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REVIEW ARTICLE

Recent advances in measuring the effects of diet on gastrointestinal physiology: Sniffing luminal gases and fecal volatile organic compounds

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Abstract

Despite the huge pool of ideas on how diet can be manipulated to ameliorate or prevent illnesses, our understanding of how specific changes in diet influence the gastrointestinal tract is limited. This review aims to describe two innovative investigative techniques that are helping lift the veil of mystery about the workings of the gut. First, the gas-sensing capsule is a telemetric swallowable device that provides unique information on gastric physiology, small intestinal microbial activity, and fermentative patterns in the colon. Its ability to accurately measure regional and whole-gut transit times in ambulant humans has been confirmed. Luminal concentrations of hydrogen and carbon dioxide are measured by sampling through the gastrointestinal tract, and such application has enabled mapping of the relative amounts of fermentation of carbohydrates in proximal-*versus*-distal colon after manipulation of the types and amounts of dietary fiber. Second, changes in the smell of feces, via analysis of volatile organic compounds, occur in response to the diet, and by the presence and therapy of irritable bowel syndrome and inflammatory bowel disease. Such information is likely to aid our understanding of what dietary change can do to the colonic luminal microenvironment, and may value-add to diagnosis and therapeutic design. In conclusion, such methodologies enable a more complete physiological profile of the gastrointestinal tract to be created. Systematic description in various cohorts and effects of dietary interventions, particularly when co-ordinated with the analysis of microbiome, are needed.

Introduction

The pivotal role that diet plays on multiple aspects of gastrointestinal physiology, biochemistry, and microbiology has excited much interest, particularly with regard to the concept that modulating what we eat may be a major preventive and therapeutic tool for gastrointestinal and non-gastrointestinal diseases. This is not a new concept and has formed the basis of many management strategies. Some, such as the gluten-free diet for celiac disease, are based on solid clinical and mechanistic grounds and form central platforms in the practice of evidence-based conservative medicine. However, there is a vast array of "internet experts" who profess almost magical efficacy of their dietary approaches without scientific rationale. One of the major stumbling blocks to progress in defining the validity of this huge pool of ideas has been the limitations of how gastrointestinal biology can be assessed. Major advances are being made in several areas of such assessment. In healthy people, the intestinal microbiome is complex and shows considerable variation. However, the fecal metabolome is remarkably constant.[1] We have proposed that it is more interesting and valuable to ask not "who is there" but rather

"what are they doing." The study of the fecal metabolome addresses this. In this review, advances in the methods of assessing the release or production of gases and volatile organic compounds (VOCs) are discussed and their implications for dietary research outlined. A subsequent review will address the assessment of barrier function and the application of intestinal ultrasound to assess the function of the gastrointestinal tract.[2] Both reviews aim to enhance the assessment of gastrointestinal function in health and disease, and with dietary manipulation.

Applying telemetric capsules—Sampling gastrointestinal gases

Since the inception of the first ingestible device, more than six decades ago,[3,4] there have been several key advances in technology, enabling the creation of miniaturized electronic devices that promise to unveil many of the previously immeasurable physiological and pathophysiological processes throughout the gastrointestinal tract in a minimally invasive manner. Capsules offer numerous capabilities, depending on the microelectronic components residing within the capsule housing, including sensors, software, and battery. The major game-changer in this space was the wireless capsule endoscope, with its various iterations, enabling imaging of almost the entire gastrointestinal tract to be performed.[5,6] Since then, numerous other devices have entered the pipeline.

The gas-sensing capsule (Atmo Biosciences, Melbourne, Australia) is one of the newer electronic ingestible devices to enter advanced stages of research and development.[7,8] The battery-operated device itself is small enough to be safely ingested (approximately 28 mm × 11 mm in size, 3.8 g in weight), as discussed in detail elsewhere.[7] The battery has an operational half-life of 4 days during which time it can measure several physiological parameters, in real time, of the relatively undisturbed gastrointestinal tract of an ambulant adult. From five sensors, these physiological parameters include hydrogen and carbon dioxide/methane concentrations, indications of oxygen level, temperature, relative humidity, capsule tumble, and changes in the physical electromagnetic properties of the environment surrounding the capsule. Measurements are transmitted from the gas-sensing capsule at a frequency of 434 MHz to a patient-worn data receiver and subsequently uploaded to a remote server *via* a mobile device for analysis and review.

Integral to the interpretation of the data generated by any ingestible device is accurate localization within the gastrointestinal tract, such that locoregional assessment can be accurately performed. These major landmarks include ingestion and excretion, both relatively easy to define, and gastroduodenal and ileocecal junction, which indicate the transition from one major region of the gut to the next. The time taken to transit from one landmark to the other can be used to assess the aspects of gastrointestinal motility, by way of transit time evaluation.[9] Acknowledging the presence of biological variation determined by tandem ingestion of gas-sensing capsules (∼12–34%),[9] the rates of transit of the capsule can be measured repeatedly under various conditions to assess the physiology of the gut. Such examples include measuring the effects of implementation of dietary changes, such as alterations in food types (solid *vs* liquid), which, for example, may alter gastric emptying time; manipulation of dietary fiber content (e.g. high fiber *vs* low fiber, fermentable *vs* poorly fermentable), which may alter whole gut and colonic transit time and administration of medications (prokinetic or anti-motility agents), and also play a role in medical diagnostics, such as work up of patients with suspected dysmotility including gastroparesis and slow transit constipation.[10–15] Key benefits to the use of the swallowable devices are that multiregional transit assessment can be performed in a single test, that they are defining physiology under physiological conditions (e.g. not fasting, no need for bowel washout or change in host behavior), and that there is clinical value in the measurements when considering, for example, which medication may be prescribed (i.e. one which acts locally *vs* more widespread) or when considering the possible origins of a patient's symptoms.

Beyond motility, the gas-sensing capsule measures the concentration of carbon dioxide/methane and hydrogen gases in real time, longitudinally along that gastrointestinal tract. The sensors cannot differentiate carbon dioxide and methane (quantified 1:1). However, methane is only relevant in the colon, where highly anaerobic conditions are needed for methanogenesis by Archaea. These gases provide insight into the unique locoregional processes occurring overall (i.e. the net effect of production and consumption of the gases) in each segment. To date, these have been explored in the stomach, small intestine, and colon.[10,11,16–18]

The gas-sensing capsule in the stomach. The gas-sensing capsule identifies the gastroduodenal junction by utilizing a combination of an increase in carbon dioxide concentration, change in capsule orientation, and detection of a change in electromagnetic properties of the environment adjacent to the capsule, with good interobserver agreement. There has also been good agreement between gas-sensing capsule and wireless motility capsule in measurement of gastric emptying time in healthy subjects and those with dysmotility.[9,11] Current normal values are based on the wireless motility capsule validation studies, where gastric emptying times of 2–5 h post-ingestion are considered normal and delayed gastric emptying time diagnosed beyond this.[19]

Analyzing the gases measured with the capsule provides unique information that might assist in evaluating gastric physiology. The gases measured at any one time may be influenced by air swallowing and eructation, ingestion of gas-containing beverages such as soft drink, the rate of gas transit along the gastrointestinal tract (i.e. moving from stomach to duodenum), the presence of passive diffusion across the luminal mucosa and into the circulation to be exhaled into the environment, and through de novo production via acid–base reactions or decarboxylation of pepsinogen-associated arginine within the parietal cell canaliculus.[20–28] An example of a potential application for measurement of gastric concentrations of gases is the observation made during preliminary studies that discrete increases in the concentrations of carbon dioxide, or bursts, measured by the capsule, are commonly observed in the stomachs of individuals, including healthy subjects and those with functional dyspepsia and gastroparesis.[10] The nature of the bursts appears to be exaggerated in subjects with delayed gastric emptying times, with both the size (measured as area-under-the-curve) and frequency of the carbon dioxide bursts being significantly greater in this

setting. It is likely that these bursts reflect carbon dioxide production secondary to acid–base reactions, with bicarbonate delivered to the stomach via duodeno-gastric reflux reacting with gastric acid, to generate carbon dioxide.

The gas-sensing capsule in the small intestine. Transit times of the gas-sensing capsule in the small intestine have also been assessed with tandem ingestion of the wireless motility capsule, using the methodology for which normal values have been obtained. There was close agreement between the two values in healthy adults with a low variance in times reported.[9,29] Potential novel application of the gas-sensing capsule is in the assessment of small intestinal bacterial overgrowth (SIBO), a highly controversial area, mainly due to the gross inadequacies of current diagnostic methods; interpretation of breath hydrogen tests is fraught with confounders, and assessing the density of bacterial populations is impractical and limited to very proximal small intestine. The measurement of carbon dioxide and/or hydrogen concentrations by the gas-sensing capsule might provide information about microbial metabolic activity right along the small intestine and provide insight into small intestinal microbiota such as the diagnosis of SIBO and its contribution to symptoms and its modulation by dietary and other therapies. In the small intestine, bacteria produce energy primarily by aerobic respiration due to sufficient oxygen being available for both aerobic and facultative anaerobic bacteria. Such metabolic activity produces carbon dioxide, whereas fermentation produces both carbon dioxide and hydrogen. The capability of the gas-sensing capsule to measure the concentrations of both gases offers two potential analytes that might reflect microbial metabolism. The current work, presented in preliminary form,[16] has been promising, but there is a large amount of work required before the methods used and true value of the gas-sensing capsule can be defined.

The gas-sensing capsule in the colon. In the colon, carbon dioxide/methane and hydrogen gases reflect the outcome of multiple processes, including fermentation by anaerobic bacteria/archaea and subsequent acid–base buffering and are influenced by the degree of passive absorption across the mucosa, into the circulation to be lost into the atmosphere via exhalation, and also due to loss per rectally as flatus.[26,30–33] Transit times in the colon have clinical implications, most obviously in their contribution to bowel habits. Since constipation

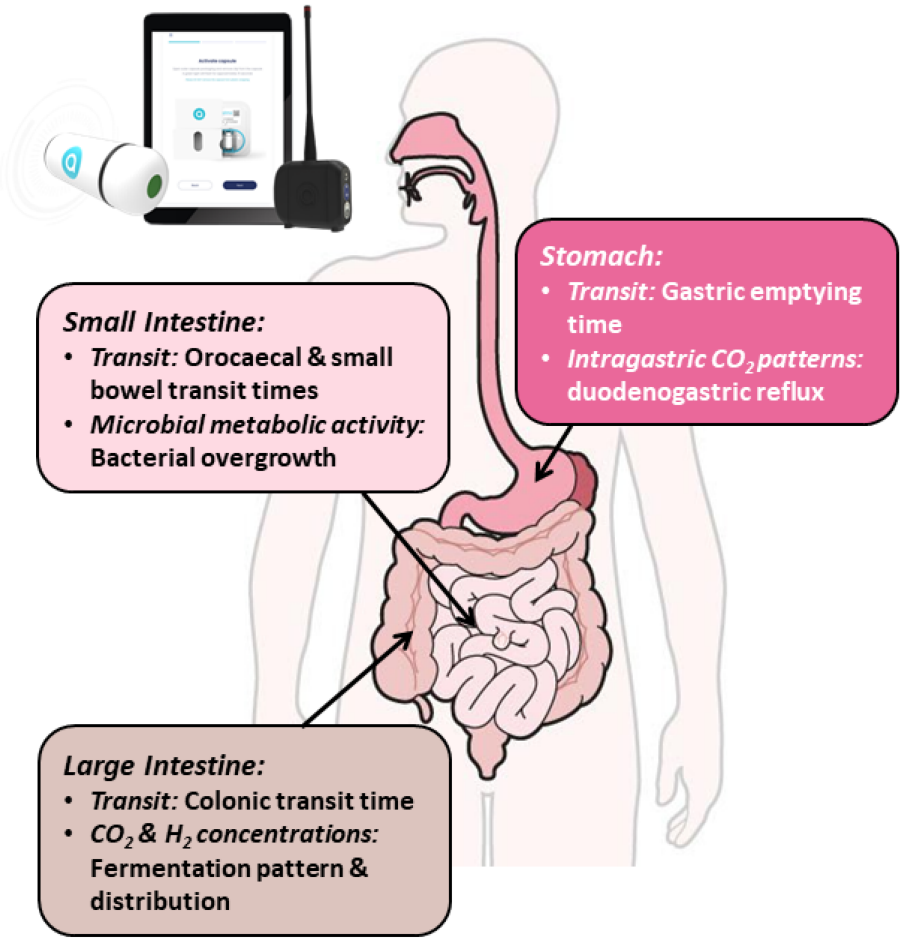

Figure 1 Potential site-specific roles for the telemetric gas-sensing capsule.

and diarrhea are major symptoms in gastroenterological practice and their therapies often involve dietary approaches or drugs that aim to hasten or slow transit, it is somewhat surprising that measurement and monitoring of transit times are not part of routine practice. Current tests of colonic transit are reserved for special circumstances, due, in part, to their expense and impracticality. Accurate evaluation of colonic transit is likely to be a major application of the gas-sensing capsule, especially as it performs well in its accuracy, safety, and acceptance. The results of the accuracy of measurement of transit times in patients with dysmotility are eagerly awaited (www.clinicaltrials.gov NCT05718505).

Gas production and distribution in the colon have large clinical importance, in terms of symptom generation and where fermentation and its subsequent delivery of health-promoting short-chain fatty acids are occurring. Hydrogen is specific to carbohydrate fermentation, and its locoregional concentrations in the colon can provide unique insights into the delivery of fermentable dietary fiber in an individual. A controlled feeding study in patients with irritable bowel syndrome (IBS) demonstrated how the hydrogen profile can reflect the patterns of fermentation induced by altering the combination of fibers that had been shown in animal studies to deliver fermentable fiber to the distal colon.[18] Likewise, a preliminary report of a study of a fiber-free enteral nutrition in healthy subjects showed how the gas-sensing capsule can detect marked slowing of transit and reduction of distal fermentation.[17] The relevance of carbon dioxide/methane concentrations, which are more likely to reflect general microbial metabolic activity, remains to be reported. Thus, the gas-sensing capsule is providing unique information of potential relevance to understanding an individual's physiology and how it can be manipulated with diet and effects subsequently monitored.

Conclusion. The gas-sensing capsule provides unique information on several aspects of gastrointestinal physiology, including the effects of dietary manipulation, which were previously unable to be examined in humans. The potential site-specific roles for the gas-sensing capsule are illustrated in Figure 1. The practicality of such an approach is evident, but further studies are needed to reinforce its value in dietary research and to show its true impact in clinical practice.

Measuring fecal volatile organic compounds—"sniffing the feces"

Patients are often embarrassed by the odor of their feces. Most of us find the odor of stool from adults and from children after weaning unpleasant. Thankfully, the feces of neonates is less offensive, which is a relief to their parents! It is unsurprising, then, that sniffing stool has not become part of the standard clinical assessment. The only time that odor is used to contribute to diagnosis is when breath malodor is observed in patients with diabetic ketoacidosis and hepatic encephalopathy. However, patients frequently report a change in the odor of their stool during relapse of inflammatory bowel disease, and nurses may be able to recognize the odor associated with *Clostridiodes difficile* infection.[34] These observations led us to the study of the gases emitted from feces.

When we began studying this topic, little was known about the composition of fecal gases. Levitt's team[35] and others had discussed methane, hydrogen, nitrogen, oxygen, carbon dioxide, and a few sulfur-based compounds, but there had been no comprehensive studies of fecal gases. Here we describe the work we have undertaken to better understand fecal gases.

Normal metabolome. Volatile compounds are emitted from feces. When contained in vials, these gases enter the space overlying feces during thermal desorption and are referred to as "fecal headspace gases." These can be analyzed using several alternative approaches. Gas chromatography–mass spectrometry (GC–MS) is the most popular and aims to identify compounds in gas. These compounds, their generation, and metabolism can then be investigated to explain their presence and how metabolic pathways may be perturbed in disease. An example of the GC–MS trace of fecal headspace is shown in Figure 2.

We propose that clinical evaluation should be based on an understanding of what is normal. Once that is established, any variation from that should prompt investigation and then the patterns of change may become indicators of disordered physiology or pathology. We undertook a detailed study of healthy volunteers and patients with diarrhea of three different etiologies.[36] We established that there is a core fecal volatile metabolome: a set of volatile organic compounds (VOCs) that were present in more than 95% of seemingly healthy donors. The core included seven fatty acids, five ketones, four aldehydes and sulfides, one alcohol, furan, thiol, and indole (acetic acid, propanoic acid, butanoic acid, pentanoic acid, hexanoic acid, 2-methylbutanoic acid, 3-methylbutanoic acid; propan-2-one, butan-2-one, heptan-2-one, butane-2,3-dione, 6-methylhept-5-en-2-one; propanal, acetaldehyde, benzaldehyde, hexanal; carbon disulfide, methylsulfanylmethane, (methyldisulfanyl)methane, (methyltrisulfanyl) methane; 4-methylphenol; 3-methylfuran; methanethiol, 1-methyl-4-prop-1-en-2-ylcyclohexene (aka limonene); 1-H indole).[36] The presence or absence of most compounds changed little in a longitudinal study of 73 donors taking an *ad lib* diet. We concluded that this core metabolome in fecal headspace gas represented the metabolism by a stable, healthy microbiome derived from the constant substrates in the human diet: amino acids, carbohydrates, and fats.[36] When fecal samples from patients with ulcerative colitis or infection with either *Campylobacter* or *C. difficile* were compared, the VOCs in the fecal headspace differed from healthy donors, and also from each other. All diarrhea smells, but each type of diarrhea appeared to have a different smell!

Effect of changing diet

Protein. Garner recruited controls, and patients with IBD and infections. During the study, she adopted a pescatarian diet for several weeks.[36] This change in the source of protein had no measurable effect on her fecal metabolome. Since then, Mitchell *et al.*[37] performed a study in which dietary protein was doubled in older men. The levels of VOCs derived from amino acids, indole, and branched-chain fatty acids (BCFA) did not change significantly, presumably because most amino acids were absorbed in the small intestine, leaving little to be fermented.

Pre-colonoscopy diet. Five healthy volunteers adopted the "white diet" that patients consume prior to bowel preparation for

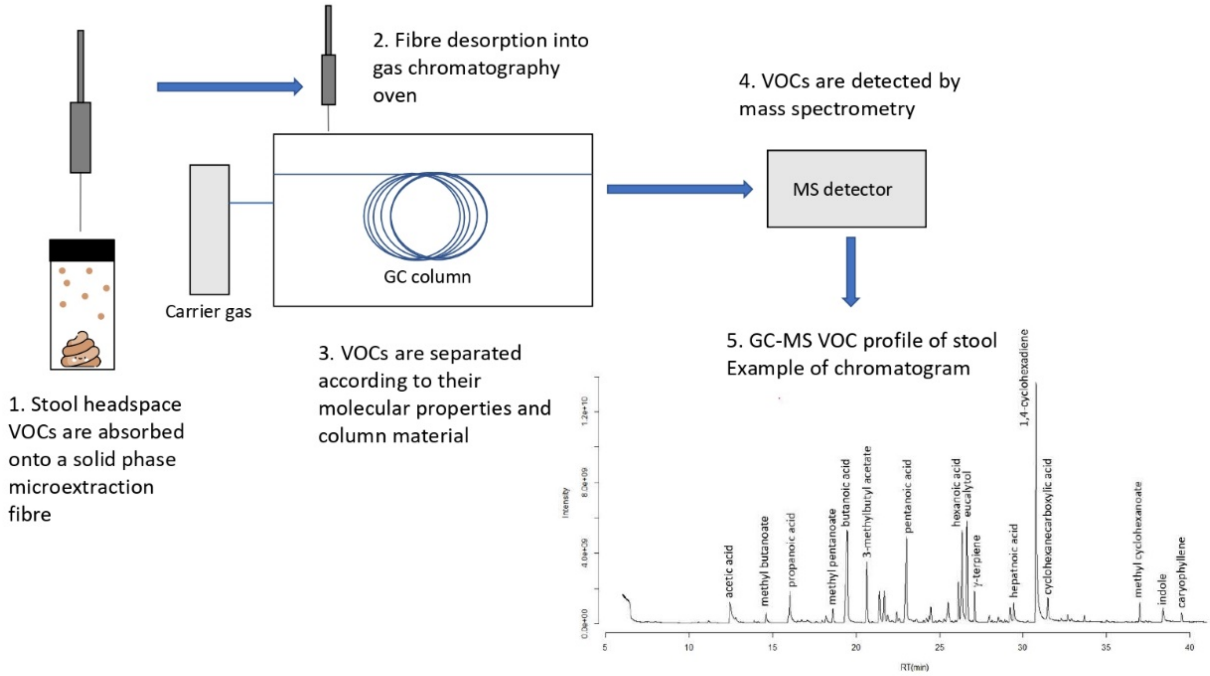

Figure 2 An example of a gas chromatography–mass spectrometry (GC–MS) workflow for analyzing fecal headspace volatile organic compounds (VOCs).

colonoscopy, avoiding red meat, fruits, and vegetables, for 3 days. Principal component analysis illustrated how the VOC pattern for most participants changed at the start and end of diet. For three, there was little change. However, two others showed a larger change, perhaps because of the greater amount of fruit or vegetables in their baseline diet. Closer scrutiny of individual VOCs found a reduction in esters (derived from fruit and vegetables) and BCFA (from amino acids) (L. Flain, unpublished data). In the same samples, little change in the bacterial microbiome based on DNA analysis was observed.[38] Hence, VOCs may represent a "real-time" indication of bacterial metabolism, allowing more rapid detection than DNA-based techniques, which also detect inactive or lysed species.[38]

4-SURE diet. This diet was designed to alter the metabolome of the colonic lumen to reduce inflammatory activity in patients with ulcerative colitis.[39] It increases the intake of fermentable indigestible carbohydrates, shifts the source of protein from animal to plant, and restricts total protein content to 70–90 g/day, which led to an increase in short-chain fatty acids (SCFA) and a reduction in BCFA. These changes were consistent with a relative shift of fermentation toward carbohydrates in preference to protein.

Fiber and FODMAPs. The influence of changes in dietary fiber content and amount has been examined in two ways. First, McDonnell investigated the impact of markedly reducing fiber intake by feeding 22 patients exclusively with Modulen, a fiber-free whole-protein powder formulation, for 4 weeks. Fecal VOC analysis showed that the concentration of SCFA fell as might be anticipated from reduced carbohydrate substrate to ferment, but the concentrations of BCFA also fell, indicating reduced protein fermentation occurred as well (M. McDonnell, unpublished data). These data illustrate how SCFAs are related to the fermentation of fiber and how BCFA production can be reduced by altering the source of protein leading to reduced amino acid fermentation. Second, we studied the effects of 2 weeks of a strict low-FODMAP (fermentable oligo-, di-, mono-saccharide, and polyol) diet in 14 healthy students to examine the effects on fecal esters. We had observed an abundance of esters in the human fecal metabolome. Esters usually have a pleasant odor and are present in fruit and vegetables. However, we have reported that esters may be generated in feces by the condensation reaction between organic acids and alcohols.[36] This may explain the increased abundance of esters in samples not stored in optimal conditions.[40] The low-FODMAP diet demonstrated a loss of esters in most of the volunteers, which may have reflected the restriction of fruit in their diet (A. Griffin, unpublished data). Thus, these studies showed that severe changes, particularly to the fiber content of the diet, may lead to a loss of metabolites.

Inflammatory bowel disease. The differences in the fecal metabolome of patient with ulcerative colitis, *Campylobacter* and *C. difficile*,[34] led to studies comparing Crohn's disease and ulcerative colitis. These two disorders were associated with qualitative analysis (presence or absence) of different fecal metabolomes.[39] Furthermore, the patterns were different in relapse and remission.[41] An inception cohort of children presenting with symptoms suggestive of inflammatory bowel disease (IBD) enabled us

to compare those in whom IBD was diagnosed ($n = 132$) and those without IBD ($n = 132$). Several SCFA were found to be in lower abundance in patients with Crohn's disease or ulcerative colitis; two other VOCs that were elevated at presentation of IBD fell when the disease was treated.[42] These findings were consistent with the smaller study by De Preter *et al.*[41] We propose that VOCs are influenced by the change in the intestinal microbiome in patients with IBD. They may have potential as biomarkers to support the diagnosis.

Calprotectin, a protein that is prevalent in neutrophils, is remarkably stable in feces. When the intestine is inflamed, for any reason, neutrophils are likely to enter the lumen, where they are degraded. The concentrations of the released calprotectin in the feces may be used to assess intestinal inflammation. Hence, the use of VOCs to define active inflammatory disease in patients with IBD may be unnecessary, unless the VOC pattern is different in Crohn's disease and ulcerative colitis, or in patients with disease with anatomical distributions. Newer data, using a quantitative analysis, rather than the previous qualitative approach, suggest that there may be differences of this nature.[42] We are investigating an alternative laboratory technique, using a GC-sensor, to compare VOCs from samples from pediatric patients with Crohn's disease and ulcerative colitis. We used the same GC-sensor to compare VOCs in active Crohn's disease and ulcerative colitis. There was clear separation.[43] We are also exploring the relationship between the specific VOCs and the microbiome in IBD.

Irritable bowel syndrome. Ulcerative colitis is, arguably, easy to diagnose, especially in young people. Patients usually have diarrhea and they often see blood in their stool. However, Crohn's disease can be harder to recognize. Pain and diarrhea, often without blood, superficially resemble IBS. NICE (National Institute for Health and Care Excellence) recommends the use of calprotectin to help "rule out" patients who do not need investigation (https://www.nice.org.uk/guidance/dg11). A "normal calprotectin" level may be used to imply a diagnosis of IBS. However, there are many other disorders that may cause abdominal discomfort and a change in bowel habit. Simply "ruling out" one cause may leave patients dissatisfied. However, patients may be left wondering what they have when a test is negative. This may lead to an unnecessary series of futile tests.[44] We have undertaken several studies of patients with a diagnosis of IBS and compared with patients with IBD, and also controls. In 2016, Ahmed *et al.*[45] reported that patients with IBS could be separated from patients with ulcerative colitis and Crohn's disease using a qualitative analysis. The IBS patients were compared with household controls. It was thought probable that such household controls would have a similar diet, and would be exposed to similar stressors, to the patient with whom they were paired. The VOCs profiles from these IBS patients were different from the household controls. This gave the first laboratory data to show that there were measurable changes in a biologic sample that could support a diagnosis of IBS.

In 2022, Vervier *et al.*[46] reported the microbiome in patients with non-constipated IBS and household controls. Participants were treated with a low-FODMAP diet. At baseline, two distinct microbial patterns were seen. One pattern (termed IBS^{H}) was similar to that found in healthy controls. The other had a pathogenic-like pattern (termed IBS^{P}). The IBS^{P} was enriched for Firmicutes, known for their fermentative properties, and contained genes encoding pathways for protein and carbohydrate metabolism. Treatment with the low-FODMAP diet led to a shift in the pattern in IBS^{P} toward normal and, with that, a reduction in the genes that were enriched. This pattern suggests microbial disturbance may underpin IBS. We are investigating the VOC profiles of these patients to determine whether VOCs can be used to predict this microbial pattern and the associated gene expressions.

Conclusion. The analysis of fecal headspace gases has revealed a relatively stable core metabolome. This metabolome may be influenced by significant changes to the diet. The metabolome is influenced by active IBD and IBS, and is responsive to the treatment of these disorders. The application of fecal sniffing, while not in routine clinical practice at present, may be a relatively simple and inexpensive way of value-adding to the diagnostic process, enhanced by their stability in feces over a 24-h period and at −80°C for many months.[40] From a research perspective, fecal gases warrant further investigation to understand the pathology of IBS, in particular, and the role of gases as biomarkers of health and disease.

Overall conclusions

With telemetric swallowable devices such as the gas-sensing capsule and analysis of fecal VOCs, a more complete physiological profile can begin to be created and then systematically described in various cohorts. The effects of various conditions, including dietary manipulations, can be better characterized. Such approaches, particularly when co-ordinated with the analysis of the microbiome, may revolutionize our view of the gastrointestinal tract and opportunity for personalized health care delivery.

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