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## REPORT

### Cortisol, Stress, and Health

Keeping levels of the stress hormone cortisol in check may help prevent illness and slow aging

By Edward R. Rosick, DO, MPH, MS



Today, we are more stressed than ever before. Men and women are working more hours, teens are committing suicide at high rates, and physicians cannot write enough prescriptions for antidepressant and anti-anxiety medications.

Although modern technology is light years ahead of that of our primitive forebears, our biological make-up has not changed appreciably for many thousands of years. Because of this, understanding how our bodies react to external and internal stressors is vitally important to the quest for optimal health and well-being.

While questions remain as to precisely how stress contributes to the disease process, research has shown that chronic stress causes a significant dysfunction of one of the most vital systems of our body—the neuroendocrine system.<sup>1-4</sup>

#### THE MIND-BODY CONNECTION

The study of brain-body interaction, or psychoneuroimmunology, is one of the most contentious fields in medicine today. While more researchers and physicians believe that the mind and body are one, a significant number of doctors still insist that the mind and body are separate entities that have only minimal interaction.

Of course, this stubbornness is not surprising, as Western medicine has long held as one of its major axioms that the mind and body are separate entities. By contrast, Chinese and other traditional medicines have always recognized the interconnectedness of the body and mind. For those who still doubt this interplay, recent scientific research proves that what happens in the mind can profoundly influence the body.

#### THE NEUROENDOCRINE CONNECTION

Scientists are just now beginning to unravel the ways in which the mind influences the body, and vice versa. The hypothalamic-pituitary-adrenal (HPA) axis plays a major role in both mind and body health. The intricate connection between the brain and endocrine system broadly influences our health, and many researchers suggest that our stressful, modern lifestyles are overtaxing the HPA axis.

Before we explore how aberrations of the HPA axis can contribute to many chronic disease states, it is important to understand how the HPA axis works. It starts with the hypothalamus, a specialized glandular area of the brain that some consider the “master gland” of the neuroendocrine system. The hypothalamus has many functions, such as controlling the body’s temperature, water balance, thirst, and hunger. It also acts as a controller of the pituitary gland, a small, bean-sized structure that sits just below the hypothalamus. During times of stress, the hypothalamus releases corticotropin-releasing factor, which in turn signals the pituitary gland to release adrenocorticotropic hormone, or ACTH. This hormone then travels through the bloodstream to the adrenals, two small, triangle-shaped glands located on the top of the kidneys. When ACTH reaches the adrenals, it causes them to release a biochemical known as cortisol.

## CORTISOL: THE STRESS HORMONE



Cortisol is, in many ways, a paradoxical hormone. A certain amount of cortisol is needed to maintain optimal health, but too much or too little can be deadly. Cortisol is involved in multiple bodily functions, including blood pressure regulation, cardiovascular and immunological function, and the metabolism of fats, proteins, and carbohydrates. In stressful situations, the body secretes cortisol at higher-than-normal rates to help break down and use fatty acids and proteins for energy production, which is especially important for optimal brain function. Unlike levels of other hormones such as testosterone and DHEA, cortisol levels generally do not decrease as we get older. In fact, some researchers now believe that many age-related problems may result from a ratio of increased

cortisol and lowered DHEA as we age.<sup>5-7</sup>

### HOW STRESS KILLS

In the 1930s, the renowned endocrinologist Hans Selye discovered that both psychological and biological stress can adversely affect human health through interactions between the mind and the adrenal glands.<sup>8</sup> Following his landmark work on the crucial link between stress and the HPA axis, in 1946 Selye published his now-classic work on the relationship between chronic stress and disease. Selye reasoned that living organisms, including humans, react in physiologically predictable ways to both physical and psychological stressors, seeking to maintain homeostasis, or a constant, dynamic metabolic equilibrium wherein all organ systems function to maintain optimal health. He termed these often-complex physiological and behavioral responses to stress the “general adaptation syndrome,” or GAS.<sup>9</sup> Selye also observed that if the stressors were continuous, the organism would ultimately “burn out” and die. He devised the following three-step model to describe the process:

- Step 1: alarm reaction. Faced with an immediate stressor (either physical or psychological), there is activation of both the “flight or fight” response and the HPA axis, leading to secretion of greater amounts of hormones such as cortisol.
- Step 2: resistance phase. If the perceived stressors are not countered in a timely fashion and the HPA axis is in a continual “on” mode in an attempt to maintain homeostasis, adrenal hypertrophy and numerous other deleterious health effects begin to occur.
- Step 3: exhaustion phase. If the perceived stress is prolonged, the adrenal glands and other organ systems begin to “burn out” and experience a precipitous decline in function. If the exhaustion phase continues long enough, the organism will die.

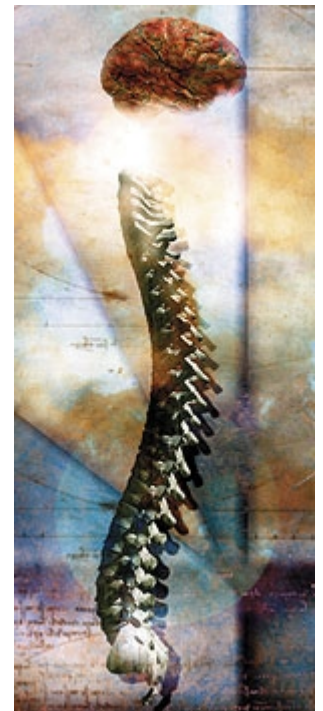
### STRESS, CORTISOL, AND ILLNESS

Taking their lead from Selye’s original work, scientists have demonstrated that both acute and chronic levels of stress contribute to elevated levels of cortisol.<sup>10-12</sup> In addition, high levels of stress are now known to be significantly linked to various illnesses, including upper respiratory infections,<sup>13</sup> exacerbation of multiple sclerosis,<sup>14</sup> and gastrointestinal disorders such as irritable bowel syndrome.<sup>15,16</sup>

Since the mid-1990s, scientists have presented provocative evidence linking cancer, stress, and elevated cortisol levels. In a 1996 case-controlled study, scientists examined hormone levels of the hypothalamic-pituitary-adrenal system in women with both early-stage and metastatic breast cancer.<sup>17</sup> Both groups had statistically higher levels of cortisol compared to women without breast cancer. Furthermore, those with metastatic breast cancer had higher cortisol levels than women with early-stage breast cancer. The authors noted, “these data provide evidence that breast cancer is associated with a hyperactive adrenal gland.”<sup>17</sup>

A more recent report in the journal *Lancet Oncology* summarized what is currently known about the complex interactions between the HPA system, stress, and cancer. According to the authors, “Evidence mainly from animal models and human studies suggests that stress and depression result in an impairment of the immune system and might promote the initiation and progression of some types of cancer...Through HPA activation, the mediators released during chronic stress suppress some non-specific and specific parts of the immune response...compromising the most important effectors of the immune response against tumors.”<sup>18</sup>

While cancer is probably the most widely feared chronic disease, heart disease remains the number-one killer of Americans. Mayo Clinic researchers examined the medical and economic costs of stress in heart disease patients.<sup>19</sup> In a study of 311 men and 70 women, the authors found that patients with the highest stress levels had markedly higher rates of rehospitalization and reoccurrence of further heart disease-related problems, including heart attacks and cardiac arrest. Concluding that psychological distress may adversely affect prognosis in heart disease patients, the authors suggested that identifying and treating psychological distress could improve outcomes in these patients.





A more recent report in the *European Heart Journal* supports the theory that stress can literally be a killer.<sup>20</sup> In this 21-year prospective study of nearly 14,000 men and women, researchers concluded, “chronic stress is an independent risk factor for [cardiovascular disease], particularly fatal stroke.” Other scientists, however, have criticized these data, indicating the need for further investigation.

Alzheimer’s disease, the most common cause of dementia in those aged 65 or older, is characterized by a progressive decline in cognition and memory. This debilitating condition currently affects over 15 million people worldwide. With the rapidly aging US population—an estimated 30% of all Americans will be 65 or older by the year 2050—projections are that 14 million people in the US alone will be affected by Alzheimer’s in the next few decades.<sup>21,22</sup> This represents a quadrupling over the current prevalence of Alzheimer’s in the US.

Although scientists continue to search for the root cause of this devastating illness, new evidence suggests that increased levels of stress, along with high levels of cortisol, may play a significant role. Research indicates that high cortisol levels may promote degeneration and death of neurons,<sup>23-25</sup> along with decreased memory function in otherwise healthy elderly men and women.<sup>26</sup> Furthermore, a recent report in the journal *Neurology* showed that chronic stress is associated with the risk of developing Alzheimer’s disease.<sup>27</sup> In this study, researchers found that people who were prone to experiencing high levels of stress had twice the risk of developing Alzheimer’s as those who were not prone to stress. The authors concluded, “proneness to experience psychological stress is a risk factor for [Alzheimer’s disease].”

While mainstream medicine offers little in the way of reducing chronic stress or high cortisol levels, making behavioral changes and using certain supplements can help you bring your stress load and high cortisol levels safely under control.

## EXERCISE COUNTERS STRESS

Humans are designed to be physically active. However, our typical twenty-first century lifestyle—sitting in front of a computer all day—is a far cry from the daily hunting and gathering activities of our ancestors. While it is common knowledge that exercise can keep our muscles and bones strong and healthy, less often recognized is that moderate exercise can also decrease stress and high cortisol levels.



A newly published study in the journal *Psychoneuroendocrinology* examined the effects of aging and fitness on the HPA axis response to stress.<sup>28</sup> The study authors hypothesized that aging is associated with a greater HPA axis reactivity to psychological stress leading to higher cortisol levels, and that exercise could ameliorate this reactivity. The researchers subjected three groups of women—categorized as “young-unfit” (aged 25-30), “older-unfit” (aged 64-67), and “older-fit” (aged 64-68)—to a battery of psychological and physical tests meant to induce stress. These tests included an EKG-monitored treadmill test, a mental arithmetic test, an anagram test, and a cold pressor test, where subjects placed their hands in a bucket of ice water for as long as they could tolerate. While cortisol levels rose in all three groups of women, those in the older-unfit group had the most significant increase. The authors concluded that “aging is associated with greater HPA axis reactivity to psychological stress, and that higher aerobic fitness among older women can attenuate these age-related changes as indicated by a blunted cortisol response to psychological stress. These findings suggest that exercise training may be an effective way of modifying some of the neuroendocrine changes associated with aging.”<sup>28</sup>



## RELAXATION AND MEDITATION

If you want to decrease stress and lower your cortisol, then taking time out each day to relax and meditate may be just the solution. Considerable scientific evidence has established that relaxation and meditation techniques are valuable therapeutics for optimal health.

An article in *Psychoneuroendocrinology* highlighted meditation’s effects on levels of various hormones, including cortisol, in otherwise healthy male subjects who were subjected to mental and physical stressors.<sup>29</sup> In this prospective, randomized study, blood samples were taken and hormone levels analyzed at the study’s onset and again four months later after the subjects had learned and practiced a meditation technique. Those who had practiced meditation had lower average cortisol levels compared to subjects who had not meditated, suggesting that meditation may help reverse the effects of chronic stress.<sup>29</sup> A paper in the journal *Psychosomatic Medicine* described how women with stage I or II breast cancer could decrease their perceived levels of stress, as well as their cortisol levels, by simple cognitive-behavioral stress-management techniques.<sup>30</sup>



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#### SUPPLEMENTS TO COMBAT CORTISOL

Exercise and meditation are two important modalities that may help many individuals manage stress-filled lives. In addition, studies suggest that effective natural supplements, such as vitamin C, fish oil, phosphatidylserine, and herbal adaptogens, may help keep the HPA axis in equilibrium, reduce elevated cortisol levels, and help optimize health.

#### **Vitamin C**

Besides its beneficial effects in maintaining proper immune system function, vitamin C has been shown to help modulate high levels of cortisol brought about by stress. A study in 2001 examined the effects of supplemental vitamin C on high cortisol levels brought about by physical stress in marathon runners.<sup>31</sup> In a randomized, placebo-controlled study, ultramarathon runners were given 500 mg a day of vitamin C, 1500 mg a day of vitamin C, or a placebo seven days before a marathon, the day of the race, and two days after the race. Researchers found that athletes who took 1500 mg per day of vitamin C had significantly lower post-race cortisol levels than those taking either 500 mg a day or placebo.<sup>31</sup>



Ginseng

Another study published in the journal *Psychopharmacology* reviewed evidence showing that vitamin C can reduce high cortisol levels brought about by psychologically induced stress.<sup>32</sup> In a randomized, double-blind, placebo-controlled trial, researchers gave 3000 mg per day of vitamin C or a placebo to 120 volunteers who were subjected to psychological stress through the Trier Social Stress Test (TSST), a commonly used assessment tool in psychological research that simulates public speaking and arithmetic tests to induce stress and raise cortisol levels. Subjects who took vitamin C had lower blood pressure, subjective stress, and cortisol measures compared to those who were given placebo.

#### **Fish Oil**

In a number of clinical tests, fish oil has been shown to reduce cardiovascular risk in women and men. Preliminary research has shown that fish oil may help individuals cope with psychological stress and lower their cortisol levels. In a study published in 2003, researchers gave seven study volunteers 7.2 grams per day of fish oil for three weeks and then subjected them to a battery of mental stress tests.<sup>33</sup> Blood tests showed that these psychological stressors elicited changes in the subjects' heart rate, blood pressure, and cortisol levels. After three weeks of fish oil supplementation, however, the rise in cortisol levels secondary to stress testing was significantly blunted, leading the authors to conclude that supplementation with omega-3 fatty acids from fish oil "inhibits the adrenal activation elicited by a mental stress, presumably through effects exerted at the level of the central nervous system."<sup>33</sup>

#### **Phosphatidylserine**

Another supplement that has been shown to be useful in combating the deleterious effects of stress is phosphatidylserine. This phospholipid constitutes an essential part of biological cellular membranes. For more than 10 years, studies have shown that phosphatidylserine is able to cut elevated cortisol levels induced by mental and physical stress. In one early study, 800 mg per day given to healthy men significantly blunted the rise in cortisol caused by physical stress.<sup>34</sup> Another paper reported that even small amounts of supplemental phosphatidylserine (50-75 mg administered intravenously) could blunt cortisol increases secondary to physical stressors.<sup>35</sup> In this study, eight healthy men had their blood drawn before and after physical stress induced by riding a bicycle ergometer. While all subjects showed increased cortisol levels, pretreatment with the 50- or 75-mg dose of phosphatidylserine significantly blunted cortisol response to the physical stressor.<sup>35</sup>

Finally, a study published in 2004 examined phosphatidylserine's effects on endocrine and psychological responses to mental stress.<sup>36</sup> The stressor used was the Trier Social Stress Test (TSST), which consists of 15 minutes of psychological stress induced via a mock job interview, followed by a mental arithmetic challenge. This double-blind study followed 40 men and 40 women, aged 20-45, for three weeks. The subjects were given either phosphatidylserine (either 400 or 600 mg daily) or a placebo

before taking the TSST. Phosphatidylserine was effective in blunting the cortisol response to stressors, with those taking 400 mg daily (but not, surprisingly, 600 mg) of phosphatidylserine showing a significantly decreased cortisol response. The authors concluded that phosphatidylserine helped dampen the effects of stress on the pituitary-adrenal axis, and may have a role in managing stress-related disorders.<sup>36</sup>

## **Herbal Adaptogens**

Plant-derived adaptogens can be a very useful in combating the mental and physical rigors of our modern lifestyle. Adaptogens work by modulating the levels and activity of hormones and brain neurochemicals that affect everything from cardiac activity to pain perception. For any herb or substance to be properly classified as an adaptogen, it should:

- produce a non-specific response and increase an individual's resistance to a wide range of deleterious stimuli
- produce a normalizing response in an individual when subjected to physiological, emotional, or mental stressors
- be non-toxic and not induce changes in the physiological, emotional, or mental state of a non-stressed individual.

One such herbal adaptogen is *Rhodiola rosea*, or rhodiola. In traditional Asian and European medicine, this herb has been used for centuries to increase physical endurance and longevity, as well as to manage fatigue, depression, and impotence. *Rhodiola*'s positive effects are thought to be mediated through the actions of rosavins and salidroside, chemical compounds found in the plant's roots. Multiple studies from the former Soviet Union have demonstrated *rhodiola*'s effectiveness in combating both physically and psychologically stressful conditions.<sup>37</sup>

Another herb that serves as an adaptogen is ginseng, which has been used throughout Asia since antiquity. It is important to note that ginseng is the name given to three different plants used as adaptogens. The most widely used ginseng is *Panax ginseng*, also known as Korean, Chinese, or Asian ginseng. *Panax quinquefolium*—or American ginseng—is also considered a “true” ginseng. However, Siberian ginseng (*Eleutherococcus senticosus*), while commonly referred to as ginseng, is not a true ginseng but a closely related plant. Yet no matter what the genus or species, all three of these plants have experimental evidence backing their adaptogenic claims. Animal studies have shown that ginsenosides, bioactive compounds in ginsengs, improve the sensitivity of the HPA axis to cortisol.<sup>38,39</sup> In addition, studies suggest that all three plants provide protection against both physical and psychological stresses.<sup>38,39</sup>

Finally, another plant that deserves mention as an adaptogen is *ginkgo biloba*. For the last 5,000 years, leaves of the *ginkgo* tree have been used to treat various medical conditions. While *ginkgo* is currently used to help combat the debilitating effects of memory decline and dementia,<sup>40-42</sup> emerging evidence suggests that it may be useful in treating the impact of stress and elevated cortisol levels. A recent double-blind, placebo-controlled study published in the *Journal of Physiology and Pharmacology* examined *ginkgo*'s effects in modulating cortisol and blood pressure levels in 70 healthy male and female subjects.<sup>43</sup> When subjected to physical and mental stressors, subjects who were given 120 mg per day of a standardized *ginkgo* extract saw smaller increases in their cortisol levels and blood pressure than did their counterparts who were given a placebo.



*Rhodiola rosea* seed heads.

## **RAISING DHEA LEVELS**

While cortisol levels stay the same or even increase as we age, levels of another vitally important hormone, DHEA, decrease with each passing year. This relationship between cortisol and DHEA has led some to suggest that these adrenal hormones may play a significant role in the aging process and its associated negative health effects. A recent paper in the *European Journal of Endocrinology* examined the pathophysiological correlates of age-related changes in the HPA axis.<sup>44</sup> The authors showed that the cortisol/DHEA ratio increases significantly as one ages, and is even higher in elderly patients who suffer from dementia. Supplemental DHEA, however, enhances the brain's resistance to stress-mediated changes, maintains functional abilities, and protects against age-related diseases. The authors concluded, “the changes of the hormonal balance [between cortisol and DHEA] occurring in aging may contribute to the onset and progression of the aging-associated neurodegenerative diseases.”<sup>44</sup>

## **CONCLUSION**

Exercise, stress management techniques such as relaxation and meditation, and nutritional supplements can help you manage stress and lower cortisol to promote optimal health and longevity. The following are scientifically supported techniques that can help support a healthy response to stress.

### **1. Behavioral techniques to lower stress and manage high cortisol levels**

- Exercise: 30-45 minutes of both anaerobic (resistance training) and aerobic (jogging, cycling) every other day.
- Meditation/relaxation: 15-30 minutes daily.

## 2. Supplements to reduce high cortisol levels secondary to stress

- Vitamin C: 1000-3000 mg/day.
- Fish oil (omega-3 fatty acids): 1-4 gm/day.
- Phosphatidylserine: 300-800 mg/day.
- Rhodiola rosea: 100-200 mg/day, standardized extract.
- Ginseng: 100-300 mg/day, standardized extract.
- Ginkgo biloba: 100-200 mg/day, standardized extract.
- DHEA: 25-50 mg/day (any hormone supplementation should be monitored by your physician).

### THE CORTISOL-OBESITY CONNECTION

Emerging studies suggest a link between central obesity—marked by abdominal fat and a high waist-to-hip ratio—and elevated cortisol levels.

One such study examined 59 healthy premenopausal women, 30 of whom demonstrated central fat distribution as determined by a high waist-to-hip ratio, and 29 of whom did not.<sup>45</sup> All 59 women participated in three sessions of psychosocial challenges on four consecutive days to gauge and measure their reaction to stress. Women with higher waist-to-hip ratios experienced the laboratory challenges as more threatening, performed more poorly on them, and reported more chronic stress. These women also secreted more cortisol than women with lower waist-to-hip ratios. The investigators noted that central fat distribution is related to greater psychological vulnerability to stress and cortisol reactivity. Furthermore, stress-induced cortisol secretion may contribute to central fat.

In a study published in 2004, researchers examined the relationship between stress levels, cortisol, and abdominal obesity in 22 obese women, 11 of whom had a binge-eating disorder.<sup>46</sup> The researchers found a positive correlation between high stress and cortisol levels and central obesity, noting, “hyperactive HPA axis due to stress raises cortisol, which may contribute to binge eating and abdominal obesity.”

Clearly, there is an intimate relationship between stress, cortisol levels, and overall health. Modulating cortisol levels may thus offer support for healthy weight management and prevent negative health outcomes associated with central obesity, such as type II diabetes.

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