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# Phosphatidylserine: Cell Membrane Nutrient for Stress Resiliency - by Lisa Canar, ND

Phosphatidylserine (PS) and other phospholipid compounds constitute the fundamental structural matrix of all cell membranes. The PS molecular structure consists of a phosphoserine head group, a glycerol backbone, and two fatty acid tails (see image).<sup>1</sup>



PS is an active and integral component of the cell membrane and is necessary for proper cell-to-cell recognition and communication. PS is known to enhance cellular metabolism and transfer of biochemical messages by regulating the function of membrane proteins and by influencing the fluidity of the membrane. PS regulates cell receptors, enzymes, ion channels, and signaling molecules, and via these functions, PS directly affects both endocrine and cognitive function.<sup>1</sup>

PS is likewise active within the cell, in membranes of secretory vesicles and the mitochondrial membrane system. PS is most concentrated in the cells of organs carrying a high metabolic demand, i.e., brain, heart, lungs, liver, and skeletal muscle.<sup>1,2</sup>

PS is also a nutrient found in high concentrations in fish, meat, egg yolk, and organ meats, with smaller amounts present in many other common foods. Supplemental PS is commonly derived from soybeans, although it may be sourced from sunflower seeds. The average daily PS intake from a Western diet is estimated to be ~130 mg. A diet high in animal protein provides ~180 mg, while a vegetarian diet supplies ~50 mg.<sup>2</sup> The body can synthesize PS only through a complex series of reactions requiring substantial energy, therefore it is considered a semi-essential nutrient.<sup>1</sup>



(Continued from page 1)

Results of numerous clinical trials indicate that supplemental PS provides metabolic support for cognitive functions that tend to decline with age, including memory, learning, language skills, concentration, reasoning, and decision making.<sup>3</sup> Indeed, PS is the only dietary supplement that holds FDA qualified health claims for reducing the risk of cognitive dysfunction and dementia.<sup>3</sup> Supplemental PS also has been shown to enhance mood, immunity, and the capacity to cope with stress.<sup>1,2</sup>

One of the primary indications for use of supplemental PS is to modulate aspects of the stress response and to improve stress adaptation. Early research in elderly patients using bovine cortex-derived PS showed benefits for conserving hypothalamic function and normalizing the hypothalamic-pituitary-adrenal (HPA) axis response.<sup>4</sup> Likewise, a recent study determined that soybeanderived PS (supplemented with essential fatty acids and antioxidant nutrients) is effective at improving mood, moderating high cortisol levels, and normalizing diurnal cortisol rhythms in a subset of elderly patients with major depression.<sup>5</sup>

Additional clinical studies in middle-aged and younger adults note similar benefits of supplemental PS in attenuating perceived stress and modulating the cortisol response relating to demanding mental tasks. In healthy young adults faced with a mental and emotional stressor, a soy-derived PScontaining supplement was able to blunt acute adrenocorticotropic hormone (ACTH) and cortisol responses while decreasing perceived mental and emotional distress. These effects were more pronounced in men than in women.<sup>6</sup> A more recent study confirmed that a soy-derived PS-containing supplement can reduce levels of perceived stress and normalize acute ACTH and cortisol responses in chronically stressed, but otherwise healthy, young men.<sup>7</sup> Another similar study of an omega-3 rich PS supplement reported a normalization (modest increase) of the cortisol response to acute stress in chronically stressed young men with depressed cortisol levels at baseline.8

Although not all studies document a normalization of cortisol levels in individuals under mental stress, the benefit of PS on the subjective perception of stress is reported more consistently.<sup>9</sup> Notably, PS may support chronically stressed students by improving the perception of stress load and enhancing mood.<sup>10</sup>

Several additional clinical trials note related benefits of supplemental PS for modulating the stress response due to strenuous exercise training. In an early study, bovine-derived PS effectively blunted the rise of cortisol and the ACTH response to strenuous exercise in healthy young men.<sup>11</sup> Likewise, a soyderived PS supplement decreased the cortisol response to intensive resistance training by 20 percent, reduced muscle soreness, and improved perception of well-being in young male athletes participating in intensive exercise training.<sup>12</sup> A more recent study confirmed and elaborated on these results, finding that soy-derived PS lowers resting cortisol levels before exercise, reduces overall cortisol output during exercise, and increases the testosterone to cortisol ratio after exercise.13

Not all studies document these improvements in cortisol response to exercise. However, the reviewed clinical trials all note benefits of PS on modulating related aspects of exercise induced stress.<sup>2</sup> In particular, supplementation with PS may improve exercise capacity and antioxidant protection,<sup>14,15</sup> as well as cognitive and overall performance related to training.<sup>16,17</sup> Dosages of PS in these studies ranged from 200-800 mg/day, and duration of supplementation ranged from 10 days to 12 weeks.

In summary, PS has been found to improve HPA axis integration by normalizing ACTH and cortisol responses to stress. As a result, PS effectively improves adaptability to stress, moderates perception of stress load, and enhances actual performance and recovery in a variety of stressful situations, including intensive exercise training and demanding mental and emotional tasks. As mentioned above, numerous clinical studies also document the benefits of PS supplementation on the enhancement of mood, immunity, and overall cognitive function.

Supplemental PS may be most beneficial for chronically stressed individuals who exhibit elevated cortisol on testing and who also suffer from anxiety, depression, or cognitive decline. PS may also help normalize cortisol output in chronically stressed patients who have low cortisol levels on testing. Additionally, PS is particularly indicated for athletes who aim to optimize performance and speed recovery after intensive training. Overall, supplemental PS can be a valuable tool for regulating the stress response in patients of all ages and fitness levels.

Medical references can be found at diagnostechs.com/Pages/NewsLetter.aspx

### **Magnesium and Stress**

Magnesium is sometimes considered the forgotten mineral, yet magnesium plays many crucial roles in human physiology. Magnesium is involved in numerous enzymatic reactions, some of which are vital for energy (ATP) production. Magnesium influences electrolyte levels inside cells by moderating cell membrane transport and cellsubstrate adherence. In addition, magnesium acts as a counterbalance to calcium, encouraging muscle relaxation by increasing reuptake of calcium after muscle contraction.<sup>1</sup> Magnesium is also necessary for normal neurological function and neurotransmitter release.<sup>2</sup> Furthermore, magnesium is a structural nutrient that maintains the health of bones and teeth.

Studies show that stress and magnesium are linked: increased stress causes urinary loss of magnesium,<sup>3</sup> and elevated catecholamine concentrations have been shown to lower serum magnesium levels.<sup>4</sup> In situations of chronic stress, increased intake of magnesium may be required to maintain adequate magnesium stores. Increased magnesium intake also has been shown to decrease neuronal overexcitation and improve reasoning coherence.<sup>5</sup> Magnesium deficient diets in animals are known to correlate with depressive and anxiogenic behaviors.<sup>6</sup>

Additionally, magnesium may help to stabilize blood sugar, restore insulin sensitivity, and normalize insulin-induced changes in cortisol output. Research shows that diabetic patients are commonly deficient in magnesium.<sup>7</sup> Supplemental magnesium has been shown to improve insulin sensitivity,<sup>8</sup> which is thought to result from improved insulin receptor signaling.<sup>9</sup> Magnesium deficiency is common in today's society, as many individuals do not consume the recommended daily intake of magnesium from food. With the benefits that come from adequate intake, magnesium supplementation may be a worthwhile consideration for individuals dealing with high levels of stress and related conditions.

### Zinc and Stress Response

Zinc is an essential trace mineral naturally present in some foods and involved in numerous aspects of cellular metabolism. Zinc plays a significant role with respect to the stress response. Proper maintenance of zinc status can help to stabilize serum cortisol levels over time,<sup>1</sup> and zinc intake has been shown to temporarily inhibit cortisol secretions.<sup>2</sup> However, in turn, prolonged stress will deplete zinc concentrations in the blood.<sup>3</sup> Zinc deficiency has been demonstrated to increase plasma cortisol and the pro-inflammatory mediators of interleukin-6 (IL-6), IL-1, and nitric oxide levels.<sup>4</sup>

Zinc is required for the catalytic activity of approximately 100 enzymes.<sup>5,6</sup> Zinc plays a role in immune function,<sup>7,8</sup> protein synthesis,<sup>9</sup> wound healing,<sup>9</sup> DNA synthesis,<sup>6,9</sup> and cell division.<sup>9</sup> Zinc supports normal growth and development during pregnancy, childhood, and adolescence,<sup>10,11</sup> and zinc is necessary for proper sense of taste and smell.<sup>12</sup> Given that the body has no specialized zinc storage system, regular daily zinc intake is required to maintain a steady state and to prevent deficiency.<sup>13</sup>

Medical references can be found at diagnostechs.com/Pages/NewsLetter.aspx



# Тесн Тагк

Quarterly updates from our Diagnos-Techs Research & Development Team

Our newly acquired Inductively Coupled Plasma Tandem Mass Spectrometer (ICP-MS/MS) provides Diagnos-Techs the ability to perform elemental analysis in clinical specimens, with unparalleled accuracy, precision and detection.

The ICP-MS/MS platform allows for trace level analysis in complex matrices with minimal sample preparation, by employing the reaction mode capability of the Agilent 8800 Triple Quad. Diagnos-Techs currently is developing and validating methods for a comprehensive suite of tests for heavy metals and other clinically relevant elements in saliva, urine, and blood. Future prospective metals panels include analyses of hair and nails.

#### Progesterone receptor activity inhibits breast cancer growth in ER/PR double-positive tumors

Researchers have now discovered why breast cancer patients whose tumors display both estrogen and progesterone receptors have a better chance of survival, a fact that has long been observed but not understood. Estrogen receptor (ER) positive breast cancer cells have increased sensitivity to estrogen. Once estrogen binds to the ER in these cells, the ER interacts with specific regions of DNA to modulate transcription of genes that promote cell division and tumor growth. Researchers have now shown that when natural progesterone binds to the progesterone receptor (PR) in these same cancer cells, the PR interacts with the ER and alters downstream effects by redirecting ER activity at specific regions within the DNA. Many genes are differentially affected by the activity of the PR/ER complex, as compared with the ER alone.

This altered expression of target genes in the cell acts as a proliferative brake, slowing tumor growth and inducing a switch to a more normal, differentiated state. Overall, the activity of natural progesterone and the PR in these breast cancer cells is associated with an inhibition of cell growth. The modulating effects of progesterone and the PR were also found to slow tumor growth in breast tumor tissue removed from women with breast cancer, and to inhibit tumor progression in an animal model using mice transplanted with human breast tumor cells. Lead researchers on this study have indicated that they are discussing a clinical trial to test whether giving natural progesterone to women with ER/PR double-positive breast cancer, alongside standard treatment, will improve clinical outcomes.1

#### Nonsteroidal anti-inflammatory drugs (NSAIDS) may be linked to infertility in women

New research suggests that certain NSAIDs may inhibit ovulation and reduce progesterone levels in young women, which could seriously undermine fertility. This study abstract and oral presentation given at the European League Against Rheumatism Congress provides preliminary evidence that use of NSAIDs may disrupt ovulation, a finding previously observed in animal studies. The report is based on a small study involving 39 women of childbearing age suffering from minor back pain. The women were assigned to one of four treatment regimens: diclofenac 100 mg/day, naproxen 500 mg twice daily, etoricoxib 90 mg/day, or placebo. Treatments were initiated on day 10 of each woman's cycle to allow adequate time for a follicle to develop in preparation for ovulation.

Before the initiation of treatment, each woman underwent an ultrasound to assess the diameter of the dominant follicle. Progesterone levels were also measured (via blood sample). After 10 continuous days on the study treatment, the women underwent another ultrasound to assess the effect of the therapy. Women treated with NSAIDs demonstrated a significant inhibition of ovulation compared with controls. Ovulation was reduced by 93% in the diclofenac group and by about 75% in both the naproxen and etoricoxib groups. All three active treatment groups saw profound decreases in progesterone levels as compared with controls. Ovulation returned to normal in treatment groups once the women stopped taking their NSAID doses.<sup>2</sup>

Medical references can be found at diagnostechs.com/Pages/NewsLetter.aspx

# Sources of Contamination in Cortisol Testing

When cortisol results are abnormally high, providers may want to check for overt and hidden sources of hormone exposure. The following list includes many common sources of potential hormone exposures that could lead to falsely elevated cortisol results. Providers should be aware that exogenous progesterone has a small cross-reactivity with cortisol measurement and is one of the more common causes of false elevations on testing. Other steroid hormone exposures may also cross-react and falsely elevate cortisol results in some situations.

# Products that officially contain steroid hormones listed in the ingredients:

- Oral corticosteroids
- Corticosteroid inhalers
- Corticosteroid-containing nose sprays (including over-the-counter products)
- Corticosteroid eye drops
- Corticosteroid ear drops
- Corticosteroid containing lip balm
- Topical corticosteroids (hydrocortisone, hemorrhoid creams, and others)
- Progesterone hormone replacement in any form
- Estrogen hormone replacement in any form
- Testosterone hormone replacement in any form
- DHEA
- Androstenedione
- Pregnenolone

# Products that DO NOT list steroid hormones in their ingredient list, but that still may contain compounds that interfere with testing:

- Topical skin creams and hand creams, especially products sold for sensitive skin
- Facial creams, anti-aging serums, wrinkle creams
- Makeup
- Eyelash lengthening mascara
- Adrenal, orchic, and ovarian glandulars (not including thyroid glandulars)

For more information on interactions with saliva hormone testing, please read **ChronoBiology Newsletter #21** in our newsletter archive at www.diagnostechs.com.

# Other relevant potential sources of contamination and test interference:

- Bleeding gums, or blood in the sample
- Anyone in the same household using topical corticosteroids, progesterone, or other hormones
- Workplace exposures (massage therapist, chiropractor, compounding pharmacist, etc.)
- Residual exposure from past progesterone cream or corticosteroid containing cream. Avoidance may require changing linens and wiping down faucet handles, door knobs or other items commonly handled after applying the cream.

# Testing guidelines to minimize the potential for contamination:

Beginning 3-5 days prior to collection, patients should avoid taking sublingual/transmucosal hormone preparations (troches, pellets, drops). Instead, they may swallow these preparations orally (for liquid preparations, mix with a few ounces of water). Beginning the entire day before collection and throughout the day of collection, patients should avoid all steroid hormones (regardless of form), and all topical skin care products, unless directed otherwise by their provider. Any testing guideline that would entail a change in dose or timing of a prescription medication is always contingent on the prescribing physician's approval.



# Meet Your Microbiota Quarterly updates from our Diagnos-Techs Microbiology Team

## **Bacterial Stool Culture Interpretation**

Gastrointestinal problems, including bacterial flora changes, may underlie numerous health conditions. Common clinical examples include irritable bowel syndrome, inflammatory bowel disease, diabetes, insulin resistance, obesity, autoimmune conditions, and allergies.

While the stool is predominantly composed of anaerobes, most of the accepted bacterial stool pathogens and opportunists grow on aerobic culture plates. Therefore, using aerobic stool cultures is a way to identify bacteria that may be contributing to symptoms in the gastrointestinal tract.

## **Culture Identification**

At Diagnos-Techs, we first isolate bacterial colonies on aerobic culture plates. We then use matrix-assisted laser desorption/ionization with time-of-flight mass spectrometry (MALDI-TOF) for precise identification of bacterial species.

In general, bacteria are identified by genus, species and, if known, the strain. Currently, we identify bacteria only to the species level, with the notable exception of *E. coli* O157. However, as bacterial identification libraries improve, we hope to identify more specific strains of toxigenic *E. coli*, as well as other bacterial strains.

About 40 percent of the dry matter in stool is composed of bacteria, many of which are still alive. As such, we expect to see moderate to heavy growth of both Gram negative and Gram positive bacteria in a healthy, normal specimen.

## **Expected Findings**

In stool culture, commonly-isolated Gram negative and Gram positive organisms include:

- Gram negative: *E. coli, Citrobacter, Klebsiella, Pseudomonas, Proteus, Enterobacter,* and others
- Gram positive: Enterococcus, Streptococcus, Bacillus, Lactococcus, and others

No growth, scant, or light growth of the total Gram negative bacteria or total Gram positive bacteria could result from a number of causes:

- Recent antimicrobial use, including herbal antimicrobials
- Loose watery stools that dilute the specimen
- Dysbiosis, where the normal flora have been displaced
- · Very low fiber or other extreme diets

## **Mixed Flora Results**

The bacteria listed under "Mixed Flora" are the bacteria growing on the culture plates in moderate to heavy amounts. These bacteria may be commensal and/or mutualistic, opportunistic, or pathogenic. It is important to note that these three categories of organisms are not distinct and may overlap.

#### Commensal and/or Mutualistic Bacteria

These include nontoxigenic *E. coli*, certain species of *Enterococcus* and *Streptococcus*, and others such as *Bacillus*, *Lactobacillus*, and *Lactococcus*.

- The majority of *E. coli* strains are commensal and may provide benefits by preventing more harmful bacteria from overgrowing.
- Some strains of Enterococcus faecium, E. faecalis, and E. coli have been used as probiotics.

#### **Opportunistic Bacteria**

These include *Citrobacter, Enterobacter, Klebsiella, Proteus, Pseudomonas,* certain species of *Streptococcus* and *Enterococcus*, certain strains of *E. coli*, and others.

#### **Bacterial Pathogens**

These include enterohemorrhagic *E. coli* (e.g., *E. coli* O157), *Salmonella, Shigella, Yersinia, Aeromonas, Vibrio,* and others (see previous issue of ChronoBiology for more information on these pathogens).

There is a common misconception that any bacteria present and reported upon testing must be eliminated. This is not correct. A healthy stool sample will contain living bacteria, and we need a healthy microbial balance present throughout the intestinal tract.

## **Clinical Relevance**

For each organism present under Mixed Flora:

- Consider current understanding of potential pathogenicity; a PubMed search can be very useful
- · Take in context with symptoms
- Evaluate a patient's risks and medical history to decide on an appropriate course of action

### Summary

- Stool culture results do not reflect the balance of flora that may be present in the small intestine.
- Stool culture does not identify all bacterial species present, only those that grow robustly on aerobic culture plates; for example *Lactobacillus* does not grow well from stool on standard culture plates.
- Stool culture cannot be used for monitoring the complete elimination of a bacterial species from the gastrointestinal tract, although in some cases there may be indications of a reduction in levels.
- Interpretation of stool culture requires a careful evaluation of the patient's symptoms and clinical history and a review of the research on any bacterial species identified to decide on an appropriate clinical course of action.

For more information, refer to our webinar on **Bacterial Stool Culture Interpretation** (Jan 2015). Notes and recordings from this webinar may be accessed and downloaded from our Webinar Archive at diagnostechs.com (account login information is required).

# ChronoBiology23



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## **Insurance Billing FAQ**

#### Which insurance do you bill?

As a courtesy we are able to bill most insurances. However, we do not bill the following insurance carriers:

- BLUE CROSS BLUE SHIELD NC
- BLUE CROSS BLUE SHIELD PA
- HMO PLANS
- KAISER
- MEDICAID/STATE INSURANCE
- PACIFIC SOURCE
- TRICARE\*
- UMR

\*For Tricare, we do not bill for "saliva only" tests.

#### Does insurance cover Diagnos-Techs' testing?

As an out-of-network provider, we cannot guarantee or verify coverage for your patient. We recommend having your patient call the insurance company to verify out-of-network benefits including deductibles and coinsurances prior to submitting insurance information for us to bill. Note that all commercial insurance claims will be processed per individual procedure billed. The patient is responsible for any difference between the insurance payment and the insurance billed charges and/or out-of-network deductibles and co-insurances.

When claims are processed out of network, the insurance carrier may pay the contracted subscriber (patient). If that is the case, the subscriber is required to reimburse Diagnos-Techs with the insurance payment.

#### Does Medicare cover Diagnos-Techs' testing?

Medicare will determine coverage based on medical necessity and frequency billed. We require an Advanced Beneficiary Notice of non-coverage to be completed prior to billing, and the referring provider needs to be located in the Medicare PECOS system.

#### Do I need to provide a diagnosis code?

Yes, ICD-10 codes are now required on all test orders billed to insurance.

Note: When insurance billing is requested, the patient pre-pay price is voided. The patient then becomes liable up to the full insurance billed charges.

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