Could Intestinal Enzyme Deficiencies be the Cause of Your Abdominal Discomfort and Diarrhea?

By Cass Nelson-Dooley, MS and Stephen Olmstead, MD

The surface area of the gut has been estimated at approximately 32 m², about half the size of a badminton court. The small intestine consists of visible 0.5 mm to 1.5 mm fingerlike projections of tissue called villi, resembling shag carpet, that increase the surface area of the intestinal tract.

The predominant cell in the small intestine is the enterocyte, a highly specialized absorptive cell. The apical or luminal side of each enterocyte consists of about 3,000 tiny microvilli. This provides another layer of minute projections inside the intestinal tube (known as the lumen) that enhance absorption of the contents of the gastrointestinal tract. The microvillus surface of the enterocyte resembles a brush when viewed under a microscope, leading to the name, “brush border.” The brush border is where the final steps of digestion and absorption occur.

THE FINAL STAGE OF DIGESTION

A number of steps are involved in effective digestion of food from macromolecules down to single molecules (“monomers”) that are capable of being transported across the gut barrier. Salivary enzymes act first on food molecules, followed by gastric processes (hydrochloric acid, gastric lipase, and pepsin) which acidify food and break it down by enzymatic hydrolysis.

When partially digested food moves from the stomach to the first section of the small intestine, or duodenum, pancreatic enzymes act to further break down very long chain food molecules (“polymers”) into smaller molecules containing 2 to 12 monomers (“dimers” and “oligomers,” respectively). The resulting chyme mixture includes short protein/peptide oligomers (oligopeptides), amino acids, linear and branched carbohydrate oligomers and polymers (oligosaccharides and polysaccharides), and lipids.

The final stage of digestion is completed by brush border enzymes (BBE). This is a critical step because dimers and oligomers cannot in most cases be transported across the gut barrier. These molecules must be further digested into monomers for absorption to occur. Once BBE break food components down into their simplest, singular components, the monomers are able to cross the gut barrier.

Microvilli are the launching pad for brush border digestive enzymes. The microvillous tips of enterocytes shed BBE-containing vesicles, which can end up in the intestinal lumen. BBE may interact with food molecules from the enterocyte membrane, from brush border membrane lined vesicles, or while the BBE are free floating or solubilized. BBE are necessary for effective final digestion and absorption of complex carbohydrates and proteins.

BRUSH BORDER ENZYMES

The brush border contains many digestive enzymes including a set of oligopeptidases (that break down oligopeptides) such as amino-peptidase, carboxypeptidase, endopeptidase, and dipeptidases, as well as a suite of oligosaccharidases (that break down oligosaccharides). The brush border also contains specialized lipid-digesting enzymes, or lipases, such as phospholipases A2 and B1, which augment pancreatic enzyme breakdown of phospholipids. Alkaline sphingomyelinase and neutral ceramidase are two additional BBE lipases. However, the brush border’s contribution to the breakdown of lipids is quite limited.

BRUSH BORDER OLIGOSACCHARIDASES

Oligosaccharidases are BBE that can break down more than one type of carbohydrate linkage. Disaccharidases fall within this category and primarily transform disaccharides into their component monosaccharides (single sugars). They are critical for the final steps of carbohydrate digestion.

Lactase is perhaps the most widely known disaccharidase and lactase deficiency the most common BBE deficiency in the form of lactase nonpersistence. Lactase deficiency causes symptoms associated with lactose intolerance: abdominal discomfort, gas, and acidic, liquid stools.3

Sucrase-isomaltase is an intestinal proenzyme that is cleaved at the brush border membrane by pancreatic protease into sucrase and isomaltase.4,5 Sucrase, in addition to cleaving sucrose into glucose and fructose, breaks down maltose. Congenital sucrase-isomaltase deficiency (CSID) is associated with diarrhea, irritability, and vomiting.

Maltoase-glucoamylase is the third major brush border oligosaccharidase.2,6 Maltoase digests maltose into its 2 constituent glucose molecules. Maltose is a disaccharide sugar found in malt, cereal
grains, and many processed foods. Maltase is not just a disacchari-
dase, but possesses much broader carbohydrate-digesting activities. 
Glucosamylase releases glucose from the ends of starch and other 
polysaccharides. Deficiency of maltase-glucosamylase is associated 
with diarrhea, although usually less severe than CSID.6,9

**BRUSH BORDER Oligopeptidases**

Brush border peptidases are enzymes that break down oligopeptide 
chains into their constituent amino acids. There are 4 types of brush 
border peptidases: dipeptidylpeptidase IV (DPP-IV), carboxypepti-
dase, endopeptidase, and the aminopeptidases A, N, and P.10 Brush 
border DPP-IV is particularly important for digestion and assimilation 
of proline-rich food proteins such as casein, collagen, and gluten.1113 
Incomplete casein and gluten digestion, respectively, are known to 
produce opioid-like exorphins called casomorphins and gluteomor-
phins (aka gliadorphins). Children with autism spectrum disorders 
(ASD) have been shown to have higher urine concentrations of 
casomorphin-7 than control children.14

Gluteomorphins are thought to play a role in psychiatric disorders.15 
In addition, immunogenic prolyl peptides from gluten may contrib-
ute to the development of celiac disease. Both children and adults 
with celiac disease have abnormally low brush border DPP-IV 
activity.16

**CONSEQUENCES OF PRIMARY BRUSH BORDER ENZYME 
DEFICIENCIES**

BBE deficiencies may be categorized as primary or secondary. Pri-
mary BBE deficiency is congenital and involves a genetic alteration 
in which the body cannot manufacture a given BBE. Primary BBE 
deficiencies are surprisingly common, the most frequent being 
deficiency of the dairy sugar-digesting enzyme lactase. Primary 
lactase deficiency can be present at birth, in preterm infants, or in 
adults later in life.17

Congenital lactase deficiency has only been reported in a few 
infants.18 They develop malabsorption with uncontrollable diarrhea 
following initiation of breastfeeding or use of lactose-containing 
formulas. Developmental lactase deficiency refers to the relative lack 
of lactase in preterm infants before a gestational age of 34 weeks.17

Adult type hypolactasia (low levels lactase) is the most common 
type of BBE deficiency.17 In most mammals, lactase is needed only 
for digestion of breast milk early in life, before weaning. Perhaps for 
this reason, hypolactasia is found in two-thirds of the human popu-
lation due to a down-regulation of lactase production during child-
hood.19 Hypolactasia manifests after lactose intake with abdominal 
discomfort, gas, and acidic, liquid stools.3 The prevalence of lactose 
tolerance is 100% in Asian and American Indian populations, 
falling to 80% in African, Middle Eastern, and Hispanic populations. 
The lowest prevalence is 5% in northwestern European populations. 
A variety of genetic mutations have been reported to be associated 
with hypolactasia in adulthood.17,20

CSID is caused by a mutation in the sucrase-isomaltase gene. CSID 
haves serious consequences because people with this BBE deficiency 
cannot break down common dietary carbohydrates such as sucrose, 
maltose, or starch.5 After ingesting these compounds, the high concen-
tration of undigested carbohydrates in the intestinal tract leads to 
a type of diarrhea known as osmotic diarrhea, where an excessive 
amount of water is drawn into the bowels. CSID also leads to mild 
steatorrhea (the excretion of an abnormal amount of fat in the feces), 
irritability, vomiting, and bacterial overgrowth in the intestinal 
tract.5,21 Bacterial feeding on undigested sucrose in the gut releases 
methane, hydrogen, and carbon dioxide, which causes abdominal 
pain and bloating.5

CSID is more common than previously thought.5 In Americans of 
European ancestry, the prevalence of people with the genetic 
mutation that causes CSID is 2% to 8%.24 Some cases of CSID may 
be missed or incorrectly diagnosed if a low-sucrose, low-starch 
diet (prescribed for food allergies or nonspecific diarrhea) resolves 
symptoms.

Primary maltase-glucoamylase deficiency is also now seen to be 
common. One study of children undergoing endoscopy for dyspep-
sia (indigestion) found that 50% had a deficiency of one or more 
disaccharidases and 28% had deficient maltase-glucoamylase.8 
In two-thirds of these cases, lack of maltase-glucoamylase was 
associated with low activity of other disaccharidases. In a large 
review of 30 American and European studies, the prevalence of 
maltase deficiency was 12.6%, sucrase deficiency 9%, and isomalt-
ase deficiency 9.1%. As expected, lactase deficiency was the most 
common at 39.2%.23 The principal finding associated with these 
deficiencies was duodenitis (inflammation of the duodenum) with 
a prevalence ranging from 6% to 24%. The study also found a clear 
correlation between increased levels of inflammation and lower 
disaccharidase activities.

**CAUSES OF SECONDARY BRUSH BORDER ENZYME 
DEFICIENCIES**

Secondary or acquired BBE deficiencies are associated with a variety 
of causes ranging from autoimmune to infectious. Any condition 
that damages microvilli could result in a secondary BBE deficiency. 
The wasting away of microvilli (villous atrophy) found in celiac 
disease is regularly associated with BBE insufficiency,24 but brush 
border disaccharidase deficiency in the absence of villous atrophy 
is also common and may in fact be an early indicator of celiac 
disease.25

Chemotherapy, radiation, and use of certain drugs are also associated 
with brush border damage, villous atrophy, and by extension 
secondary BBE deficiencies.5 The angiotensin II receptor blocker 
olmesartan, used for high blood pressure, can cause villous atrophy 
and malabsorption.26 Codeine inhibits sucrase activity,27 and the 
histamine-2 (H2) receptor antagonist ranitidine used to treat ulcers 
binds to sucrase, inhibiting its activity.28

Gastroenteritis caused by a variety of pathogens does structural 
damage to the brush border and impairs BBE activity.4 Both Yersinia 
enterocolitica and rotavirus damage brush border structure caus-
ing villous atrophy and reduced BBE activities, which may persist 
after resolution of the acute infection.29,30 Shiga toxin, produced by 
Shigella dysenteriae and enterohemorrhagic strains of Escherichia 
coli, inhibits brush border functional protein synthesis and directly 
damages the intestinal epithelium, reducing BBE activity by 50%.31 
Acquired immunodeficiency syndrome (AIDS) is regularly asso-
ciated with severe lactase and sucrase-isomaltase deficiencies.32 
Colonization of the proximal small intestine with the waterborne 
pathogen Giardia lamblia leads to microvillus shortening, villous 
atrophy, and reduced disaccharidase and protease activities.33

Animal models of induced inflammatory bowel disease (IBD) reveal 
that proinflammatory cytokines decrease the synthesis of sucrase-
isomaltase in the small intestine.4 Persons with small intestinal 
bacterial overgrowth (SIBO) typically present with gas, abdominal 
discomfort, flatulence, and diarrhea, symptoms that also characterize 
disaccharidase deficiencies. A dog model of spontaneous SIBO is 
associated with villous atrophy, but preserved disaccharidase
activities. However, infants with congenital disaccharidase insufficiency experience SIBO. Furthermore, some people with SIBO have marked reductions in BBE activities. Cell cultures of bacteria sampled from people with SIBO show significantly reduced lactase, sucrase, and maltase activities. In a Russian study of 386 patients with postinfectious irritable bowel syndrome (IBS), 36.5% had moderate or severe lactase deficiency and all had SIBO. The fact that cigarette smoking is associated with depressed brush border disaccharidase activities highlights how common BBE deficiencies are as well as the sensitivity of the brush border to environmental toxins. Deficient activities of brush border lactase, sucrase, and alkaline phosphatase have been called “biomarkers for intestinal damage,” which attests to the link between BBE and intestinal mucosal health. BBE activities are used to gauge intestinal brush border health or injury in the medical literature. While there are some exceptions, the disaccharidases lactase, maltase, and sucrase are suppressed when there is damage to the brush border but return to normal levels when the brush border begins to repair. The falloff and restoration of disaccharidase activity is directly correlated with mucosal injury and mucosal healing in cases of celiac disease and infectious enteritis.

**SUPPORTING BRUSH BORDER FUNCTION WITH ENZYME REPLACEMENT**

Primary and secondary BBE deficiencies can be effectively managed with enzyme replacement. Practical support entails furnishing enzymes with essential BBE activities. These include enzymes with glucoamylase and isomaltase activities, important disaccharidases, and a protein-peptidase complex with DPP-IV activity.

**Glucoamylase** is a brush border carbohydrate that catalyzes the hydrolysis of starch and other polysaccharides. It has isomaltase activity, making it an excellent enzyme for the digestion of amylopectin and isomaltose carbohydrates. glucoamylase functions in concert with other BBE such as sucrase and maltase to liberate glucose for absorption in the intestinal tract.

**Lactase**, a member of the beta-galactosidase enzyme family, breaks apart a bond in lactose yielding its component β-D-galactose and β-D-glucose monosaccharides. Its presence is essential to relieve symptoms if lactase-deficient individuals consume foods and beverages containing lactose.

**Maltase**, also known as alpha-glucosidase, is an enzyme that specifically digests maltose into its 2 constituent glucose molecules. However, far from being a limited disaccharidase, maltase possesses much broader carbohydrase activities. It cleaves bonds in amylose and amylopectin and can also digest isomaltose and glycogen (a storage form of glucose found in liver and skeletal muscle tissue).

**Sucrase (invertase)** has the distinctive ability to break down the glycosidic bond in sucrase disaccharides yielding glucose and fructose. Sucrose, commonly known as refined table sugar, is an important disaccharide made by plants, but not animals. In humans, sucrase is complexed with the enzyme isomaltase in the brush border microvilli. Sucrase derived from plant or microbial sources, often used to treat CSID, has no isomaltase activity.

**Protease/Pepitidase Complex with DPP-IV activity** has both endo- and exopeptidase functions. Protease activity fulfills the brush border function of converting protrypsin into trypsin, an important proteolytic enzyme. Endo- and exopeptidase functions ensure proteins are digested to yield amino acids and oligopeptides. Complete digestion of proline-rich proteins such as casein and gluten is facilitated by DPP-IV, a unique mammalian, membrane-bound, serine-type exopeptidase. DPP-IV aids in the absorption of proline-rich proteins. DPP-IV enzymes are widely distributed throughout the body where they serve to regulate peptides involved in neurotransmission, immunity, and hormonal activity.

DPP-IV is critical to the catabolic inactivation of exorphins, bioactive peptides with morphine-like opioid effects. Exorphins derive primarily from dietary casein, gluten, and soy and may in part be responsible for the neurological and behavioral symptoms seen in persons with ASD and gluten sensitivities. The DPP-IV activity present in the protease/peptidase complex provides for complete digestion of proline-rich proteins and efficient breakdown of dietary exorphins.

**SUPPORTING BRUSH BORDER FUNCTION WITH PROBIOTICS**

The probiotic yeast *Saccharomyces boulardii* is well documented to provide a host of benefits in IBD and IBS. It can be effectively used to prevent and treat *Clostridium difficile* disease and to reduce the risk of antibiotic-associated and traveler’s diarrhea. It antagonizes an array of pathogens including *Candida* organisms.

*S. boulardii* significantly increases the activity of intestinal disaccharidase enzymes including sucrase-isomaltase, lactase, and maltase-glucoamylase. It also stimulates activities of other intestinal BBE such as alpha-glucosidases, alkaline phosphatases, and aminopeptidases. Within the intestinal lumen, *S. boulardii* secretes a sucrase with such high activity that *S. boulardii* has been proposed as a treatment for CSID. *S. boulardii* has also been found to secrete a leucine aminopeptidase that boosts the breakdown of small N-terminal peptides. This enzyme may reduce the development of allergies to dietary proteins, especially after recovery from acute gastroenteritis, decreasing the likelihood of persistent diarrhea.

*Lactobacillus* and *Bifidobacterium* probiotics with demonstrable lactase activities have been used for decades to manage lactose intolerance. There is evidence that treatment with strains of *Lactobacillus casei* and *Bifidobacterium breve* may confer benefits in lactose intolerance for up to 3 months after discontinuation of the probiotics. *Lactobacillus rhamnosus* GG has been shown to significantly restore BBE in mice infected with *Giardia*. The probiotic both prevented BBE damage when administered prophylactically and raised BBE when administered in parallel with *Giardia* inoculation. A probiotic mixture containing *Bifidobacterium* strains, *Lactobacillus* strains, and *Streptococcus thermophilus*, known to reverse intestinal injury and normalize gut barrier function, increased BBE activity in mice and humans with colitis.

**BENEFITING FROM BRUSH BORDER ENZYME SUPPORT**

The final stages of carbohydrate and protein digestion and absorption are heavily dependent on BBE. Primary and secondary BBE deficiencies are common and clinically manifest as intestinal gas, abdominal discomfort, flatulence, and diarrhea, mimicking symptoms of IBS. Digestive enzyme replacement for primary BBE deficiencies has been shown to be effective. The conditions most likely to benefit from BBE support include lactase deficiency, celiac disease, SIBO, giardiasis, maladaptation, malabsorption, postchemotherapy and radiation, and gastroenteritis. Dietary changes, BBE replacement, and supplementation with *S. boulardii*, *Bifidobacterium*, and *Lactobacillus* probiotics may improve BBE activities, digestion, absorption, and overall gastrointestinal health.

**REFERENCES:**
Cardiovascular disease (CVD) is the number one cause of death in the United States according to the Centers for Disease Control and Prevention (CDC).1 Corresponding to the high level of cardiovascular mortality, individuals in modern society are subjected to excessive amounts of chronic stress lending support to the possibility that stress is implicated in the development and worsening of CVD.

The cardiovascular effects of mental stress may involve elevations in heart rate, blood pressure, and cardiac output.2 The fact that there is a high prevalence of anxiety and mood disorders in people who have heart disease3 also lends merit to the idea that emotional stress is a risk factor for cardiovascular conditions. In this article, we will explore the connection between stress and CVD and discuss the natural options for reducing stress and enhancing heart health.

EMOTIONAL STRESS AND YOUR HEART
Coronary artery disease in adults is almost always caused by coronary artery atherosclerosis. When the heart is acutely or chronically deprived of necessary blood flow by atherosclerotic processes, ischemic heart disease occurs. Angina pectoris, heart attacks, ischemic cardiomyopathy, and most cases of sudden cardiac death all fall under the category of ischemic heart disease due to coronary artery disease. These disorders are the most serious forms of CVD.

Acute and chronic mental stress may induce heart attacks or sudden cardiac death or worsen underlying CVD.4 Many people who have coronary artery disease develop myocardial ischemia (lack of oxygen to the heart) when subjected to emotional stress.3,4 Researchers have observed that mental stress during daily life, including reported feelings of tension, frustration, and sadness, can have more than double the risk of myocardial ischemia in the following hour.5 Mental stress-induced myocardial ischemia is linked to a 3-fold higher occurrence of fatal and nonfatal cardiac events.6,7

In numerous studies, intense mental stress or anger is associated with the onset of acute cardiac events, such as heart attack or sudden cardiac death. Studies have shown that a significant number of patients were angry or stressed hours before they experienced cardiac arrest.8,9 Furthermore, an increased incidence of heart attacks occurs after an acutely stressful event such as the loss of a loved one.10 Scientists report that being under a high-pressure deadline at work is associated with a 6-fold increase in the likelihood of having a heart attack during the next 24 hours.11

Acute stress is also associated with cardiac rhythm changes. This was evident for the 30 days after the September 11, 2001 attacks on the World Trade Center when there was a significant increase in life-threatening ventricular arrhythmias among patients with implanted cardioverter defibrillators in the New York area.12 Additionally, acute psychological stress can result in electrocardiogram (ECG) T-wave alternans,13 which is an established sign of cardiac rhythm instability and, in sensitive individuals, increases susceptibility to serious ventricular arrhythmias and sudden cardiac death.14

Chronic stress is equally damaging to the heart and is associated with an elevated risk of ischemic heart disease.15 The effects of chronic psychological stress may last for a long time after the cause of stress dissipates. Males around the age of puberty who survived

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the siege of Leningrad in the 1940s suffered from hypertension and a greater risk of mortality from CVD later in life compared to Russians who did not live in the besieged city.

This is consistent with studies investigating the association between posttraumatic stress disorder (PTSD) and vascular diseases. Scientists have observed that women with the greatest PTSD symptoms are nearly twice as likely to experience venous thromboembolism (a type of blood clot) compared with women who were never exposed to trauma. In addition, veterans suffering from PTSD have a 25% to 50% elevated rate of heart attacks and heart failure compared with veterans who do not have PTSD. Nonveterans diagnosed with PTSD are 3.4 times more likely to suffer heart failure compared to those not diagnosed with PTSD.

A possible mechanism by which mental stress induces CVD is by weakening of the blood vessel lining, or endothelium. The extent of endothelial dysfunction caused by stress is associated with changes in the systemic vascular resistance response, which has been linked with oxygen deprivation to the heart as well as other heart-related problems. Endothelial dysfunction can occur for up to 1.5 hours after exposure to a mental stressor. Over time, these episodes of impairment could progressively lead to CVD. Nitric oxide (NO) may offer another connection between CVD and stress. NO is involved with the relaxation of blood vessels and maintenance of normal blood pressure, so imbalanced levels can lead to impaired cardiovascular function. At the same time, NO plays a role in regulating secretion of cortisol, the “stress hormone.” Additionally, neuronal nitric oxide synthase (nNOS) suppresses cortisol receptors in the hippocampus of the brain and may be involved in regulating activity of the hypothalamic-pituitary adrenal (HPA) axis. Cortisol receptors and the HPA axis play important roles in your body’s response to stress.

Intense psychological stress may also trigger cardiomyopathy. Stress-induced cardiomyopathy is characterized by symptoms similar to a heart attack such as chest pain and ECG abnormalities, but usually does not involve blockage of the coronary arteries. Stress cardiomyopathy is a known trigger of acute heart failure, lethal ventricular arrhythmias, and ventricular rupture.

MENTAL STRESS AND CARDIAC TISSUE DAMAGE
Myocardial ischemic reperfusion injury occurs when blood flow to the heart is stopped and then subsequently restored. Ischemic reperfusion injury is the major cause of cardiac tissue damage in heart attacks, sudden cardiac death, and cardiac bypass surgery and is implicated in the morbidity and mortality related to ischemic heart disease and heart attacks. Both acute and chronic stress have an impact on reperfusion injury. Interestingly, rodent models indicate acute stress may actually reduce the risk of arrhythmia due to myocardial ischemia reperfusion injury. On the other hand, chronic stress increases the risk of arrhythmias and ischemic injury to the heart.

HOW HIGH STRESS HORMONE LEVELS DAMAGE THE HEART
The HPA axis, which is involved in the fight-or-flight response to stress, plays a role in the association between CVD and stress. Psychological stress signals the hypothalamus to produce corticotropin releasing hormone (CRH), which in turn triggers the adrenal glands to release cortisol into the systemic circulation. Research indicates elevated CRH levels may also contribute to endothelial dysfunction.
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SHIELDING THE HEART FROM THE CARDIAC CONSEQUENCES OF STRESS

Beyond foundational support with nutrients like vitamin D, which has been found to be protective of the heart, a number of specific nutrients can reduce the effects of stress, protect the heart from stress-related damage, and help maintain healthy blood pressure.

L-CITRULLINE

L-Citrulline, an NO precursor, can help compensate for stress-related declines in NO. Many studies indicate this amino acid can support healthy blood pressure. In one study, researchers investigated the effects of 6 g/day of L-citrulline or a placebo in 16 healthy overweight or obese males evaluated at rest and during performance of an isometric handgrip exercise. L-Citrulline reduced aortic systolic blood pressure and systemic arterial stiffness in response to exercise-induced stress.

GRAPE SEED EXTRACT

Grape seed extract (GSE) is well researched in both humans and animal models for its antihypertensive effects. Researchers conducted a randomized, double-blind, placebo-controlled study of middle-aged adults with prehypertension. A total of 29 subjects were first given a placebo for 2 weeks, then switched to juice containing either 0 mg or 300 mg/day of GSE for 6 weeks, followed by 4 weeks of no treatment.

Systolic blood pressure (upper number) fell a significant 5.6% after 6 weeks of GSE supplementation and diastolic blood pressure (lower number) declined by 4.7%. Blood pressure reverted back to baseline levels during the 4-week period of no treatment. Participants with higher initial blood pressure experienced the greatest declines, almost double the effect size. Grape seed polyphenols have high antioxidant activity and enhance blood circulation by strengthening capillaries. Some studies also indicate GSE can enhance endothelial function.

TAURINE

The amino acid taurine protects the heart and has antistress effects. Taurine is critically important for cardiovascular function. In chronic heart failure patients, taurine supplementation stabilizes vital signs and improves cardiovascular function. One of taurine’s primary roles in the heart is influencing the mitochondrial respiratory chain. Researchers have noted that the impairment of respiratory chain function in taurine-deficient hearts leads to reduced energy metabolism and lowered generation of ATP, the molecule that serves as a fuel for the muscles of our bodies, including cardiac muscle. Taurine also exerts antistress effects, which include normalizing stress hormone levels in rodents. Additionally, life stress scores in female college students were reduced after taurine supplementation.

MAGNESIUM

Like taurine, the essential mineral magnesium possesses a dual role in that it protects the heart and guards against the effects of stress. Higher serum magnesium concentrations are associated with reduced risk of developing heart failure, while low magnesium intake has been linked to a greater likelihood of future heart failure-related hospitalizations. In patients with chronic kidney disease, there is a strong association between serum magnesium and coronary artery calcification, with higher magnesium levels having a protective effect. And one study found persons with higher serum magnesium levels had a 48% lower risk of hypertension than did people with lower magnesium levels.

Beyond its heart-protective abilities, magnesium is critically important to help the body cope with stress. Magnesium plays a role in regulating the HPA axis, and magnesium deficiency worsens stress reactions such as anxiety. Researchers found that magnesium-deficient mice showed signs of being more stressed then controls during anxiety tests. Magnesium deficiency also led to changes in HPA axis function.

Both mental and physical stress create a vicious circle where an excessive amount of magnesium is expelled from the body, thus reducing the ability to cope with stress. Conversely, supplementation with magnesium protects the nervous system against the negative effects of stress.

L-THEANINE

L-Theanine is an amino acid found in green tea. Current evidence proposes that L-theanine causes alpha-wave brain activity, which is associated with relaxation. We discussed in detail L-theanine’s antistress effects in last month’s article about stress and immunity. L-Theanine’s relaxation properties may benefit the heart as well. In spontaneously hypertensive rats, intraperitoneal administration of L-theanine resulted in a significant decrease in blood pressure. L-Theanine also protects against cerebrovascular disease such as strokes and triggers the production of NO from endothelial cells, facilitating dilation of the arteries.

ASHWAGANDHA

Ashwagandha (Withania somnifera) is a powerful antioxidant, anti-inflammatory, and heart-protective botanical. It is an adaptogen known for its ability to strengthen the adrenal glands during stress. In an animal study, scientists demonstrated that ashwagandha extract can protect against pulmonary hypertension. It has also been shown to suppress cell death after ischemia-reperfusion and increase levels of endogenous antioxidants, maintain antioxidant status in the heart, and restore altered blood flow in animal models of heart attacks.

SUPPORTING HEART HEALTH DURING STRESS

Acute and chronic mental stress can produce profound changes in the cardiovascular system, leading to ischemia and hypertension. Heightened activity of the HPA axis and the sympathetic nervous system can contribute to the adverse effects of stress on the heart. Specific nutrients such as L-citrulline and GSE protect the heart, while taurine, magnesium, and ashwagandha extract have both heart-protective and antistress properties. L-theanine can be used when you’re stressed to produce a state of relaxation while at the same time benefiting the heart.

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Mitochondrial Support for Autism Spectrum Disorders

By David Wolfson, ND

Despite over a half century of research, autism remains one of the most poorly understood neurological disorders. A condition with wide variations in clinical and genetic presentation, the neurochemical basis of autism remains elusive, even as its prevalence continues to rise. According to the Centers for Disease Control and Prevention (CDC), autism currently affects 1 child in 68.1 This is up 30% from their previous estimate of 1 child in 88 in 2012,1 and some evidence points to an even higher prevalence rate.2

In recent years, research has established a link between autism and dysfunction of the mitochondria, the powerhouses of cells. Pathological processes associated with autism such as increased oxidative stress, heightened inflammatory responses, and immune dysregulation all adversely impact mitochondrial function. Impaired mitochondrial energy production may then exacerbate the neurological deficits of autism. Disturbed mitochondrial function may thus result from, and further contribute to, the development of autism.

This article reviews the current research regarding autism and the functioning of mitochondria and proposes a number of approaches to support and promote mitochondrial health.

**AUTISM BACKGROUND**

Autism belongs to a group of neurodevelopmental conditions known as autism spectrum disorders (ASD). While its origin remains unclear, ASD is believed to be an inherited disorder in which genetic, epigenetic, and environmental factors combine to produce abnormal neurobehavioral patterns.3 Often diagnosed early in life, children with ASD are characterized by social withdrawal, communication deficits, and repetitive or restrictive behavior patterns. Ancillary conditions including seizures, gastrointestinal symptoms, and immune dysfunction are commonly found in ASD.4,6 Neurobehavioral disorders related to autism and grouped under the ASD heading include Asperger Syndrome, Rett Syndrome, and Childhood Disintegrative Disorder.7

Some people with ASD present with severe behavioral and neurological deficits, while others exhibit only mild or sporadic impairments in social interactions. Children with ASD may display characteristic symptoms before the age of one, or appear to progress normally for their first year or more and then experience a sudden “regression” of social and/or language skills.8 The differences in incidence, severity, and timing of ASD symptoms is mirrored by the incidence, severity, and timing of ASD symptoms.8 The differences in incidence, severity, and timing of ASD symptoms is mirrored by the severity of ASD symptoms.8 The differences in incidence, severity, and timing of ASD symptoms is mirrored by the severity of ASD symptoms.8 The differences in incidence, severity, and timing of ASD symptoms is mirrored by the severity of ASD symptoms.8 The differences in incidence, severity, and timing of ASD symptoms is mirrored by the severity of ASD symptoms.8

**WHAT MANY PEOPLE WITH AUTISM HAVE IN COMMON**

Many people with ASD share common pathological features. Increased oxidative stress markers, for example, are frequently found in autistic children,10-12 and sometimes their parents.11 In some studies, oxidative stress levels positively correlate with the severity of ASD symptoms.14,15

ASD patients also have a tendency toward heightened inflammatory responses. Increased expression of proinflammatory cytokines (proteins important in immunity and inflammation) such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma have been measured in the blood and tissues of ASD patients.16,17 Researchers have also reported neuroinflammatory processes in brain and cerebrospinal fluid (CSF) samples obtained from people with autism at autopsy.18

Immune dysregulation is another commonly observed feature in ASD. Whether due to maternal autoantibodies, exposure to

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environmental toxins or other factors, researchers have theorized that chronic dysregulated immune function plays a major role in the overproduction of cytokines and ensuing neuroinflammation that occurs in ASD.19

It is interesting to note that each of these abnormalities—oxidative stress, inflammation, and immune dysregulation—can impair the health and function of cellular mitochondria. Oxidative free radicals, for example, may damage proteins and lipids in mitochondrial membranes, inhibit bioenergetic processes within mitochondria, and alter DNA in ways that affect mitochondrial structure and function.20 Over the last 10 years, research on the role of mitochondria in neuropsychiatric disease has increased considerably, and a good portion of this research supports a link between mitochondrial dysfunction and the development of ASD.11

WHAT ARE THE MITOCHONDRIA AND HOW DO THEY FUNCTION?
Mitochondria are often referred to as the “powerhouses” of cells because they convert nutrients and oxygen into energy. A mature human cell may contain relatively few or many thousands of mitochondria depending on its energy requirements.

Mitochondria are bounded by an outer phospholipid membrane similar in nature to the cellular membrane. Inside the mitochondrion, an inner membrane encloses a gel-filled matrix. The folds, or cristae, of this inner membrane, along with the matrix, contain the enzymes and protein complexes associated with cellular respiration, the process that produces energy in the body. Energy derived from mitochondrial respiration is essential for virtually all life functions including cellular reproduction, muscle contraction, production of digestive and metabolic enzymes, synthesis and secretion of hormones, and transmission of nerve impulses.

Mitochondria produce energy by metabolizing the breakdown products of carbohydrates, fats, and proteins. Digestion of each of these macronutrients in the gastrointestinal tract yields energy-rich molecules that are absorbed and delivered to cellular mitochondria to be broken down.

Glucose, produced from carbohydrate digestion, is the principal high-energy molecule obtained from the diet. Once absorbed and brought to the body’s cells, glucose can either be stored as glycogen, converted to other biomolecules such as lipids or amino acids, or burned for energy. Glucose used for energy production first undergoes a degradation process known as anaerobic glycolysis in the cellular cytoplasm. Anaerobic glycolysis yields a small amount of energy along with two molecules of pyruvic acid. In the presence of oxygen, pyruvic acid can pass from the cytoplasm into the mitochondria and be further metabolized to produce a substantially greater amount of energy.21

The two primary energy-producing pathways within the mitochondria are the Krebs cycle and the electron transport chain (ETC). In the Krebs cycle, metabolites of pyruvic acid are sequentially stripped of carbon and hydrogen atoms. The removed carbons combine with oxygen to form carbon dioxide (CO₂), most of which is exhaled as a waste product through the lungs. The hydrogen atoms, along with the electrons they bear, are delivered to the ETC where they are passed through a series of carrier complexes and ultimately combine with oxygen to become water (H₂O).

At key steps along the ETC, energy is released from the electrons being passed from one carrier complex to the next. Most of the energy extracted in the ETC is converted to heat to help maintain normal body temperature. The remainder is used to generate the high-energy storage molecule, adenosine triphosphate (ATP). This process, known as “oxidative phosphorylation,” yields up to 38 molecules of ATP per molecule of glucose. By comparison, anaerobic glycolysis generates only 6 to 8 molecules of ATP, demonstrating the enormous energy benefits cells (and higher organisms) enjoy by using aerobic mitochondrial respiration.21

While energy production is the principal activity of mitochondria, these organelles also play an important role in the life and death cycle of cells. Disruption of mitochondrial function or damage to mitochondrial DNA (mtDNA) can result in mitochondrial membranes becoming more permeable leading to leakage of harmful agents from the mitochondria into the rest of the cell. These agents can then trigger a process known as apoptosis, or programmed cell death.22 Maintaining adequate intramitochondrial levels of antioxidants such as L-glutathione is an important factor in preventing oxidative damage to mitochondria and the subsequent initiation of events leading to apoptosis.23,24

WHY MITOCHONDRIAL FUNCTION IS IMPORTANT IN AUTISM
Neurons are more dependent on mitochondria for survival than most other cells as their capacity to produce energy from anaerobic glycolysis is very limited.25 Neuronal signaling is also an energy-intensive process that requires large inputs of ATP.26 It is not surprising therefore that impaired mitochondrial function has been linked with a wide variety of neurological and neuropsychiatric disorders, ASD among them.27,28

Over the past several decades, approximately 100 studies have appeared in the medical literature implicating mitochondrial dysfunction in the development of autism.11 While it is beyond the scope of this article to comprehensively assess such a vast body of literature, a brief review of the relevant findings can be presented.

Since 1985, many studies involving ASD patients have reported abnormal biomarkers suggestive of a mitochondrial disorder. One of the more common findings is elevated blood and tissue levels of lactic acid.11,19-22 Although excess lactic acid can derive from a number of sources, it is widely considered an indicator of impaired aerobic oxidation within mitochondria.23 Other abnormal biomarkers observed in ASD patients and suggesting mitochondrial pathology include high levels of pyruvic acid,30,32,34,36 low levels of L-carnitine,32,33,37,38 and the presence of antimitochondrial antibodies.39 In some studies, the degree of biomarker abnormality has been shown to be linked to the severity of ASD symptoms.33,38

A GENETIC LINK
Although mitochondrial dysfunction may result from pathological processes such as excessive oxidative stress, inflammation, or immune dysregulation, as mentioned earlier, it may also arise due to genetic factors. A number of studies have observed mutations in mtDNA obtained from the blood or tissues of persons with ASD. In one case study, researchers identified a pathogenic mtDNA mutation in a sibling pair where the male presented with ASD and the female was diagnosed with a degenerative neurological condition known as Leigh syndrome.40 Other scientists examined 5 children with ASD and found 2 had a mtDNA mutation in their tissues, while the same mutation was found in maternal tissue samples from 2 of the other children (the fifth child did not display this particular mutation, but had significant depletion of mtDNA in her skeletal muscle).41

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In a larger trial involving 449 subjects and matched controls without ASD, researchers demonstrated a significant association between autism and genetic mutations known as single-nucleotide polymorphisms (SNPs) on one gene important in the mitochondrial ETC. And, finally, several research studies encompassing almost 1,000 subjects with ASD have reported finding SNPs within another gene important in mitochondrial function.

**WEAKENED ENERGY PRODUCTION**

Beyond biomarkers and gene mutations, perhaps the most direct evidence of mitochondrial involvement with ASD can be found in studies showing defects in mitochondrial energy-production pathways. Such defects have been observed in both peripheral and central nervous system tissues of patients with ASD.

In one study, scientists found deficiencies in mitochondrial ETC Complexes III and IV in skeletal muscle tissue from a 3-year old autistic child. A similar study reported deficiencies of mitochondrial Complexes I, IV, and V in deltoid muscle biopsies from 6 of 11 ASD children. Likewise, researchers analyzed skeletal muscle samples from 25 patients with ASD and discovered Complex I deficiencies in 64% and Complex III deficiencies in 20% of the subjects. And a 2010 study reported in the prestigious journal *JAMA* examined white blood cells from 10 autistic children and found impaired activity of ETC Complexes I and V in 6 and 4 of the subjects, respectively.

In recent years, evidence has also begun to emerge of such defects appearing in the brains of ASD patients. Using postmortem samples from brain tissue banks, scientists measured mitochondrial proteins from the temporal lobe of 20 ASD subjects (ages 3 to 60) and 25 control subjects (ages 2 to 65). The temporal lobe is a brain region involved with auditory processing, language, social perception, and facial recognition. Significant reductions in proteins associated with mitochondrial respiratory chain Complexes I, III, IV, and V, along with significantly diminished mitochondrial antioxidant capacity, were observed only in the ASD subjects. Interestingly, these abnormalities were seen primarily in ASD children under 10 years old, a time period when critical neurodevelopmental processes are taking place.

Two research groups have demonstrated abnormal gene expression related to mitochondrial function in the brains of ASD patients. One group of researchers reported a notable downregulation of genes linked to mitochondrial ATP synthase (the enzyme responsible for synthesizing ATP) and ETC Complexes I and III in ASD cerebellar and occipital brain tissues. Another group of scientists examined tissue from various brain regions of ASD patients and observed reduced expression of 11 genes associated with ETC Complex I, 5 genes each associated with Complexes III and IV, and 7 genes associated with Complex V.

Other researchers measured ETC complex levels in the cerebellum and frontal, parietal, temporal, and occipital lobes of 7 children and adults with ASD and 7 age-matched controls. They found significant reductions of Complexes III and V in the cerebellum, Complex I in the frontal lobe, and Complexes II, III, and V in the temporal lobe of ASD patients compared to control subjects. As in an earlier study, the affected brain regions in this study also exhibited evidence of heightened oxidative stress, and the observed mitochondrial defects appeared only in children, not adults, suggesting a normalization of mitochondrial dysfunction may occur over time.

**MITOCHONDRIA OFTEN, BUT NOT ALWAYS INVOLVED**

Mitochondrial dysfunction is not apparent in all cases of autism. In fact, some investigators have failed to find associations between autism and mitochondrial abnormalities. One group of researchers found no evidence of a mitochondrial gene mutation commonly reported to affect autistic patients. Other scientists looked for specific evidence of a defect in mitochondrial Complex 1 in both ASD and schizophrenia patients and found only the schizophrenic subjects to be affected. Such studies are in the minority, however, as most research probing the involvement of mitochondrial pathology in ASD has yielded positive findings.

A recent review article estimates 30% to 50% of children with ASD display evidence of mitochondrial dysfunction. This large subset of ASD cases (numbering in the millions) may benefit from medical and nutritional interventions designed to support proper functioning of mitochondria.

**COENZYME Q10**

Coenzyme Q10 (CoQ10), or ubiquinone, serves multiple functions in the body, but is best known as an electron carrier in the ETC. It is also the only fat-soluble antioxidant produced within the body. As part of the mitochondrial respiratory chain, CoQ10 plays an integral role in the production of energy. As an antioxidant with widespread distribution in the body, CoQ10 inhibits the oxidation of vital structures such as DNA, membrane phospholipids, and circulating lipoproteins, and also helps regenerate vitamin E.

Although CoQ10 is endogenously synthesized and found in both plant and animal foods, a number of factors including aging, chronic illness, and use of statin medications can deplete CoQ10 from the body. Additionally, recent evidence suggests mutations in genes responsible for CoQ10 biosynthesis and distribution are associated with specific genetic factors linked to autism and other neurological disorders.

Supplementation with CoQ10 restores plasma levels of the nutrient and exerts a beneficial effect in a variety of conditions associated with impaired mitochondrial function, including neuropsychiatric disorders. Supplemental CoQ10 is available in both an oxidized ubiquinone form and a reduced ubiquinol form. According to available evidence, orally ingested ubiquinone is reduced to ubiquinol either during or after absorption from the intestinal tract, but has poorer bioavailability than ubiquinol.

While research is scarce, both ubiquinone and ubiquinol have been studied as potential treatments for ASD. In a randomized, double-blind, placebo-controlled trial, scientists incorporated 50 mg of ubiquinone into a comprehensive multinutrient supplement that was administered to 72 children and adults with ASD. A matched control group of 69 subjects received placebo. At 3 months, multiple markers of antioxidant status had improved in the nutrient group. Subjects receiving the supplement also exhibited significantly improved face recognition. Significant reductions in proteins associated with auditory processing, language, social perception, and facial recognition were observed only in the ASD subjects. Interestingly, these abnormalities were seen primarily in ASD children under 10 years old, a time period when critical neurodevelopmental processes are taking place.

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greater improvements on the Parental Global Impressions-Revised (PGI-R) scale, and on subscores for hyperactivity, throwing tantrums, and receptive language.65

In a smaller, uncontrolled trial, researchers supplemented 24 ASD children ages 3 to 6 with 50 mg/day of ubiquinol for one week, increasing the dose to 100 mg/day for the remainder of the study. After 3 months, average plasma CoQ10 levels had risen significantly from 0.51 to 3.02 µmol/L. In the subset of children who achieved plasma CoQ10 levels of >2.5 µmol/L, a variety of symptom improvements was observed including better parental and overall communication, increased play with friends, improved sleep, decreased food rejection, and less aggressiveness and self harm.66

L-CARNITINE AND ACETYL-L-CARNITINE

L-Carnitine is a naturally occurring molecule found in animal-source foods and also synthesized in the body from the amino acids L-lysine and L-methionine. The primary function of L-carnitine is to transport fatty acids across the inner mitochondrial membrane into the matrix for oxidation. As mentioned earlier, abnormally low levels of L-carnitine are often observed in ASD patients. In some instances, this may be due to specific genetic defects that compromise L-carnitine synthesis.

A recent case study reported on a 4-year old boy with ASD and developmental regression who had deletions in a gene that encodes for a key enzyme involved in L-carnitine synthesis. Supplementation with L-carnitine at 200 mg/kg/day led to normalization of plasma carnitine levels, recovery of interactive, language, and motor skills, return of preregression milestones, and achievement of new developmental milestones.67

In biological systems, L-carnitine exists in either a free form or as acetyl-L-carnitine (ALC). A number of studies have reported benefits of ALC supplementation for Fragile X syndrome, an inherited condition commonly associated with mental retardation, attention deficit hyperactivity disorder (ADHD), and autistic behavior.68 In one double-blind, placebo-controlled, multicenter trial, the effects of 1,000 mg/day of ALC or placebo were examined in 51 male children with Autism Spectrum Disorder (ASD). After one year, significant improvements in hyperactivity, attention, and socialization were observed in the ALC group compared to the placebo group.69

N-ACETYL-L-CYSTEINE

N-Acetyl-L-cysteine (NAC) is an antioxidant that scavenges a number of free radicals including hypochlorous acid, hydrogen peroxide, and hydroxyl radicals. Of particular importance to mitochondria, NAC functions as a precursor to the detoxifying and antioxidant compound L-glutathione, which plays a critical role in preventing oxidative damage within mitochondria. Depletion of L-glutathione typically results in mitochondrial dysfunction and apoptotic cell death.24,70

Mitochondrial L-glutathione is especially vulnerable to oxidation and depletion because of its proximity to the free radicals generated by the ETC and also because mitochondria lack the specific enzymes required for endogenous L-glutathione synthesis.22 Supplemental NAC has been shown to help maintain optimal levels of mitochondrial L-glutathione and preserve mitochondrial function under conditions of experimentally induced cellular stress, tissue injury, and L-glutathione depletion.71-73

In humans, NAC demonstrates clinical benefits in a number of disorders associated with depleted L-glutathione and/or mitochondrial dysfunction, including ASD. Two double-blind, placebo-controlled trials have examined the use of NAC as an adjunct to risperidone in children with ASD. One trial administered 1,200 mg/day of NAC, the other 600 to 900 mg/day, and both used the irritability subscale of the Aberrant Behavior Checklist (ABC) as their main outcome measure. In the higher-dose study, children taking NAC showed significantly less irritability after 8 weeks than did those taking placebo.74 The lower-dose trial also demonstrated a significant decrease in irritability after 10 weeks of NAC treatment, as well as marked reductions in the hyperactivity and noncompliance subscores of the ABC.75

A third randomized, blinded, placebo-controlled trial tested NAC alone in a group of 29 children with ASD. In this study, the NAC dose was increased from 900 to 1,800 mg/day over a 12-week period. At week 12, significant improvements were noted in children taking NAC for multiple outcome measurements including irritability on the ABC, stereotypical behavior on the Repetitive Behavior Scale-Revised (RBS-R), and social cognition and autistic mannerisms on the Social Responsiveness Scale (SRS).76

CREATINE

Creatine is an endogenously produced amino acid-like substance that plays an important role in replenishing ATP. Creatine is transformed to high-energy creatine phosphate by excess ATP generated in the mitochondrial respiratory chain. When tissues expend energy, ATP is used and adenosine diphosphate (ADP) is formed. Creatine phosphate quickly re-synthesizes ATP from ADP to ensure an adequate supply of energy.

In skeletal muscle, under conditions of impaired mitochondrial ATP production, supplemental creatine helps maintain a normal energy status. Creatine’s importance in supporting ATP levels is not limited to muscle tissue, however. Observations of animals and humans with inborn errors of creatine metabolism suggest a deficiency of energy-rich creatine phosphate may have even more of a damaging impact on brain function than on muscle function.77 Persons with defective creatine synthesis display a variety of neurological symptoms including mental retardation, extrapyramidal movements, speech disability, epilepsy, and ASD.77-79

Of note, children with ASD have been found to have significantly reduced levels of creatine and creatine phosphate in several brain regions compared to control children.80 These findings suggest creatine supplementation may be of benefit for ASD patients who display evidence of creatine-dependent defects in energy metabolism. While there are currently no published clinical trials examining the effects of creatine supplementation in ASD, some research suggests use of creatine monohydrate in children with neuromuscular diseases related to mitochondrial dysfunction may lead to improvements in physical and mental symptoms.81,82

PROTECTING THE MITOCHONDRIA IS CRITICALLY IMPORTANT IN AUTISM

ASD is a pervasive developmental disorder with a poorly understood origin. Several decades of research have identified a number of shared pathologic features in ASD, most notably increased oxidative stress, heightened inflammatory responses, and dysregulation of immune function. Genetic abnormalities also appear to be common in ASD and likely account for its high degree of heritability. All of these shared features can adversely impact mitochondrial function, impairing cellular energy production and exerting a disproportionately damaging effect on neurological health.

Natural agents like CoQ10, L-carnitine, and creatine play critical roles in mitochondrial energy production, and antioxidants like

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NAC help protect mitochondria from oxidative damage. Studies suggest supplementation with these nutrients may provide benefit for persons with mitochondrial pathology, including patients with ASD.

REFERENCES:
**DID YOU KNOW?**

- Sirtuins, molecules known to contribute to lifespan, play a critical role in maintaining cartilage homeostasis, and use of sirtuin-activating phytochemicals such as resveratrol may reduce cartilage breakdown in osteoarthritis and other degenerative joint conditions.

- *Rhodiola rosea* is a potential selective estrogen receptor modulator and may have a role to play in the amelioration of menopause-related fatigue, stress, depression, cognitive decline, memory impairment, cardiovascular disease, osteoporosis, and cancer.

- Higher folate concentrations in obese pregnant women are associated with a reduced risk of overweight or obesity in their offspring.

- Bilberry inhibits inflammation and reduces disease activity in ulcerative colitis patients.

- N-acetyl-L-cysteine, alpha-lipoic acid, and bromelain may have a role to play in reducing the symptoms of endometriosis, according to a mouse model of the disease in which administration of these three nutrients reduced the number and size of endometriotic cysts.

- Berberine reduces waist circumference, improves insulin sensitivity, lowers triglyceride levels, and inhibits some of the other metabolic and hormonal abnormalities in women with polycystic ovary syndrome (PCOS).

- Sedating antihistamines, such as Benadryl®, exacerbate restless leg syndrome.

- Drinking hot tea, coffee, or other beverages above 149 degrees Fahrenheit (65 degrees Celsius) is associated with an increased risk of tumors in the esophagus.

- A derivative of the flavonoid quercetin (quercetin-3 β-O-D-glucoside, or Q3G) was found to inhibit the Ebola virus in mice when administered 30 minutes before viral challenge. Q3G targeted the early processes involved in viral entry and demonstrated antiviral activity against two species of Ebola.

- Excessive daytime sleepiness and fatigue in older adults is associated with brain atrophy, disturbed sleep, lower cognitive scores, and a greater number of medical comorbidities.