

Review of: "Candida and Long Covid"

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This excellent work on Candida and Long Covid has been continuously improved, and the newest version covers all important aspects of the many connections that link Candida and Long Covid. The review focuses on the relevant molecular mechanisms and mediators that implicate Candida and Candida overgrowth in the development of Long Covid and its often devastating consequences:

- Zonulin, a circulating protein associated with increased intestinal and endothelial permeability, seems to be a central player. Proteases secreted by Candida stimulate the secretion of Zonulin, paving the way for the development of autoimmune diseases that are a hallmark of Long Covid.
- Candida hyphal walls express proteins that are analogous to gliadin/gluten (celiac disease antibodies) and to GPCRs (Crohn's disease antibodies) that can trigger anti-gliadin and anti-GPCR autoantibody formation. These two autoantibody-producing pathways both stimulate the release of zonulin.
- The spike protein S on SARS-CoV-2 can bind to ACE2 receptor-bearing cells and Toll-like receptor 4-bearing cells. The latter can also activate zonulin.
- A hypothetical pathophysiologic model is proposed with the central role of Candida overgrowth as a consequence of Covid-19 in promoting the genesis of Long Covid and associated autoimmune diseases, as well as dementia, cancer, and many other chronic diseases of premature aging.

The author proposes supplementation with a triple play of a prebiotic, probiotic, and postbiotic that may help to stop the development of the disease.

Since the pandemic, we have seen excess morbidity and mortality worldwide that presents a great challenge to science and society. Poor nutrition may be one decisive culprit leading to reductions in health span and even life expectancy. Research has to focus on nutrition and supplementation to restore, maintain, and improve health, fitness, and resistance to opportunistic invasive pathogens such as Candida.

This comprehensive and conclusive review can help to establish solutions to the problems of poor nutrition, opportunistic invasive pathogens, and associated chronic diseases.

- The altered tryptophan metabolism, with induction of indoleamine-2,3-dioxygenase, is now discussed in detail, and approaches to normalize enhanced tryptophan consumption associated with the formation of toxic kynurenine metabolites such as quinolinic acid are proposed.
- The review demonstrates in detail all the changes in GPCR signaling associated with Candida and Long Covid. Gq-

coupled GPCRs mediate all chemokine signals from T cells and antibodies to Gq-coupled GPCRs, induced by lectin-bound hyphal mannans, may represent a decisive pathway to Long Covid, as the lectin receptor domain may be part of the Gq-coupled GPCR signaling. Anti-inflammatory approaches are needed.

- Tryptophan depletion is induced by interferon- γ , which leads to the formation of toxic kynurenine metabolites such as anthranilic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid. Quinolinic acid is a potent excitotoxin with pro-inflammatory effects, whereas anthranilic acid, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid can act as oxidotoxins that alter the immune response. Long Covid is associated with the depletion of tryptophan and the accumulation of the toxic kynurenines. Candida fuels this vicious cycle of self-destruction. Antioxidant protection and anti-inflammatory modulation of the immune system are needed. The exhaustion of tryptophan has to be stopped, and normal signaling can be restored.
- The linkage of the NLRP3 inflammasome to Candida overgrowth and spike protein S accumulation adds additional credence to the hypothesis of Candida and Long Covid coupling. The NLRP3 inflammasome links Candida and Long Covid to dementia, cancer, autoimmunity, and obesity initiated by candidalysin and the spike protein S.
- The rapid increase in autoimmune diseases over the last half century leads to exhaustion and has to be stopped in order to increase resistance to infection and to restore symbiosis. This can be done with better nutrition and superior supplementation.
- Up to 65% of the persons affected by Long Covid have persistent spike protein S and antibodies to host AT1Rs, α 1-adrenergic, β 2-adrenergic receptors, and muscarinic cholinergic receptors that characterize Long Covid and may be due to invasive mannans.

Detoxification with regulation and regeneration by nutrition and supplementation can aid the restoration of health and well-being. The extended review gives an overview of the changes that are induced by Candida and Long Covid.

The endogenous molecular mechanisms and mediators of premature aging and degenerative diseases are identified and characterized to orchestrate supplementation that helps to restore normal signaling and symbiosis.