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REVIEW

Methane on Breath Testing Is Associated with Constipation: A Systematic Review and Meta-analysis

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Abstract

Background A growing body of literature suggests an association between methane and constipation. Studies also link degree of methane production to severity of constipation and have shown constipation is improved following antibiotics.

Aims We aim to conduct a systematic review and meta-analysis to examine the cumulative evidence regarding the association between methane and constipation.

Methods A literature search was performed using MEDLINE and Embase to identify studies where the presence (or absence) of methane was assessed in constipated subjects. Search terms included "methane," "breath test," "constipation," "motility," "transit," "irritable bowel syndrome" and/or "IBS." Pooled odds ratios were generated using a random effects model. In a separate analysis, studies that measured intestinal transit in methane and non-methane subjects were systematically reviewed.

Results Nine studies met inclusion criteria for the meta-analysis. Among these, 1,277 subjects were examined by breath testing ($N = 319$ methane producers and $N = 958$ methane non-producers). Pooling all studies, a significant association was found between methane on breath test and constipation (OR = 3.51, CI = 2.00–6.16). Among adults only, methane was significantly associated with constipation (OR = 3.47, CI = 1.84–6.54). Similar results were seen when only examining subjects with IBS (OR = 3.60, CI = 1.61–8.06). The systematic review identified eight additional papers which all demonstrated an association between methane and delayed transit.

Conclusions We demonstrate that methane present on breath testing is significantly associated with constipation in both IBS and functional constipation. These results suggest there may be merit in using breath testing in constipation. Moreover, methane may be used to identify candidates for antibiotic treatment of constipation.

Keywords Methane · Breath test · Transit · Constipation

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Introduction

The human gut is an elaborate microbial ecosystem where 10^{14} bacteria are established within the first year of life [1, 2]. These flora are progressively altered throughout adulthood by endogenous and exogenous factors [3, 4]. Dietary intake significantly influences gut microbiota, but genetic predisposition is still the most important factor in the development of gut microbiota [5–7]. Improved techniques for examining the bacterial composition of the human gut are increasing the ability to identify and subsequently classify enteric bacteria and their relevance in human health and disease [8–10].

Functional bowel disorders are a group of chronic gastrointestinal conditions of unknown etiology, characterized by altered bowel function, abdominal discomfort, and varying gastrointestinal symptoms depending on the organ of involvement [11, 12]. The most common is irritable bowel syndrome (IBS), affecting roughly one in five individuals worldwide and 14% of the U.S. population [13–15]. The diagnosis of IBS is based on the presence of specific symptoms in the absence of a detectable organic cause [16]. These criteria permit sub-categorization of IBS on the basis of the more predominant symptom.

Interestingly, a growing body of literature has accumulated over the last decade suggesting that patients with functional bowel disorders have significant alterations in their intestinal microbiota. Much of the initial work in this area has been centered on the lactulose breath test (LBT), which measures two gases exclusively produced by fermentation in the gastrointestinal tract: hydrogen and methane [17]. Methane gas is produced by methanogenic bacteria, which are extremely fastidious and difficult to culture. The most common methanogenic colonizer of humans is *Methanobrevibacter smithii* [18–20]. Among studies of breath testing in functional disease, methane on breath testing is found to be associated with a constipation phenotype, constipation-predominant IBS (C-IBS) [21].

Recently, we have demonstrated that methane gas as produced by gut bacteria was able to slow small intestinal transit by nearly 70% in an in vivo model of transit [22].

The association between methane and constipation has gained such clinical significance that the presence of methane on breath testing can be confidently utilized as a valid tool in the diagnosis of C-IBS [23]. This suggests that methane has an active role in the development of constipation.

While methane appears to be associated with, and perhaps contributing to, constipation, what is more important is that it potentially identifies a subgroup of functional bowel patients that respond to antibiotic therapy directed at eliminating or reducing the production of this gas. In this study, we conduct a systematic review of the literature and meta-analysis to examine the cumulative evidence regarding the association between methane and constipation.

Methods

Search Methodology and Abstract Review

Using MEDLINE and Embase (January 1950 to January 2010), a comprehensive search was performed for abstracts matching one or more of the following search terms: "methane," and/or "breath test," "constipation," "motility," "transit," "irritable bowel syndrome" and/or "IBS." Within these results, the prevalence of methane (based on breath testing via gas chromatography) in a population with comparison to the presence or absence of constipation as the predominating symptom (including C-IBS and/or functional constipation) was required for inclusion in the final analysis. During the search, studies that measured intestinal transit in methane and non-methane subjects were also identified. After the initial literature search, abstracts meeting a priori criteria were eligible for full paper review.

Data Extraction and Analysis

Studies meeting inclusion and exclusion criteria were analyzed by two reviewers independently. During the data collection process, extracted data included the size of the study population, case and control groups, and the number of constipated, non-constipated subjects in both methane positive and negative groups. The substrate and criteria for a positive breath test were noted for each study. Any disagreement over study inclusion or identification of relevant data within a particular study, during any stage of the review process, was resolved by third-party consensus.

Statistical Analysis

Summary effect estimates (pooled odds ratios) were generated using the DerSimonian and Laird random-effects model to produce more conservative estimates [24, 25]. Where cell counts equaled zero, a validated approach to add 0.5 to each of the cells of the 2×2 table for a study was applied [26]. For each evaluation, forest plots were generated containing odds ratios, 95% confidence intervals, and weights for each study, followed by an overall pooled odds ratio. Heterogeneity and I^2 statistics were calculated to evaluate the extent to which odds ratios varied between studies. Funnel plots were generated to assess evidence of significant publication bias or small-study effects within the studies included in each evaluation. Harbord's test, the modified version of Egger's test for binary data, was used to test for funnel plot asymmetry [27]. All statistical analyses were performed using Stata Version 10 (StataCorp, College Station, TX).

Results

Paper Selection Outcome

The initial search strategy generated 705 abstract titles, of which 44 matched the search term criteria for paper review. After application of paper review, nine manuscripts then proceeded to full review as they met all eligibility requirements (Fig. 1) [21, 23, 28–34]. Seven of nine studies involved IBS patients only, and one study involved children [29]. The remaining study examined functional constipation in non-IBS subjects [34]. The definition of methane positivity for each study is summarized in Table 1.

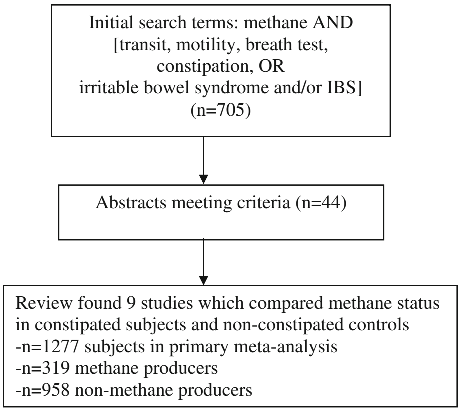

Fig. 1 Flowchart of paper selection for meta-analysis

Though they met the initial search criteria, the following five studies were excluded upon paper review. A brief explanation regarding the exclusion of these studies is as follows. Rana et al. examined methane status in 154 IBS patients and 286 healthy controls, however, it was not reported which of the IBS patients had C-IBS, so the paper was excluded from the meta-analysis [35]. Soares et al. examined methane status in children with constipation; the absence of a control group of subjects without constipation disqualified the study from the meta-analysis [36]. Grover et al. performed breath testing on 158 subjects with IBS and 34 healthy controls, but intestinal gas predominance rather than methane status was reported, thus not meeting the inclusion criteria [37]. Pimentel et al. examined methane production in 23 patients with IBS, however, “area under the curve” was reported in lieu of a conventional measure of gut transit [22]. Kajs et al. examined methane status and time to first bowel movement after a single meal, an inadequate measure of gut transit to be included in the systematic review [38].

Meta-Analysis of Methane and Constipation

In total, nine studies were included in the meta-analysis. This included a total of 1,277 subjects (319 methane producers and 958 methane non-producers). Pooling all these studies, a significant association was observed between methane on breath test and constipation. The presence of

Table 1 Summary of papers meeting criteria for meta-analysis

Study	Relevant sample size (total *n* [methane])	Study population	Rome criteria	Type of breath test	Definition for methane positive
Peled et al. [28]	32 (11)	32 subjects with IBS	NA	NA	Breath methane concentration at least 1 ppm
Fiedorek et al. [29]	107 (35)	67 encopretic or constipated children and 40 healthy controls	NA	NA	Breath methane >3 ppm (at least 1 ppm above ambient air, which is 1.8 ppm)
Pimentel et al. [30]	231 (35)	120 with C-IBS and positive LBT, 11 with D-IBS and positive LBT	1	Lactulose	Breath methane >20 ppm within 90 min of lactulose
Pimentel et al. [30]	50 (12)	26 D-IBS cases, 12 C-IBS cases, and 12 cases with IBS-like symptoms	2	Lactulose	Breath methane >20 ppm, or any rise in concentration within 90 min of lactulose administration
Majewski et al. [31]	204 (32)	149 IBS-D cases, 30 IBS-C cases, 25 IBS-other cases	2	Glucose	Methane >20 ppm when baseline less than 10 ppm or for any increase of 12 ppm
Bratten et al. [32]	224 (44)	224 subjects with IBS; 40 healthy controls	2	Lactulose	Breath methane ≥ 1 ppm at baseline or anytime during the test
Parodi et al. [33]	130 (35)	51 IBS-D cases, 31 IBS-C cases, 48 IBS-mixed cases	3	Glucose	Methane excretion higher than 10 ppm in basal condition or after administration of glucose
Hwang et al. [23]	56 (28)	24 C-IBS cases, 23 D-IBS cases, 9 IBS-mixed/other cases	1	Lactulose	Any detection of methane above 5 ppm
Attaluri et al. [34]	202 (87)	96 patients with non-IBS chronic constipation cases, 106 controls	3	Glucose	Baseline methane ≥ 3 ppm

IBS irritable bowel syndrome, *C-IBS* constipation-predominant irritable bowel syndrome, *D-IBS* diarrhea-predominant irritable bowel syndrome, *LBT* lactulose breath test, *NA* not applicable

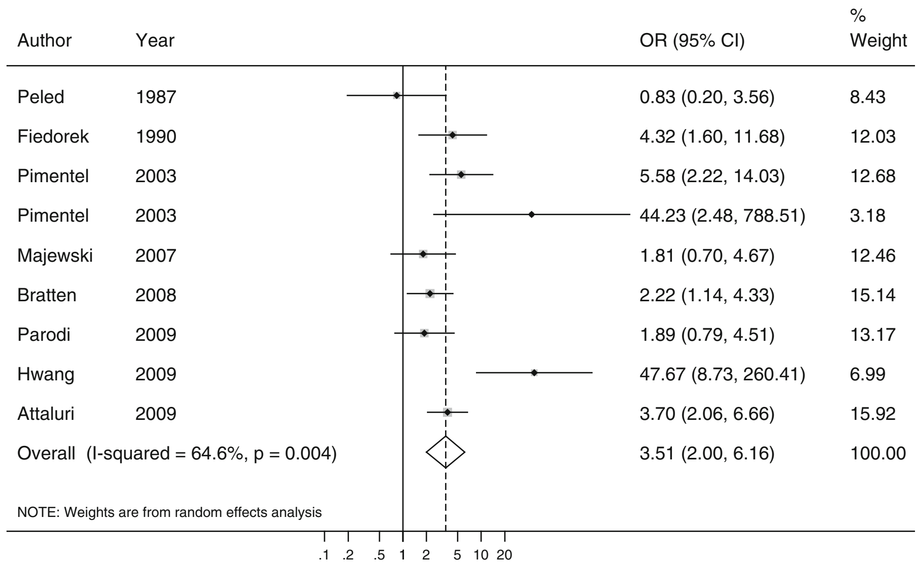

Fig. 2 Forest plot for the total group meta-analysis

methane was more often associated with a constipation phenotype (OR = 3.51, CI = 2.00–6.16; Fig. 2). For all nine studies, heterogeneity was moderate with I-squared equal to 65%, and Harbord's modified test for small-study effects suggested no evidence of significant publication bias ($P = 0.887$).

The original nine studies in the meta-analysis were sub-analyzed to determine whether the association between methane and constipation remained when other variables were removed. When only adults were considered, methane remained significantly associated with constipation (OR = 3.47, CI = 1.84–6.54; Fig. 3). Similarly, when only studies of IBS subjects were analyzed, methane remained significantly associated with constipation, i.e. constipation-predominant IBS (OR = 3.60, CI = 1.61–8.06; Fig. 4).

Intestinal Transit

In addition, the systematic review identified eight papers that examined intestinal transit in the presence of methane (Table 2) [39–46]. While studies could not be combined for meta-analysis due to markedly different techniques (bowel frequency, orocecal, colonic, and whole gut transit time), all eight studies demonstrated that the presence of methane was associated with significant slowing of intestinal transit irrespective of the measure used.

Discussion

In this systematic review and meta-analysis, the relationship between methane and intestinal transit was evaluated

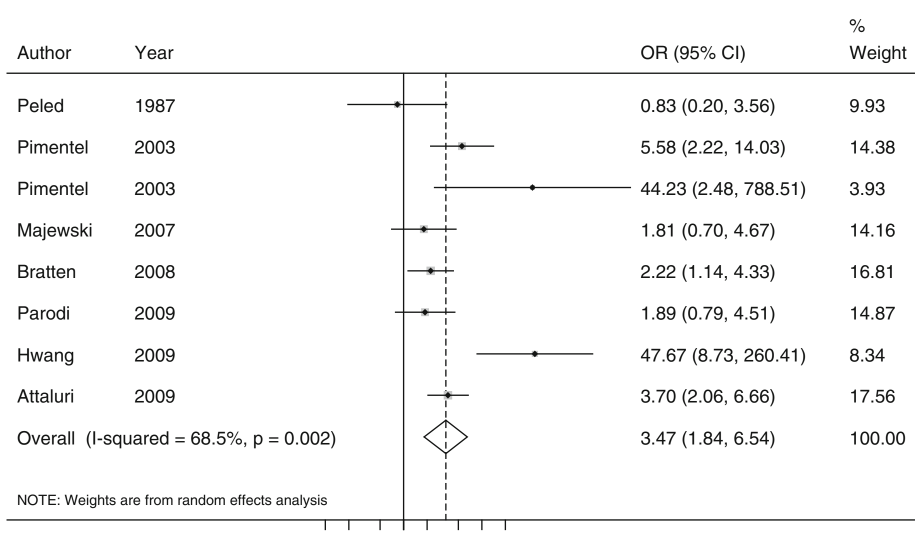

Fig. 3 Forest plot for the adult group meta-analysis

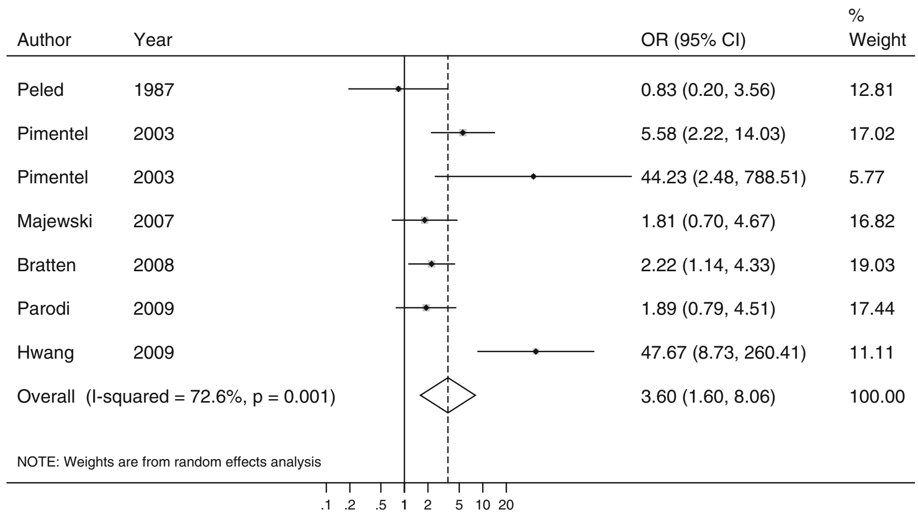

Fig. 4 Forest plot for the irritable bowel syndrome (IBS) group meta-analysis

Table 2 Systematic review summarizing papers that measure transit in patients with and without methane on breath testing

Study	Measure of transit	Controls	Methane producers	*P* value
Stephen et al. [39]	Whole gut transit time (h)	48.6 ± 6.6	84.6 ± 11.7	0.05*
Cloarec et al. [40]	Orocecal transit time (m)	68 ± 24	111 ± 52	0.005*
Rumessen et al. [41]	Orocecal transit time (m)	60	75	0.1
Oufir et al. [42]	Whole gut transit time (h)	50	95.5	0.05*
Soares et al. [43]	Colonic transit time (h)	61	80.5	0.05*
Levitt et al. [44]	Stool frequency (bm/day)	1.11 ± 0.06	1.03 ± 0.08	0.1
Morken et al. [45]	Whole gut transit time (h)	95 ± 8	141 ± 14	0.005*
Chatterjee et al. [46]	Stool frequency (bm/day)	1.96 ± 1.40	1.17 ± 0.86	0.05*

* Indicates significance

in subjects with functional constipation and IBS. The results demonstrate that methane on breath testing is more common in patients presenting with symptoms of functional constipation or C-IBS compared to non-constipated controls. Among studies that objectively examine intestinal transit, methane was associated with a delayed transit.

Over the last decade, numerous studies have emerged demonstrating a relationship between intestinal bacteria and functional bowel disease. Specifically, data suggest a higher prevalence of small intestinal bacterial overgrowth in IBS on the basis of breath testing [47]. While there has been controversy about breath testing in IBS, this recent meta-analysis appears to demonstrate that subjects with IBS have a higher prevalence of abnormality. Moreover, a recent study by Posserud et al. revealed that among 162 IBS subjects, there was a higher number of coliform bacteria in the jejunum, although this did not exceed 10^5 cfu/mL [48]. These data are the basis for a series of controlled studies demonstrating the efficacy of antibiotic treatment in IBS [18, 49, 50]. This antibiotic approach has rendered both immediate and long-term alleviation of IBS symptoms.

While a bacterial abnormality such as bacterial overgrowth is included in the differential diagnosis of diarrhea-predominant irritable bowel syndrome (D-IBS), bacteria would not be an intuitive cause of constipation. However, over the past few years, the same breath testing studies in IBS have revealed that this may be the case. During breath testing, two gases (hydrogen and methane) are measured that distinguish bacterial from human metabolism. Methane was observed to be associated in IBS with a higher prevalence of C-IBS [23]. In follow-up to this finding, further investigation demonstrated that methane gas itself may be important in the manipulation of transit. In one study, infusion of methane into the intestinal tract resulted in nearly 70% slowing of transit in all animals tested [22]. This effect is supported by the systematic review. In Table 2, studies that have examined transit in IBS have universally demonstrated an association between methane gas on breath test and slower transit.

In this meta-analysis, the importance of methane in subjects with C-IBS is further corroborated. The data in these studies come from various investigators and countries. What is interesting is that the association between methane also appears to extend to patients with general non-IBS constipation as well [34, 36]. The importance of this meta-analysis is that it suggests that methane may be useful in trying to understand the pathophysiology of constipation—methane could potentially be used as a diagnostic test for conditions of constipation [23]. More importantly, if methane is a cause of this constipation, as suggested by Table 2, testing for methane may be useful in determining patients who may benefit from an antibiotic approach. This has already been demonstrated [49, 50].

Although the meta-analysis supports the association between methane and constipation, there are some pitfalls with this study. First, there is significant heterogeineity among studies. These include differences in criteria to define IBS as well as varied definitions of positive breath test for methane. In addition, it needs to be clearly stated that methane does not account for all constipation in these patients. Thus, methane is not the exclusive cause of constipation in IBS, although in one study among constipated patients, those with methane had a greater severity of constipation compared to constipation-IBS subjects without methane [46].

In conclusion, in this meta-analysis, methane is demonstrated to be significantly associated with a constipation phenotype in functional bowel patients. This finding is potentially very important in the pathophysiology of C-IBS and constipation in general. In the future, demonstration of methane in the breath of a patient with constipation may direct the approach to treatment.

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