ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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New Developments and the Role of Gravity in the Pathogenesis of Irritable Bowel Syndrome

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G&H How did the idea of gravity playing a role in irritable bowel syndrome come about?

BS It began after contemplating a family member who has been experiencing diminishing functional status while residing in an assisted-living facility. As she was spending more and more time lying flat in bed for prolonged periods, she simultaneously developed abdominal discomfort, bloating, and constipation. Her experience highlighted for me that the human body is not supposed to be lying flat all the time, and there is something about our relationship to gravity that affects the configuration and function of the gastrointestinal (GI) tract because humans evolved to stand up. With movement of 90 degrees in relation to Earth's pull, every strand in the body had to evolve, over time, to manage the downward pull of gravity. It is worth noting that we only stood up in the very last stages of our evolutionary history, so it is likely that some of us reside in bodies that are better able to manage the force of gravity than others. What is lower back pain, for example, if not a form of gravity intolerance? Or heart failure? Or vertigo? The list of gravity intolerance conditions is long. Thinking about this in relation to irritable bowel syndrome (IBS) pathogenesis prompted me to research what is known about our relationship to gravity and led to the gravity hypothesis of IBS. I wrote about this hypothesis in a paper published in 2022 to help inspire new ways of thinking about this oftentimes recalcitrant condition.

G&H How do the gravity resistance mechanisms in the gravity hypothesis help determine IBS susceptibility?

BS I started my inquiry by understanding physically how humans manage gravity in the GI system specifically in the abdominal cavity. This is not to infer that IBS is entirely a physical issue, or all in the gut; it is simply a starting point. In the abdominal cavity, most of our viscera are suspended by the mesentery, a structure that has a unique configuration in every person, just like any other organ. Normally, our intestines are not haphazardly spooled at the bottom of a sack. They are more like a functional stack. Analogous to a marionette on strings—how the marionette is animated by the way the strings hold up its appendages and accoutrements—the intestinal system arrays out in an intricate and delicate configuration that allows it to function in relation to gravity. The mesenteric suspension system is 1 of at least 4 gravity resistance mechanisms of the GI tract that I discuss in the paper. Another mechanism is the spinal column, which is like a chassis that holds up the entire body, and the antigravity extensor muscles that run up and down the back and the rest of the body that enable the body to stand upright. The mesentery comes together right around the lumbar spine within the abdominal cavity, and the visceral stack is held upright by straightening the spine and hoisting our innards. Standing upright also brings up the rib cage and

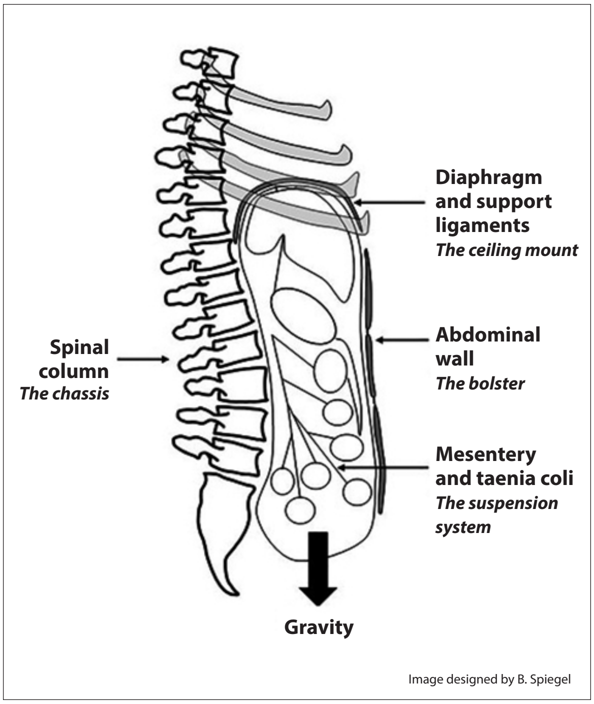

Figure 1. Four gravity resistance mechanisms of the gastrointestinal tract.

diaphragm, which is a third mechanism. The diaphragm has ligaments that act like a ceiling mount to suspend the abdominal contents, like a tacked-up sack of potatoes. It makes sense that disorders of the spinal column such as scoliosis, lordosis, kyphosis, and vertebral fractures are associated with GI problems. A curved or torqued spinal column may essentially squeeze the abdominal cavity and change the configuration of its contents. What can happen next is the intestines can become kinked, twisted, or backed up. This can lead to changes in the flow within the intestinal system, resulting in overgrowth of bacteria, which then can cause gas formation, bloating, and change serotonin levels in the gut that sensitizes the nerves. There are studies supporting each of these assertions, although they are not typically thought of as a continuous, integrated mechanism of GI distress. Thinking about the physical phenomena that happen in relation to gravity, there is also the anterior abdominal wall, the last of the 4 gravity resistance mechanisms that I considered in the paper. A key function of the abdominal wall is to keep the abdominal stack in its upright configuration so that gravity does not cause it to fold down too far and bulge out and change its configuration (Figure 1).

For each mechanism described, gravitational force (g-force) resistance is at the center. An example of an abnormality in g-force resistance mechanisms is Ehlers-Danlos syndrome (EDS), a condition characterized by a stretchy suspension system. Almost all patients with EDS have IBS-like symptoms; almost all have bacterial overgrowth. In fact, one study suggests that up to half of people with IBS may in fact have hypermobile joints and stretchy ligaments. This raises the question of whether one's relationship to gravity and tolerance of gravity *in part* contributes to some people having chronic GI symptoms and others not. Consider how some astronauts when floating in space experience abdominal pain, bloating, and constipation. Many studies discuss why this is and why the microbiome appears to change in a zero-gravity environment. It is almost like there is a Goldilocks zone, where some gravity is needed because humans evolved in it, but too much gravity for certain people can be a problem, as can too little. During flight, some people get jet belly (abdominal distention, pain, bloating), a common condition in upper altitudes resulting from a variation in one's experience of gravity. The pressure differentials by altitude are determined by relative differences in g-force that change as one moves in altitude or even, to a much smaller degree, latitude.

G&H What is the g-force cube?

BS I mentioned *g-force resistance.* This relates to how well the physical body systems can resist the pull of gravity or tolerate gravity and is one of 3 factors that may determine IBS susceptibility, with the other 2 being *g-force detection* and *g-force vigilance* (Figure 2). Embryologically, we develop along 3 layers: the endoderm, the mesoderm, and the ectoderm. The focus so far in this discussion has been on the mesoderm—the embryological layer that holds the body together, like the glue of our body, including the bones, muscles, tendons, and ligaments. Mesodermal structures do a lot of work to help us manage gravity. So fundamental is g-force resistance to human existence that most of the time humans are unaware of its presence until they are made aware of it (eg, by falling or tripping). The question is what happens when there is mechanical vulnerability and how does this affect gravity management? The hypothesis is that pain in the mesodermal structures may be a sign of gravity intolerance (ie, that alignment with this fundamental force of nature is not optimized, and the farther a joint or an intestinal system stretches out of line with gravity, the more pain it generates). The intestinal system being pulled down leads to secondary consequences, which I mentioned. Bacterial overgrowth, for example, is a consequence, in part, of physical abnormalities in the gut related to gravity, as is EDS.

Problems with gravity management also affect the nerves and this is the second part of the g-force cube, which is g-force detection or sensitivity, a problem related to the embryological ectoderm, which gives rise to the

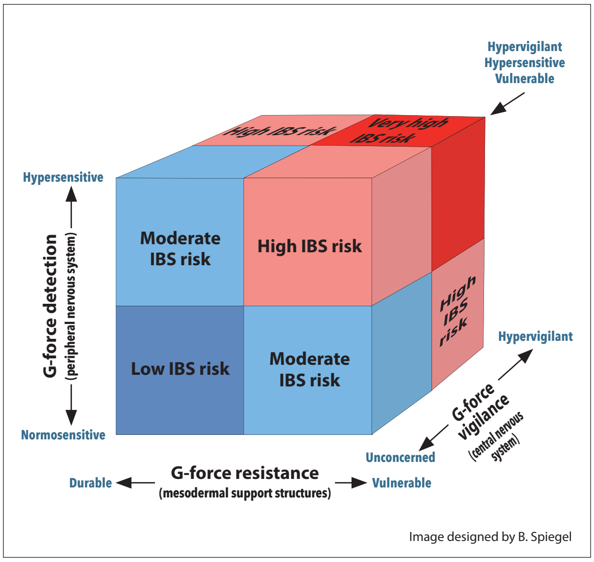

Figure 2. The g-force cube is a model showing how IBS susceptibility can be determined by 3 factors: g-force resistance; g-force detection; and g-force vigilance. These factors jointly define 8 IBS susceptibility profiles, ranging from very low risk (durable, normosensitive, unconcerned) to very high risk (vulnerable, hypersensitive, hypervigilant).

IBS, irritable bowel syndrome.

nervous system. Some people are much more sensitive to these kinds of phenomena than others. One universal gut sensation is the feeling of falling; being on a roller coaster, for example, everyone experiences butterflies. The question is, when feeling abdominal butterflies, is it a good or bad feeling? The difference can be seen, for example, when riding a roller coaster, people who smile in glee are *g-force-tolerant,* whereas people who feel extreme distress are *g-force-vigilant*. That sensitivity then determines how many signals are sent to the brain and central nervous system. The third part is the brain's reaction or g-force vigilance. How vigilant is the brain at detecting these signals as a threat? The hypothesis is that people with IBS and people with related conditions, such as fibromyalgia, postural tachycardia syndrome (POTS), and EDS, are affected by all 3 g-force factors and are highly likely to have mechanical vulnerability, hypersensitivity, and hypervigilance. In the paper, I describe how these factors jointly define 8 IBS susceptibility profiles.

G&H Can gravity explain the link between IBS and associated comorbidities?

BS EDS, POTS, and fibromyalgia commonly overlap, and they all have in common a form of gravity intolerance as well as abnormalities in serotonin function. In fact, altering serotonin levels is often effective in managing all those conditions. Serotonin is a pleiotropic hormone or neurotransmitter. Without it, humans could not stand up or survive in gravity. Serotonin is vital for the baroreceptor reflex that maintains blood pressure, alters cerebrospinal fluid levels with upward and downward movement, and maintains vestibular function. When looked at through the lens of gravity, it seems like serotonin might have evolved, in part, to be a gravity management substance. The fact that 90% to 95% of serotonin is created in the gut, under this hypothesis, suggests that the gut functions as the center of our gravity-management systems. Other reasons why serotonin may have this role and why all these comorbidities may share that abnormality are discussed in the hypothesis paper.

G&H Why are some people better designed to carry the abdominal load than others?

BS The idea is that like any other organ system, there are many natural variations in humans. Understanding the musculoskeletal comorbidities of IBS is an area that has been underdeveloped in the literature. There is very little research looking at the physical structures of patients with IBS compared with patients without IBS (eg, examining differences in the spine and its relationship to the bowels, differences in the insertion points of various tendons in the diaphragm and the falciform ligament or in the mesentery and intra-abdominal wall, and so forth). In the hypothesis paper, I use the analogy of an abdominal crane to describe the structures that work together to hoist the viscera within the abdominal cavity as a framework for future evaluation.

G&H Does the gravity hypothesis negate the significance of other factors thought to be important in IBS, like motility and visceral sensation?

BS That is a great question because, in a way, thinking about gravity unifies various meritorious evidence-based theories. My goal is not to undermine any of the existing theories but to try and think about how they can all be true at once. It is perplexing on the surface that so many different, seemingly incompatible theories about IBS can all coexist and have evidence to support them. The hypothesis paper contains explanations for how these theories can be linked to gravity. For example, there is no doubt that bacterial overgrowth plays a central role in IBS, but why it occurs in people with IBS remains a point of considerable debate and research. Kinked, twisted intestines will, like a kinked garden hose, become backed up and have abnormalities in the microbiome, a change in serotonin levels, which will activate metabolites, have sensitive nerves, and so on. That is just one example of how gravity interrelates with that theory. There are other theories about the brain-gut axis and about hypersensitivity, the amygdala and hypervigilance, as well as stress and cortisol. All those responses may in fact have evolved to help manage gravity. To assume that patients with IBS have only a bad mesentery, for example, would be shortsighted. Instead, the paper explores how the entire gut-brain system, as an *integrated whole,* manages gravity. In the paper, I discuss how people who are afraid of falling will have abdominal butterflies even before they fall because of the perceived threat, and what that might mean in terms of central hypervigilance in comparison to other people without fear of falling (like rock climbers) who remarkably seem to have quite opposite brains on functional magnetic resonance imaging scans, for instance.

G&H How do the effects of gravity strain help explain certain neuropsychological features of IBS?

BS One effect of gravity strain may be the neuropsychological symptoms of IBS. Often patients with IBS describe feeling anxious, a rapid heart rate, lightheaded, dizziness, and fatigued. What may be causing these feelings is the baroreceptor response, which is a set of receptors in the aortic arch of the carotid artery that are constantly monitoring whether our blood pressure is adequate. What the baroreceptor is really doing is telling the body if it has enough pressure to manage living in gravity. When there is not enough pressure because of gravity, the pressure falls. The baroreceptors fire off, and the nervous system fires up, the person becomes tachycardic, symptoms develop, and the person becomes nervous and shaky. It has been shown that people with IBS have very sensitive baroreceptors, as do people with POTS (which commonly overlaps with IBS), people with fibromyalgia, and people with EDS. This quartet of conditions share not only abnormalities in serotonin biology but also sensitivity to blood pressure and circulating volume. This literally is gravity intolerance—the body not quite knowing whether it is sufficiently managing this force of nature. The relationship between IBS, EDS, POTS, fibromyalgia, and certain IBS symptoms is further explored in the paper.

G&H What other new hypotheses regarding IBS pathogenesis do you find exciting and worthwhile for our readers to know about?

BS The work of Dr Emeran A. Mayer, who was my mentor at University of California, Los Angeles, stands out as a real highlight for me. Dr Mayer and colleagues have been working on the notion of the brain-gut axis for many years and positioning IBS in part as a breakdown in the bidirectional communications between the brain, the gut, and the microbiome. I think the gravity hypothesis is quite consistent with and bolsters the brain-gut axis evidence-based model. The hypothesis proposes that the systems managing this relationship between the brain and the gut evolved to manage gravity. Examining these systems at this level can help further understanding of why they may have come about and how different theories of IBS pathogenesis may coexist.

G&H What are the next steps for studying gravity in IBS?

BS I would begin by surveying IBS patients about their experiences in relation to gravity. The next step would be to test whether strategies to relieve g-force strain on the gut (eg, hypopressive abdominal exercise, use of tilt tables or inverted yoga positions, adjusting sleeping positions, float tank therapy, osteopathic manipulative therapies, core strength training) help IBS patients or affect their disease in a meaningful way. There is already evidence to support some of these interventions. The gravity hypothesis is a testable model to help improve understanding of how multiple ideas on IBS pathogenesis can be true simultaneously. The paper lists 30 different experiments that could be implemented to test this hypothesis.

It is not about changing gravity; it is about changing one's relationship to gravity that is important. Evidence shows that activities that improve how one interacts with gravity, such as exercise, tai chi, and visceral weight loss, can be beneficial to health and can help patients with IBS, but it is not known why. The gravity hypothesis might help answer this question. Enhancing our understanding of IBS can help us advance the care of our patients.

Disclosures
Dr Spiegel has no relevant conflicts of interest to disclose.

Suggested Reading

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