F. Esposito

CLINICAL MANIFESTATIONS OF STRESS-MEDIATED AND INFECTION-RELATED CORTISOL DYSREGULATION – THE ROLE OF GUNAVIT B5 PLUS IN RESTORING STRUCTURAL BALANCE AND FUNCTIONAL INTEGRITY

SUMMARY

The hypothalamic-pituitary-adrenal (HPA) Axis is the primary mechanism by which the Central Nervous System interacts with the Endocrine System. In response to environmental stressors, including viral infections, the HPA Axis mobilizes the appropriate metabolic resources to meet specific demands. The final effector hormone of the HPA Axis is cortisol. Cortisol release increases markedly upon awakening and then gradually decreases throughout the day, reaching a minimum around midnight.

– Alterations in this specific pattern of cortisol secretion are associated with adverse health consequences, including sleep disorders and chronic inflammatory diseases, the origin of which may be related to a sensitized cortisol response. Diet and nutritional status play a key role in restoring order to a cortisol-related organ system that does not respond physiologically to external stimulation.

– In this article, our focus is on four components in particular: selenium (in its organic form of selenium-methionine), as a trace element constituting several selenium-proteins involved in the modulation of oxidative stress, phosphatidylserine, a membrane phospholipid promoting correct apoptosis and amplifying antioxidant enzymatic activity, vitamin D which, in synergy with selenium, mitigates the inflammatory response, and vitamin B5 whose role as an energy booster is crucial for the production of glutathione and thus for reducing oxidative stress.

KEY WORDS

STRESS, SELENIUM, PHOSPHATIDYLSERINE, VIT. D, VIT. B5, GUNAVIT B5 PLUS, CORTISOL, HPA AXIS, NUTRACEUTICS, MICRONUTRIENTS

INTRODUCTION

Cortisol is a powerful anti-inflammatory hormone produced by the adrenal glands in the fasciculated area of the cortical portion. Its dysfunction can lead to widespread inflammation following the reactivation of an acute reaction to stress with various origins.

– Generally speaking, high levels of cortisol are associated with diets that are high in animal protein and carbohydrates with a high insulin-sensitive glycaemic index inducing the production of further cortisol.

Despite stress being an inevitable part of life, a prolonged or excessive response to pain or various factors can intensify sympathetic and neuroendocrine activity, deplete cortisol and perpetuate widespread pain and inflammation.

Following acute stress, high cortisol levels may help to reinforce fear-based emotional memories for even unexpected, previously unknown events, conditioning a physiological response to stress, making it sensitised.

– A hypervigilant response to stressful stimuli may lead to frequent or pro-

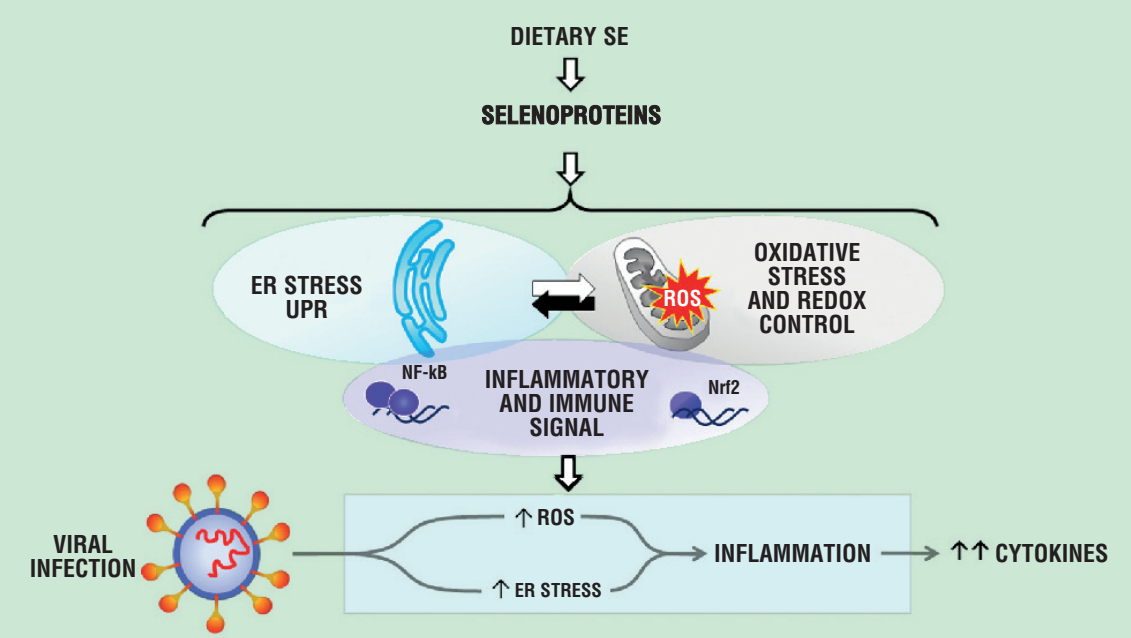

FIG. 1

Graph retrieved from: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/selenium-and-viral-infection-are-there-lessons-for-covid19/BE3AC78D5C92725BE83C4E474ECBB548.

longed activation of the **hypothalamic-pituitary-adrenal (HPA) Axis**.

Following a chronic reactivation of the HPA, cortisol dysfunction may encourage the transmission of pain through altered modulation or the repeated activation of nociceptors by pro-inflammatory mediators.

The reactivation of a stress response triggers the release of pro-inflammatory sympathetic catecholamines.
Cortisol's compromised anti-inflammatory functions can intensify and prolong the short-term physiological inflammatory response.

– The side effects of systemic inflammation may include **1)** autoimmune susceptibility, **2)** widespread oxidative damage, **3)** the accumulation of free radicals produced by the inflammation itself, with the related tissue degeneration.

Osteoporosis, **myopathies**, and **idiopathic neuropathies** are common manifestations of systemic inflammation, and pain is a common effect of these conditions.

– Viral infections can induce various physiological changes in the human Endocrine System, resulting in a cytokine-mediated activation of the HPA Axis to increase the production of cortisol, thus modulating the immune response.

Any virus that causes systemic viraemia and inflammation can stimulate the HPA Axis to release cortisol, through early pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) and T-cell related cytokines, INF-γ, and IL-2.

These mediators act on the hypothalamic cells that produce CRH (corticotropin-releasing hormone), the anterior pituitary and the adrenal cortex to increase glucocorticoids during viral disease.

• At the moment, the Coronavirus disease (COVID-19, SARS-CoV-2) mainly involves the lungs, leading to pneumonia, which is often complicated by acute respiratory distress syndrome, and sepsis.

The pathogen enters the pneumocyte using the host's angiotensin-converting enzyme 2 (ACE2) as a receptor.

Binding results in the *down*-regulation of ACE2 and the ineffective conversion of the pro-thrombotic angiotensin II (the levels of which are directly proportional to those of cortisol and the proportion of *spike* proteins on the surface of the Coronavirus), into angiotensin I.

Furthermore, the enzyme is expressed on the arterial and venous endothelial cells of many organs, including the adrenal glands.

– It is common knowledge that the severe course of the disease is associated with an overreaction of the immune system with a mass release of cytokines and chemokines ('cytokine storm'), which can be correlated with HPA dysfunction.

Elevated cytokines also trigger the induction of hyaluronan synthase 2 (HAS2) in alveolar epithelial cells (type 2) and fibroblasts.
– Thus, the synthesis of **hyaluronan** occurs, which has a high water-binding capacity of up to 1,000 times its molecular weight, resulting in the accumulation of fluid in the lungs, which correlates with the development of respiratory distress syndrome.

– COVID-19 therefore constitutes a universal threat requiring rapid, favourable and safe measures to reduce the risk of infection, suppress the development of virulence, strengthen the immune system and support healing.

– It is known that individuals living in areas with a low selenium intake or inadequate nutrition, and patients with pre-existing comorbidities are at particularly high risk of becoming infected with COVID-19 or other viral infections.

The optimum status of **selenium** (100 µg per day) promotes increased T-cell proliferation, NK *(natural killer)* cell activity and innate cell functions.

– Selenium supports a stronger vaccine response and solid immunity to pathogens.
It also suppresses severe inflammation in tissues such as the lungs and intestines.

• Clinical studies have shown that selenium supplementation modulates the inflammatory response in patients with respiratory distress syndrome by restoring the antioxidant status of the lungs and suppressing the levels of IL-1β and IL-6.

Selenium supplementation inhibits the pathogen-induced activation of the transcription factor NF-kB and its downstream release of pro-inflammatory cytokines.

In humans, dietary selenium is incorporated into 25 selenium-proteins, including glutathione peroxidase, selenium F protein, selenium proteins K and S, and thioredoxin reductase.

These play crucial roles in molecular pathways such as **1)** the response to oxidative stress or endoplasmic reticulum stress, **2)** the response to unfolded proteins, and **3)** the immune and inflammatory response involving NF-kB and the nuclear factor erythroid-2-related factor (Nrf2 regulating the gene expression of a wide variety of antioxidant cytoprotective enzymes).

– In human studies and animal models, it has been observed that the crossed dialogue between these pathways is crucial for producing an adequate response to viral infections; low selenium concentration is linked to a less efficient response to RNA virus infection.

FIG. 1 shows how reduced selenium-protein expression, resulting from a low/sub-optimal selenium status, may alter molecular pathways involved in stress responses and contribute to an +aggressive pro-inflammatory environment leading to a worse prognosis of viral disease.

– As observed, the decline in selenium status leads to insufficient protective selenium enzymes, particularly glutathione peroxidase, an enzyme consisting of selenium and glutathione.
Glutathione peroxidase is an enzyme belonging to the class of oxidoreductases.

By reducing the amount of hydrogen peroxide in water, it converts the reduced form of glutathione (GSH) into **glutathione disulfide (GSSG)**, the oxidised form of glutathione.
– In other words, the glutathione is oxidised. The oxidised GSSG is then 'recharged' or regenerated by NADPH (a reduced form of NADP+), turning into GSH (a reduced form of glutathione).

If there is a selenium and glutathione deficiency, an insufficient inactivation of peroxides as precursors of reactive oxygen species (ROS) occurs, resulting in a **serious disturbance to the redox balance**.

Glutathione peroxidase itself, however, interacts inhibitively with the MPRO protease of SARS-CoV-2, a protease which is necessary for the formation and production of virus components.
MPRO is directly involved in the proteolysis of glutathione peroxidase and other important selenium proteins (thioredoxin reductase and glutamate cysteine ligase), which, when deactivated or structurally demolished, **do not** guarantee the adequate removal of free radicals.

– In order for there to be a powerful regeneration and activation of the glutathione peroxidase, it is necessary to increase the amount of energy required to produce glutathione, i.e. to ensure two molecules of ATP for the production of each glutathione molecule.

To do this, it is necessary to enhance the Krebs cycle through the first component that enters it, i.e. acetyl coenzyme A.

The latter is derived from pantothenic acid, i.e. vitamin B5.

– The expected consequences of an increase in acetyl-CoA content in the mitochondria are the stimulation of pyruvate oxidation, the functioning of the Krebs cycle and the oxidation of fatty acids.
It also appears that vitamin D3 plays the role of upregulating the thioredoxin-reductase (selenium-containing protein that regenerates NADPH) and glutamate-cysteine ligase (the first enzyme of the glutathione biosynthetic pathway).
The overexpression of glutathione, glutathione peroxidase, superoxide dismutase, and the downregulation of NADPH oxidase are induced by vitamin D3 to reduce oxidative stress.

The effective over-regulation of so-called selenium proteins by vitamin D3 requires the presence of an adequate level of selenium, however.

The full potential of vitamin D3 with respect to COVID-19 or other viral infections can only be considered in combination with an optimal selenium intake.

Chronic stress also reduces **cortisol-binding globulin (CBG)**.

– CBG is a glycoprotein synthesised in the liver and secreted into the bloodstream where it binds with high affinity to glucocorticoid hormones, such as

cortisol in humans and corticosterone in laboratory rats.
In mammals, 95% of circulating glucocorticoids are bound to CBG (80%) and albumin (15%), and only 5% of the free fraction is able to enter the CNS.

During stress, the concentration of glucocorticoids increases significantly (the free fraction increases even more) once the CBG is saturated.

The observed pronounced increase in ACTH and cortisol during stress can be explained by a decrease in CBG in chronically stressed individuals.

– A membrane phospholipid known as phosphatidylserine, physiologically and temporarily externalised as a marker during apoptosis, first causes the normalisation of CBG levels under these conditions, followed by the normalisation of HPA Axis activity and reactivity.

During viral infections, another impairment of the structural and functional aspect of the cell membrane also occurs.

– Viral infections create structural membrane damage that leads to abnormal permanent exposure of phosphatidylserine on the outer cell surface (scramblases activate caspases which inactivate the flippases that bring phosphatidylserine back to the membrane after the apoptosis signal).

– The balance between the internalisation and externalisation of phosphatidylserine is equal to the balance between pro-inflammation and anti-inflammation.

If phosphatidylserine is extended out of the cell's *bilayer* phospholipid structure, apoptosis occurs and cellular activity shifts towards a suppression of immune response (a suppression that viruses promote) in favour of an extended cellular and tissue synthesis pathway, when instead there must be a correct balance between the apoptotic signal, and immediate macrophage phagocytosis, with the subsequent reentry of the phosphatidylserine into the membrane structure.

In such a compromised system, it would be crucial to strengthen the membrane phosphatidylserine, repairing and sustaining the cellular apoptotic defence mechanism and the apoptotic cell elimination mechanism, the first defence strategy against pathogens and the interleukin-mediated inflammatory state.

The efficient elimination of apoptotic cells from the airways by phagocytes is essential for the effective resolution of inflammation and a return to pulmonary homeostasis.
– A disruption in this process would lead to a secondary necrosis of accumulated apoptotic cells, the release of necrotic cell debris, and the subsequent uncontrolled inflammatory activation of the innate immune system by the released 'Damage-associated molecular patterns' (DAMPS).

In other words, during sepsis or inflammatory events, phosphatidylserine exposure may be over-regulated on cell surfaces throughout the body, including endothelial cells, platelets, erythrocytes, neutrophils, lymphocytes, and extracellular micro-particles.

– Within the context of a SARS-CoV-2 infection, the intracellular conditions required for the activation of scramblases can be triggered by the viral infection itself, down modulation of ACE2 and the resulting increase in angiotensin II directly related to circulating cortisol levels.

With phosphatidylserine overexpressed, such structural membrane disruption would lead to the formation of clots and the activation of the extrinsic coagulation pathway by association with factor VII.

• By administering phosfatidylserine in the appropriate dosages, the cell membrane is structurally and functionally repaired, therefore competitively preventing abnormal externalisation and thus blocking the activation of inflammatory and pro-coagulant processes.

Furthermore, the phosphatidylserine **intensifies** the antioxidant action of glutathione peroxidase, it **regulates** the release of interleukin-1ß, it **normalises** the production levels of cortisol in response to stress, it **promotes** the differentiation of T-lymphocytes in the interleukin-10 producing form, the antagonist of pro-inflammatory Interleukins.

In appropriate dosages, phosphatidylserine safely **shuts down** or **reverses** biochemical elevations and the structural deterioration of nerve cells, it **supports** human cognitive functions such as short-term memory formation, long-term memory consolidation, the ability to learn and recall information, attention focus, and concentration.
It also supports locomotory functions, especially quick reactions and reflexes.

▶ At appropriate dosages and in synergy, the administration of selenium (in the organic selenium-methionine form), phosphatidylserine, vitamins B5 and D3 **(GunaVit B5 PLUS)** triggers a virtuous mechanism aimed at combating the symptoms related to **chronic stress** and **infections** and those consisting of chronic fatigue, muscular and joint pain, insomnia, hair and memory loss, difficulties concentrating, increased histamine reactivity, atypical skin rashes, dyspnoea, synovitis and thyroiditis.

A vitamin B5 deficiency also lowers the available acetylcholine, the neurotransmitter also used by the Parasympathetic Nervous System.

– The uncontrolled and increased sympathetic tone subsequently causes hypertension, tachycardia, atrial arrhythmias, and a 'hyperadrenergic' state known to influence heart disease, and strokes.

– A vitamin B5 deficiency leads to a reduced production of cortisol where it acts as an anti-inflammatory mediator,

thus leading to increased arthritic pain, myalgia, fatigue, headaches, depression, insomnia, and widespread 'pro-inflammatory' effects on the Immune System.

The combination of vitamins D and B5 creates an intestinal environment favourable to the repopulation of *Actinobacteria*, *Bacteroidetes*, *Firmicutes* and *Proteobacteria* that make up the normal human microbiome.

A deficiency in the action of glutathione peroxidase promotes angiotensin II-induced left ventricular hypertrophy, dilatation, and ventricular dysfunction, highlighting a crucial physio-pathological role for ROS in the development of cardiovascular diseases.
– When the cortisol-mediated response is repeated and exacerbated, cortisol can *invade* the receptors for mineralocorticoids, thus triggering an aldosterone-like reaction.

In the case of COVID-19, activation (associated with cortisol) of the mineralocorticoid receptor in the virus-infected epithelial and endothelial cells stimulates the release of ATP, which then acts on the purinergic receptors.

In the lungs, this can cause a non-productive cough through the purinergic receptors on the affected vagal nerves.

On the other hand, in endothelial cells it can stimulate: **1)** the exocytosis of the Weibel-Palade Bodies* containing angiopoietin-2, which is involved in the pathogenesis of acute respiratory distress syndrome (ARDS), and **2)** the Von Willebrand factor (VWF), which mediates platelet adhesion to the endothelium and thus coagulation.

* **Editor's note**: Weibel-Palade Bodies are cytoplasmic organelles found in the endothelium cells of blood vessels, and of the heart.

CONCLUSIONS

Nutritional therapy is an important part of patient care, for surviving viral infections or other stress-promoting conditions, and for a better and shorter recovery as a result.

In addition, controlling malnutrition and optimal nutritional supplementation are essential steps to ensure the Immune System works in the best way possible.
– Patients with malnutrition are more likely to belong to poor socio-economic groups.
Therefore, nutritional supplementation is important for at-risk groups and fragile individuals such as the elderly with relatively weak immune systems.
People with a weak immune system are more prone to bacterial and/or viral infections.

– Early and adequate nutritional supplementation, together with pharmacological treatment and clinical collaboration, are essential when it comes to restoring both the structural and functional balance in health, and promoting a general state of well-being. ■

References

– Argañaraz G.A. *et* Al. – Phosphatidylserine inside out: a possible underlying mechanism in the inflammation and coagulation abnormalities of COVID-19. Cell Commun Signal. **2020** Dec 27;18(1):190. doi: 10.1186/s12964-020-00687-7.
– Audo R. *et* Al. – Phosphatidylserine Outer Layer Translocation Is Implicated in IL-10 Secretion by Human Regulatory B Cells. PLoS One. **2017**; 12(1): e0169755.
– Ayari H. *et* Al. – Mutual amplification of corticosteroids and angiotensin systems in human vascular smooth muscle cells and carotid atheroma. J Mol Med (Berl). **2014** Nov;92(11):1201-8. doi: 10.1007/s00109-014-1193-7. Epub 2014 Aug 5.
– Bermano G. *et* Al. – Selenium and viral infection: are there lessons for COVID-19? Br J Nutr. **2021** Mar 28;125(6):618-627. doi: 10.1017/S0007114520003128. Epub 2020 Aug 6.
– Dutta S. *et* Al. – Before the "cytokine storm": Boosting efferocytosis as an effective strategy against SARS-CoV-2 infection and associated complications. Cytokine & Growth Factor Reviews 63(10). Jan **2022**. doi: 10.1016/j.cytogfr.2022.01.002
– Edwards C. – New Horizons: Does Mineralocorticoid Receptor Activation by Cortisol Cause ATP Release and COVID-19 Complications? J Clin Endocrinol Metab. **2021** Mar; 106(3): 622-635. Published online 2020 Nov 28. doi: 10.1210/clinem/dgaa874.
– Erol A. – Importance of Efferocytosis in COVID-19 Mortality. Infect Drug Resist. **2022** Mar 10;15: 995-1007. doi: 10.2147/IDR.S348639. PMID: 35299855; PMCID: PMC8922362.
– Gominak S.C. – Vitamin D deficiency changes the intestinal microbiome reducing B vitamin production in the gut. The resulting lack of pantothenic acid adversely affects the immune system, producing a "pro-inflammatory" state associated with atherosclerosis and autoimmunity. Med Hypotheses. **2016** Sep; 94:103-7. doi: 10.1016/j.mehy.2016.07.007. Epub 2016 Jul 14.
– Grabiec A.M. & Hussell T. – The role of airway macrophages in apoptotic cell clearance following acute and chronic lung inflammation. Semin Immunopathol. **2016** Jul;38(4):409-23. doi: 10.1007/s00281-016-0555-3. Epub 2016 Mar 8.
– Hellhammer J. *et* Al. – A soy-based phosphatidylserine/phosphatidic acid complex (PAS) normalizes the stress reactivity of hypothalamus-pituitary-adrenal-axis in chronically stressed male subjects: a randomized, placebo-controlled study. Lipids Health Dis. **2014**; 13: 121. Published online 2014 Jul 31. doi: 10.1186/1476-511X-13-121.
– Kara E. *et* Al. – Chronic Stress, Cortisol Dysfunction, and Pain: A Psychoneuroendocrine Rationale for Stress Management in Pain Rehabilitation. Phys Ther. **2014** Dec; 94(12): 1816-1825. Published online 2014 Jul 17. doi: 10.2522/ptj.20130597.
– Linani A. *et* Al. – Exploring Structural Mechanism of COVID-19 Treatment with Glutathione as a Potential Peptide Inhibitor to the Main Protease: Molecular Dynamics Simulation and MM/PBSA Free Energy Calculations Study. Int J Pept Res Ther **2022**; 28(2):55. doi: 10.1007/s10989-022-10365-6. Epub 2022 Jan 21.
– Moghaddam A. *et* Al. – Selenium Deficiency Is Associated with Mortality Risk from COVID-19. Nutrients. **2020** Jul 16;12(7):2098. doi: 10.3390/nu12072098.
– Mrityunjaya M. *et* Al. – Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19. Front Immunol. **2020**; 11: 570122. Published online 2020 Oct 7.

doi: 10.3389/fimmu.2020.570122.
– Seale L.A. *et* Al. – A role for selenium-dependent GPX1 in SARS-CoV-2 virulence. Am J Clin Nutr. **2020** Aug 1;112(2):447-448. doi: 10.1093/ajcn/nqaa177.
– Shimura T. *et* Al. – Increase in serum levels of phosphatidylserine-specific phospholipase A1 in COVID-19 patients. Cell Mol Immunol. **2021** Sep;18(9):2275-2277. doi: 10.1038/s41423-021-00744-2. Epub 2021 Jul 28.
– Slyshenkov V.S. *et* Al. – Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. FEBS Lett. **2004** Jul 2;569(1-3):169-72. doi: 10.1016/j.febslet.2004.05.044.
– Sm S. *et* Al. – Curative role of pantothenic acid in brain damage of gamma irradiated rats. Indian J Clin Biochem. **2018** Jul;33(3):314-321. doi: 10.1007/s12291-017-0683-0. Epub 2017 Aug 7.
– Taylor E.W. & Radding W. – Understanding Selenium and Glutathione as Antiviral Factors in COVID-19: Does the Viral M pro Protease Target Host Selenoproteins and Glutathione Synthesis? Front Nutr. **2020** Sep 2;7:143. doi: 10.3389/fnut.2020.00143. eCollection 2020.
– Yahaya M. *et* Al. – Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: A cross-sectional comparative study in Jigawa, Northwestern Nigeria. SAGE Open Med. **2021** Feb 1; 9:2050312121991246. doi: 10.1177/2050312121991246. eCollection 2021.
– Zhang J. *et* Al. – Selenium and selenoproteins in viral infection with potential relevance to COVID-19. Redox Biol. **2020** Oct; 37: 101715. Published online 2020 Sep 10. doi: 10.1016/j.redox.2020.101715.

author

Dr. Felice Esposito
– Clinical Nutritionist
– Certified Sonographer (Ultrasound Internist and Doppler)
Borgosatollo (BS), Italy