietas bajas en residuos están asociadas con un menor volumen de contenido colónico(127), y posiblemente este es el caso con la dieta baja en FODMAP. La sobrecarga intestinal de FODMAP ha mostrado incrementar el volumen de contenido dentro del intestino delgado(220), pero aún no se ha comprobado si el contenido intestinal en una dieta baja en FODMAP es menor que una dieta normal sin exceso de FODMAP.

Efecto del prebiótico B-GOS en los síntomas - mecanismos

La mejora en los síntomas relacionados con el gas debido a la suplementación con el prebiótico B-GOS en nuestro estudio es consistente con observaciones anteriores(221). Sin embargo, los mecanismos por los cuales el B-GOS mejora los síntomas no están claros. Como se sabe el prebiótico B-GOS, es un producto no absorbible y fermentable; en consecuencia, sirve como sustrato para la microbiota colónica y al inicio de su administración aumenta la producción de gas intestinal. Sin embargo, la administración continua de b-GOS provoca un fenómeno de adaptación, lo que resulta en una disminución progresiva en la producción de gas a los niveles pre-administración después de 2 semanas de tratamiento(212,213) y un cambio en el perfil de la microbiota intestinal(212,221), que probablemente sea la causa de la adaptación. Además, B-GOS ha mostrado efectos

antiinflamatorios y también podría reducir la hipersensibilidad visceral, una característica en pacientes con trastornos funcionales digestivos que los lleva a presentar síntomas en respuesta a contenidos intestinales normales(78,222). No se sabe si los efectos de la administración de B-GOS sobre los síntomas y la microbiota son específicos de este producto o son comunes a otros prebióticos.

La mejoría de los síntomas persistió 2 semanas después de terminar la administración de B-GOS. Este efecto posterior probablemente esté relacionado con los cambios en la microbiota, y actualmente no tenemos datos que indiquen cuanto tiempo puede persistir. Al contrario, los síntomas empeoraron a las 2 semanas de haber interrumpido la dieta baja en FODMAP, lo que refleja el cese del efecto en el ambiente intraluminal de la dieta baja en FODMAP cuando se sustituye por la dieta habitual de los pacientes.

Efectos de la dieta baja en FODMAP y el prebiótico B-GOS en la composición de la microbiota.

Los efectos beneficiosos potenciales de B-GOS en la microbiota incluyen el aumento de *Lachnospiraceae*, que produce butirato y otros grasos de cadena corta, y la disminución de *Bilophila wadsworthia*, una bacteria reductora de sulfatos que se ha encontrado que desempeña un papel en individuos que se quejan de flatulencias excesivas(125) y se ha asociado con inflamación intestinal en modelos experimentales(173). Los cambios en la microbiota inducidos por la dieta baja en FODMAP fueron totalmente diferentes a los inducidos por B-GOS, sobretodo en relación a la abundancia de bifidobacterias (disminuyó con la dieta baja en FODMAP y aumento con B-GOS) y *Bilophila wadsworthia* (aumentó con la dieta baja en FODMAP y disminuyó con B-GOS).
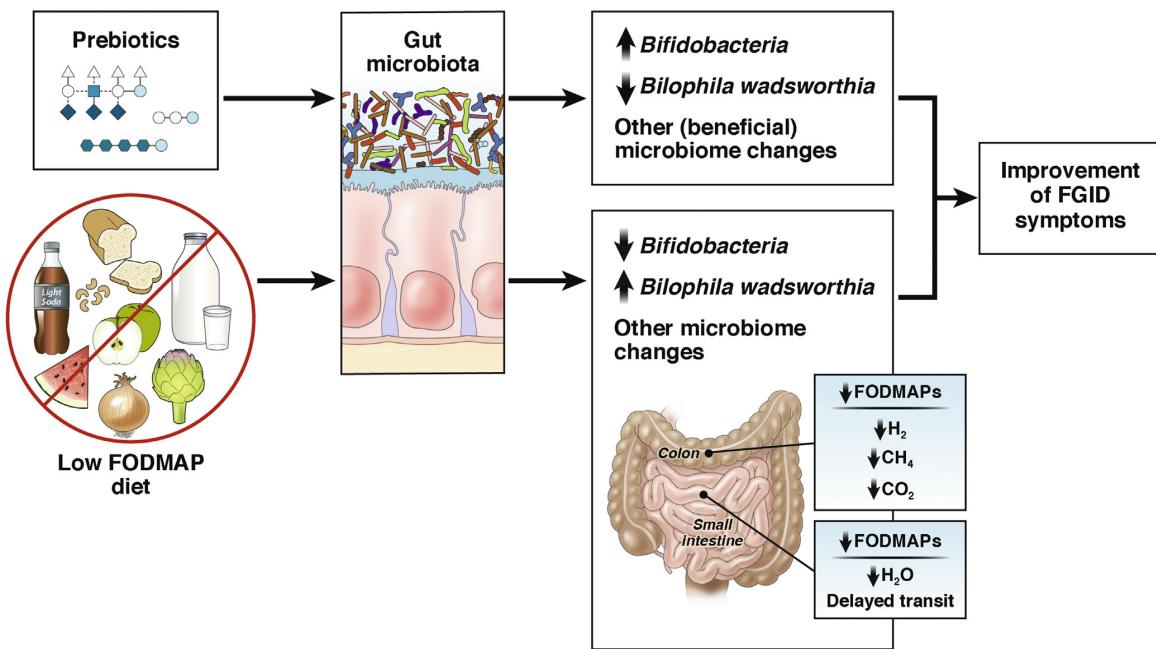
Tomada de Simrén M (223)

Efectos de la dieta baja en FODMAP y el prebiótico B-GOS en la producción de gas intestinal

El volumen de gas recolectado con una sonda rectal después de una comida de prueba no se vio afectada por los tratamientos. Esta inesperada falta de diferencias podría deberse a que la comida de prueba con la recolección del gas se administró después de 3 días de dieta alta en residuos, lo que proporcionó una sobrecarga colónica y difuminó el efecto del tratamiento. De hecho, la producción de gas intestinal depende no solo de las cargas de residuos fermentados recientemente, sino también de la anteriores(126).

Relación entre corrección de la disinergia defecatoria en pacientes dispépticos y la mejoría de sus síntomas

El segundo estudio muestra que en pacientes con dispepsia funcional y disinergia defecatoria, la corrección de la defecación produce un alivio significativo de la dispepsia. Estos datos apoyan nuestra hipótesis e indican que los síntomas tipo distrés postprandial en

la dispepsia funcional se agravan con el estreñimiento concomitante. Para este estudio se reclutaron pacientes cuyo síntoma principal era pesadez epigástrica asociada con la ingesta de alimentos; los pacientes también referían estreñimiento asociado. El estreñimiento se manifestó como esfuerzo defecatorio y sensación de evacuación incompleta sin alteración del hábito intestinal. Los pacientes presentaron una contracción anal paradójica y un test de expulsión del balón alterado. La efectividad del biofeedback anorrectal para el tratamiento de la disinergia defecatoria se ha demostrado anteriormente(174,177,224). De hecho, para probar nuestra hipótesis, incluimos para el análisis sólo aquellos pacientes con una corrección efectiva de la defecación, que lo comparamos con un grupo control. La cantidad de fibra en el grupo control era relativamente pequeña, y de hecho, no produjo un empeoramiento de los síntomas.

Estudios previos han demostrado que la corrección de la disinergia defecatoria mejora el estreñimiento y también puede mejorar los síntomas concomitantes del SII(179). Los pacientes con DF y SII comparten algunos mecanismos fisiopatológicos comunes, como la hipersensibilidad del tracto digestivo. La mayoría de los estudios han demostrado hipersensibilidad gástrica en la dispepsia funcional e hipersensibilidad intestinal y colónica en el SII; sin embargo, la disfunción sensorial puede estar extendida y los síntomas específicos dependen del territorio afectado y la presencia de disfunciones motores asociadas(4,29,58,78,88). Por lo tanto, la corrección del estreñimiento puede tener beneficio en ambas condiciones, es decir el síndrome de intestino irritable y la dispepsia funcional.

La flatulencia un síntoma que no se incluye en las clasificaciones actuales de los trastornos funcionales digestivos, mejoró de forma significativa al corregir la disinergia de la defecación, y esta sensación subjetiva se confirmó por la reducción en el número de evacuaciones anales de gas, que puede servir como un marcador objetivo de respuesta al tratamiento. Se puede suponer que corregir la defecación alterada facilitaría la evacuación anal de gas. El hecho de que los resultados se movieran en dirección opuesta sugiere que la defecación alterada puede resultar en un proceso de fermentación continua (y en la producción de gas), y este efecto se evitaría mediante una defecación normal. Aunque no se pudo detectar un aumento en el contenido del colon para respaldar esta explicación, después de la corrección de la disinergia defecatoria, algunas mejoras clínicas se relacionaron con indirectamente con el volumen del contenido del colon.

6. CONCLUSIONES

1. Los factores que determinan el contenido intestinal, tanto la dieta como el hábito deposicional, influyen sobre los síntomas digestivos funcionales.

2. Los residuos fermentables de la dieta influyen sobre los síntomas digestivos y la microbiota intestinal. Los prebióticos producen una adaptación de la microbiota y mejoran los síntomas digestivos aún después de interrumpir el tratamiento. Sin embargo, los FODMAPs tienen una acción opuesta y tienden a empeorar los síntomas digestivos: la restricción de FODMAPs en la dieta disminuye los síntomas, pero este efecto está asociado con un deterioro de la microbiota y los síntomas revierten al interrumpir la dieta restrictiva.

3. En pacientes con dispepsia funcional y estreñimiento, la corrección del estreñimiento mejora los síntomas dispépticos, lo que indica que en pacientes susceptibles el estreñimiento induce o predispone a los síntomas dispépticos.

4. Distintos síndromes funcionales digestivos comparten una base fisiopatológica común que involucra el contenido intestinal.

7. LÍNEAS DE INVESTIGACIÓN DE FUTURO

Los estudios incluidos en esta tesis doctoral han demostrado que tanto una dieta baja en residuos como un prebiótico mejoran los síntomas digestivos. En un estudio futuro se evaluará la eficacia de las dos estrategias combinadas, es decir una dieta baja en residuos combinada con un prebióticos. La hipótesis es que la combinación tendrá un efecto sinérgico positivo sobre los síntomas digestivos y además el prebiótico paliará los efectos negativos de la dieta baja en residuos.

El efecto positivo que tiene la corrección del estreñimiento sobre los síntomas de dispepsia funcional probablemente se debe a su influencia sobre el contenido intestinal. En un estudio próximo se evaluará el efecto de una dieta baja en residuos, potencialmente con un efecto sobre el contenido intestinal análogo al que tuvo la corrección del estreñimiento, sobre los síntomas dispépticos.

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