Long COVID & Sexual Health

ACA-CDID 2023 DABCI Symposium

Saturday, April 15th, 3:30-5:30

Nikolas Hedberg, DC, DABCI, DACBN

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Bio

- Nikolas Hedberg, DC, DABCI, DACBN
- Taught DABCI Infectious Disease Module x3 – DABCI Orlando
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- Practice – Immune Restoration Center in Asheville, NC
- Moss Nutrition – Chief Medical Officer

COVID-19 General Prevention

- Core:
- Vitamin D+K 5-10,000 IU/day
- Multivitamin (zinc, selenium, B's, A, E)
- Vitamin C: 500 mg bid
- Icelandic Cod Liver Oil: 1 teaspoon/day or 3 softgels/day
- Cs-4 Cordyceps: 500 mg bid
- Probiotic
- High potassium diet
- 1.2 – 1.5 grams protein/kg bw (increases phagocytosis, improves NK cell activity, increases immunoglobulin production)

- Core + Boosters:
- NAC 700 mg: 1 qd or Liposomal Glutathione 500 mg – 1 teaspoon/day
- Immune Formula (Echinacea, Goldenseal, Astragalus, Ligustrum, Andrographis, Olive Leaf, Shisandra, Amla, Lysine): 1 bid
- Curcumin 250 mg bid, Black Cumin Seed Oil 500 mg qd, or Resveratrol + Quercetin 225 mg qd if there is an ongoing inflammatory process.

Acute Phase

- Vitamin D+K 5-10,000 IU and Multivitamin
- Cod Liver Oil 1 teaspoon or 3 softgels tid
- Zinc 30 mg + 1 mg copper: 1 bid
- Increase NAC 700 mg to 1 tid or Liposomal Glutathione 1 tsp tid
- Vitamin C 1,000 mg every hour to bowel tolerance in 6-15 doses
- Immune Formula (Echinacea, Goldenseal, Astragalus, Ligustrum, Andrographis, Olive Leaf, Shisandra, Amla, Lysine): 2 tid
- Cs-4 Cordyceps: 1,000 mg tid
- Melatonin 3 mg at bedtime
- Selenomethionine 200 mcg tid
- Curcumin 500 mg bid or Black Cumin Seed Oil Softgels 1,000-3,000 mg/day in 2-3 divided doses
- Resveratrol + Quercetin 225 mg tid.
- Probiotic 1 tid

Acute Phase - Optional

- Marshmallow Root 1 scoop bid. Mix with honey and drink slowly. (Cough, sore throat)
- Gingko Biloba 120 mg bid (Blocks SARS-CoV-2, anti-inflammatory, antioxidant, prevents cerebral infarctions and microcirculation damage.)
- Nattokinase 100 mg bid or Bromelain 500 mg bid
- PEA 600 mg bid + Luteolin 100 mg bid
- Berberine 500 mg bid

The Journal of Nutrition
Nutrition and Disease

Palmitoylethanolamide Reduces Proinflammatory Markers in Unvaccinated Adults Recently Diagnosed with COVID-19: A Randomized Controlled Trial

Samantha N Fessler,[1] Li Liu,[1,2] Yung Chang,[2,3] Theresa Yip,[2,3] and Carol S Johnston[1]

Participants were stratified by age, sex, and BMI and randomly assigned by coin toss to receive 600 mg Levagen+ twice daily (LEV) or placebo tablets twice daily (CON) for 4 wk. The primary outcomes were the 4-wk change between groups for IL-6, C-reactive protein, ferritin, intercellular adhesion molecule 1, soluble P-selectin (sP-selectin), and neutrophil/lymphocyte ratio.

Results: After 4 wk of supplementation, sP-selectin, IL-1β, and IL-2 concentrations were significantly reduced in the LEV group compared with the CON group.

Conclusions: Overall, PEA supplementation produced anti-inflammatory effects in individuals recently diagnosed with COVID-19 who were nonhospitalized.

viruses

MDPI

Article

The Combination of Bromelain and Acetylcysteine (BromAc) Synergistically Inactivates SARS-CoV-2

Javed Akhter [1,2,†], Grégory Quéromès [3,†], Krishna Pillai [2,†], Vahan Kepenekian [1,4,†], Samina Badar [1,5], Ahmed H. Mekkawy [1,2,5], Emilie Frobert [3,6,‡], Sarah J. Valle [1,2,5,‡] and David L. Morris [1,2,5,*,‡]

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† These authors contributed equally to this work.
‡ These authors contributed equally to this work.

Abstract: Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection is the cause of

molecules

MDPI

Article

Degradative Effect of Nattokinase on Spike Protein of SARS-CoV-2

When cell lysates transfected with S protein were incubated with nattokinase, the S protein was degraded in a dose- and time-dependent manner. Immunofluorescence analysis showed that S protein on the cell surface was degraded when nattokinase was added to the culture medium. Thus, our findings suggest that nattokinase exhibits potential for the inhibition of SARS-CoV-2 infection via S protein degradation.

Natto is a popular traditional Japanese food made from soybeans fermented by *Bacillus subtilis* var. *natto*. Nattokinase is found in natto [4] and is one of the most important extracellular enzymes produced by *B. subtilis* var. *natto* [5]. Nattokinase consists of 275 amino acids and is approximately 28 kDa [6,7]. Nattokinase inactivates plasminogen activator inhibitor-1 and increases fibrinolysis [8]. It also decreases the plasma levels of fibrinogen, factor VII, cytokines, and factor VIII [9]. Nattokinase has the highest clot-dissolving potency among naturally known anticoagulants [10]. A clinical trial demonstrated that oral consumption of nattokinase was not associated with any adverse effects [11]. Thus, nattokinase is now considered an efficient, secure, and economical enzyme that has drawn central attention in thrombolytic drug studies [12,13]. In addition, nattokinase is used in the treatment of some tumors [14,15].

Biochemical and Biophysical Research Communications 570 (2021) 21–25

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Natto extract, a Japanese fermented soybean food, directly inhibits viral infections including SARS-CoV-2 *in vitro*

Mami Oba [a], Wen Rongduo [a, b], Akatsuki Saito [c, d], Tamaki Okabayashi [c, d], Tomoko Yokota [a], Junko Yasuoka [a], Yoko Sato [a], Koji Nishifuji [e], Hitoshi Wake [a, f], Yutaka Nibu [g], Tetsuya Mizutani [a, b, *]

Interestingly, our results show that both SARS-CoV-2 and BHV-1 treated with a natto extract were fully inhibited infection to the cells. We also found that the glycoprotein D of BHV-1 was shown to be degraded by Western blot analysis and that a recombinant SARS-CoV-2 receptor-binding domain (RBD) was proteolytically degraded when incubated with the natto extract. In addition, RBD protein carrying a point mutation (UK variant N501Y) was also degraded by the natto extract.

International Journal of Biological Macromolecules 226 (2023) 780–792

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Ginkgolic acids inhibit SARS-CoV-2 and its variants by blocking the spike protein/ACE2 interplay

Yusen Xiang [a,1], Guanglei Zhai [b,1], Yaozong Li [c,d], Mengge Wang [a], Xixiang Chen [a,e], Ruyu Wang [a], Hang Xie [f], Weidong Zhang [a,g], Guangbo Ge [a], Qian Zhang [h], Yechun Xu [i], Amedeo Caflisch [c], Jianrong Xu [e,j,*], Hongzhuan Chen [a,*], Lili Chen [a,*]

Our pseudovirus assay showed that one of the compounds, Ginkgolic acid C17:1 (GA171), significantly inhibits the entry of original SARS-CoV-2 and its variants into the ACE2-overexpressed HEK293T cells.

frontiers in Pharmacology

REVIEW
published: 23 September 2020
doi: 10.3389/fphar.2020.581840

COVID-19: Is There Evidence for the Use of Herbal Medicines as Adjuvant Symptomatic Therapy?

A total of 39 herbal medicines were identified as very likely to appeal to the COVID-19 patient. According to our method, the benefits/risks assessment of the herbal medicines was found to be positive in 5 cases (**Althaea officinalis (Marshmallow)**, Commiphora molmol (Myrrh), Glycyrrhiza glabra (Licorice), Hedera helix (English ivy), and Sambucus nigra (Black elderberry), promising in 12 cases (Allium sativum (Garlic), Andrographis paniculata, Echinacea angustifolia, Echinacea purpurea, Eucalyptus globulus essential oil, Justicia pectoralis (Water willow), Magnolia officinalis, Mikania glomerata, Pelargonium sidoides, Pimpinella anisum (Anise), Salix sp (White willow bark), Zingiber officinale (Ginger)), and unknown for the rest.

ILLUSTRATION BY DAVID PARKINS

THE MYSTERY IN MICRO-CLOTS

Tiny blood clots might explain some of long COVID's puzzling array of symptoms. But many researchers worry about people seeking unproven therapies. **By Cassandra Willyard**

Nature **608**, 662-664 (2022)

doi: https://doi.org/10.1038/d41586-022-02286-7

Angiogenesis
https://doi.org/10.1007/s10456-022-09850-9

ORIGINAL PAPER

Persistent capillary rarefication in long COVID syndrome

Irina Osiaevi[1] · Arik Schulze[1] · Georg Evers[1] · Kimon Harmening[1] · Hans Vink[2] · Philipp Kümpers[3] · Michael Mohr[1] · Alexandros Rovas[3]

All participants underwent sublingual videomicroscopy using sidestream dark field imaging. A newly developed version of Glycocheck™ software was used to quantify vascular density, perfused boundary region (PBR-an inverse variable of endothelial glycocalyx dimensions), red blood cell velocity (VRBC) and the microvascular health score (MVHS™) in sublingual microvessels with diameters 4-25 µm.
Although dimensions of the glycocalyx were comparable to those of healthy controls, a µm-precise analysis showed a significant decrease of vascular density, that exclusively affected very small capillaries. Plotting VRBC of capillaries and feed vessels showed that the number of capillaries perfused in long COVID patients **was comparable to that of critically ill COVID-19 patients** and did not respond adequately to local variations of tissue metabolic demand. MVHS was markedly reduced in the long COVID cohort (healthy 3.87 vs. long COVID 2.72 points; p = 0.002).

Conclusions: Our current data strongly suggest that COVID-19 leaves a persistent capillary rarefication even 18 months after infection.

Long COVID

"CAUSES"

Persistent virus/antigens

T-cell abnormalities

Other amyloid-inducing metabolites

Endotheliitis

Platelet hyperactivation

Coagulopathies, especially fibrin amyloid microclots

Decreased O_2 delivery to tissues

Respiration/mitochondrial dysfunction

Oxidative stress

Autoantibodies

Gut Dysbiosis
Autonomic Dysfunction
Dendritic Cell Deficiency

"EFFECTS"

CNS dysfunction

Chest pain

Breathlessness

Fatigue

POTS, tachychardia

Brain fog

Post-exertional malaise

PMID: 36043493

PMID: 36672687

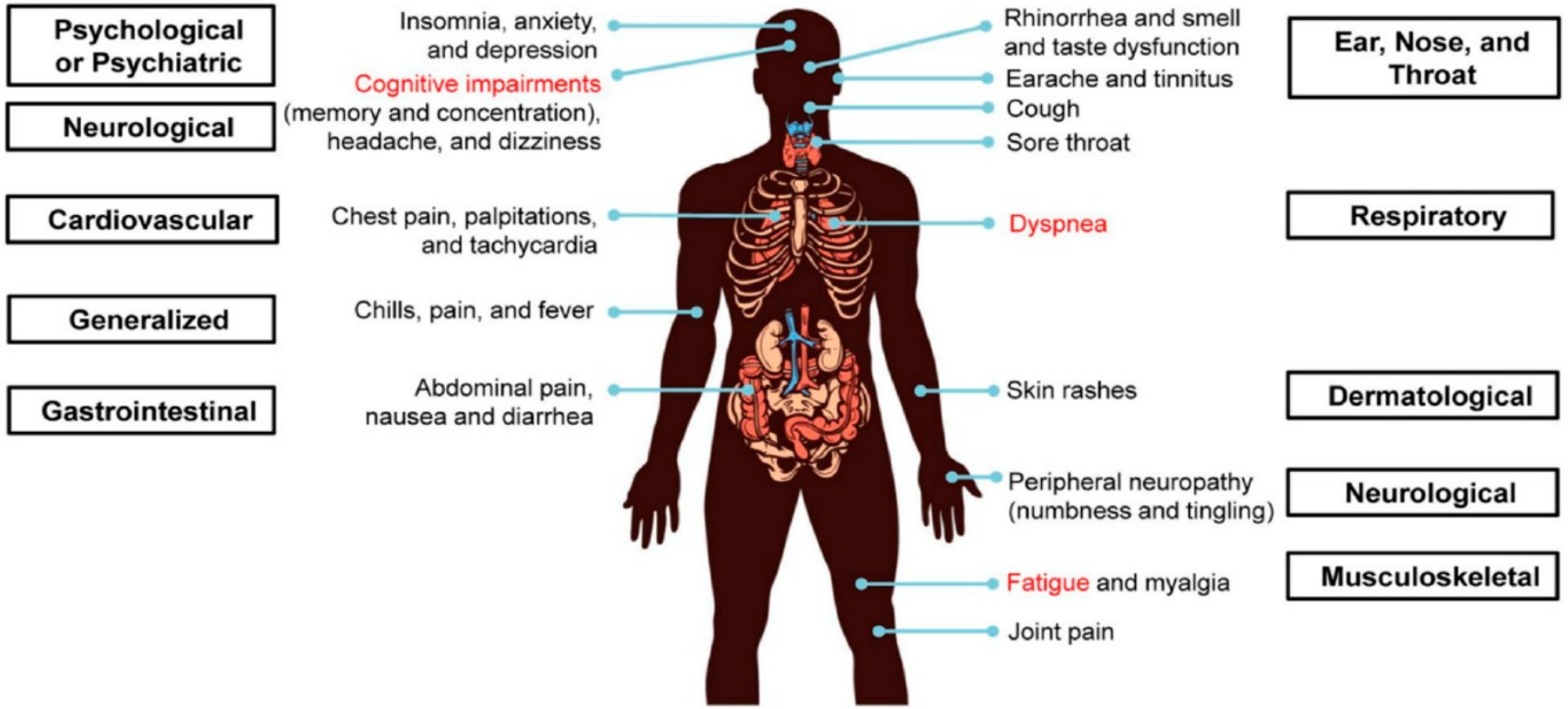


Figure 1. Symptoms of long-COVID-19. Multiple organ systems are affected, such as psychological

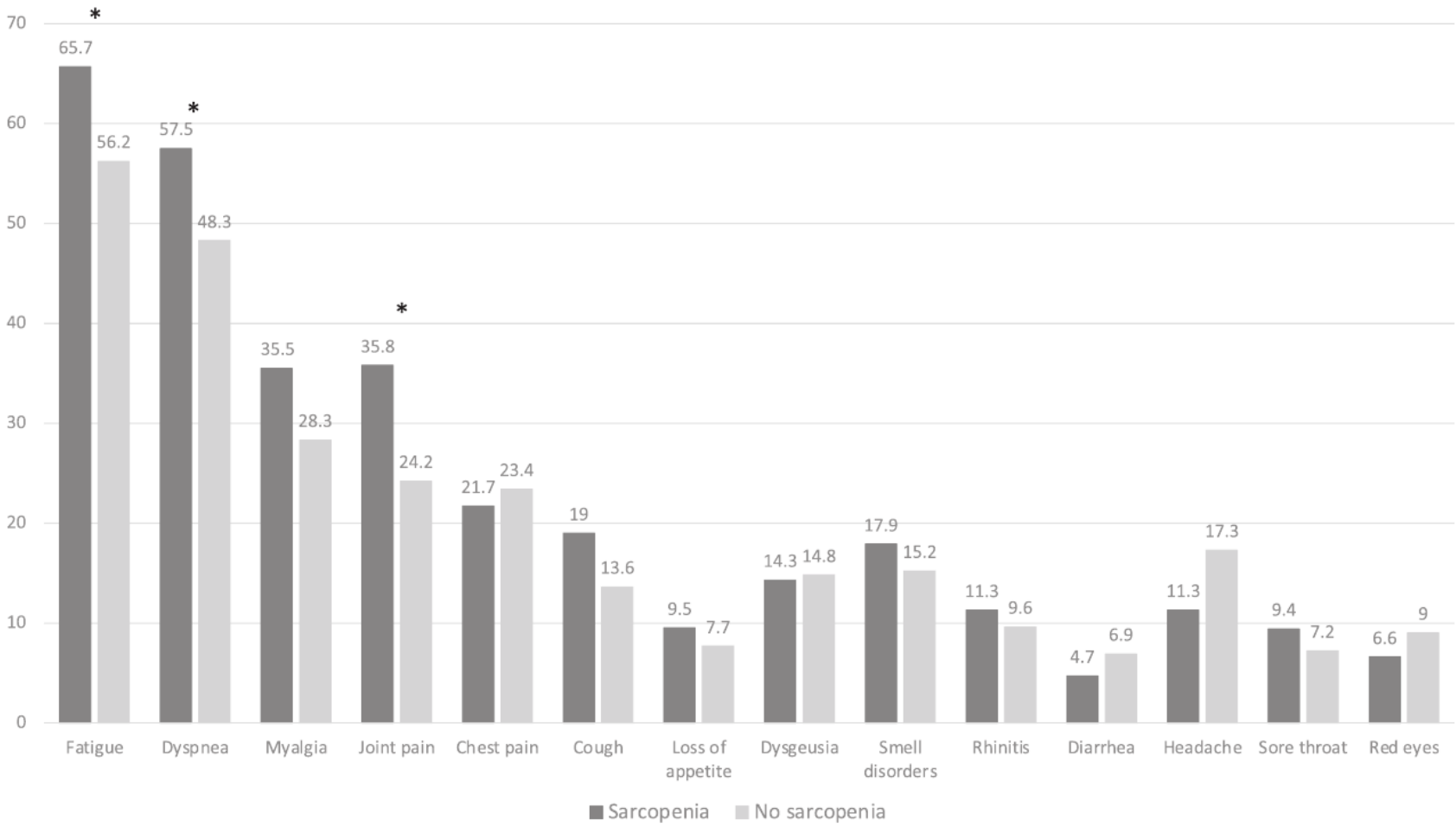


Figure 2 Prevalence of persistent COVID-19-related symptoms according to the presence of sarcopenia ($^{*}\leq 0.05$).

PMID: 35698920

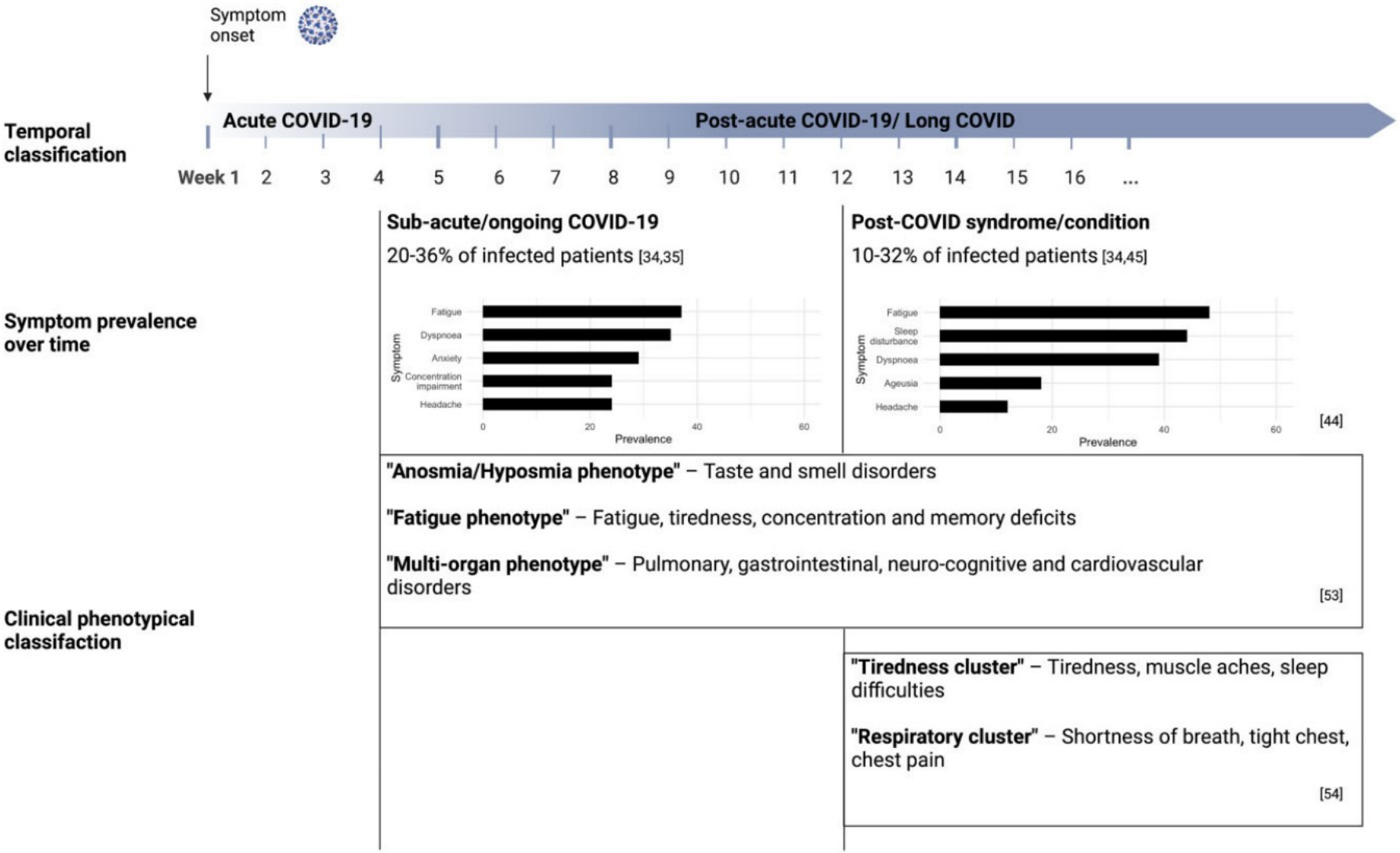
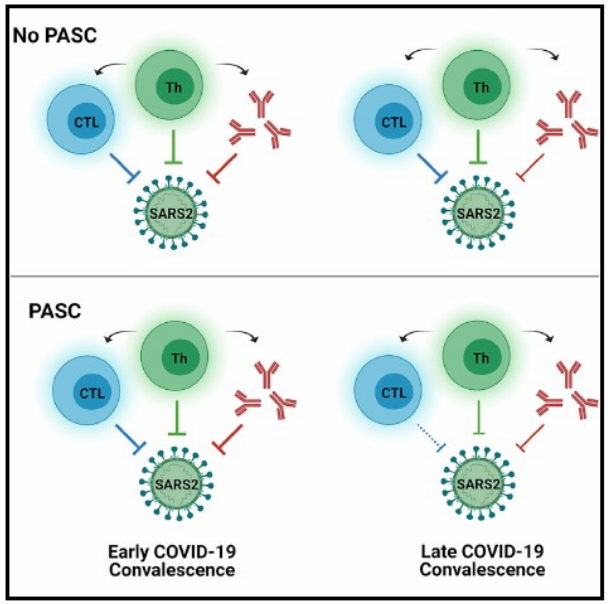


Figure 1. Time course of long COVID, dominant symptoms over time and proposed clinical phenotypes (Created with BioRender.com). PMID: 36846561

Cell Reports

Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms

Graphical abstract



Highlights

- The magnitude of early CD4$^+$ T cell responses correlates with severity of COVID-19
- Prior lung disease correlates with higher SARS-CoV-2-specific CD8$^+$ T cell responses
- PASC is associated with a decline in N-specific interferon-γ-producing CD8$^+$ T cells
- Neutralizing capacity correlates with SARS-CoV-2-specific CD4$^+$ T cell responses

Authors

Michael J. Peluso, Amelia N. Deitchman, Leonel Torres, ..., Bryan Greenhouse, Rachel L. Rutishauser, Timothy J. Henrich

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In brief

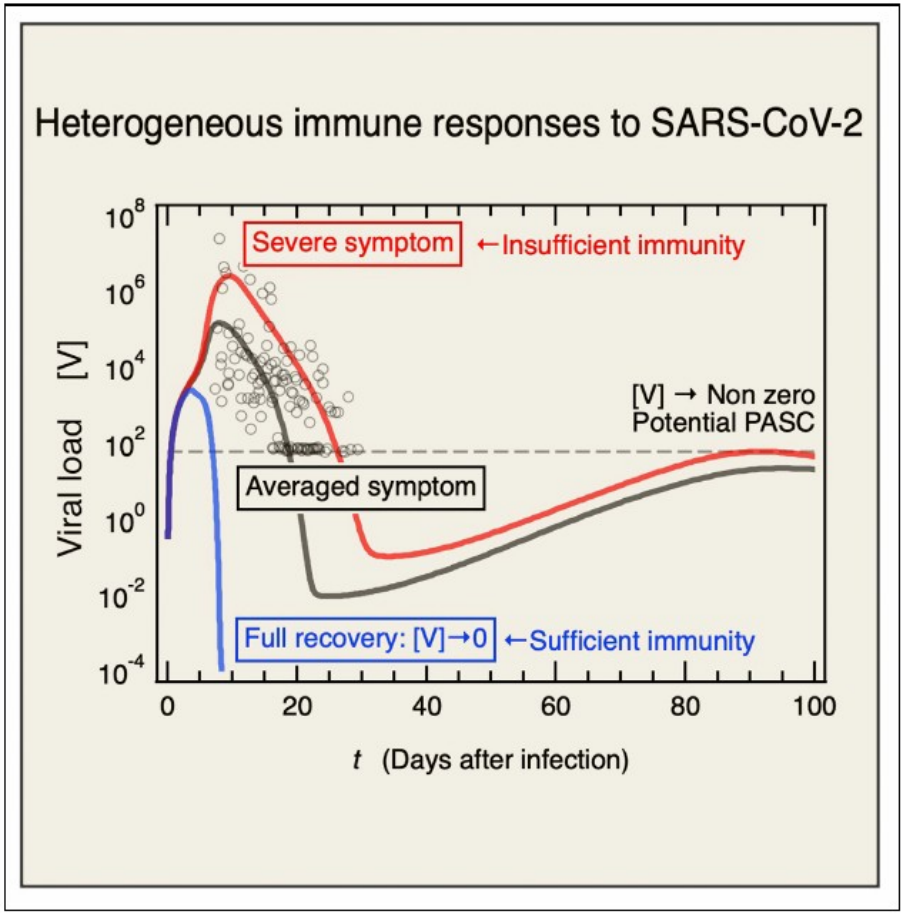
CD4$^+$ and CD8$^+$ T cell responses following natural infection with COVID-19 are stable over 8 months. Individuals with PASC demonstrate a lower frequency of CD8$^+$ T cells expressing CD107a, a marker of degranulation, and a more rapid decline in the frequency of N-specific interferon-γ-producing CD8$^+$ T cells.

iScience

CellPress
OPEN ACCESS

Article

Immune response to SARS-CoV-2 in severe disease and long COVID-19



Tomonari Sumi,
Kouji Harada

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Highlights

Systemic SARS-CoV-2 infection owing to ACE2 expression on a wide range of cell types

Persistent viral infection can be ongoing within the host even if it is not severe

Long-term dendritic cell deficiency is owing to viruses that cannot be removed by the host

Ongoing persistent viral infection within the host potentially causes long COVID or PASC

PMID: 36293160

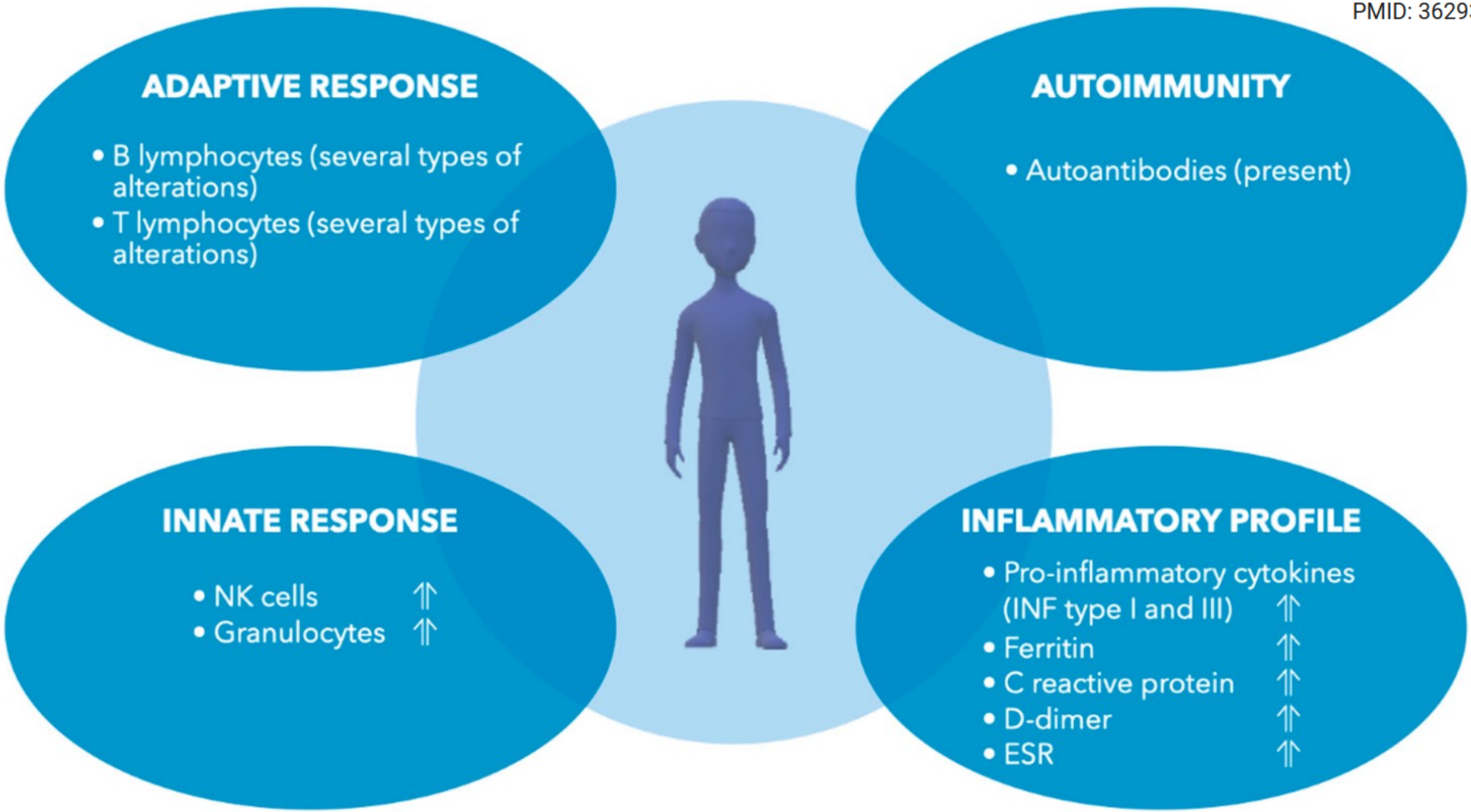

Figure 2. Immunological and inflammatory alterations described in long COVID-19.

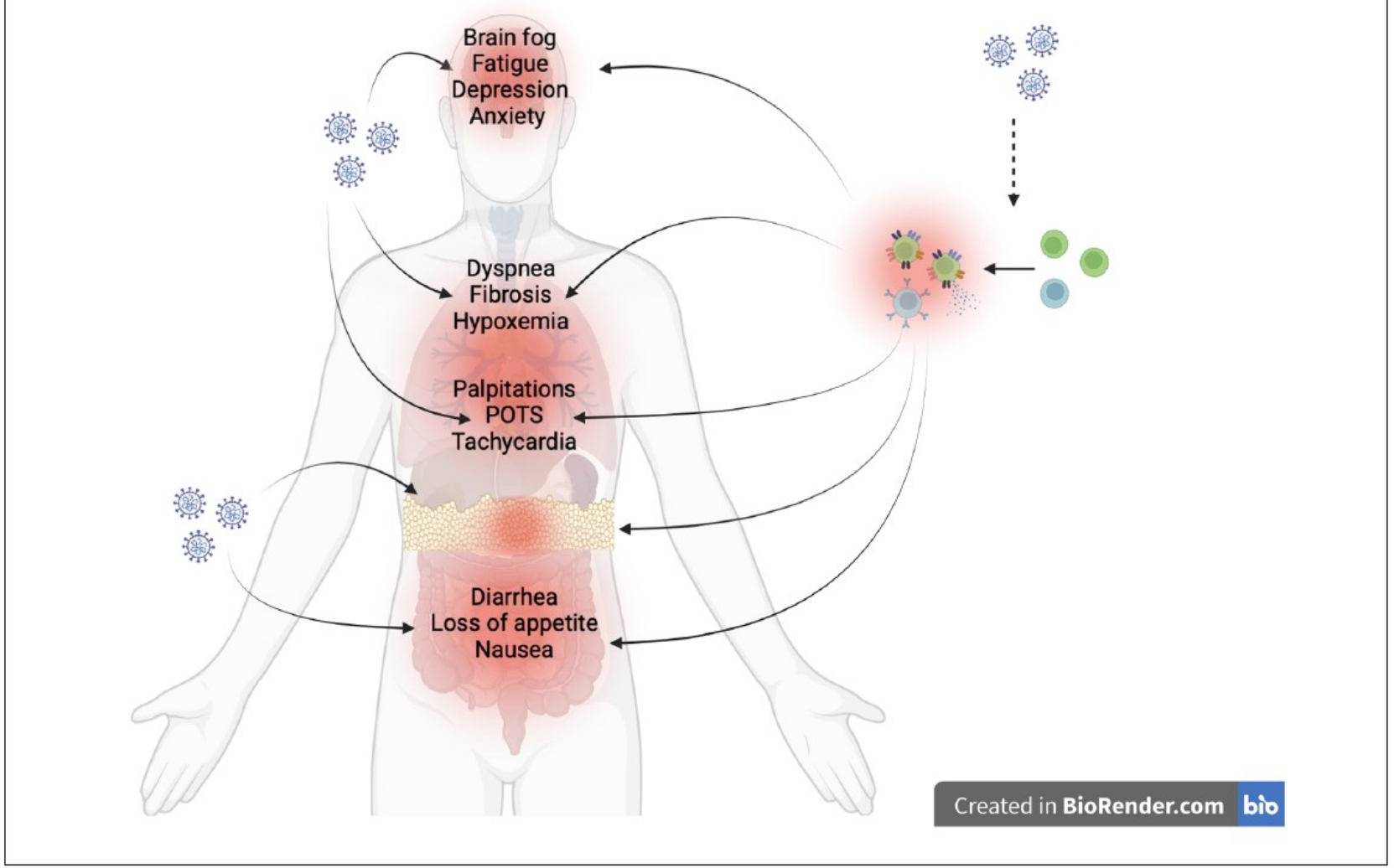

Figure 5. Proposed mechanism for how viral reservoirs and dysregulated immune responses contribute to the development of long COVID.

Persistent antigen contributes to cell population changes such as a decrease in naïve T and B cells and an increase in effector cells, as well as increased expression of activation and exhaustion markers as the immune system attempts to regulate this chronic activation state. We propose that viral reservoirs contribute to this dysregulation and lead to both localized and systemic inflammation depending on where antigen is located. Several groups have demonstrated antigen persistence in a variety of tissues (e.g., brain, lungs, heart, adipose, gastrointestinal tract) in SARS-CoV-2-infected patients both acutely and chronically. In addition, several groups have demonstrated tissue-specific immune responses and inflammation in relation to corresponding organ-specific symptoms.

PMID: 36879504

frontiers | Frontiers in Cellular and Infection Microbiology

ORIGINAL RESEARCH
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doi: 10.3389/fcimb.2022.922422

Cytokine Profiles Associated With Acute COVID-19 and Long COVID-19 Syndrome

OPEN ACCESS

Edited by:
Viviane Fongaro Botosso, Butantan Institute, Brazil

Reviewed by:

Maria Alice Freitas Queiroz[1†], *Pablo Fabiano Moura das Neves*[2†], *Sandra Souza Lima*[1],

In the post-COVID-19 group, subjects with long COVID-19 had higher levels of IL-17 and IL-2 ($p<0.05$), and subjects without sequelae had higher levels of IL-10, IL-6 and IL- 4 ($p<0.05$). Our results suggest that advanced age, comorbidities and elevated serum IL-6 levels are associated with severe COVID-19 and are good markers to differentiate severe from mild cases. Furthermore, high serum levels of IL-17 and IL-2 and low levels of IL-4 and IL-10 appear to constitute a cytokine profile of long COVID-19, and these markers are potential targets for COVID-19 treatment and prevention strategies.

BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Mast cell activation syndrome and the link with long COVID

Soumya Arun[1,2]
Abbie Storan[2,3]
Bethan Myers[4]

Author details can be found at the end of this article

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Abstract

Mast cells are innate immune cells found in connective tissues throughout the body, most prevalent at tissue–environment interfaces. They possess several cell-surface receptors which react to various stimuli and, after activation, release many mediators including histamine, heparin, cytokines, prostaglandins, leukotrienes and proteases. In mast cell activation syndrome, excessive amounts of inflammatory mediators are released, in response to triggers such as foods, fragrances, stress, exercise, medications or temperature changes. Diagnostic markers may be difficult to assess because of their rapid degradation; these include urinary N-methyl histamine, urinary prostaglandins D2, DM and F2α and serum tryptase (which is stable) in the UK. Self-management techniques, medications and avoidance of triggers may improve quality of life. Treatments include mast cell mediator blockers, mast cell stabilisers and anti-inflammatory agents. 'Long COVID' describes post-COVID-19 syndrome when symptoms persist for more than 12 weeks after initial infection with no alternative diagnosis. Both mast cell activation syndrome and long COVID cause multiple symptoms. It is theorised that COVID-19 infection could lead to exaggeration of existing undiagnosed mast cell activation syndrome, or could activate normal mast cells owing to persistence of viral particles. Other similarities include the relapse–remission cycle and improvements with similar treatments. Importantly, however, aside from mast cell disorders, long COVID could potentially be attributed to several other conditions.

Key words: Long COVID; Mast cell activation syndrome; Multiple symptomatology; Post-acute sequelae SARS-CoV-2 infection

Submitted: 28 February 2022; accepted following double-blind peer review: 31 May 2022

Introduction

Mast cell activation syndromes are a heterogeneous group of conditions which sit within a broad spectrum of disorders associated with oversensitive or inappropriately activated mast cells (Figure 1). Mast cell activation syndrome is characterised by widespread, multisystem, episodic symptoms. These symptoms result from chronic inappropriate activation of mast cell receptors rather than increased production of inflammatory mediators (Table 1). Mast cell activation syndrome can occur in both adults and children, and the prevalence may be as high as 17% in some countries (Molderings et al, 2013; Akin, 2017).

This article describes what mast cell activation syndrome is and how it is linked to long COVID.

Mast cells

Mast cells are haematopoietically-derived innate immune cells which reside in connective tissues throughout the body. They are most prevalent at tissue–environment interfaces such

How to cite this article:
Arun S, Storan A, Myers B. Mast cell activation syndrome and the link with long COVID. Br J Hosp Med. 2022. https://doi.org/10.12968/hmed.2022.0123

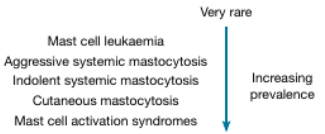

Figure 1. Spectrum of mast cell activation disease. From Afrin and Molderings (2014).

Neurological or neuropsychiatric
Anxiety
Depression
Migraines
Pins and needles
Numbness
Brain fog
Fatigue
Behavioural issues

Dermatological
Itching
Burning
Flushing
Rashes
Hives
Swelling

Gastrointestinal
Dysphagia
Abdominal pain
Diarrhoea
Constipation
Appetite loss
Bloating
Reflux
Vomiting or nausea
Dumping syndrome
Food intolerances

Ear, nose and throat
Visual impairment
Hearing impairment
Loss of taste/smell
Nasal congestion

Respiratory
Dyspnoea
Wheezing
Anaphylaxis
Coughing
Sore throat
Throat swelling

Immunological
Severe reactions to existing
Allergies
Development of new allergies

Musculoskeletal
Joint and muscle pain
Loss of bone mass

Cardiovascular
Chest pain
Palpitations
Low blood pressure
Fainting

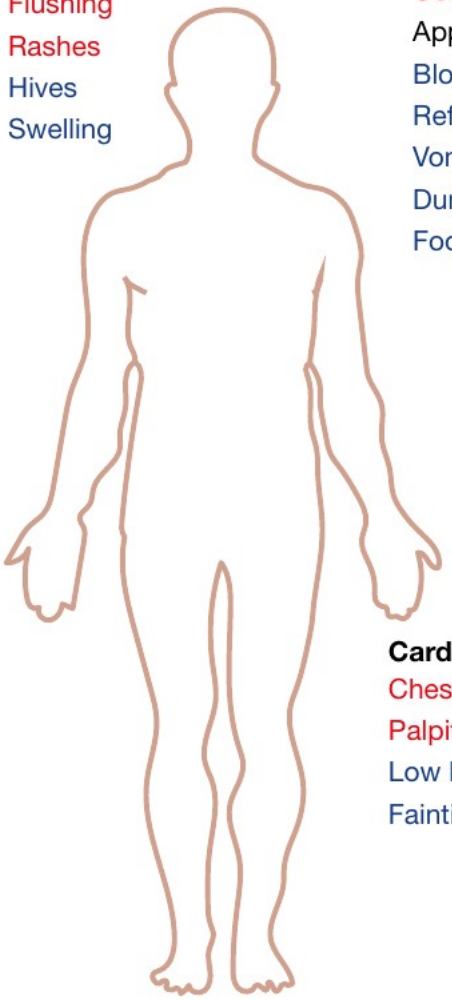

Figure 4. Long COVID symptoms. Those highlighted in red are shared with mast cell activation syndrome, and those highlighted in blue are general symptoms of mast cell activation syndrome.

LETTERS
https://doi.org/10.1038/s41590-021-01113-x
nature immunology

Check for updates

Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection

Chansavath Phetsouphanh[1,7]✉, David R. Darley[2,7], Daniel B. Wilson[3], Annett Howe[1], C. Mee Ling Munier[1], Sheila K. Patel[4], Jennifer A. Juno[5], Louise M. Burrell[4], Stephen J. Kent[5,6], Gregory J. Dore[1,2], Anthony D. Kelleher[1,2,7]✉ and Gail V. Matthews[1,2,7]✉

Patients with LC had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection. Combinations of the inflammatory mediators IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with LC with 78.5-81.6% accuracy. This work defines immunological parameters associated with LC and suggests future opportunities for prevention and treatment.

IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with LC with 78.5–81.6% accuracy. This work defines immunological parameters associated with LC and suggests future opportunities for prevention and treatment.

Acute COVID-19, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by a broad spectrum of clinical severity, from asymptomatic to fatal[1,2]. The immune response during acute illness contributes to both host defense and pathogenesis of severe COVID-19 (ref. [3]). Pronounced immune dysregulation with lymphopenia and

of initial diagnosis)[4–6], with 95.6% and 84.5% of participants completing subsequent month 4 (median, 128 days) and month 8 (median, 232 days) visits (Table 1). Of the 147 patients recruited (70.5% through ADAPT sites and 29.5% externally), 31 participants (21.08%) were designated as LC based on the occurrence of one of three major symptoms (fatigue, dyspnea or chest pain) at month 4 (Supplementary Table 1). These participants were age and gender matched with 31 asymptomatic matched controls (MCs) from the same cohort who did not report symptoms at month 4 after infection but were symptomatic during the acute phase of the infection

antioxidants

MDPI

Article

Antioxidant Genetic Profile Modifies Probability of Developing Neurological Sequelae in Long-COVID

Marko Ercegovac [1,2,†], Milika Asanin [1,3,†], Ana Savic-Radojevic [1,4], Jovan Ranin [1,5], Marija Matic [1,4], Tatjana Djukic [1,4], Vesna Coric [1,4], Djurdja Jerotic [1,4], Nevena Todorovic [5], Ivana Milosevic [1,5], Goran Stevanovic [1,5], Tatjana Simic [1,4,6], Zoran Bukumiric [1,7,*] and Marija Pljesa-Ercegovac [1,4,*]

Neurological examination and antioxidant genetic profile (SOD2, GPXs and GSTs) determination, as well as, genotype analysis of Nrf2 and ACE2, were conducted on 167 COVID-19 patients. Only polymorphisms in GSTP1AB and GSTO1 were independently associated with long-COVID manifestations. Indeed, individuals carrying GSTP1 Val or GSTO1 Asp allele exhibited lower odds of long-COVID myalgia development, both independently and in combination. Furthermore, the combined presence of GSTP1 Ile and GSTO1 Ala alleles exhibited cumulative risk regarding long-COVID myalgia in carriers of the combined GPX1 LeuLeu/GPX3 CC genotype. Moreover, individuals carrying combined GSTM1-null/GPX1LeuLeu genotype were more prone to developing long-COVID "brain fog", while this probability further enlarged if the Nrf2 A allele was also present.

frontiers in Immunology

ORIGINAL RESEARCH
published: 10 January 2022
doi: 10.3389/fimmu.2021.746021

Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection

Bruce K. Patterson[1*], *Edgar B. Francisco*[1], *Ram Yogendra*[2], *Emily Long*[1], *Amruta Pise*[1], *Hallison Rodrigues*[1], *Eric Hall*[3], *Monica Herrera*[3], *Purvi Parikh*[4], *Jose Guevara-Coto*[5,6], *Timothy J. Triche*[7], *Paul Scott*[7], *Saboor Hekmati*[7], *Dennis Maglinte*[7], *Xaiolan Chang*[8], *Rodrigo A. Mora-Rodríguez*[5] and *Javier Mora*[5]

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Edited by:

The levels of both intermediate (CD14+, CD16+) and non-classical monocyte (CD14Lo, CD16+) were significantly elevated in PASC patients up to 15 months post-acute infection compared to healthy controls. A statistically significant number of non-classical monocytes contained SARS-CoV-2 S1 protein in both severe and PASC patients out to 15 months post-infection. Cells from 4 out of 11 severe COVID-19 patients and 1 out of 26 PASC patients contained ddPCR+ peripheral blood mononuclear cells, however, only fragmented SARS-CoV-2 RNA was found in PASC patients.

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Original research

Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome

Qin Liu,[1,2,3,4] Joyce Wing Yan Mak ,[1,2,3] Qi Su,[1,2,3,4] Yun Kit Yeoh ,[1,4,5] Grace Chung-Yan Lui,[2,6] Susanna So Shan Ng,[2] Fen Zhang ,[1,2,3,4] Amy Y L Li,[1,2,3] Wenqi Lu,[1,2,3,4] David Shu-Cheong Hui,[6] Paul KS Chan,[1,5] Francis K L Chan ,[1,2,3,4] Siew C Ng [1,2,3,4]

Gut microbiota composition at admission was associated with occurrence of PACS. Patients without PACS showed recovered gut microbiome profile at 6 months comparable to that of non-COVID-19 controls. Gut microbiome of patients with PACS were characterised by higher levels of Ruminococcus gnavus, Bacteroides vulgatus and lower levels of Faecalibacterium prausnitzii. Persistent respiratory symptoms were correlated with opportunistic gut pathogens, and neuropsychiatric symptoms and fatigue were correlated with nosocomial gut pathogens, including Clostridium innocuum and Actinomyces naeslundii. Butyrate-producing bacteria, including Bifidobacterium pseudocatenulatum and Faecalibacterium prausnitzii showed the largest inverse correlations with PACS at 6 months.

including *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii* showed the largest inverse correlations with PACS at 6 months.

Conclusion These findings provided observational

- These findings provide new insights into the intricate association between the gut microbiome and the long-term sequelae after COVID-19 infection.

JCI insight

RESEARCH ARTICLE

Inflammation-type dysbiosis of the oral microbiome associates with the duration of COVID-19 symptoms and long COVID

John P. Haran,[1,2,3] Evan Bradley,[1,3] Abigail L. Zeamer,[2,3] Lindsey Cincotta,[1] Marie-Claire Salive,[1] Protiva Dutta,[1] Shafik Mutaawe,[1] Otuwe Anya,[1] Mario Meza-Segura,[2] Ann M. Moormann,[4] Doyle V. Ward,[2,3] Beth A. McCormick,[2,3] and Vanni Bucci[2,3]

[1]Department of Emergency Medicine, [2]Department of Microbiology and Physiological Systems, [3]Program in Microbiome Dynamics, and [4]Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, USA.

Given the role of the microbiome in mediating inflammation, we aimed to examine the relationship between the oral microbiome and the duration of long COVID symptoms. Of the patients followed, 63% developed ongoing symptomatic COVID-19 and 37% went on to long COVID. Patients with prolonged symptoms had significantly higher abundances of microbiota that induced inflammation, such as members of the genera Prevotella and Veillonella, which, of note, are species that produce LPS. The oral microbiome of patients with long COVID was similar to that of patients with chronic fatigue syndrome. Altogether, our findings suggest an association with the oral microbiome and long COVID, revealing the possibility that dysfunction of the oral microbiome may have contributed to this draining disease.

Introduction

The oral cavity holds the second largest microbial community in the human body, after the gut, with over 1000 species of commensal bacteria residing therein (1). Dysbiosis or disrupted homeostasis caused by an imbalance in the microflora in the oral cavity has been linked to many other systemic inflammatory or infectious diseases (2). There is mounting evidence that links oral bacterial species to systemic diseases including

Authorship note: JPH and EB

nature communications

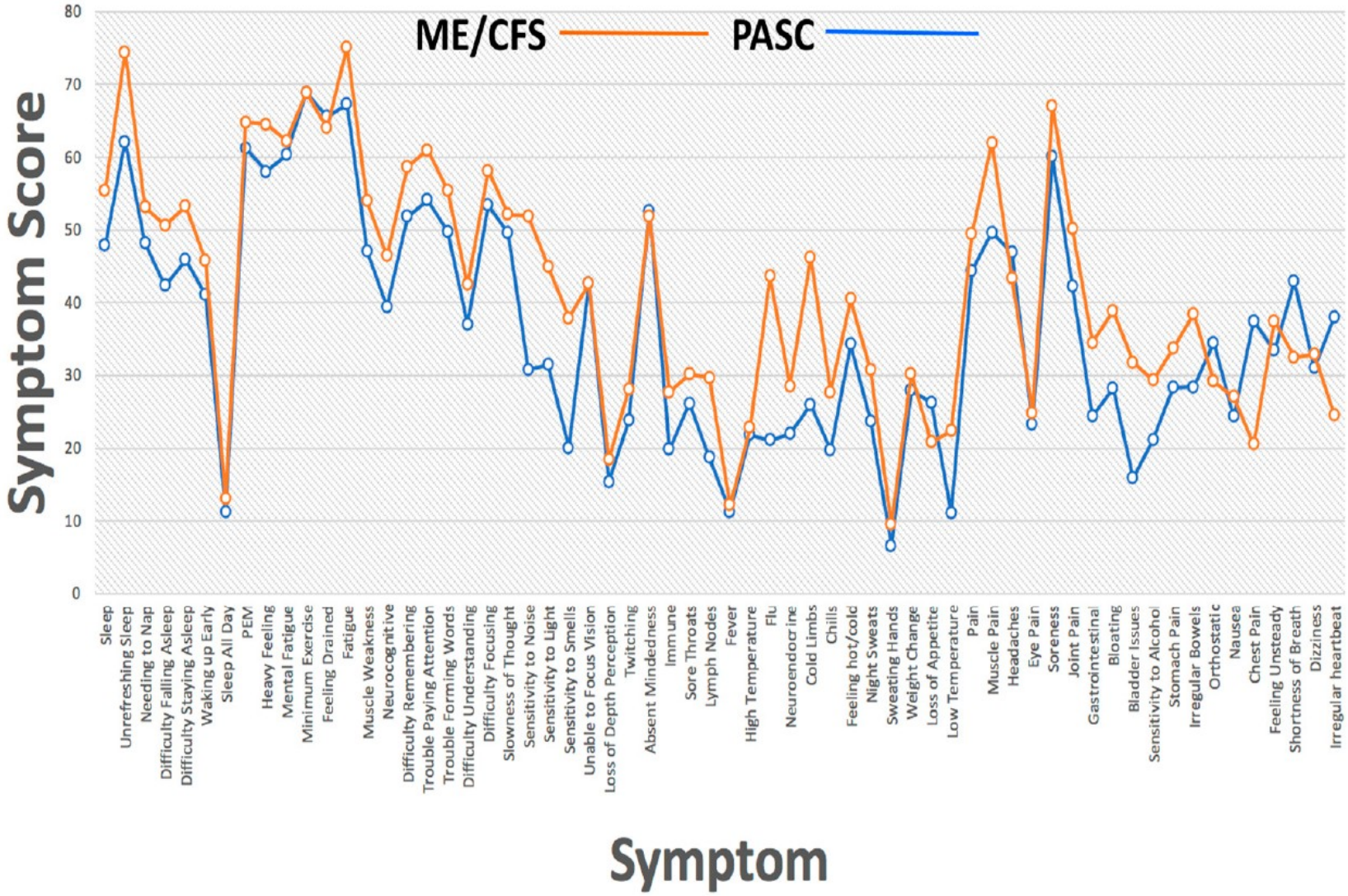
Article

https://doi.org/10.1038/s41467-022-32507-6

A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity

In a prospective observational cohort study, we analyze clinical and laboratory parameters in 42 post-COVID-19 syndrome patients (29 female/13 male, median age 36.5 years) with persistent moderate to severe fatigue and exertion intolerance six months following COVID-19. Further we evaluate an age- and sex-matched postinfectious non-COVID-19 myalgic encephalomyelitis/chronic fatigue syndrome cohort comparatively. Most post-COVID-19 syndrome patients are moderately to severely impaired in daily live. 19 post-COVID-19 syndrome patients fulfill the 2003 Canadian Consensus Criteria for myalgic encephalomyelitis/chronic fatigue syndrome. Disease severity and symptom burden is similar in post-COVID-19 syndrome/myalgic encephalomyelitis/chronic fatigue syndrome and non-COVID-19/myalgic encephalomyelitis/chronic fatigue syndrome patients. Hand grip strength is diminished in most patients compared to normal values in healthy. Association of hand grip strength with hemoglobin, interleukin 8 and C-reactive protein in post-COVID-19 syndrome/non-myalgic encephalomyelitis/chronic fatigue syndrome and with hemoglobin, N-terminal prohormone of brain natriuretic peptide, bilirubin, and ferritin in post-COVID-19 syndrome/myalgic encephalomyelitis/chronic fatigue syndrome may indicate low level inflammation and hypoperfusion as potential pathomechanisms.

Symptom Profiles for ME/CFS and PASC



PMID: 36672687

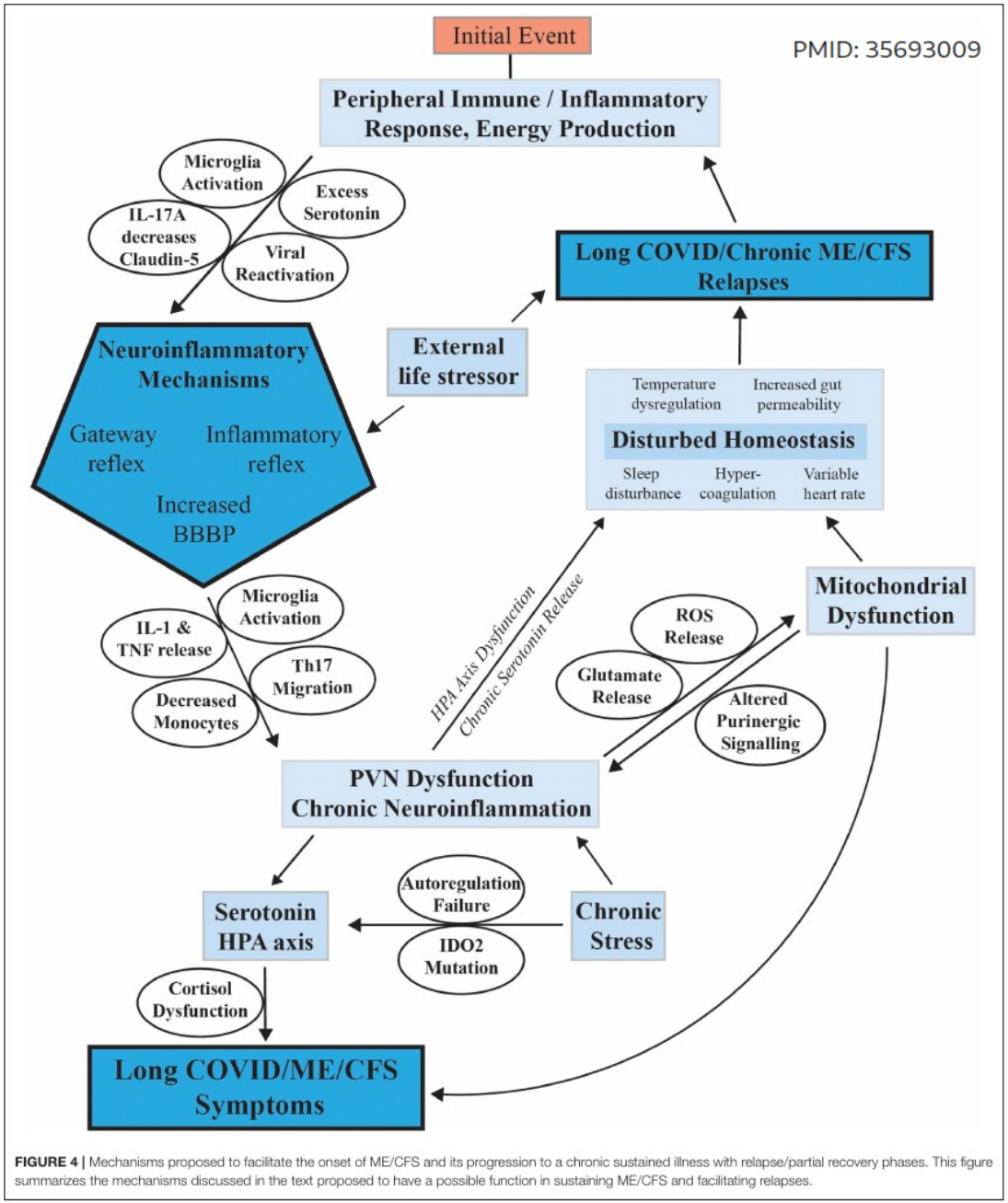


FIGURE 4 | Mechanisms proposed to facilitate the onset of ME/CFS and its progression to a chronic sustained illness with relapse/partial recovery phases. This figure summarizes the mechanisms discussed in the text proposed to have a possible function in sustaining ME/CFS and facilitating relapses.

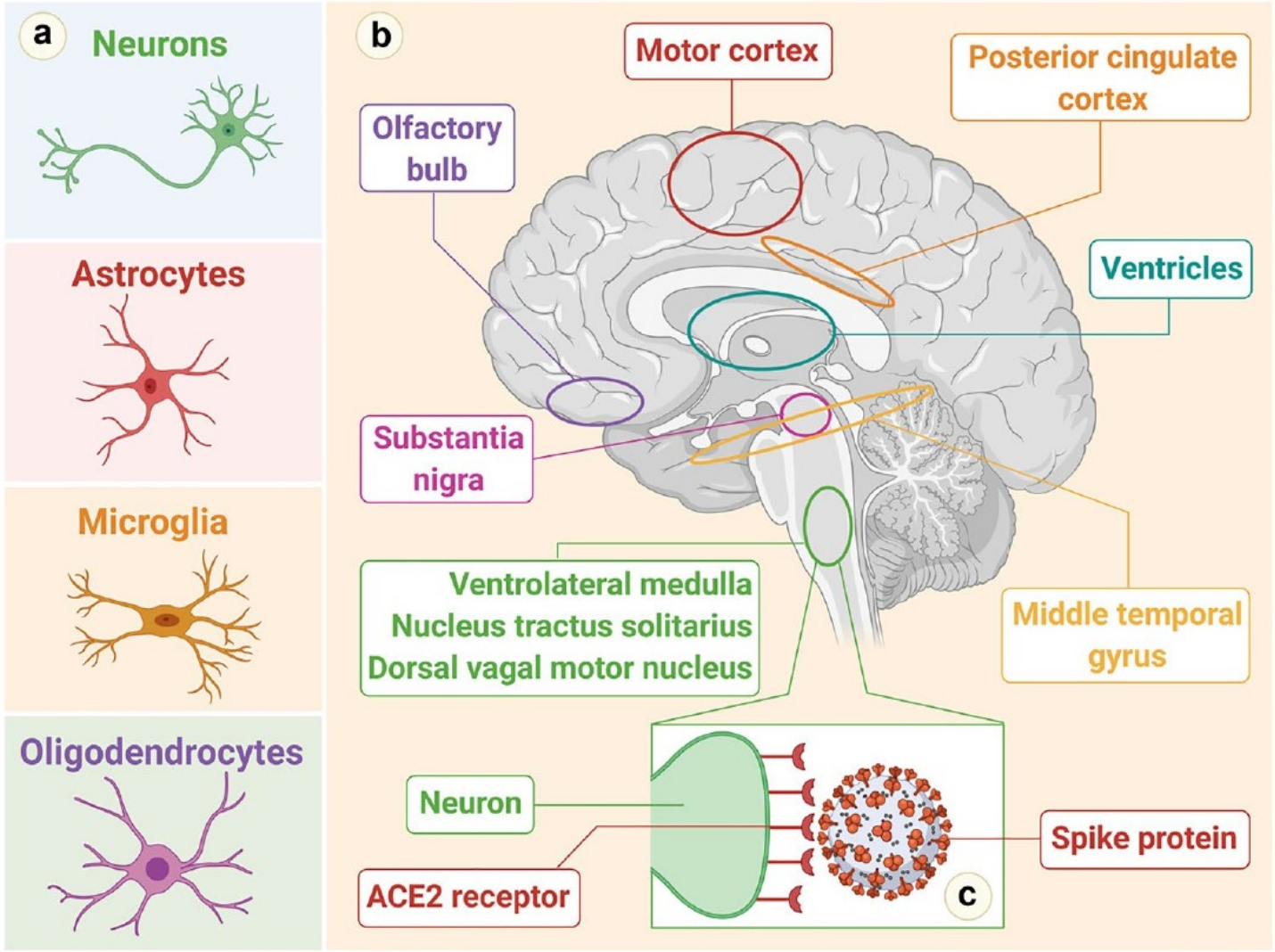


Fig. 2 **a** Human cells that express ACE2 receptors in the CNS. **b** Brain areas that express ACE2 receptors. **c** Binding of SARS-CoV-2 to a neuron (ACE2 receptors on a medullary neuron binding to the SPIKE protein on SARS-CoV-2)

PMID: 33464535

Biochemical Journal (2022) **479** 1653–1708
https://doi.org/10.1042/BCJ20220154

PORTLAND PRESS

Review Article

The potential role of ischaemia–reperfusion injury in chronic, relapsing diseases such as rheumatoid arthritis, Long COVID, and ME/CFS: evidence, mechanisms, and therapeutic implications

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Ischaemia-reperfusion (I-R) injury, initiated via bursts of reactive oxygen species produced during the reoxygenation phase following hypoxia, is well known in a variety of acute circumstances. We argue here that I-R injury also underpins elements of the pathology of a variety of chronic, inflammatory diseases, including rheumatoid arthritis, ME/CFS and, our chief focus and most proximally, Long COVID. Ischaemia may be initiated via fibrin amyloid microclot blockage of capillaries, for instance as exercise is started; reperfusion is a necessary corollary when it finishes. Such microclot-based phenomena can explain both the breathlessness/fatigue and the post-exertional malaise that may be observed in these conditions, as well as many other observables. The recognition of these processes implies, mechanistically, that therapeutic benefit is potentially to be had from antioxidants, from anti-inflammatories, from iron chelators, and via suitable, safe fibrinolytics, and/or anti-clotting agents.

Biochemical Journal (2022) **479** 1653–1708
https://doi.org/10.1042/BCJ20220154

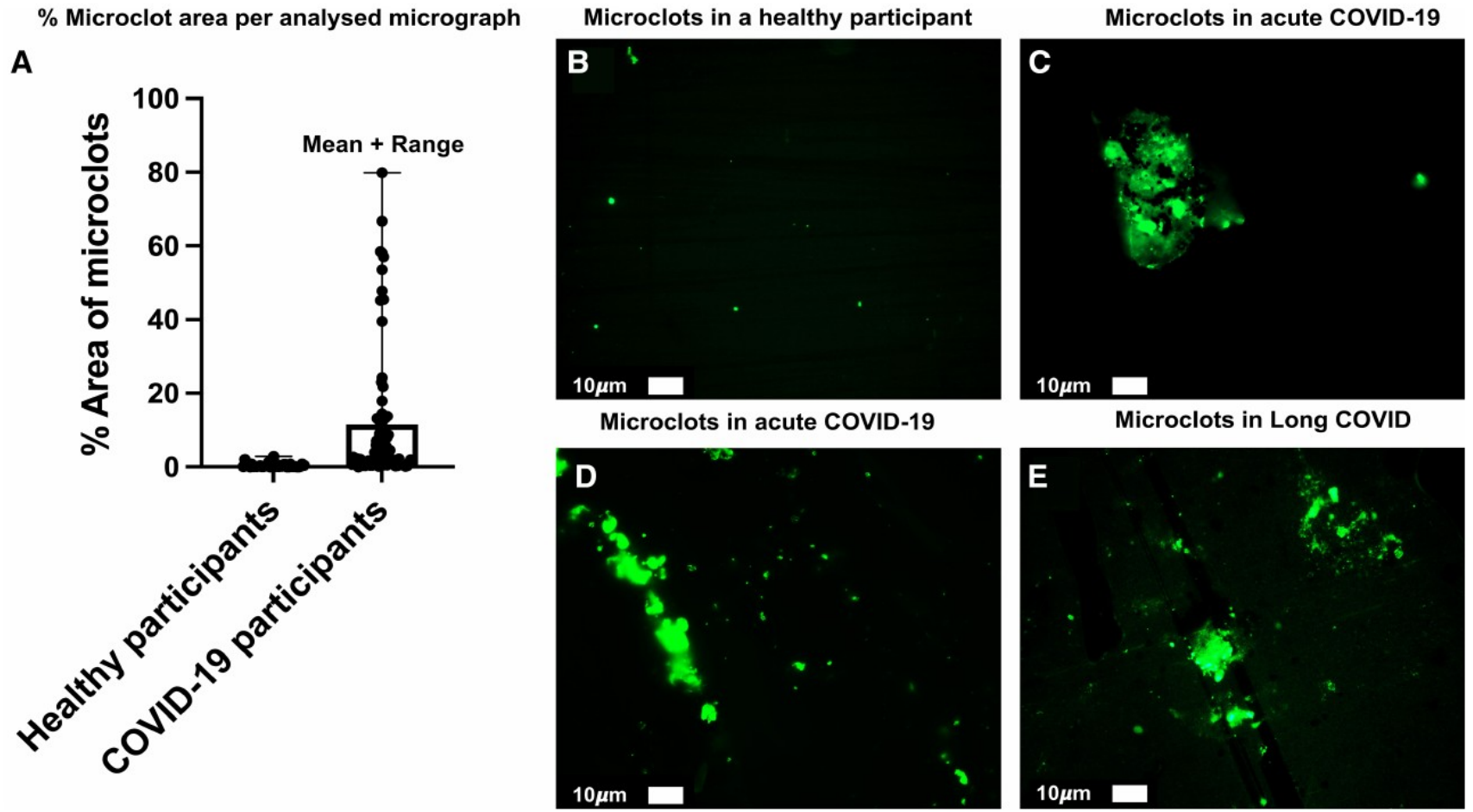

Figure 7. (**A**) % area distribution of microclots in plasma from participants with acute COVID-19 (taken from raw data as in [87]). (**B**) Representative micrograph of microclots in plasma from a healthy individual. (**C**,**D**) Representative micrographs of microclots in plasma from acute COVID-19 participants (taken from raw data as in [87]). (**E**) Representative micrograph of microclots in plasma from participants with Long COVID (taken from raw data in [422]).

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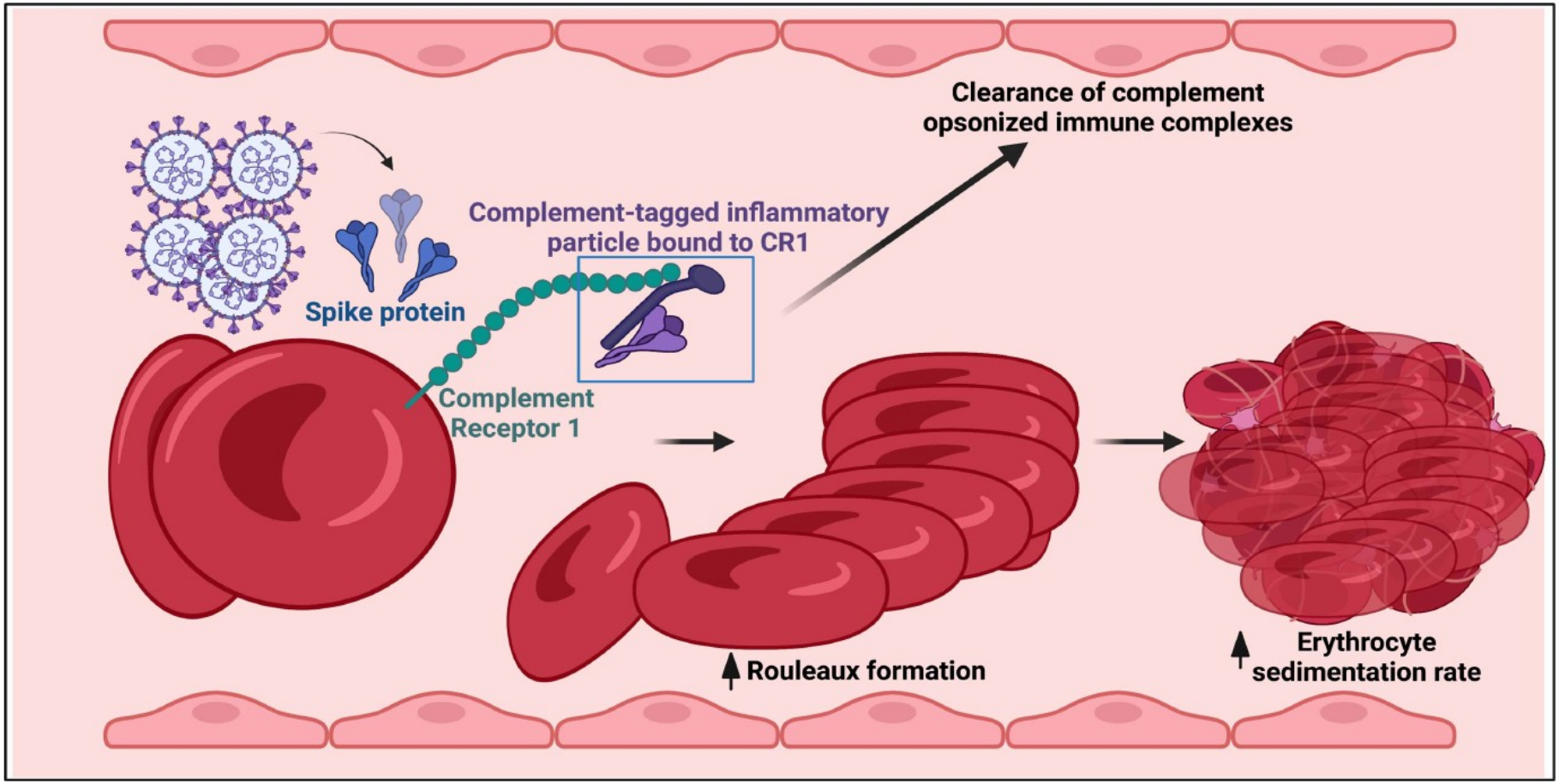

Figure 8. Immune complex formation on erythrocytes during COVID-19 and Long COVID: a hypothesis.
Created with BioRender (https://biorender.com/).

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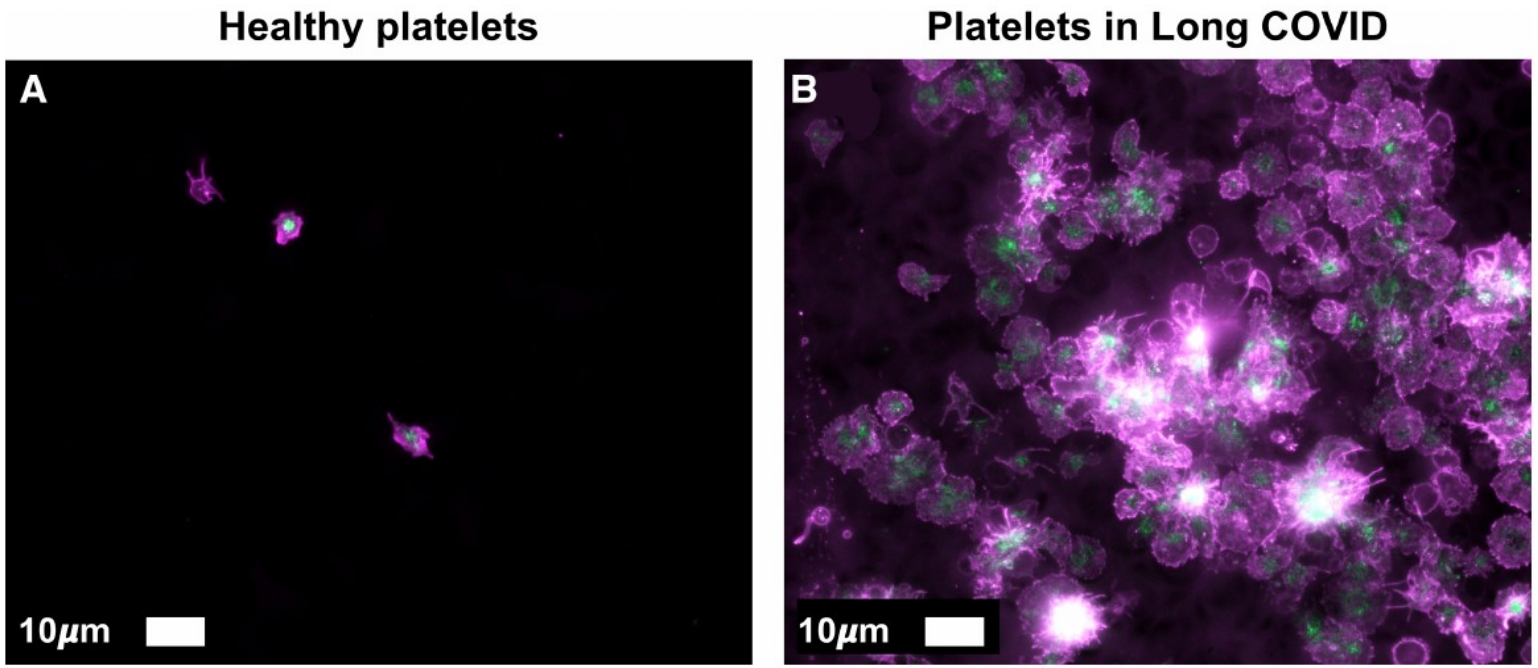
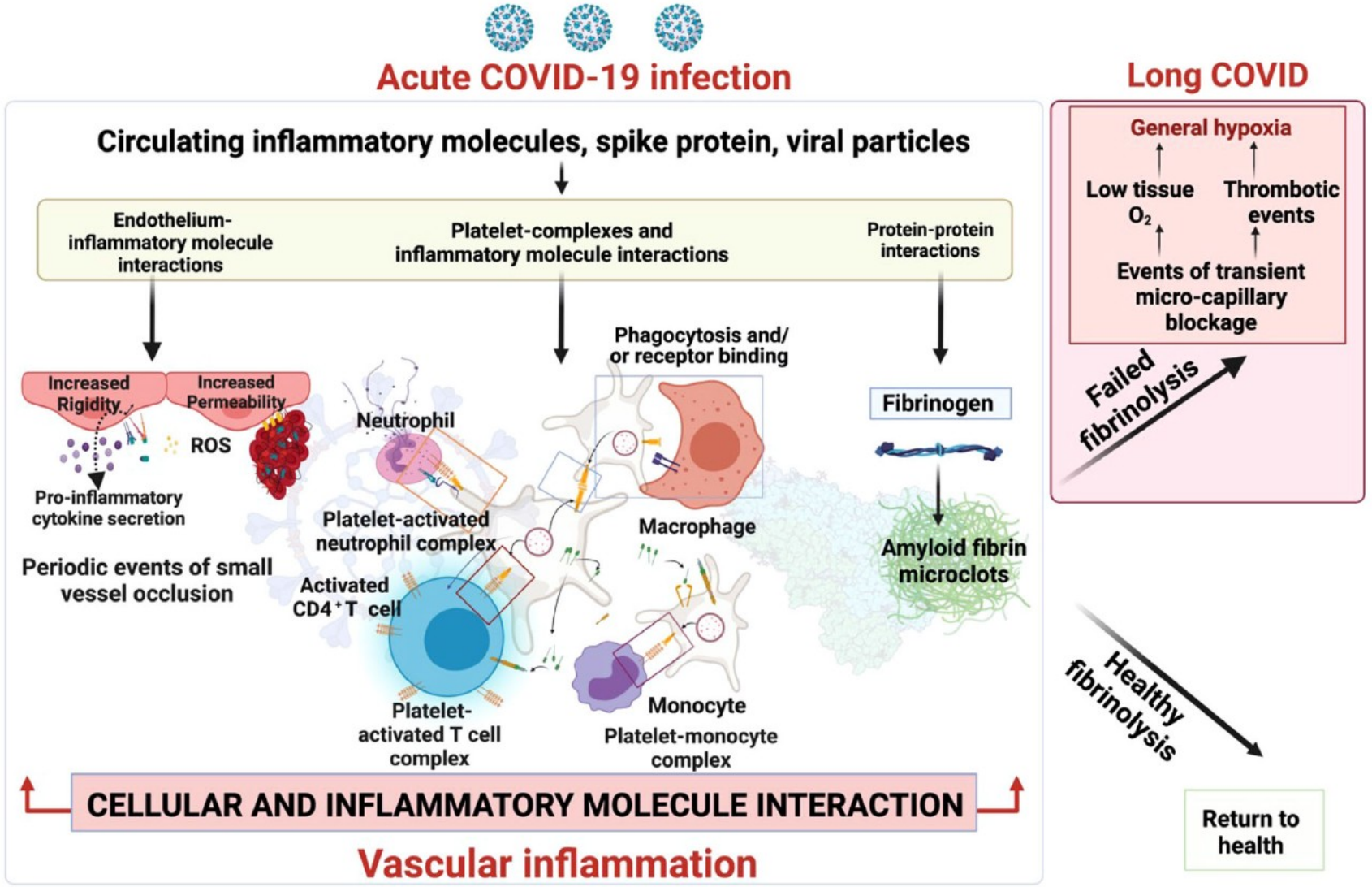


Figure 11. Platelet hyperactivation noted in a healthy individual (A) and an individual with Long COVID with severe platelet hyperactivation (B).

Haematocrit samples were exposed to the two fluorescent markers, CD62P (PE-conjugated) (platelet surface P-selectin) (IM1759U, Beckman Coulter, Brea, CA, U.S.A.) and PAC-1 (FITC-conjugated) (340507, BD Biosciences, San Jose, CA, U.S.A.). CD62P is a marker for P-selectin that is either on the membrane of platelets or found inside them. PAC-1 identifies platelets through marking the glycoprotein IIb/IIIa (gpIIb/IIIa) on the platelet membrane. Samples were viewed using a Zeiss Axio Observer 7 fluorescent microscope with a Plan-Apochromat 63x/1.4 Oil DIC M27 objective (Carl Zeiss Microscopy, Munich, Germany). (Unpublished data; Ethics from Stellenbosch University Human Ethics Committee (HREC) number 9521.).



PMID: 36412084

FIGURE 1 Clotting pathologies in long COVID. ROS, reactive oxygen species. Created with BioRender.com.

International Journal of
Molecular Sciences

MDPI

Article

Post-COVID-19 Syndrome: Retinal Microcirculation as a Potential Marker for Chronic Fatigue

Sarah Schlick [1,†], Marianna Lucio [2,†], Gerd Wallukat [3], Alexander Bartsch [1], Adam Skornia [1], Jakob Hoffmanns [1], Charlotte Szewczykowski [1], Thora Schröder [1], Franziska Raith [1], Lennart Rogge [1], Felix Heltmann [1], Michael Moritz [1], Lorenz Beitlich [1], Julia Schottenhamml [1], Martin Herrmann [4,5], Thomas Harrer [4,5], Marion Ganslmayer [6], Friedrich E. Kruse [1], Robert Lämmer [1], Christian Mardin [1,*,‡] and Bettina Hohberger [1,*,‡]

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† These authors contributed equally to this work.
‡ These authors contributed equally to this work.

Citation: Schlick, S.; Lucio, M.; Wallukat, G.; Bartsch, A.; Skornia, A.;

Abstract: Post-COVID-19 syndrome (PCS) is characterized by persisting sequelae after infection with

THERAPEUTIC ADVANCES in
Gastroenterology

Meta-analysis

Gastrointestinal manifestations of long COVID: A systematic review and meta-analysis

Ther Adv Gastroenterol
2022, Vol. 15: 1–18
DOI: 10.1177/17562848221118403

Arup Choudhury, Raseen Tariq, Anuraag Jena, Elissa Kinzelman Vesely, Siddharth Singh, Sahil Khanna and Vishal Sharma

GI symptoms in patients were seen in 12% after COVID-19 and 22% as part of long COVID. Loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain were the five most common GI symptoms of long COVID.

with COVID-19 and those with long COVID, respectively. The frequencies of abdominal pain, nausea/vomiting, loss of appetite, and loss of taste were 0.14 (95% CI, 0.04–0.38, $I^2 = 96\%$), 0.06 (95% CI, 0.03–0.11, $I^2 = 98\%$), 0.20 (95% CI, 0.08–0.43, $I^2 = 98\%$), and 0.17 (95% CI, 0.10–0.27, $I^2 = 95\%$), respectively, after COVID-19. The frequencies of diarrhea, dyspepsia, and irritable bowel syndrome were 0.10 (95% CI, 0.04–0.23, $I^2 = 98\%$), 0.20 (95% CI, 0.06–0.50, $I^2 = 97\%$), and 0.17 (95% CI, 0.06–0.37, $I^2 = 96\%$), respectively.

Conclusion: GI symptoms in patients were seen in 12% after COVID-19 and 22% as part of long COVID. Loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain were the five most common GI symptoms of long COVID. Significant heterogeneity and small number of studies for some of the analyses are limitations of the systematic review.

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nature communications

Article

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Long-term gastrointestinal outcomes of COVID-19

Received: 18 July 2022

Accepted: 20 January 2023

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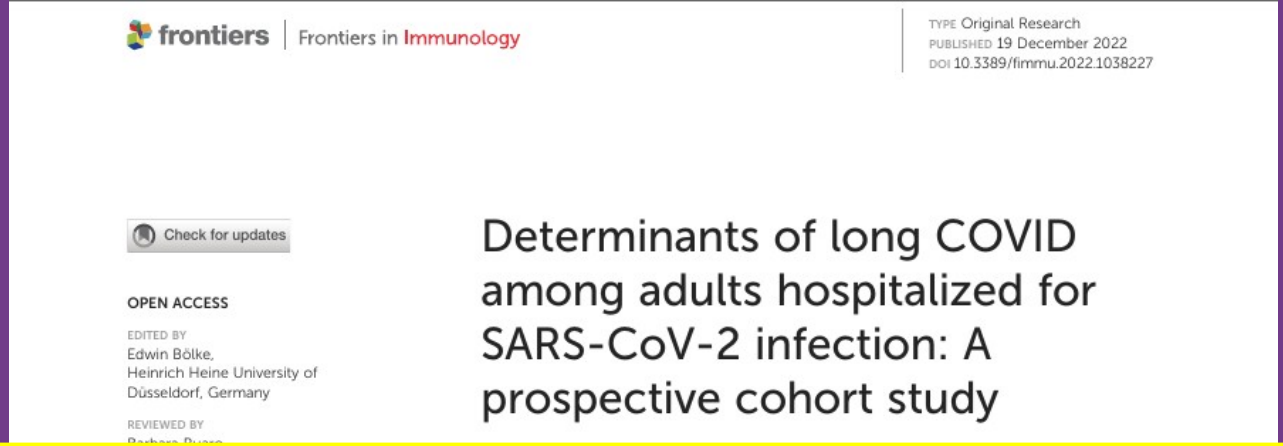
We show that beyond the first 30 days of infection, people with COVID-19 exhibited increased risks and 1-year burdens of incident gastrointestinal disorders spanning several disease categories including motility disorders, acid related disorders (dyspepsia, gastroesophageal reflux disease, peptic ulcer disease), functional intestinal disorders, acute pancreatitis, hepatic and biliary disease. The risks were evident in people who were not hospitalized during the acute phase of COVID-19 and increased in a graded fashion across the severity spectrum of the acute phase of COVID-19 (non-hospitalized, hospitalized, and admitted to intensive care).


frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 19 December 2022
DOI 10.3389/fimmu.2022.1038227

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EDITED BY
Edwin Bölke,
Heinrich Heine University of
Düsseldorf, Germany

REVIEWED BY

Determinants of long COVID among adults hospitalized for SARS-CoV-2 infection: A prospective cohort study

After correcting for comorbidities and COVID-19 severity, the risk of developing long COVID was lower in the 109 subjects admitted to the hospital in the third wave of the pandemic than in the 215 admitted during the first wave. Univariable analysis revealed female sex, diffusing capacity of the lungs for carbon monoxide (DLCO) value, body mass index, anxiety and depressive symptoms to be positively associated with COVID-19 sequelae at 1 year. Following logistic regression analysis, DLCO was the only independent predictor of residual symptoms. In the subgroup of subjects with normal DLCO (> 80%), for whom residual lung damage was an unlikely explanation for long COVID, the presence of anxiety and depressive symptoms was significantly associated to persistent symptoms, together with increased levels of a set of pro-inflammatory cytokines: interferon-gamma, tumor necrosis factor-alpha, interleukin (IL)-2, IL-12, IL-1β, IL-17. In logistic regression analysis, depressive symptoms and IL-12 levels 1-year after hospital discharge were independently associated with persistence of symptoms. Conclusions: Long COVID appears mainly related to respiratory sequelae, prevalently observed during the first pandemic wave. Among patients with little or no residual lung damage, a cytokine pattern consistent with systemic inflammation is in place.

Table 1 | Summary of candidate treatments and supporting evidence

PMID: 36639608

Symptoms and/or biological mechanism	Treatments	Supporting evidence	Comments
Postexertional malaise	Pacing	ME/CFS literature	Exercise, cognitive behavioural therapy and graded exercise therapy are contraindicated
POTS	Pharmacological: β-blockers, pyridostigmine, fludrocortisone, midodrine	POTS and ME/CFS literature	Options can be prioritized on the basis of a specific constellation of symptoms
	Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings	POTS and ME/CFS literature	–
Immune dysfunction	Intravenous immunoglobulin	ME/CFS literature	Consider consulting an immunologist on implementation
Cognitive dysfunction	Cognitive pacing	ME/CFS literature	Consider implementation alongside pacing physical exertion
Cognitive dysfunction	Postconcussion syndrome protocols	ME/CFS and postconcussion syndrome literature	–
Fatigue	Coenzyme Q_{10}, D-ribose	ME/CFS literature	–
Pain, fatigue, neurological symptoms	Low-dose naltrexone	ME/CFS and other literature	Substantial anecdotal reports of success within the patient community
Fatigue, unrefreshing sleep, brain fog	Low-dose aripiprazole	ME/CFS literature	–
Autoimmunity	BC007	Long COVID case report	Neutralizes G protein-coupled receptor autoantibodies
Abnormal clotting	Anticoagulants	Long COVID pilot study	Additional trials in progress

Abnormal clotting	Apheresis	ME/CFS literature, long COVID pilot study	–
Viral persistence and antivirals (COVID-19)	Paxlovid	Long COVID case reports	No active trials, despite strong evidence for viral persistence
Viral persistence and antivirals (reactivations such as of EBV, HCMV and VZV)	Valaciclovir, famciclovir, valganciclovir and other antivirals	ME/CFS literature	–
Endothelial dysfunction	Sulodexide	Long COVID pilot study	–
Gastrointestinal symptoms	Probiotics	Long COVID pilot study	Resolved gastrointestinal and other symptoms
Dysautonomia	Stellate ganglion block	Long COVID case report	Effects may wane over time and require repeated procedures
Endothelial function, microcirculation, inflammatory markers and oxidative stress	Pycnogenol	COVID-19 pilot study	–
MCAS	H_1 and H_2 antihistamines, particularly famotidine	Long COVID case reports, MCAS literature	Expected to treat symptoms, not underlying mechanism
Autonomic dysfunction	Transcutaneous vagal stimulation	Long COVID pilot study	–

EBV, Epstein–Barr virus; HCMV, human cytomegalovirus; MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic tachycardia syndrome; VZV, varicella zoster virus.

PMID: 36639608

PMID: 36514781

TABLE 2 Putative mechanism and suggested treatment of long COVID in multiple systems

Involvement	Putative mechanism	Suggested treatment
Pulmonary and respiratory involvement	1. Pulmonary fibrosis 2. Severe cytokine storm	1. Antifibrotic drug 2. Administration of antihistamines reagent
Neurological involvement	1. Brain hypoxemia 2. Neuronal necrosis 3. Mitochondrial dysfunction 4. Neurotoxicity caused by inflammatory responses and cytokine release	1. Antidepressants 2. Pain medications 3. Mitochondrial modulator: MitoQ 4. Free radicals scavenger: vitamin C, vitamin E, and CoQ10 5. Immunomodulatory therapy[196]
Olfactory involvement	1. Viral infection on sustentacular cells 2. Cytokines released by vascular injury 3. Down-regulation of genes related to olfactory receptor	1. Smell treatment 2. Anti-inflammation treatment 3. Drug therapy: oral steroids, alpha-lipoic acid, sodium citrate, omega 3 fatty acids, and intranasal vitamin A
Vascular involvement	1. Viral infection on perivascular cardiomyocytes and pericytes 2. High pro-inflammatory cytokine response	1. Administration of antihistamines reagent[197] 2. Administration of anticoagulant: heparin 3. Immunomodulatory therapy and blockade of pro-inflammatory cytokines

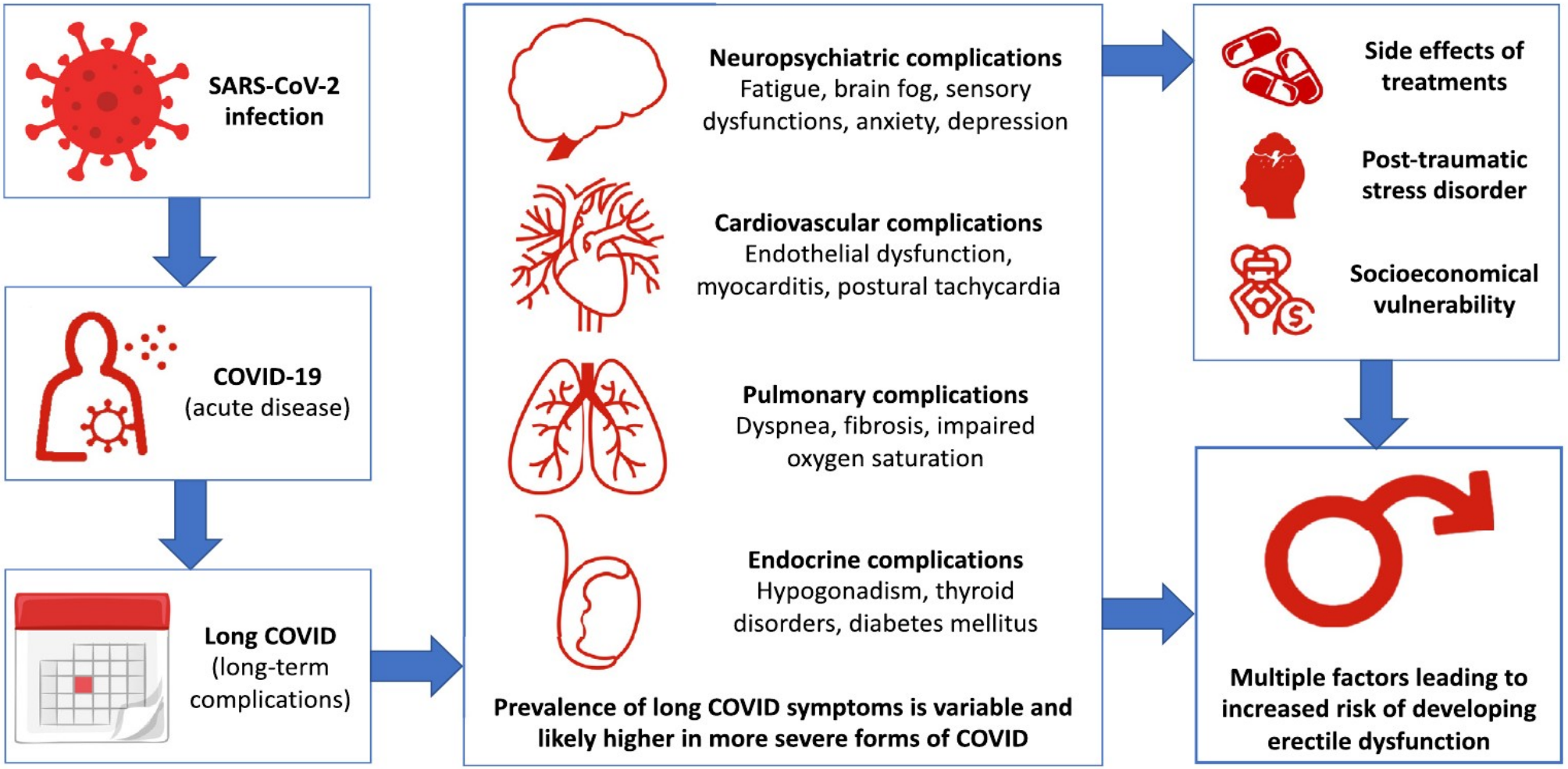

Figure 1. The pathophysiology of erectile dysfunction in long COVID: mechanisms and progression. Figure 1 is available in color online at www.smr.jsexmed.org.

PMID: 34933829

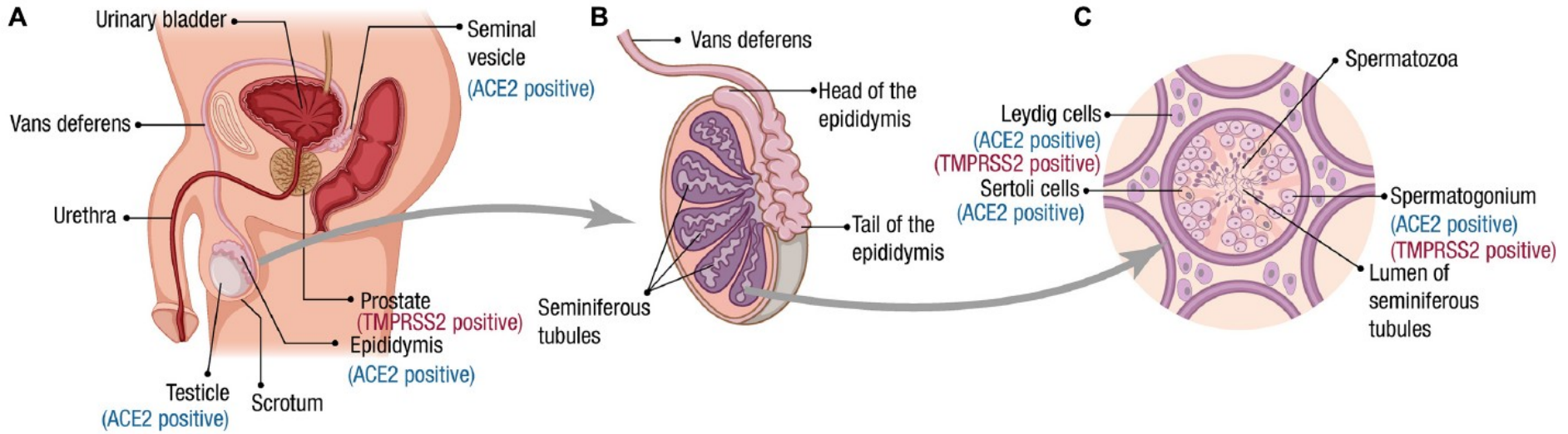

FIGURE 1 | Male reproductive tract, spermatogenesis, and SARS-CoV-2 receptor expression. **(A)** Scheme of the male reproductive system composition. The organs for which ACE2 and TMPRSS2 expression has been reported at RNA and/or protein level are indicated. **(B)** The testes are composed mainly by seminiferous tubules (up to 90% of the testis volume). Immotile sperm flow from the lumen of the seminiferous tubules into the epididymis via the rete testis. During the passage through the epididymis to the vas deferens, the spermatozoa mature and acquire their motility. **(C)** A transverse section of seminiferous tubules is illustrated. The cells for which ACE2 and TMPRSS2 expression has been reported at the RNA and/or protein level are indicated. Spermatogenesis occurs within the seminiferous tubules. Spermatogonia (diploid primordial germ cells) are located near the basal lamina of the seminiferous tubules. When spermatogonia divide by a first mitotic division, they produce diploid primary spermatocytes. Half of these primary spermatocytes will remain near the basal lamina dividing mitotically to allow the production of new spermatozoa during the whole male's reproductive lifespan. The other half migrate toward the lumen of the seminiferous tubules and undergo meiosis I, generating haploid secondary spermatocytes, which divide through meiosis II to produce haploid spermatids. A final stage called spermiogenesis produces mature sperm cells (spermatozoa) capable of fertilizing an egg. Leydig cells produce the hormone testosterone.

PMID: 35003013

PMID: 35003013

TABLE 1 | Major RNA viruses found in the male reproductive tract, their consequences, and cell receptors used for viral entry.

RNA virus	Family	Main impact in the male reproductive tract reported	Virus shedding in human semen	Main cell receptor	References
HIV	*Retroviridae*	Orchitis, infertility, sexual transmission	Acute stage: 61–100% Chronic stage: 81–100%	CD4	Dejucq and Jégou, 2001; Salam and Horby, 2017; Liu et al., 2018; Le Tortorec et al., 2020
Zika virus (ZIKV)	*Flaviviridae*	Orchitis, infertility, risk of sexual transmission	Acute stage: 50–68%	AXL receptor	Musso et al., 2015; Mead et al., 2018; Strange et al., 2019; Le Tortorec et al., 2020
Hepatitis viruses C	*Flaviviridae*	Alteration of sperm parameters.	Acute stage: 29–39% Chronic stage: 32–46%	NA	Liu et al., 2018; Le Tortorec et al., 2020
Mumps virus (MuV)	*Paramyxoviridae*	Orchitis, testicular atrophy, infertility	NA	Sialic acid, AXL, and MER receptor tyrosine kinases	Dejucq and Jégou, 2001; Liu et al., 2018
Ebola virus (EBOV)	*Filoviridae*	High risk of sexual transmission.	Acute stage: 73–100%	Different molecules reported, including integrins, C-type lectins, and AXL	Soka et al., 2016; Deen et al., 2017; Perry et al., 2018; Schindell et al., 2018; Le Tortorec et al., 2020
Influenza virus	*Orthomyxoviridae*	Orchitis.	NA	Sialic acid	Dejucq and Jégou, 2001; Liu et al., 2018
SARS-CoV	*Coronaviridae*	Orchitis.	NA	ACE2	Zhao et al., 2003; Xu et al., 2006
SARS-CoV-2	*Coronaviridae*	Testicular damage, orchitis, epididymitis, impaired spermatogenesis	Only two reports among many studies detected viral RNA in semen and in 6–15%% of the patients	ACE2	Li D. et al., 2020; Li H. et al., 2020; Paoli et al., 2020; Ma et al., 2021

Original Article
Male sexual health and dysfunction

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The World Journal of MEN's HEALTH

COVID-19 Endothelial Dysfunction Can Cause Erectile Dysfunction: Histopathological, Immunohistochemical, and Ultrastructural Study of the Human Penis

Eliyahu Kresch[1], Justin Achua[1], Russell Saltzman[2], Kajal Khodamoradi[1], Himanshu Arora[1], Emad Ibrahim[1], Oleksandr N. Kryvenko[1,3,6], Vania Wolff Almeida[4], Fakiha Firdaus[1],

TEM showed extracellular viral particles ~100 nm in diameter with peplomers (spikes) near penile vascular endothelial cells of the COVID-19 (+) patients and absence of viral particles in controls. PCR showed presence of viral RNA in COVID-19 (+) specimens. eNOS expression in the corpus cavernosum of COVID-19 (+) men was decreased compared to COVID-19 (-) men. Mean EPC levels from the COVID-19 (+) patients were substantially lower compared to mean EPCs from men with severe ED and no history of COVID-19.

Conclusions: Our study is the first to demonstrate the presence of the COVID-19 virus in the penis long after the initial infection in humans. Our results also suggest that widespread endothelial cell dysfunction from COVID-19 infection can contribute to ED.

PLOS ONE

RESEARCH ARTICLE

Erectile dysfunction after COVID-19 recovery: A follow-up study

Kawintharat Harirugsakul[1], Sorawit Wainipitapong[2], Jeerath Phannajit[3], Leilani Paitoonpong[4], Kavirach Tantiwongse[1]*

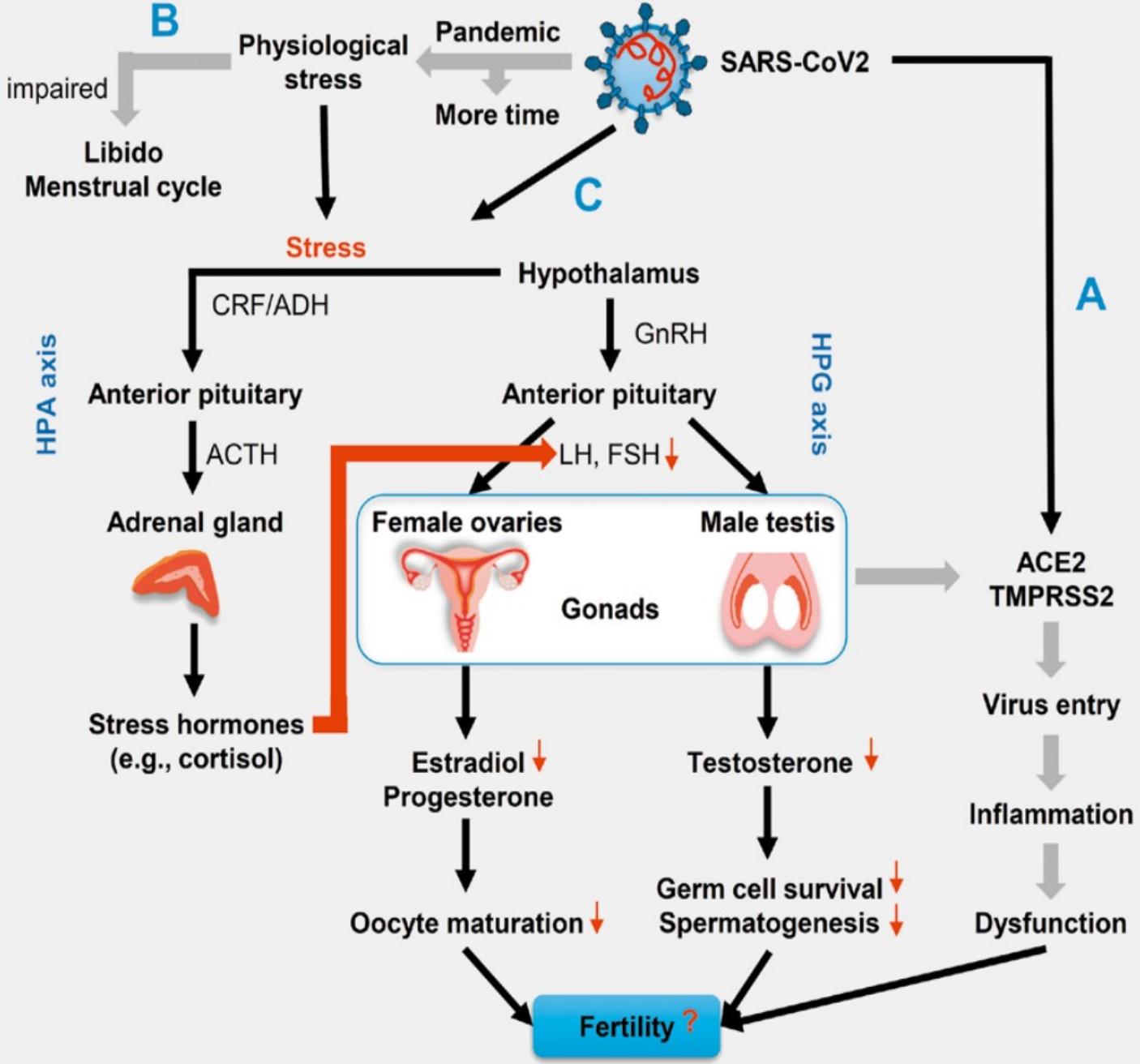
1 Division of Urology, Department of Surgery, Faculty of Medicine, Chulalongkorn University and King

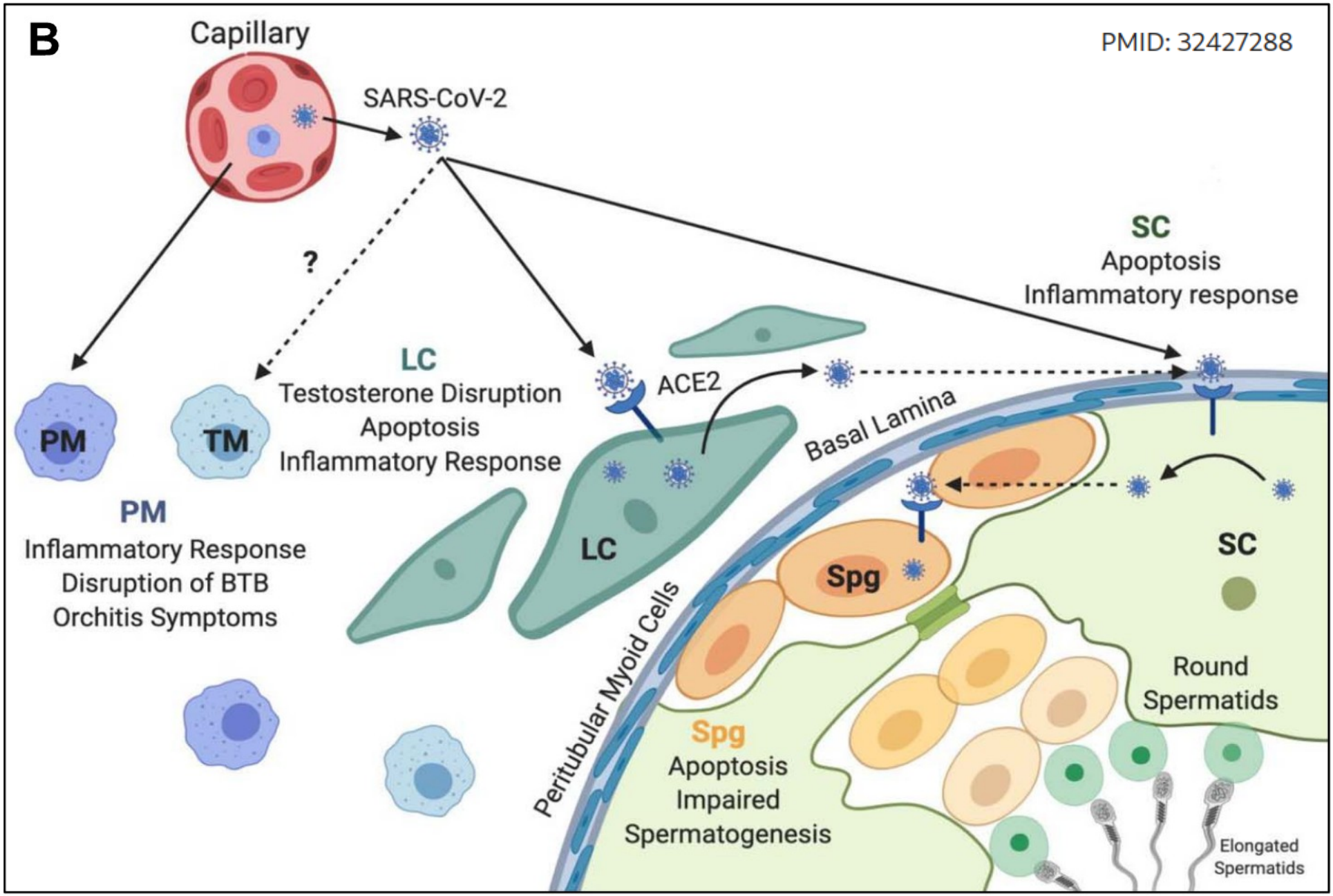
We enrolled all COVID-19 male patients, who were hospitalized from May to July 2021, and declared to be sexually active within the previous two weeks.

Results: ED prevalence at three months after recovery was 50.3%, which was significantly lower compared with ED prevalence at baseline (64.7%, P = 0.002). Logistic regression, adjusted for BMI, medical comorbidities, and self-reported normal morning erection, showed a significant association between ED at three months and age above 40 years and diagnosis of major depression.

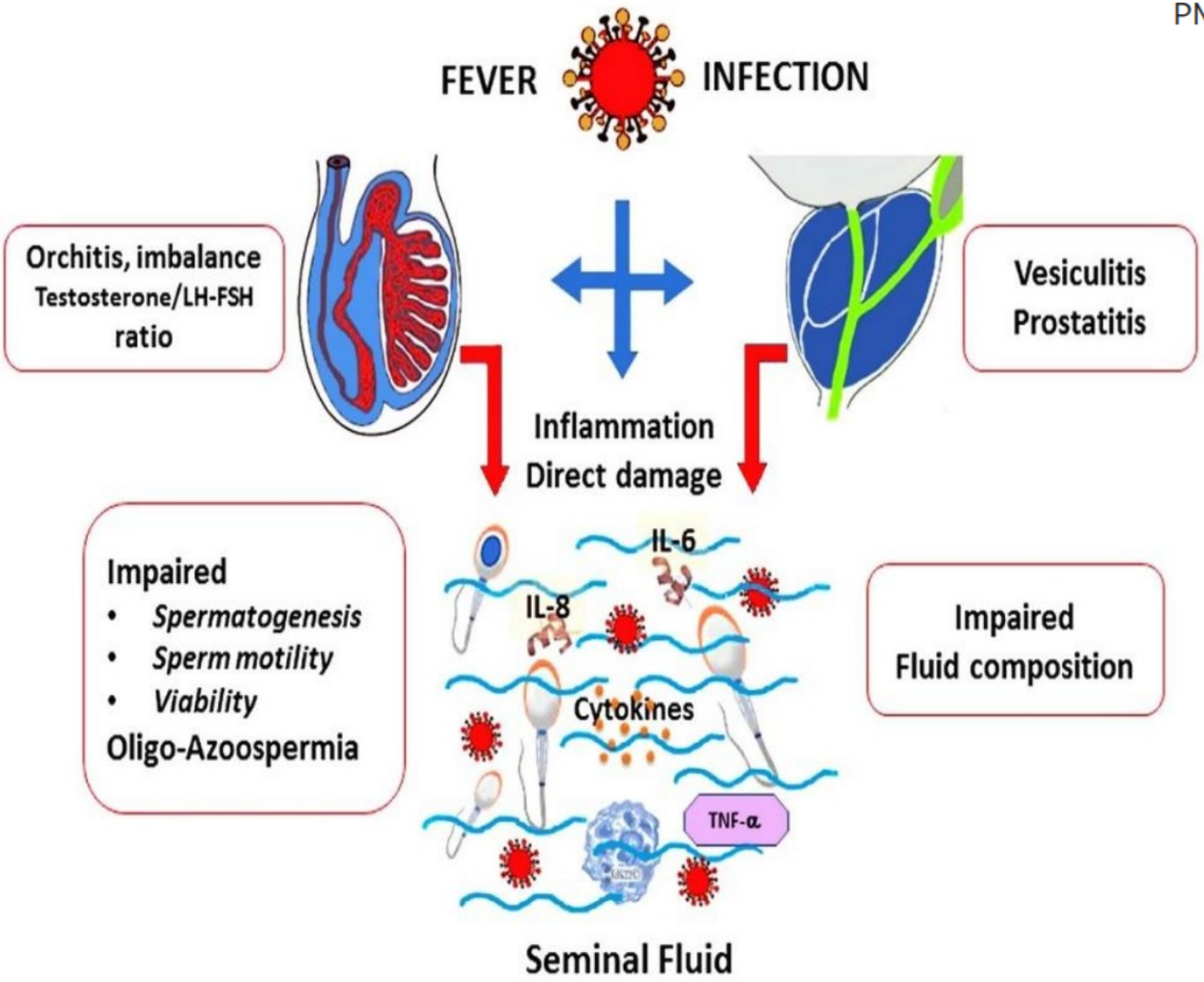
Conclusion: Our study showed a high ED prevalence during the third month of recovery from COVID-19. The predicting factors of persistent ED were age over 40 years and diagnosis of major depression during acute infection.

PMID: 35853464




B
Capillary
SARS-CoV-2
PMID: 32427288
?
SC
Apoptosis
Inflammatory response
LC
Testosterone Disruption
Apoptosis
Inflammatory Response
ACE2
PM
TM
PM
Inflammatory Response
Disruption of BTB
Orchitis Symptoms
Basal Lamina
LC
SC
Spg
Peritubular Myoid Cells
Round
Spermatids
Spg
Apoptosis
Impaired
Spermatogenesis
Elongated
Spermatids

PMID: 36560392



Abstract: Since SARS-CoV-2 infection was first identified in December 2019, it spread rapidly and a global pandemic of COVID-19 has occurred. ACE2, the receptor for entry into the target cells by SARS-CoV-2, was found to abundantly express in testes, including spermatogonia, Leydig and Sertoli cells. However, there is no clinical evidence about whether SARS-CoV-2 infection can affect male gonadal function so far. In this study, we compared the sex-related hormones between 81 reproductive-aged men with SARS-CoV-2 infection and 100 age-matched healthy men, and found that serum luteinizing hormone (LH) was significantly increased, but the ratio of testosterone (T) to LH and the ratio of follicle stimulating hormone (FSH) to LH were dramatically decreased in males with COVID-19. Besides, multivariable regression analysis indicated that c-reactive protein (CRP) level was significantly associated with serum T:LH ratio in COVID-19 patients. This study provides the first direct evidence about the influence of medical condition of COVID-19 on male sex hormones, alerting more attention to gonadal function evaluation among patients recovered from SARS-CoV-2 infection, especially the reproductive-aged men.

Key words: SARS-CoV-2, COVID-19, male gonadal function, sex-related hormones, reproductive system

THE AGING MALE
2022, VOL. 25, NO. 1, 202–216
https://doi.org/10.1080/13685538.2022.2104833

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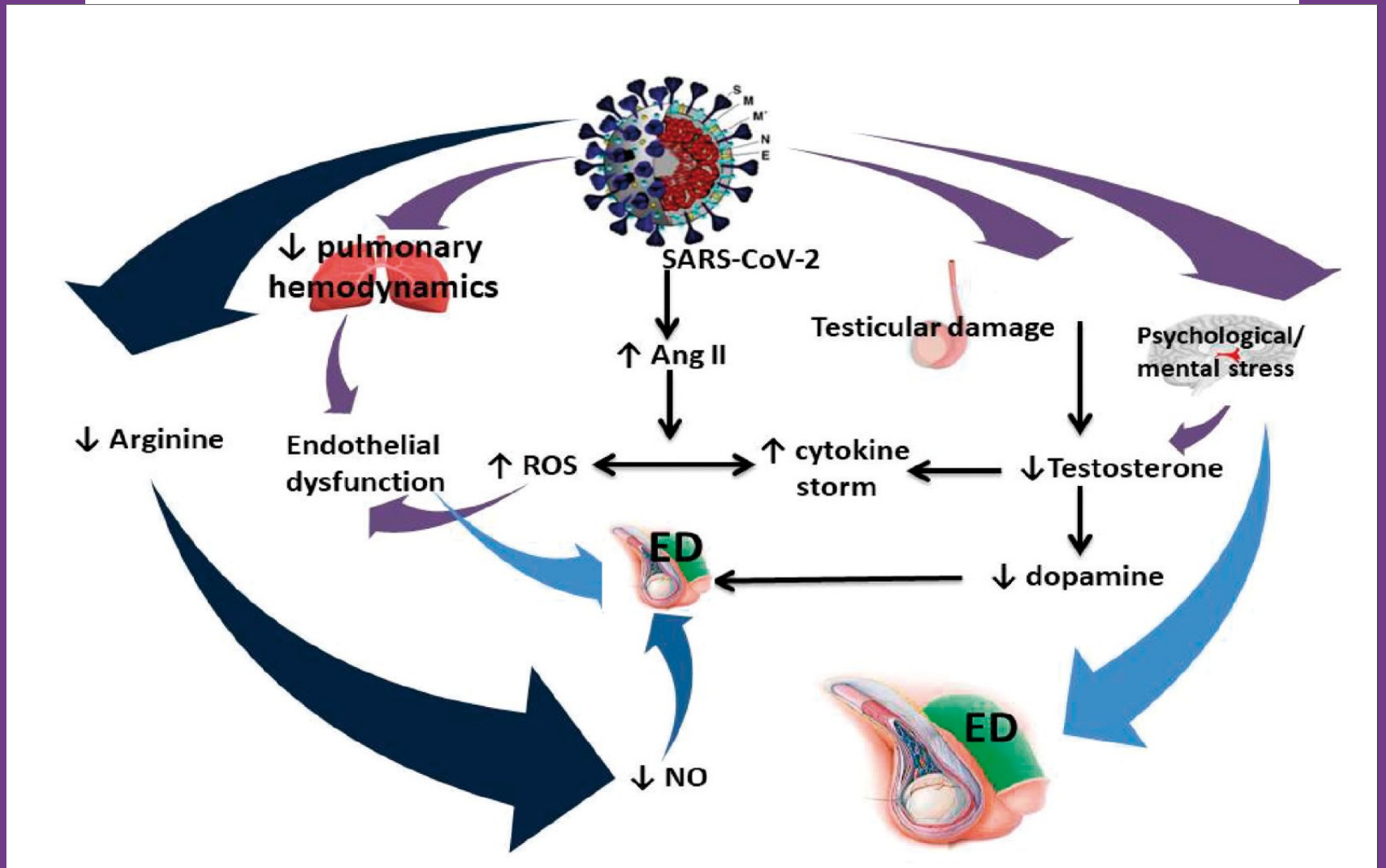
REVIEW ARTICLE

OPEN ACCESS Check for updates

Impact of COVID 19 on erectile function



Pharmacological Research 183 (2022) 106360

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Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Combining L-Arginine with vitamin C improves long-COVID symptoms: The LINCOLN Survey

We designed a nationwide multicenter clinical study (LINCOLN: L-Arginine and Vitamin C improves Long-COVID), in which a survey assessing several symptoms that have been associated with Long-COVID was administered to COVID-19 survivors. Patients were divided in two groups, with a 2:1 ratio: the first group included patients treated with L-Arginine + Vitamin C, whereas the second group was treated with a multivitamin combination (alternative treatment).

Results: 1590 patients were initially enrolled, of which 1390 completed the study. Following a 30-day treatment with L-Arginine + Vitamin C, the survey revealed that patients in this treatment group had significantly lower scores compared to the other group. When examining effort perception, we observed a significantly lower value ($p<0.0001$) in patients receiving L-Arginine + Vitamin C compared to the alternative-treatment arm.

1.6 grams of L-Arginine twice a day and 500 mg of Vitamin C twice a day.

nutrients

MDPI

Article

Effects of L-Arginine Plus Vitamin C Supplementation on Physical Performance, Endothelial Function, and Persistent Fatigue in Adults with Long COVID: A Single-Blind Randomized Controlled Trial

A single-blind randomized, placebo-controlled trial was conducted in adults aged between 20 and 60 years with persistent fatigue attending a post-acute COVID-19 outpatient clinic. Participants were randomized 1:1 to receive twice-daily orally either a combination of 1.66 g l-arginine plus 500 mg liposomal vitamin C or a placebo for 28 days. The primary outcome was the distance walked on the 6 min walk test. Secondary outcomes were handgrip strength, flow-mediated dilation, and fatigue persistence. At 28 days, l-arginine plus vitamin C increased the 6 min walk distance and induced a greater improvement in handgrip strength compared with the placebo. The flow-mediated dilation was greater in the active group than in the placebo. At 28 days, fatigue was reported by two participants in the active group and 21 in the placebo group. l-arginine plus vitamin C supplementation improved walking performance, muscle strength, endothelial function, and fatigue in adults with long COVID. This supplement may, therefore, be considered to restore physical performance and relieve persistent symptoms in this patient population.

frontiers in Medicine

ORIGINAL RESEARCH
published: 19 March 2021
doi: 10.3389/fmed.2021.635255

Analysis of Ovarian Injury Associated With COVID-19 Disease in Reproductive-Aged Women in Wuhan, China: An Observational Study

Ting Ding[1], Tian Wang[1], Jinjin Zhang[1], Pengfei Cui[1], Zhe Chen[1], Su Zhou[1], Suzhen Yuan[1], Wenqing Ma[1], Minli Zhang[1], Yueguang Rong[2], Jiang Chang[3], Xiaoping Miao[3], Xiangyi Ma[1†] and Shixuan Wang[1*†]*

[1] Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetrical and Gynecological Diseases,

Our results indicate that although no obvious menstrual cycle change was observed, women affected by COVID-19 have a significantly lower serum AMH level and higher T/PRL level, suggesting a poor ovarian reserve and abnormal reproductive hormones compared to the age-matched healthy unaffected women. Hierarchical linear regression showed that COVID-19 disease was likely to be an independent risk factor respecting ovarian function as represented by AMH, T, and PRL levels, even after adjusted for age, menstrual cycle, and parity variations.

This observed ovarian injury may be caused directly by coronavirus binding to the ACE2 receptor and entering the cell through TMPRSS2, leading to a cytopathic effect mediated by local replication of the SARS-CoV-2. The available evidence suggests that ACE2 is widely expressed in the ovary, uterus, vagina, and placenta. ACE2 can be detected in ovaries from humans to animals and our data also verify the expression of ACE2 and TMPRSS2 in the human ovary.

Cureus

Open Access Original Article

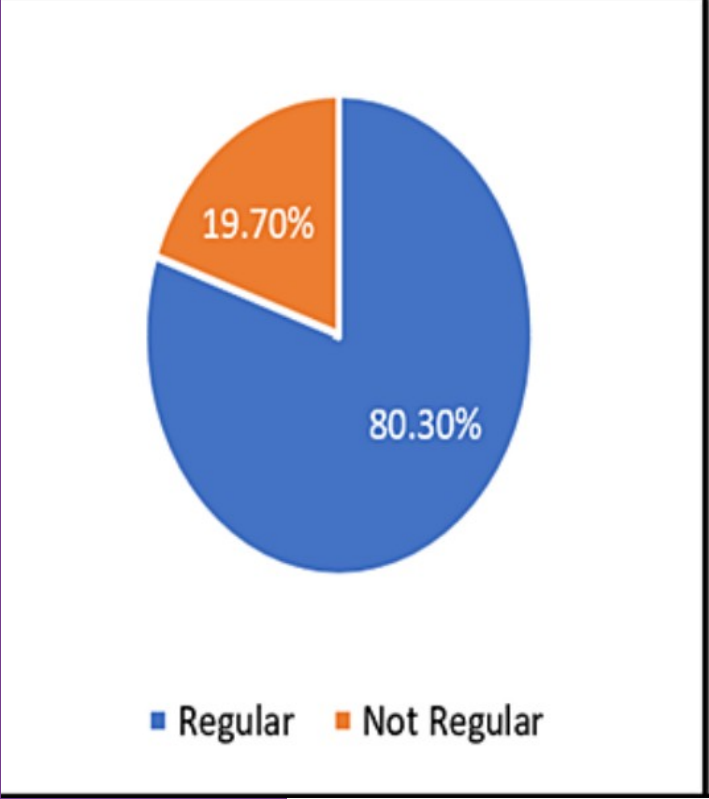
DOI: 10.7759/cureus.32431

Determining the Effect of COVID-19 on the Menstrual Cycle Among Women of Reproductive Age Group in the Jazan Region: A Cross-Sectional Study

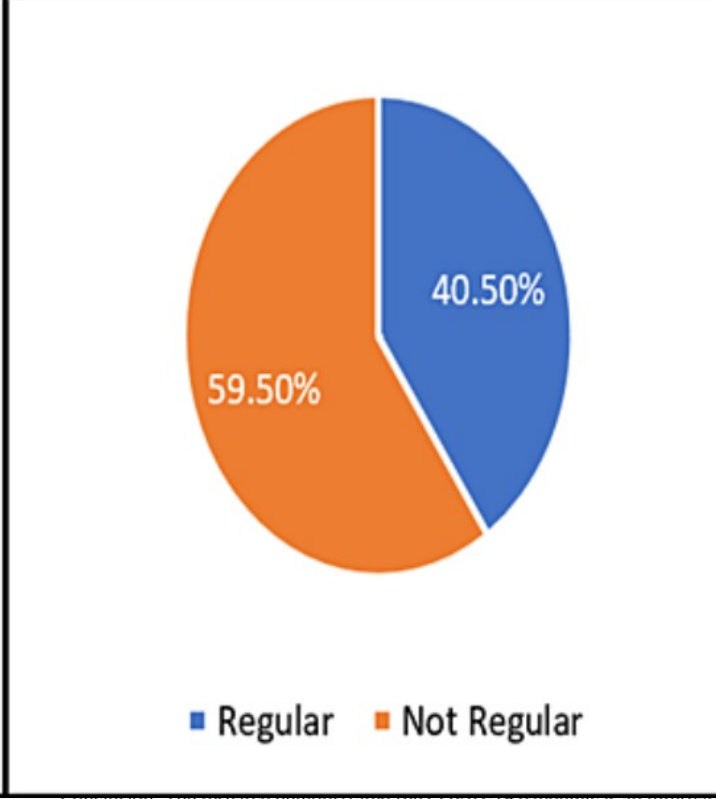
Review began 12/02/2022
Review ended 12/07/2022
Published 12/12/2022

Uma H. Chourasia [1], Ali H. Khormi [1], Hanan A. Jawkhab [2], Shahad I. Zoli [2], Kholoud A. Assiri [2], Shaden A. Thurwi [2], Saleha H. Alhazmi [2], Altaf A. Alhazmi [3], Jawahir M. Homadi [4], Raneem K. Zakri [2], Nada Y. Kenani [2], Ibrahim M. Dighriri [5]

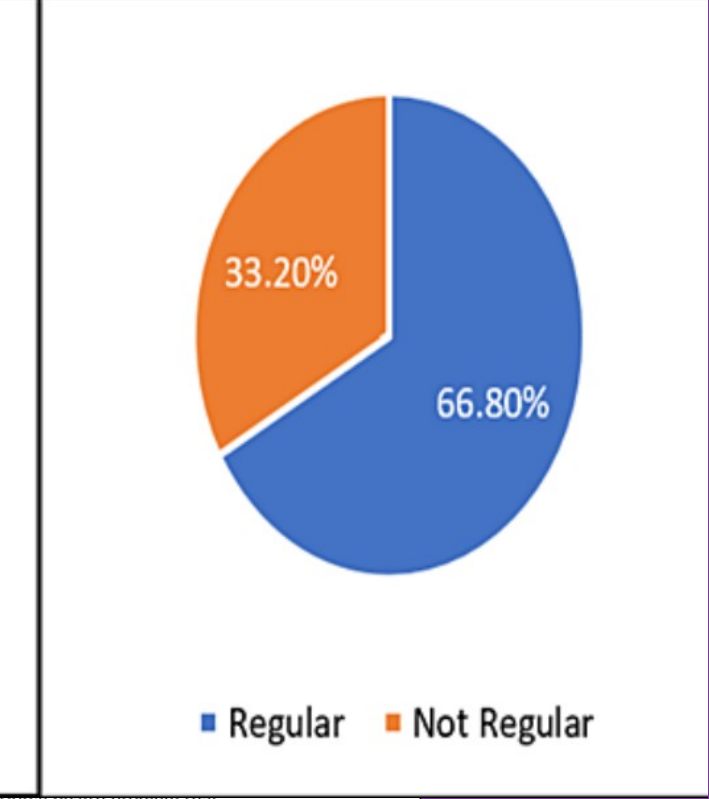
Menstruation prior to COVID-19 infection



Menstruation during COVID-19 infection



Menstruation after COVID-19 infection



Elsevier Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Maturitas. 2021 Oct; 152: 74.
Published online 2021 Oct 18.
doi: 10.1016/j.maturitas.2021.08.026

PMCID: PMC8522980

Long Covid and menopause - the important role of hormones in Long Covid must be considered

48% of women had been experiencing symptoms for more than 6 months. 50% of women reported that their periods had stopped or changed since their infection and 80% stated that their periods had not returned to how they were before their Covid infection.

Interestingly, 62% of responders reported that their symptoms of Long Covid were worse on the days before their periods which is when hormone levels are usually at their lowest. The vast majority of women, 70%, had thought that some of their Long Covid symptoms could be a result of either their perimenopause or menopause. However, 84% of women had never been asked by a healthcare professional about whether or not they could be perimenopausal or menopausal.

Medical Science

25(112), June, 2021

Premature ovarian failure - A long COVID sequelae

Sparsh Madaan[1], **Arpita Jaiswal**[2]✉, **Sunil Kumar**[3], **Dhruv Talwar**[4], **Dhruva Halani**[1]

To Cite:
Madaan S, Jaiswal A, Kumar S, Talwar D, Halani D. Premature ovarian failure-A long COVID sequelae. *Medical Science*, 2021, 25(112), 1286-1290

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✉**Corresponding author**

ABSTRACT

Ever since its emergence since 2019, Coronavirus Disease 2019 (COVID-19) has brought the healthcare setup down with its burden of varied appearance and presentation. It can lead to a severe disease with respiratory distress syndrome along with hypercoagulability and various neurological complications. There has been an emergence of a large population of patients who develop a subsequent long term disease known as "long-COVID' which is thought to be secondary to chronic tissue inflammation. We Report a case a 34-year-old female who was infected with COVID-19 12 months back and presented with infertility as a post COVID sequelae. This is the first case report linking Ovarian Failure with COVID-19 in our knowledge.

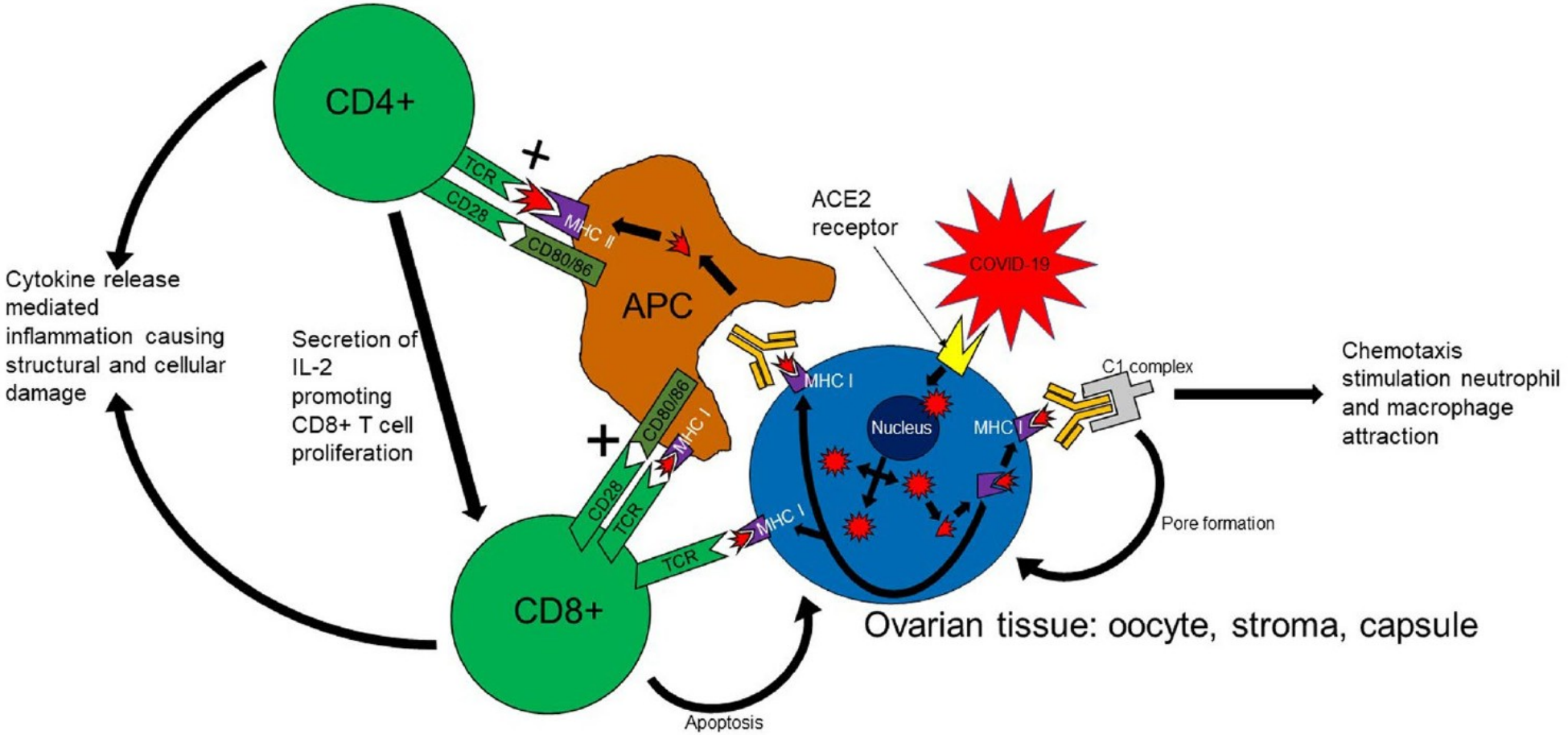
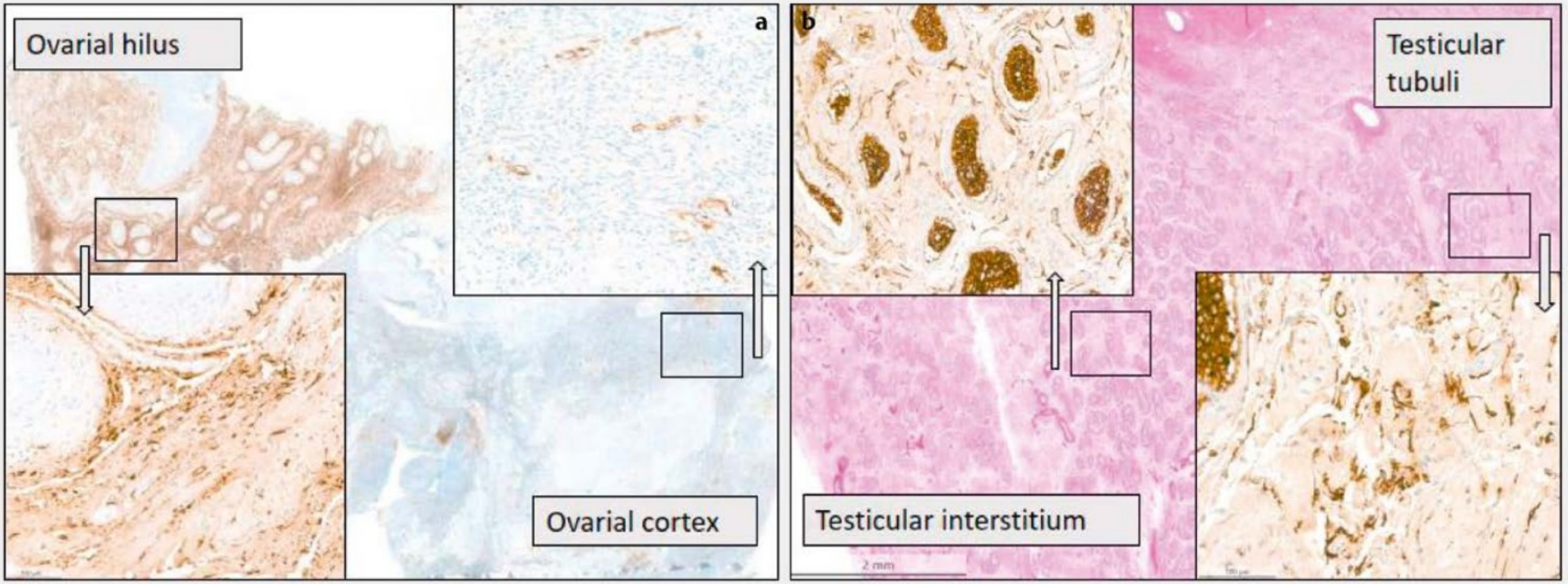


FIGURE 1 Possible mechanism of COVID-19 induced premature ovarian insufficiency

PMID: 35853464



▶ **Fig. 2** Differential ACE2 expression in ovary and testis: **a**: Representative histology from the ovary of an 87-year-old patient who died from SARS-CoV-2 infection and revealed detectable SARS-CoV-2-RNA (not shown) in post-mortem ovarian tissue at autopsy. Immunostaining for ACE2 shows a prominent expression in ovarian stromal cells of hilus (left side of the image) and a weak expression in some cortical stromal cells (right side of the image). **b**: Representative histology from the testis of a 56-year-old patient who died from SARS-CoV-2 infection. The background shows a conventional HE-stain of the autopsy sample. Immunostaining for ACE2 demonstrates a strong expression in all cellular elements of the tubuli (Sertoli and spermatogonia, left side of the image) and a middle-strong expression in the Leydig cells in the testicular interstitium (right side of the image).

Case Study #1

- 47 yof
- COVID-19 – severe pneumonia, ventilator for a few weeks and hospitalization for a month. Oxygen for 11 months.
- Overweight and difficulty losing weight
- No menstrual cycle for 11 months after COVID-19
- Edema – can't wear rings
- Insomnia, wakes up in a panic
- Fatigue – significant afternoon crash through the evening.
- No libido
- Brain fog
- Poor cognitive function, memory issues
- Belching, bloating, gas, inconsistent bowel movements
- Mold exposure – headaches, fatigue, difficulty breathing
- ACE score: 4

- Lung scarring from COVID-19 – dx pulmonary fibrosis
- Deep vein thrombosis in the left brachial vein
- Park Ranger – Now has to work at a desk job.
- Previous dx: Hashimoto's, endometriosis, hypochlorhydria, insulin resistance, low iron w/borderline anemia, migraines, gall bladder removed, sleep apnea.
- Meds: Tirosint, Lexapro, Eletriptan, Spironolactone
- Oral contraceptives 15 years
- "Dozens of antibiotics"
- Antacids for 5 years
- Feels worse after histaminic foods

Stool Analysis

H. pylori		
	Result	Normal
Helicobacter pylori	**4.2e2**	<1.0e3
Virulence Factor, babA	**N/A**	Negative
Virulence Factor, cagA	**N/A**	Negative
Virulence Factor, dupA	**N/A**	Negative
Virulence Factor, iceA	**N/A**	Negative
Virulence Factor, oipA	**N/A**	Negative
Virulence Factor, vacA	**N/A**	Negative
Virulence Factor, virB	**N/A**	Negative
Virulence Factor, virD	**N/A**	Negative

Normal Bacterial Flora

	Result		Normal
Bacteroides fragilis	**2.37e10**		1.60e9 - 2.50e11
Bifidobacterium spp.	**2.07e9**		>6.70e7
Enterococcus spp.	**2.68e5**		1.9e5 - 2.00e8
Escherichia spp.	**9.33e3**	**Low**	3.70e6 - 3.80e9
Lactobacillus spp.	**6.25e6**		8.6e5 - 6.20e8
Clostridia (class)	**5.39e5**	**Low**	5.00e6 - 5.00e7
Enterobacter spp.	**9.18e6**		1.00e6 - 5.00e7
Akkermansia muciniphila	**1.86e5**	**High**	1.00e1 - 5.00e4
Faecalibacterium prausnitzii	**<dl**		1.00e3 - 5.00e8

Phyla Microbiota	Result		Normal
Bacteroidetes	**3.10e11**	**Low**	8.61e11 - 3.31e12
Firmicutes	**4.09e10**	**Low**	5.70e10 - 3.04e11
Firmicutes:Bacteroidetes Ratio	**0.13**		<1.00

Opportunistic Bacteria

Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	**7.73e4**		<1.50e5
Enterococcus faecalis	**<dl**		<1.00e4
Enterococcus faecium	**<dl**		<1.00e4
Morganella spp.	**<dl**		<1.00e3
Pseudomonas spp.	**8.36e2**		<1.00e4
Pseudomonas aeruginosa	**8.47e2**	**High**	<5.00e2
Staphylococcus spp.	**<dl**		<1.00e4
Staphylococcus aureus	**5.02e2**	**High**	<5.00e2
Streptococcus spp.	**6.22e3**	**High**	<1.00e3
Methanobacteriaceae (family)	**5.44e7**		<5.00e9

Potential Autoimmune Triggers	Result		Normal
Citrobacter spp.	**<dl**		<5.00e6
Citrobacter freundii	**<dl**		<5.00e5
Klebsiella spp.	**<dl**		<5.00e3
Klebsiella pneumoniae	**<dl**		<5.00e4
M. avium subsp. paratuberculosis	**<dl**		<5.00e3
Prevotella spp.	**1.39e7**		<1.00e8
Proteus spp.	**<dl**		<5.00e4
Proteus mirabilis	**<dl**		<1.00e3
Fusobacterium spp.	**1.07e9**	**High**	<1.00e8

Intestinal Health

Digestion	Result		Normal
Steatocrit	**<dl**		<15 %
Elastase-1	**>750**		>200 ug/g

GI Markers	Result		Normal
b-Glucuronidase	**327**		<2486 U/mL
Occult Blood - FIT	**0**		<10 ug/g

Immune Response	Result		Normal
Secretory IgA	**210**	Low	510 - 2010 ug/g
Anti-gliadin IgA	**62**		0 - 157 U/L

Inflammation	Result		Normal
Calprotectin	**9**		<173 ug/g

	Iron Bind.Cap.(TIBC)	412	
	UIBC [01]	390	
▼	**Iron** [01]	**22**	**Low**
▼	**Ferritin** [01]	**11**	**Low**

CBC With Differential/Platelet

	Test	Current Result and Flag	
	WBC [01]	7.9	
	RBC [01]	4.71	
	Hemoglobin [01]	12.0	
	Hematocrit [01]	38.3	
	MCV [01]	81	
▼	**MCH** [01]	**25.5**	**Low**
▼	**MCHC** [01]	**31.3**	**Low**
▲	**RDW** [01]	**16.2**	**High**
	Platelets [01]	357	
	Neutrophils [01]	65	
	Lymphs [01]	23	
	Monocytes [01]	7	
	Eos [01]	3	
	Basos [01]	2	
	Neutrophils (Absolute) [01]	5.2	
	Lymphs (Absolute) [01]	1.8	
	Monocytes(Absolute) [01]	0.5	
	Eos (Absolute) [01]	0.2	
	Baso (Absolute) [01]	0.1	
	Immature Granulocytes [01]	0	
	Immature Grans (Abs) [01]	0.0	

C-Reactive Protein, Cardiac	**3.78**	**High**	mg/L	0.00 - 3.00	01
Relative Risk for Future Cardiovascular Event					
		Low		**<1.00**	
		Average		**1.00 - 3.00**	
		High		**>3.00**	
Homocyst(e)ine	5.5		umol/L	0.0 - 15.0	01
.					01
Thyroid					01
TSH	**0.332**	**Low**	uIU/mL	0.450 - 4.500	01
Thyroxine (T4)	6.6		ug/dL	4.5 - 12.0	01
T3 Uptake	**22**	**Low**	%	24 - 39	01
Free Thyroxine Index	1.5			1.2 - 4.9	
Triiodothyronine (T3)	100		ng/dL	71 - 180	01
Triiodothyronine (T3), Free	3.1		pg/mL	2.0 - 4.4	01
Reverse T3, Serum [A]	19.0		ng/dL	9.2 - 24.1	01
T4,Free(Direct)	1.08		ng/dL	0.82 - 1.77	01
Thyroid Peroxidase (TPO) Ab	**221**	**High**	IU/mL	0 - 34	01
Thyroglobulin Antibody	**2.4**	**High**	IU/mL	0.0 - 0.9	01
Thyroglobulin Antibody measured by Beckman Coulter Methodology					
.					01
Immunoassay					01

Glucose, Serum	**120 H**	65 - 100	mg/dL
Urea Nitrogen	12	6 - 23	mg/dL
Creatinine, S	0.9	0.5 - 1.2	mg/dL

[A] Hemoglobin A1c%	**6.2 H**	<5.7	%

IRF%	**21.70 H**	2.30 - 15.90	%	
RET#	**0.1100**	0.0200 - 0.100	x10E6/uL	
Reticulocyte	2.4	0.6 - 2.6	%	

Cholesterol, Total	**206.0 H**	0.0 - 200.0	mg/dL	207.0
Optimal Range <200	Intermediate 200-240	High Risk >240		
LDL Calculated	**106.0 H**	0.0 - 100.0	mg/dL	104.4
Optimal Range <100	Intermediate 100-130	High Risk >130		
Cholesterol, HDL	54.0	>35.0	mg/dL	52.0
High Risk Range: <35, Optimal Range: >/=50				
Triglycerides	**230.0 H**	<150.0	mg/dL	253.0
Optimal Range <150	Intermediate 150-200	High Risk >200		
Non-HDL- C	**152 H**	0 - 130	mg/dL	155
VLDL	**46.0 H**	0.0 - 30.0	mg/dL	50.6
CHO/HDL Ratio	3.8	0.0 - 5.0		4.0

ACTH	**5.2 L**	7.2 - 63.3	pg/mL

ACTH measurement is not recommended for patients who have been administered cosyntropin (ACTH(1-24)) because the results may be falsely elevated or depressed.

Amylase	**26.0 L**	28.0 - 100.0	IU/L
Lipase	26	13 - 60	IU/L
Magnesium, Serum	2.3	1.6 - 2.6	mg/dL
Uric Acid	5.4	2.4 - 5.7	mg/dL

ESR	17	0 - 20	mm/hour
ANA IFA	**Positive**	Negative	
ANA Pattern & Titer	**See Not**		

Homogeneous 1:80

FSH	2.6		mIU/mL

Male:	1.5-12.4 mIU/mL
Female:	
Follicular	3.5-12.5 mIU/mL
Ovulatory	4.7-21.5 mIU/mL
Luteal	1.7-7.7 mIU/mL
Postmenopausal	25.8-134.8 mIU/mL

LH	2.3		mIU/mL

Adult Male :	1.7-8.6 mIU/mL
Adult Female:	
Follicular	2.4-12.6 mIU/mL
Ovulation	14.0-95.6 mIU/mL
Luteal	1.0-11.4 mIU/mL
Postmenopausal	7.7-58.5 mIU/mL

Progesterone	<0.1		ng/mL

Male:	0.0-0.50 ng/mL
Female:	
Follicular Phase	0.1- 0.9 ng/mL
Luteal Phase	1.8-23.9 ng/mL
Postmenopausal	< 0.1 ng/mL
Oral Contraceptives	0.34-0.92 ng/mL
Pregnancy:	
First Trimester	11- 44.3 ng/mL
Second Trimester	25.4-83.3 ng/mL
Third Trimester	58.7-214 ng/mL

Estradiol	264.00		pg/mL	

Male
7.6-42.6 pg/mL
Female
Follicular Phase 12.5-166 pg/mL
Mid-Cycle 85.8-498 pg/mL
Luteal Phase 43.8-211 pg/mL
Postmenopausal <54.7 pg/mL
Pregnancy: 1st trimester: 215.0 to >4300.0

Testosterone, T	<5	<73.0	ng/dL	
Testosterone, F (Calc)	<0.1	0.0 - 2.2	ng/dL	
Testosterone, F (Calc)	<0.1	0.0 - 2.2	ng/dL	
DHEA-Sulfate	62.6	35.4 - 256.0	ug/dL	
Cortisol, Serum	**4.6 L**	6.0 - 18.4	ug/dL	

Cortisol AM: 6.02-18.4
Cortisol PM: 2.68-10.5

Intact PTH	25.1	15.0 - 65.0	pg/mL	
Folic Acid	14.6	>4.5	ng/mL	
Vitamin B12	701.0	232.0 - 1245.0	pg/mL	
Vitamin D 25-OH	92.7	30.0 - 100.0	ng/mL	

Treatment Plan

- Paleo/Low Histamine Diet
- Continue water aerobics and walking outdoors
- GammaCore vagus nerve stimulation
- EMST150 + IA150 for pulmonary rehab
- Microcirculation Strategies

Pulmonary Rehab - EMST150

Inspiratory Adapter

Supplementation

- Black Cumin Seed Oil Softgels: 1,000-3,000 mg/day
- Vitamin D+K 5,000
- Probiotics
- Betaine HCL: 750-2,250 mg/meal
- Chelated iron 27 mg tid (waited one month)
- Buffered Vitamin C taken with iron
- Selenomethionine 200 mcg qd
- Reginator + HMB Powder
- Cod Liver Oil: 3 softgels
- Magnesium-l-threonate
- Phosphatidylserine: 100 mg tid
- Rhodiola, Ashwagandha, Korean ginseng, Eleuthero
- CS-4 Cordyceps 1,000 mg tid
- Licorice + Rehmmania with breakfast
- NAC 700 mg tid
- Melatonin 3 mg before bed

Microcirculation

- Green leafy vegetables
- 85%-92% dark chocolate. 20 grams/day maximum. Be careful with patients who have issues with histamine or caffeine.
- Blueberries, strawberries, raspberries, and blackberries
- 1/2-1 clove of fresh garlic
- Turmeric and ginger as spices
- Green tea – 3-4 cups/day
- Beetroot juice or supplements
- Black Cumin Seed Oil
- Curcumin
- Grape Seed Extract
- Mango Extract
- Ginkgo Biloba
- Korean Ginseng

Glucose, Serum	83	65 - 100	mg/dL	
Urea Nitrogen	12	6 - 23	mg/dL	
Creatinine, S	0.7	0.5 - 1.2	mg/dL	
For patients >49 years of age, the reference				
Hemoglobin A1c%	5.5	<5.7	%	5.7
Higher for people identified as African- American.				
Bun/Creat Ratio	See Note	9.00 - 23.00	Ratio	
BUN/Creatinine ratio is not applicable.				
Sodium, Serum	141.0	134.0 - 145.0	mmol/L	
Potassium, S	4.6	3.5 - 5.3	mmol/L	
Chloride, Serum	102.0	96.0 - 112.0	mmol/L	
CO2	26.0	19.0 - 32.0	mmol/L	
Anion Gap	See Note	8.0 - 16.0	mmol/L	
Anion gap is not applicable				

Is there a role for the adrenal glands in long COVID?

Waldemar Kanczkowski[1], *Felix Beuschlein*[2] *and Stefan R. Bornstein*[1,3]✉

Taken together, adrenal gland insufficiency in patients with COVID-19 might be induced through different mechanisms, including vascular damage, viral replication, inflammatory factors and improper tapering off of long-term steroid replacement. In conclusion, SARS-CoV-2 targets the adrenal gland and can cause adrenal insufficiency in some patients. Furthermore, numerous patients with COVID-19 have received glucocorticoid treatment over an extended period of time, therefore we believe that adrenal gland insufficiency needs to be considered and carefully ruled out in all patients with COVID-19 and long COVID.

Distinguishing features of Long COVID identified through immune profiling

Jon Klein, Jamie Wood, Jillian Jaycox, Peiwen Lu, Rahul M. Dhodapkar, Jeff R. Gehlhausen, Alexandra Tabachnikova, Laura Tabacof, Amyn A. Malik, Kathy Kamath, Kerrie Greene, Valter Silva Monteiro, Mario Peña-Hernandez, Tianyang Mao, Bornali Bhattacharjee, Takehiro Takahashi, Carolina Lucas, Julio Silva, Dayna Mccarthy, Erica Breyman, Jenna Tosto-Mancuso, Yile Dai, Emily Perotti, Koray Akduman, Tiffany J. Tzeng, Lan Xu, Inci Yildirim, Harlan M. Krumholz, John Shon, Ruslan Medzhitov, Saad B. Omer, David van Dijk, Aaron M. Ring, David Putrino, Akiko Iwasaki

doi: https://doi.org/10.1101/2022.08.09.22278592

Analysis of circulating immune mediators and various hormones also revealed pronounced differences, with levels of cortisol being uniformly lower among participants with Long COVID relative to matched control groups. Integration of immune phenotyping data into unbiased machine learning models identified significant distinguishing features critical in accurate classification of Long COVID, with decreased levels of cortisol being the most significant individual predictor.

medicina

MDPI

Case Report

Possible Adrenal Involvement in Long COVID Syndrome

Ciro Salzano [1], Giovanna Saracino [2] and Giuseppe Cardillo [2,*]

[1] Unit of Internal Medicine, San Giovanni Bosco Hospital, ASL-NA1, Via Filippo Maria Briganti, 255, 80144 Napoli, Italy; cirosalzano89@gmail.com
[2] Medylab–Advanced Biochemistry, Viale Martiri di Nassiriya, 14, 81030 Lusciano, Italy; giovanna.saracino.83@gmail.com
* Correspondence: giuseppe.cardillo.75@gmail.com

Abstract: *Background*: A significant number of patients with COVID-19 experience prolonged symptoms, known as Long COVID. The most frequent symptoms are fatigue and cognitive dysfunction. We describe a patient suffering from Long COVID in whom adrenal involvement was highlighted. *Methods*: The patient described Long COVID symptoms that persist 3 months after the negativization of the molecular swab test. The main symptoms were weakness, brain fog, dizziness, and muscular and joint pain. All routine lab panels for inflammation, anemia, and thyroid and liver function were conducted. Moreover, salivary cortisol and DHEA-S determinations were used to compute the adrenal stress index (ASI). *Results*: All tests were negative, except the ASI that showed very low levels of free cortisol. The patient started hydrocortisone acetate supplementation. *Conclusion*: Long COVID symptoms could be explained by an adrenal involvement, due to a COVID-19 action on adrenal glands and by a iatrogenic side effect of high glucocorticoid therapy during the COVID-19 infection. Salivary cortisol determination is effective for establishing a correct recovery plan.

Keywords: Long COVID; salivary cortisol and DHEA-S; adrenal insufficiency

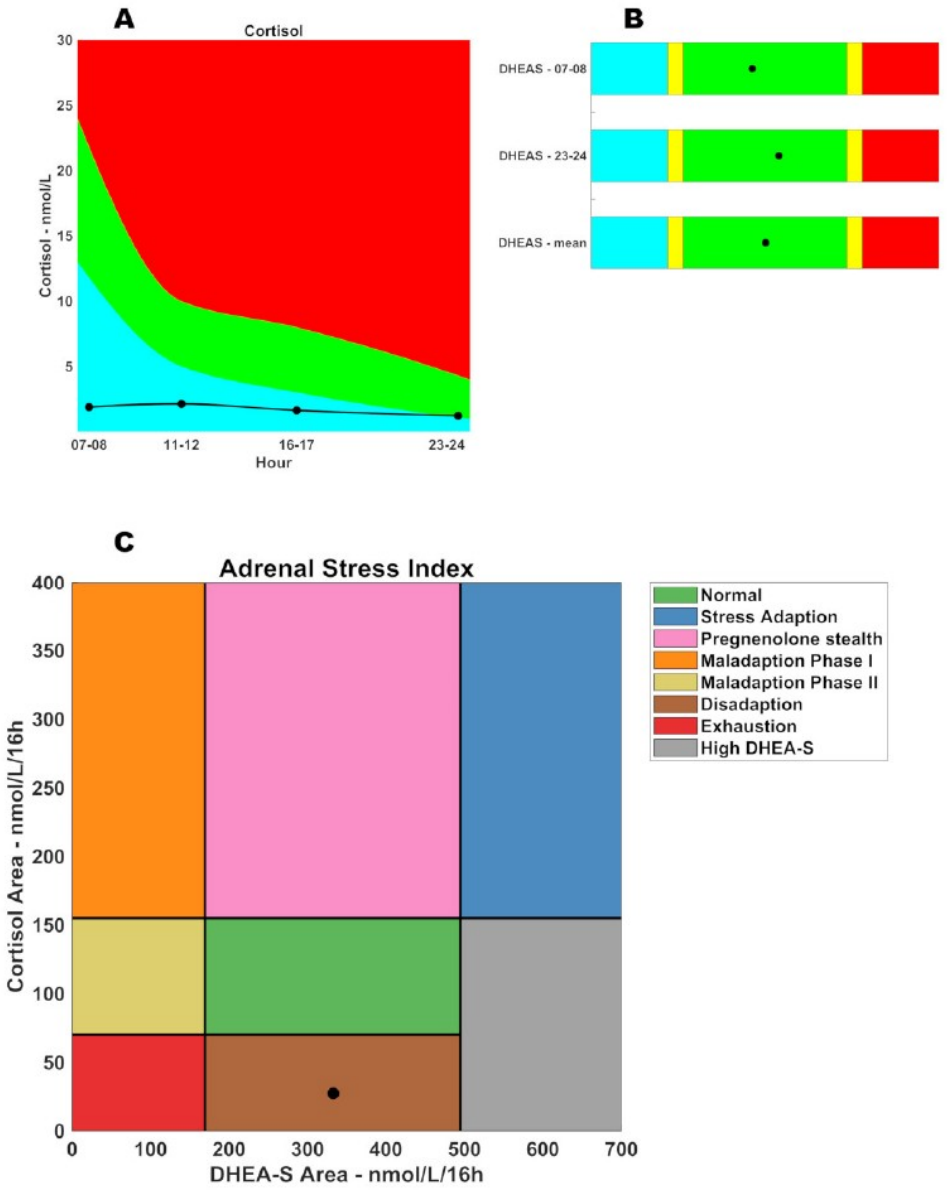


Figure 1. Adrenal Stress Index (ASI). (**A**) Circadian salivary cortisol; (**B**) circadian salivary DHEA-S; (**C**) ASI phase graph.

pharmaceuticals

MDPI

Article

Efficacy of Adaptogens in Patients with Long COVID-19: A Randomized, Quadruple-Blind, Placebo-Controlled Trial

One hundred patients with confirmed positive SARS-CoV-2 test, discharged from COVID Hotel isolation, Intensive Care Unit (ICU), or Online Clinics, and who experienced at least three of nine Long COVID symptoms (fatigue, headache, respiratory insufficiency, cognitive performance, mood disorders, loss of smell, taste, and hair, sweatiness, cough, pain in joints, muscles, and chest) in the 30 days before randomization were included in the study of the efficacy of a fixed combination of adaptogens Rhodiola, Eleutherococcus, and Schisandra supplementation for two weeks. Adaptogens decreased the duration of fatigue and pain for one and two days, respectively, in 50% of patients. The number of patients with lack of fatigue and pain symptoms was significantly less in the treatment group than in the placebo group on Days 9 and 11. Significant relief of severity of all Long COVID symptoms over the time of treatment and the follow-up period was observed in both groups of patients, notably decreasing the level of anxiety and depression from mild and moderate to normal, as well as increasing cognitive performance in patients in the d2 test for attention and increasing their physical activity and workout (daily walk time). However, the significant difference between placebo and adaptogen treatment was observed only with a workout (daily walk time) and relieving respiratory insufficiency (cough). A clinical assessment of blood markers of the inflammatory response (C-reactive protein) and blood coagulation (D-dimer) did not reveal any significant difference over time between treatment groups except significantly lower IL-6 in the treatment group. Furthermore, a significant difference between the placebo and treatment was observed for creatinine: adaptogens significantly decreased blood creatinine compared to the placebo, suggesting prevention of renal failure progression in Long COVID. In this study, we, for the first time, demonstrate that adaptogens can increase physical performance in Long COVID and reduce the duration of fatigue and chronic pain.

Cordyceps sinensis

FIGURE 1 | *Cordycepin sinensis* in the soil (left). Traditional Chinese herb *Dong Chong Xia Cao* decoction pieces (right).

Cordyceps sinensis

- Anti-inflammatory
- Inhibits platelet aggregation
- Anti-tumor
- Anti-fibrotic
- Anti-oxidant
- Anti-hyperglycemic
- Hypolipidemic
- Immuomodulatory
- Neuroprotective
- Anti-leukemic
- Analgesic
- Anti-hypertension
- Anti-infertility
- Cardioprotective
- Nephroprotective
- Metabolic regulation
- Anti-tussive
- Antimicrobial
- Anti-arthritic
- Hepatoprotective
- Anti-hypoxia
- Cytotoxic activities
- Anti-osteoporotic
- Corticosteroid supportive
- Adaptogen
- Anti-fatigue
- Anti-viral

Received: 19 June 2020 | Revised: 25 August 2020 | Accepted: 13 September 2020
DOI: 10.1002/ptr.6890

Check for updates

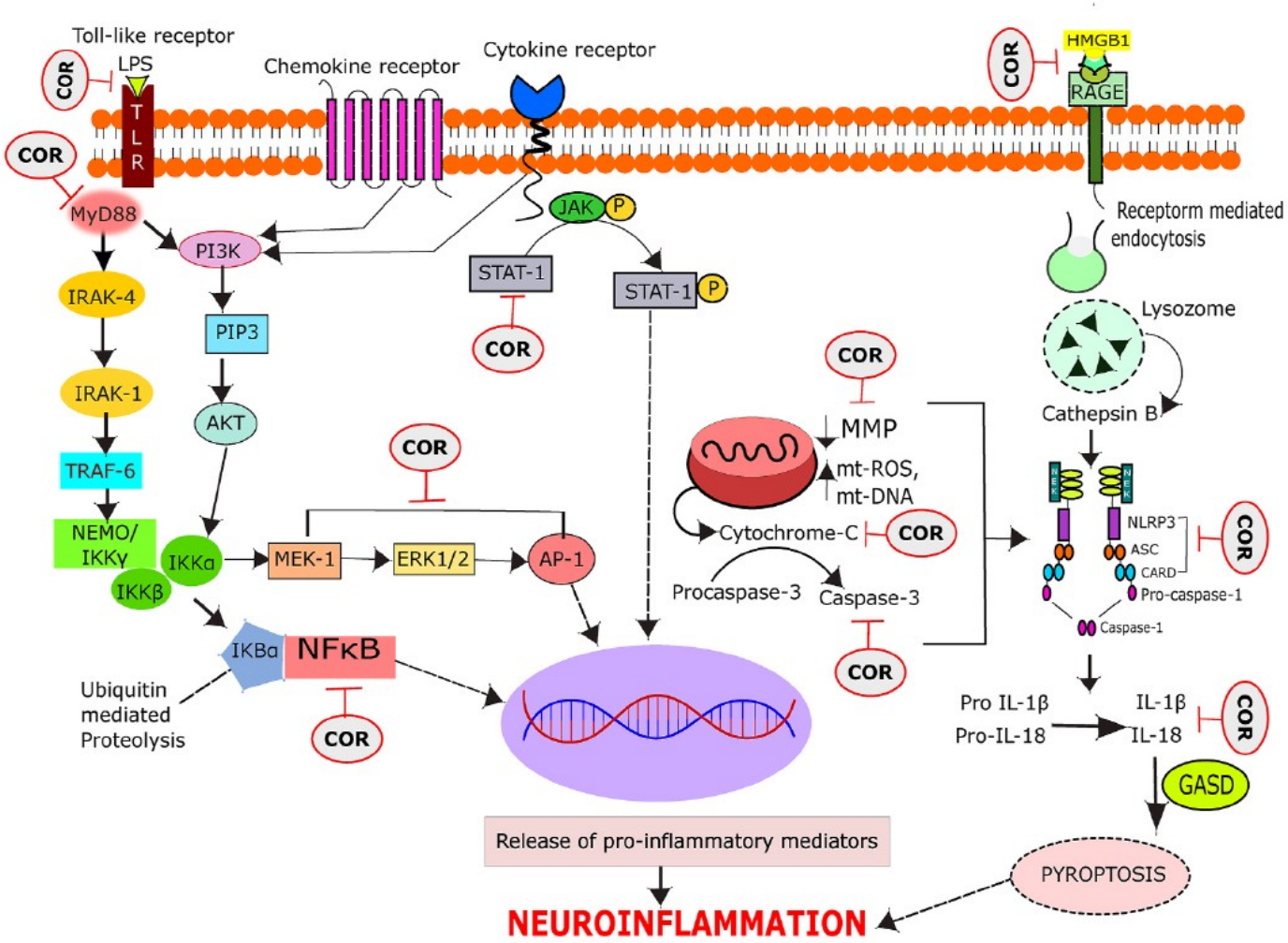
REVIEW

WILEY

Anti-inflammatory effects of cordycepin: A review

Lu Tan[1] | Xiaominting Song[1] | Yali Ren[1] | Miao Wang[1] | Chuanjie Guo[1] | Dale Guo[1] | Yucheng Gu[2] | Yuzhi Li[1] | Zhixing Cao[1] | Yun Deng[1]

The results from our review indicate that cordycepin exerts protective effects against inflammatory injury for many diseases including acute lung injury (ALI), asthma, rheumatoid arthritis, Parkinson's disease (PD), hepatitis, atherosclerosis, and atopic dermatitis. Cordycepin regulates the NF-κB, RIP2/Caspase-1, Akt/GSK-3β/p70S6K, TGF-β/Smads, and Nrf2/HO-1 signaling pathways among others. Moreover, cordycepin enhanced immunity, inhibited the proliferation of viral RNA, and suppressed cytokine storms, thereby suggesting its potential to treat COVID-19 and other viral infections.



PMID: 34297967

Fig. 1. Schematic representation of underlying neuroinflammatory mechanisms and the targets pertinent to cordycepin.

Abbreviations: COR: cordycepin; LPS: lipopolysaccharide; MyD88: myeloid differentiation primary response protein; IRAK-4: interleukin 1 receptor associated protein kinase-4; IRAK-1: interleukin receptor associated protein kinase-1; TRAF-6: tumor necrosis factor receptor associated factor-6; NEMO: nuclear factor kappa-B essential modulator; IKKγ: inhibitor of nuclear factor kappa B kinase gamma; IKKα: inhibitor of nuclear factor kappa B kinase alpha; IKKβ: inhibitor of nuclear factor kappa B kinase beta; IKBα: nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor alpha; NF-κB: nuclear factor kappa light chain enhancer of activated B cells; PI3K: phosphoionositide-3-kinase; PIP3: phosphotidylionositol-3,4,5-trisphosphate; AKT: protein kinase B; MEK-1: mitogen activated protein kinase kinase; ERK1/2: extracellular signal regulated kinase; AP-1: activator protein-1; JAK: janus kinase; P: phosphorylation; STAT-1: signal transducer and activator of transcription-1; MMP: mitochondrial membrane potential; mt-ROS: mitochondrial reactive oxygen species; mt-DNA: mitochondrial DNA; HMGB1: high mobility group box protein-1; RAGE: receptor for advanced glycation end products; NLRP3: nod-like receptor pyrin domain containing protein 3; ASC: apoptosis associated speck like protein containing a caspase recruitment domain; CARD: caspase activation and recruitment domain; GASD: gasdermin.

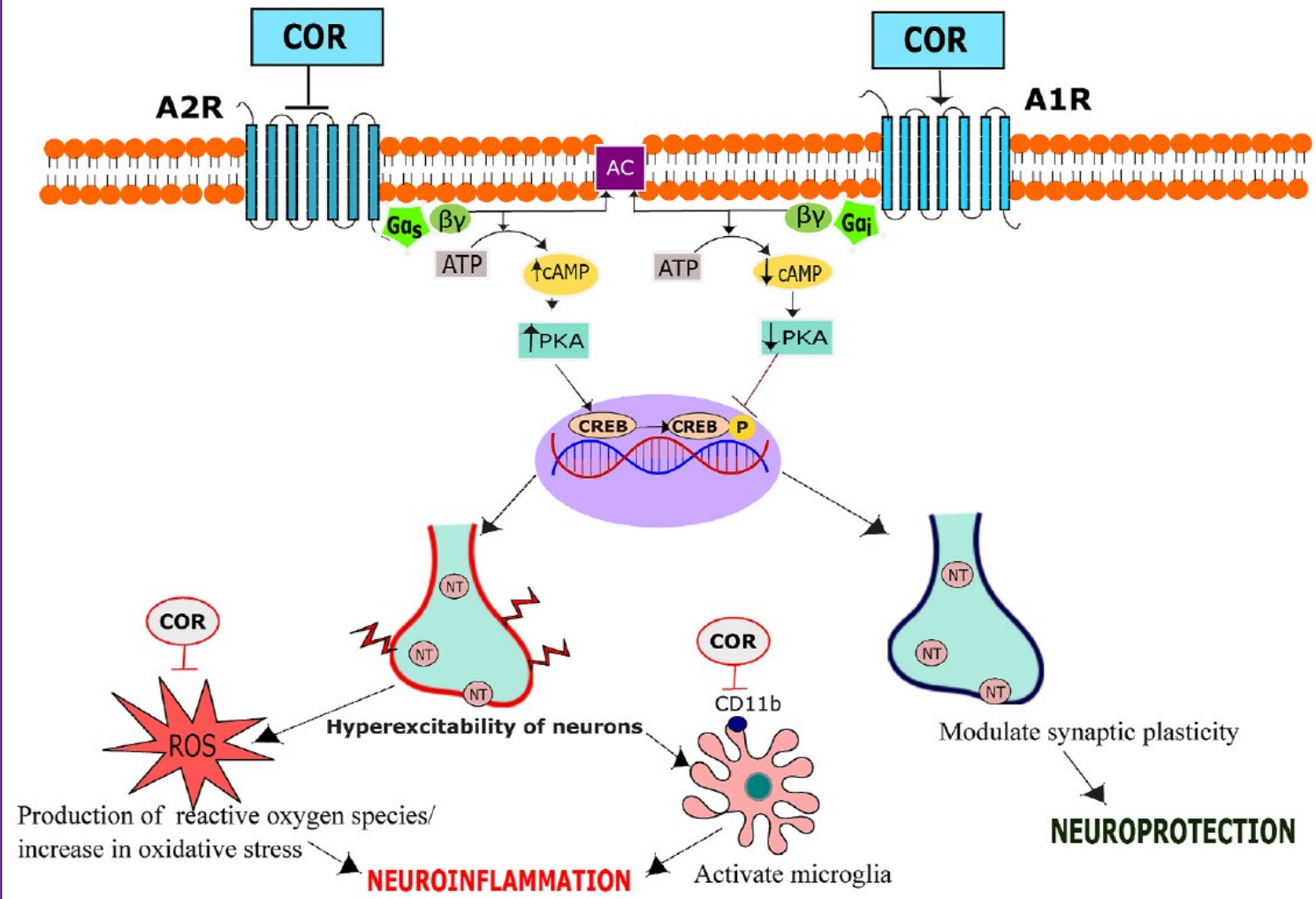


Fig. 2. Schematic representation of adenosine receptor signalling mechanism of cordycepin; Abbreviations: A2R: adenosine 2 receptor; A1R: adenosine 1 receptor; Gαs: stimulatory G-protein α subunit; Gαi; inhibitory G-protein α subunit; βγ: beta-gamma complex of G-protein; AC: adenylyl cyclase; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; CREB: cAMP-response element-binding protein; P: phosphorylation; NT: neurotransmitter; ROS: reactive oxygen species; CDD11b: microglial marker.

PMID: 34297967

The *in Vivo* Effect of *Cordyceps sinensis* Mycelium on Plasma Corticosterone Level in Male Mouse

Sew-Fen LEU,[a] Chi-Hsien CHIEN,[b] Chi-Yu TSENG,[b] Yu-Ming KUO,[b] and Bu-Miin HUANG*,[b]

[a] *National Laboratory Animal Breeding and Research Center, National Science Council, Taipei, Taiwan, Republic of*

Results illustrated that plasma corticosterone levels were significantly induced by F2 at 0.02 mg/g body weight with 7 d feeding in immature mice, and by CS at 0.02 mg/g body weight with 3 d feeding and F3 at 0.02 mg/g body weight for 7 d feeding in mature mice, respectively ($p<0.05$).

PHARMACEUTICAL BIOLOGY
2022, VOL. 60, NO. 1, 404–416
https://doi.org/10.1080/13880209.2022.2033275

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RESEARCH ARTICLE

OPEN ACCESS Check for updates

Cordycepin mitigates spermatogenic and redox related expression in H_2O_2-exposed Leydig cells and regulates testicular oxidative apoptotic signalling in aged rats

Spandana Rajendra Kopalli[a,b], Kyu-Min Cha[c], Jae Youl Cho[d], Si-Kwan Kim[b] and Sushruta Koppula[b]

COR treatment significantly inhibited the H2O2-induced decrease in the percentage of viable cells and reduced the malondialdehyde (MDA) content. Further, the decreased antioxidant enzymes (glutathione-S-transferase mu5, glutathione peroxidase 4 and peroxiredoxin 3), spermatogenesis-related factors (nectin-2 and inhibin-α) and testosterone levels in H2O2-exposed TM3 cells were significantly ameliorated by COR.

Conclusion: COR might be developed as a potential agent against ageing-associated and oxidative stress-induced male infertility.

nutrients

MDPI

Article

Cordycepin, an Active Constituent of Nutrient Powerhouse and Potential Medicinal Mushroom *Cordyceps militaris* Linn., Ameliorates Age-Related Testicular Dysfunction in Rats

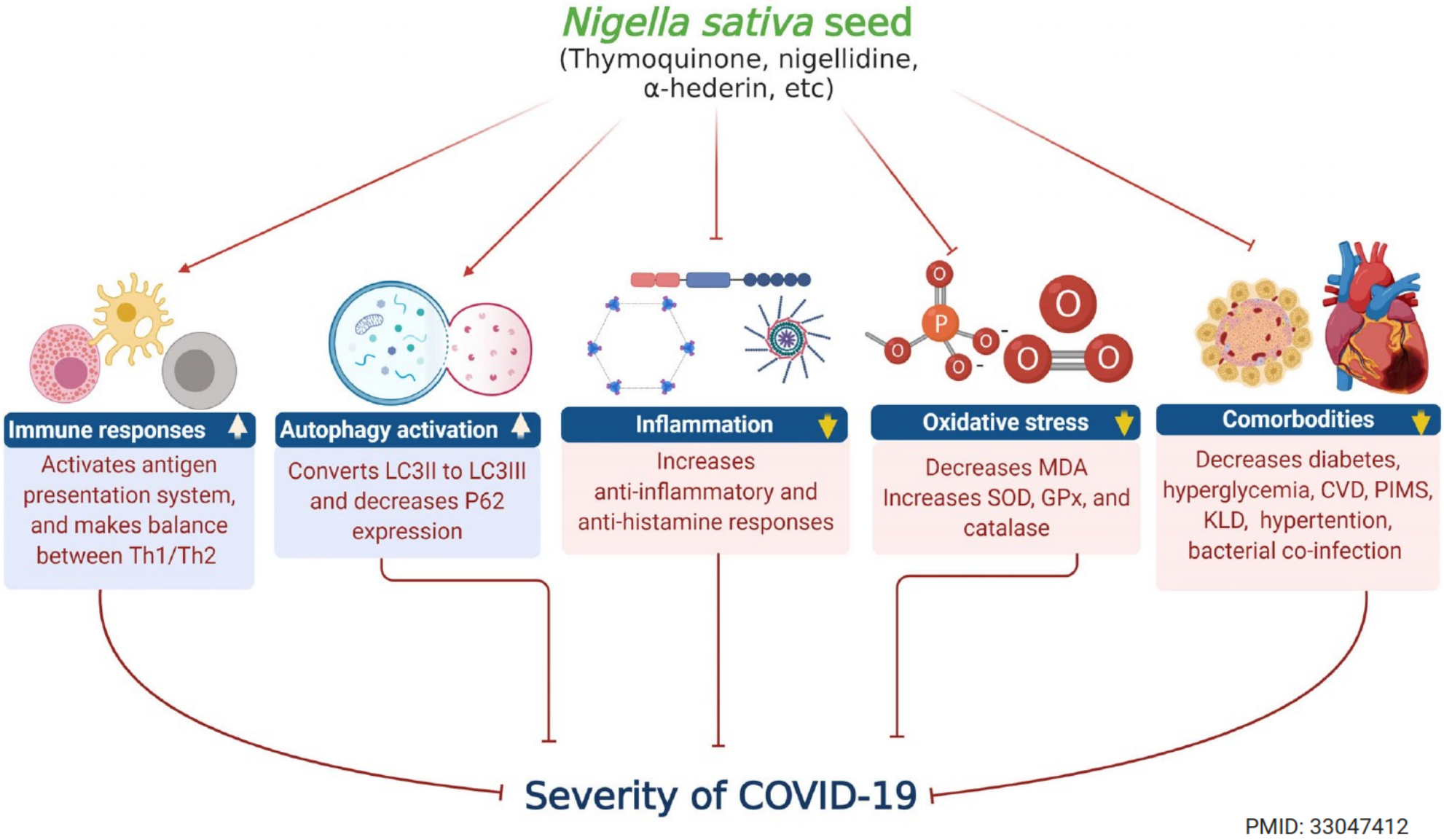
Compared with the AC group, the COR-treated group exhibited improved sperm motility, progressiveness, and average path/straight line velocity. Alterations in spermatogenesis-related protein and mRNA expression were significantly ameliorated in the COR-20 group compared with the AC group. The altered histone deacetylating SIRT1 and autophagy-related mTORC1 molecular expression in aged rats were restored in the COR-20 group. In conclusion, the results suggest that COR holds immense nutritional potential and therapeutic value in ameliorating age-related male sexual dysfunctions.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Life Sciences 75 (2004) 1051–1062
Life Sciences
www.elsevier.com/locate/lifescie

In vivo stimulatory effect of *Cordyceps sinensis* mycelium and its fractions on reproductive functions in male mouse

Yuan-Li Huang[a], Sew-Fen Leu[b], Bi-Ching Liu[a], Chia-Chin Sheu[c], Bu-Miin Huang[a,*]

Cordyceps sinensis (CS), an Ascomycetes fungus parasitic to Lepidoptera larvae, has been traditionally used as nutritious food for the enhancement on sexual performance and the restitution of impairment in sexual function in Chinese society. Results illustrated that CS significantly induced plasma testosterone levels both in immature and mature mice in 3 and/or 7 days treatment. F2 and F3 at 0.02 and/or 0.2 mg/g body weight for different feeding duration could also significantly stimulated plasma testosterone levels both in immature and mature mice. Taken together, these studies illustrate that CS and its fractions significantly stimulated in vivo mouse testosterone production.



PMID: 34073784

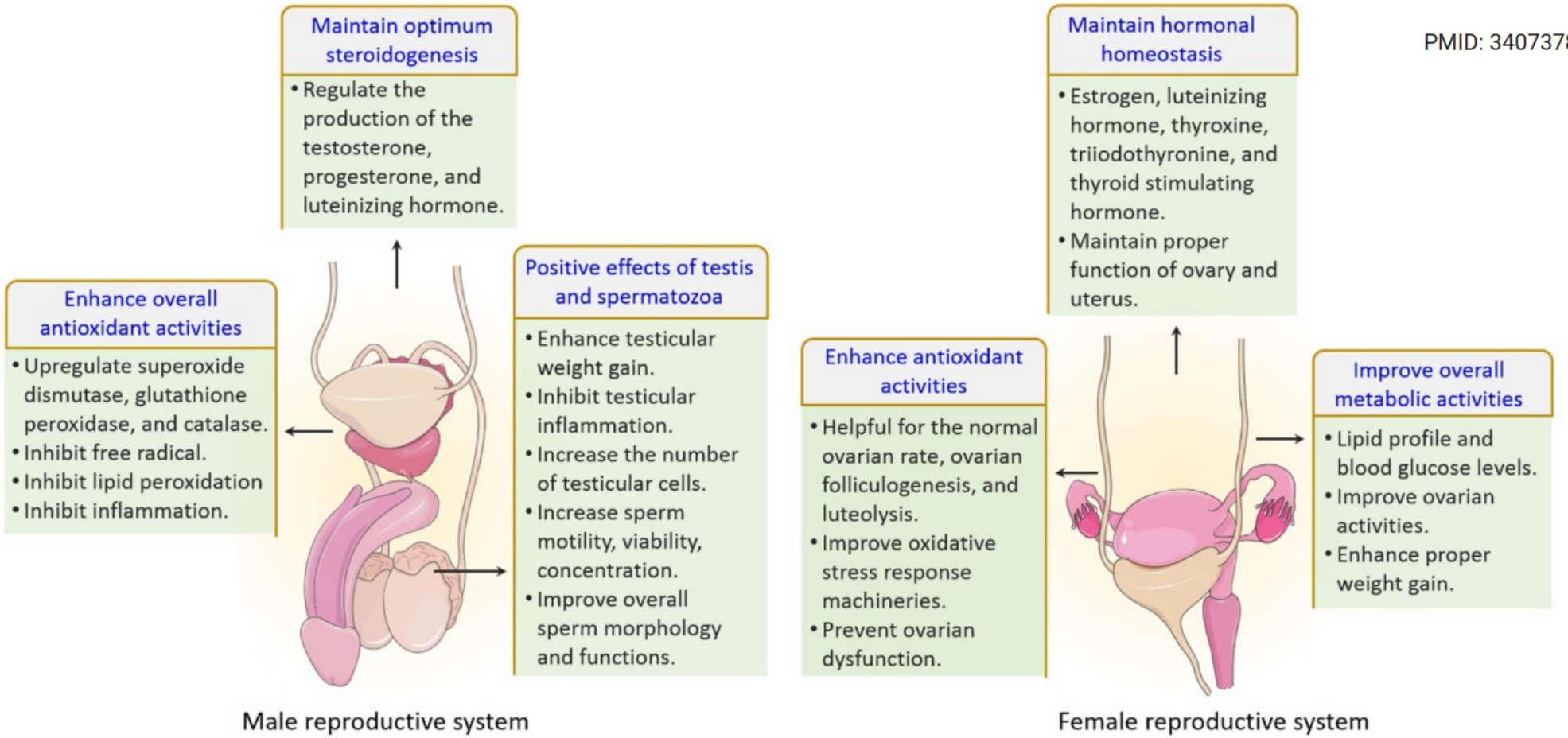


Figure 5. Hypothetical illustration showing black cumin action mechanism on reproduction. At the molecular level, black cumin exhibits its beneficial effects on reproduction via three major pathways: (1) adjust hormonal homeostasis, (2) enhance antioxidant capacity of reproductive tissue/cells, and (3) facilitate proper growth and maturation of germ cells and associated organs. A more detailed description of black cumin action can be found in the main text.

Nordin *et al. BMC Complementary and Alternative Medicine* (2019) 19:290
https://doi.org/10.1186/s12906-019-2706-2

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Effect of *Nigella sativa* and its bioactive compound on type 2 epithelial to mesenchymal transition: a systematic review

[illegible]

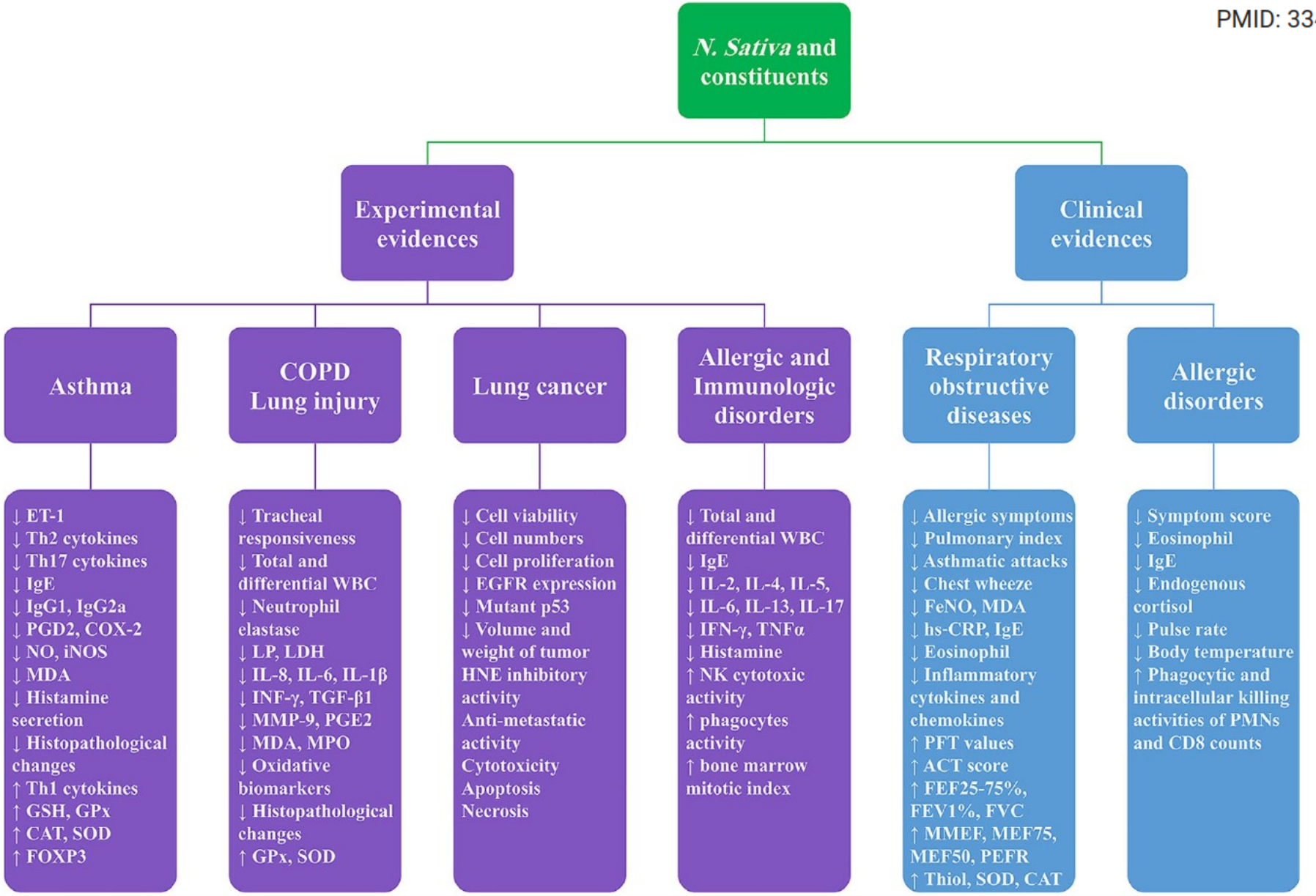
Epithelial to mesenchymal transition (EMT) of type 2 is defined by the balance between wound healing and tissue fibrosis, which is dependent to the state of inflammation. Majority of the studies, reported better wound healing rate or significant prevention of tissue inflammation and organ fibrosis following Nigella sativa or thymoquinone treatments. Alternatively, in terms of fibrosis and inflammation, studies included reported reversal of pathological changes related to EMT after treatment with Nigella sativa or thymoquinone.

Nigella sativa and thymoquinone have been shown to promote wound healing, attenuate tissue inflammation, and prevent organ fibrosis via regulation of the EMT process.

Table 2 Effect of *Nigella sativa* and thymoquinone on organ fibrosis

References	Experimental model	Treatment	Outcome measures	Results	Conclusion
Myocardial Fibrosis					
Pei et al. 2018 [38]	Doxorubicin (Dox)-induced heart failure in Sprague-Dawley rats.	50 mg/kg/day oral TQ.	1. Left ventricular functions. 2. Atherosclerotic lesion. 3. Fibrosis markers. 4. Apoptosis markers.	Treatment of TQ reverses Dox-induced pathological changes in the heart via inhibition of fibrosis and apoptosis.	TQ mitigates Dox-induced cardiac damage and fibrosis.
Pulmonary Fibrosis					
Abidi et al. 2017 [23]	Bleomycin-induced pulmonary fibrosis in Wistar rats.	1 mg/kg/day oral NSO.	1. Physical measurements. 2. Histological evaluation. 3. Liver metabolites. 4. Urine metabolites. 5. Expression of TGF-β1.	Treatment with NSO reverse bleomycin-induced pathological changes via induction of TGF-β1.	NSO have shown to resolve BLM-induced PF due to its anti-inflammatory and anti-fibrotic properties
Pourgholamhossein et al. 2016[42]	Paraquat-induced lung fibrosis in NMRI mice.	20 mg/kg/day and 40 mg/kg/day oral TQ.	1. Histological evaluation. 2. Oxidative stress analysis. 3. Hydroxyproline content. 4. Gene expression.	Treatment with TQ reverses paraquat-induced lung fibrosis inhibition of fibrosis and antioxidant activity.	TQ is able to reduce pulmonary fibrosis via its anti-fibrotic property.

PMID: 33455047



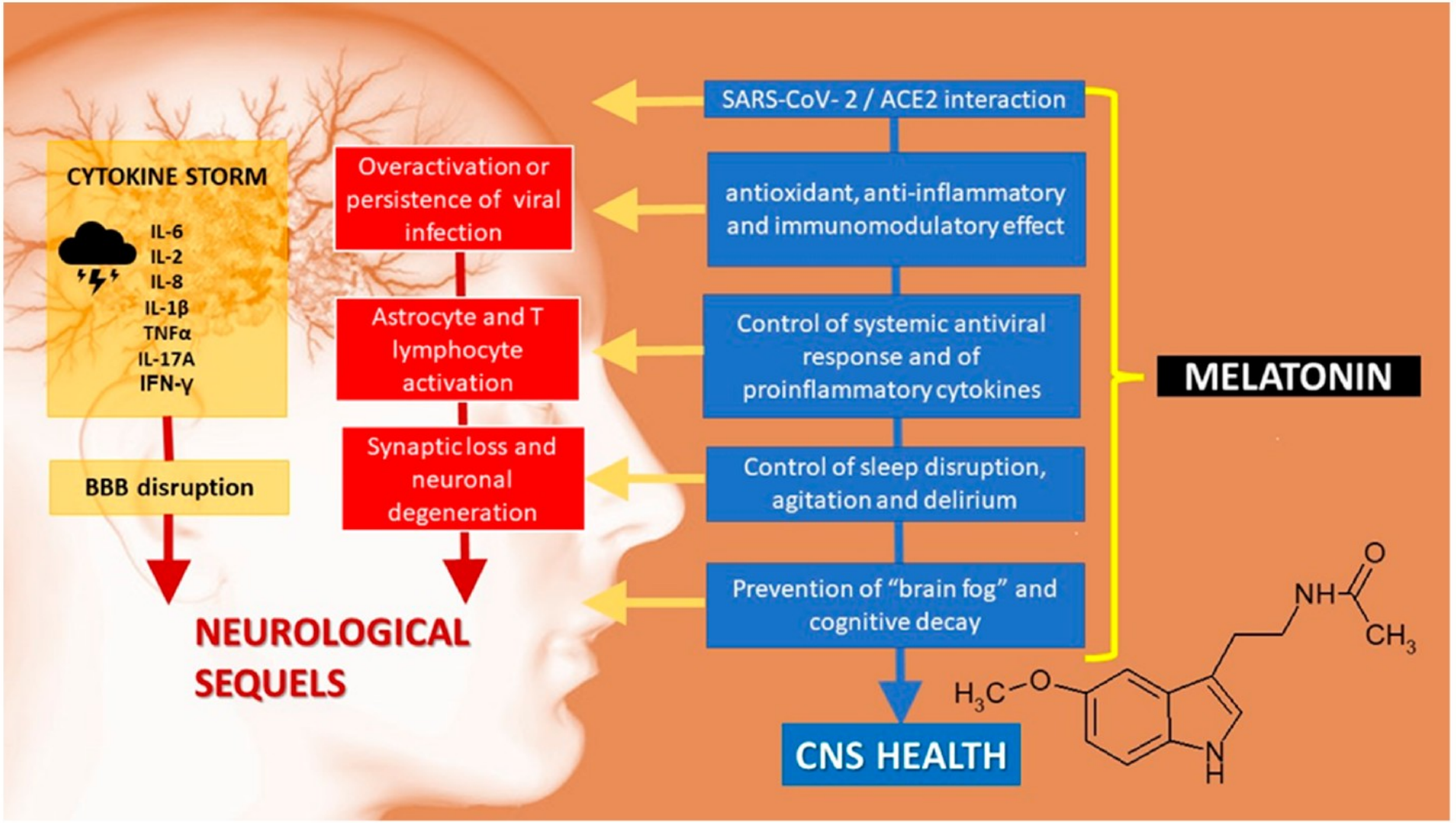
biomolecules

MDPI

Review

Possible Application of Melatonin in Long COVID

Daniel P. Cardinali [1], Gregory M. Brown [2] and Seithikurippu R. Pandi-Perumal [3,*]



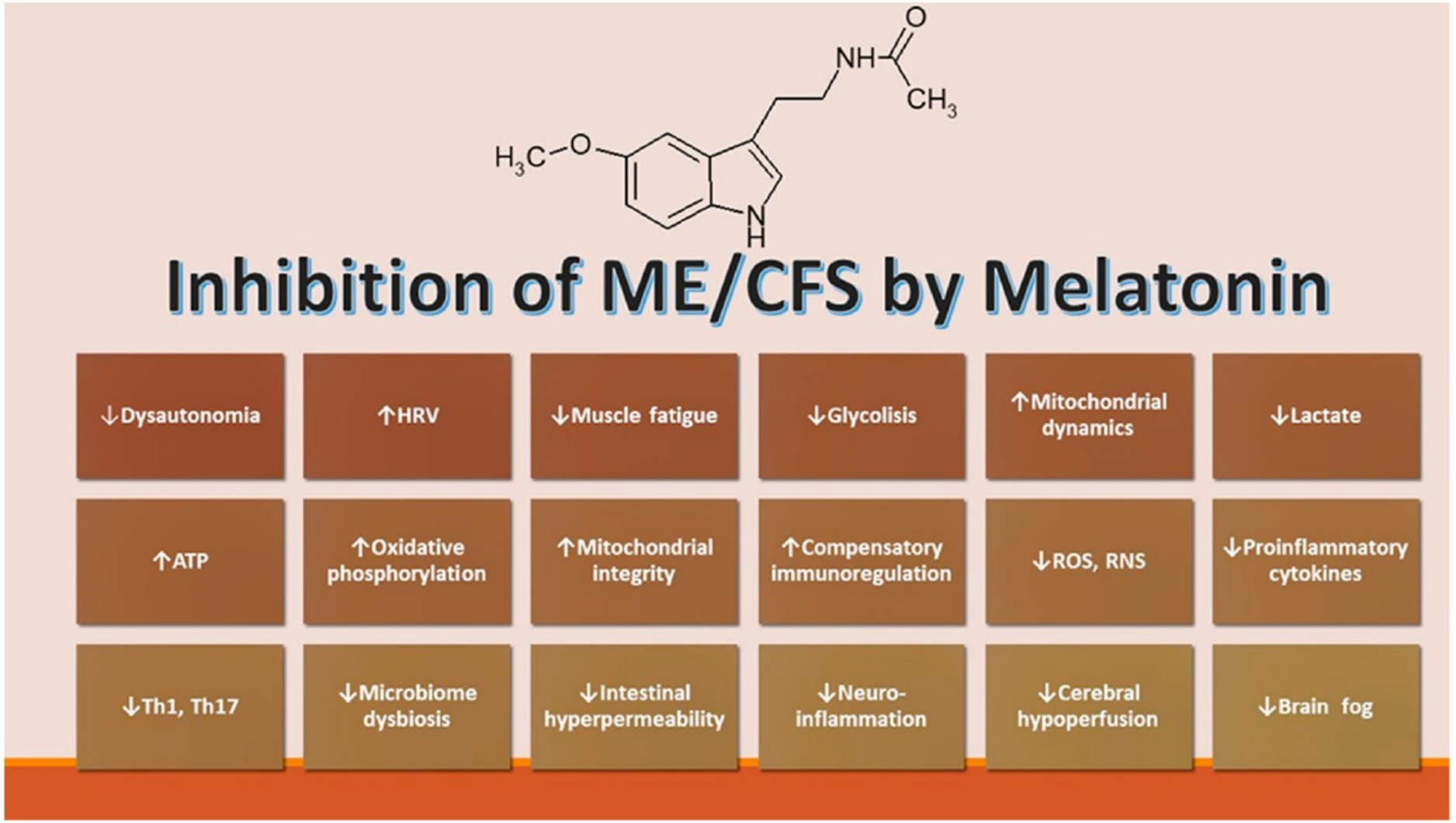


Figure 2. Putative activity of melatonin in ME/CFS. HRV: heart rate variability.

Brain, Behavior, & Immunity - Health 20 (2022) 100412

Contents lists available at ScienceDirect

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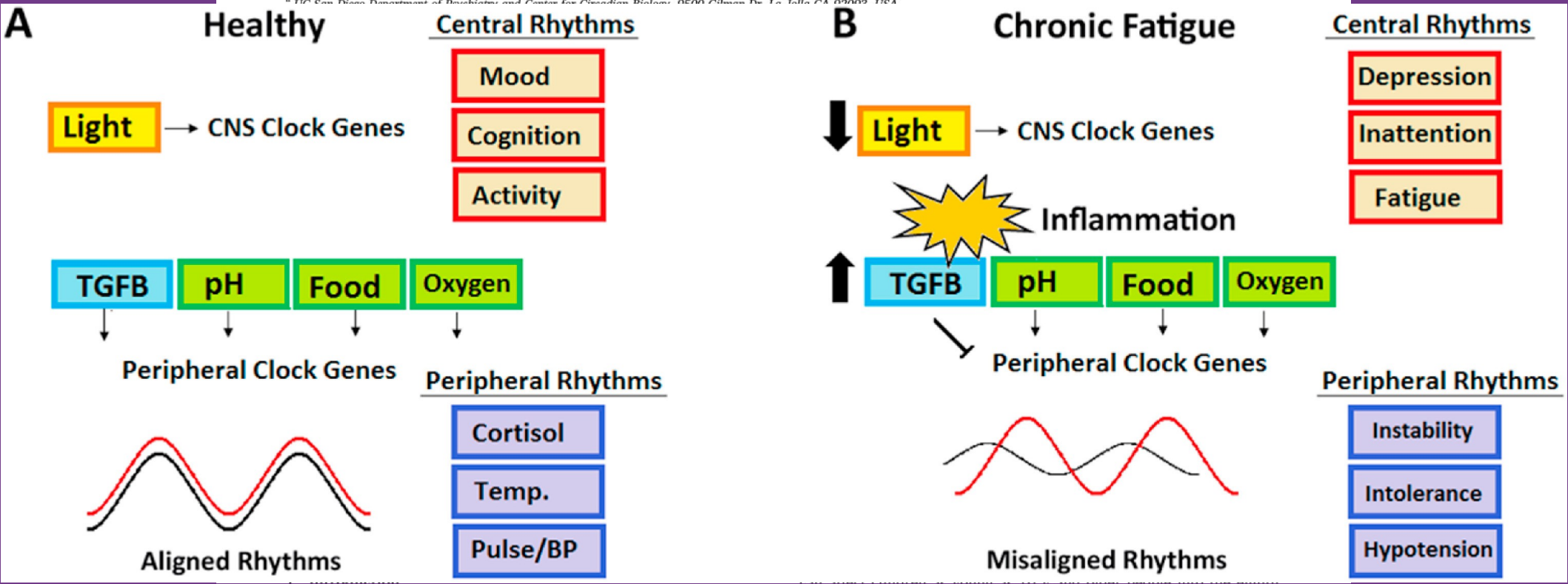
journal homepage: www.editorialmanager.com/bbih/default.aspx

Circadian rhythm disruption in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Implications for the post-acute sequelae of COVID-19

Michael J. McCarthy [a,b,*]

[a] UC San Diego Department of Psychiatry and Center for Circadian Biology, 9500 Gilman Dr. La Jolla CA 92093, USA



Role of Nuclear Factor Erythroid 2 (Nrf2) in the Recovery of Long COVID-19 Using Natural Antioxidants: A Systematic Review

PMID: 36009268

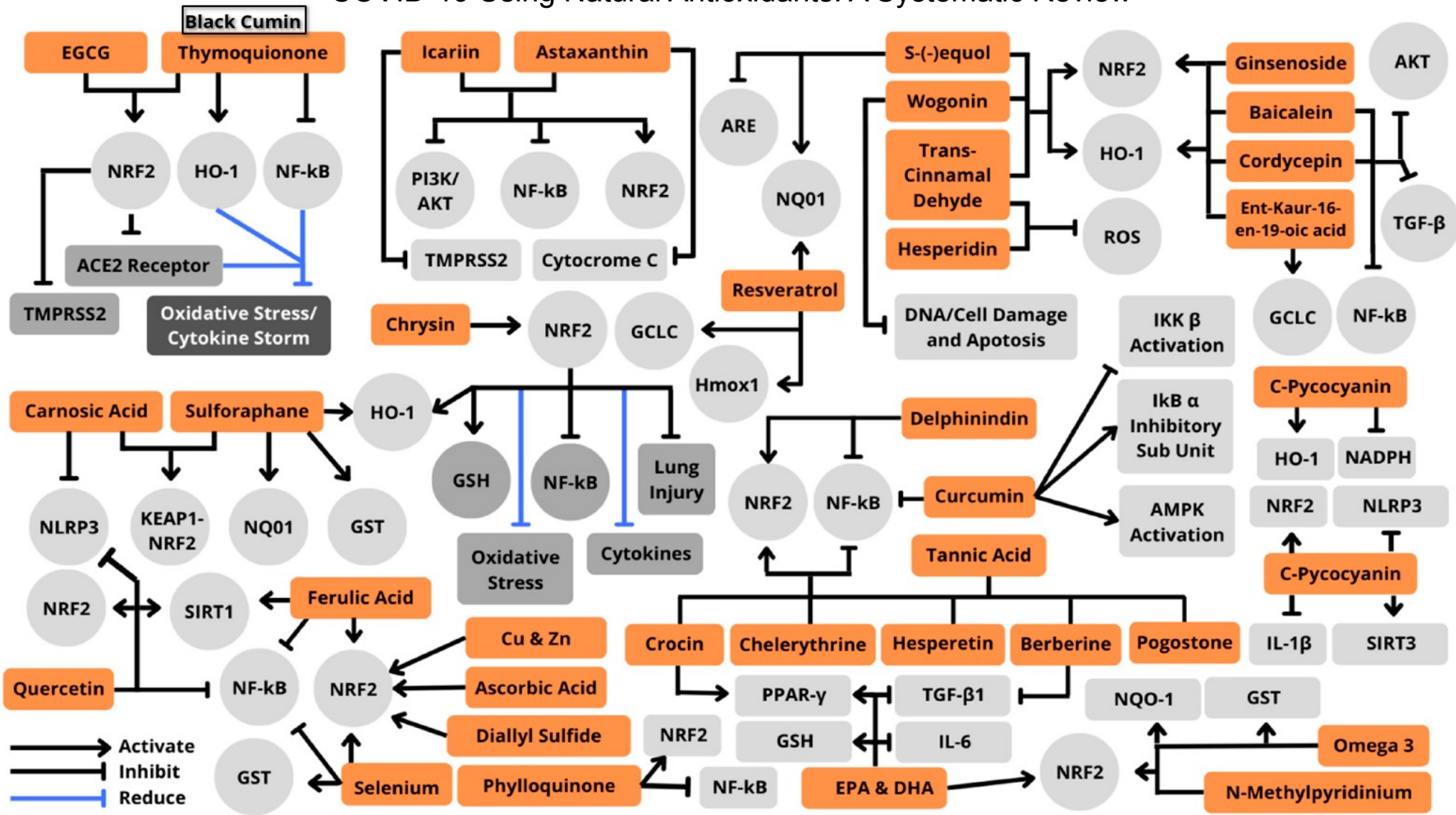


Figure 9. Mechanism of natural antioxidant compounds in Nrf2 activation.

viruses

MDPI

Article

Impaired Vagal Activity in Long-COVID-19 Patients

Domenico Acanfora [1,*], Maria Nolano [2,3], Chiara Acanfora [1,4], Camillo Colella [1], Vincenzo Provitera [3], Giuseppe Caporaso [3], Gabriele Rosario Rodolico [5], Alessandro Santo Bortone [6], Gennaro Galasso [7] and Gerardo Casucci [1,*]

[1] Department of Internal Medicine, San Francesco Hospital, Viale Europa 21, 82037 Telese Terme, Italy; acanforachiara@gmail.com (C.A.); cacolella@virgilio.it (C.C.)

To verify the dysautonomia hypothesis in Long-COVID-19 patients, we studied heart rate variability using 12-lead 24-h ECG monitoring in 30 Long-COVID-19 patients and 20 No-COVID patients. Power spectral analysis of heart rate variability was lower in Long-COVID-19 patients. Dysautonomia may explain the persistent symptoms in Long COVID-19 patients. The persistence of a procoagulative state and an elevated myocardial strain could explain vagal impairment in these patients.

Advances in Neurology and Neuroscience Research
Volume 2
Article ID: 100011
DOI: 10.51956/ANNR.100011

EMRES PUBLISHERS

Research Article

Transcutaneous Auricular Vagus Nerve Stimulation (tVNS) can Reverse the Manifestations of the Long-COVID Syndrome: A Pilot Study

Verbanck P[1,2*], Clarinval AM[2], Burton F[2], Corazza F[3], Nagant C[3] and Cheron G[1,2]

[1]Laboratory of Neurophysiology & Movement Biomechanics, Université Libre de Bruxelles, Belgium

[2]Human Waves c/o PsyPluriel, Belgium

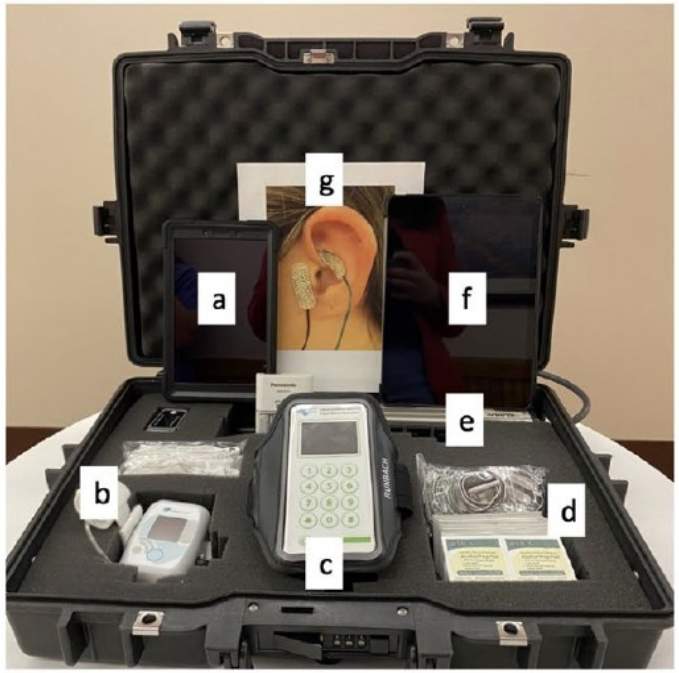
[3] Laboratory of Translational Research, Centre Hospitalier Universitaire Brugmann, Université Libre de Bruxelles, Belgium

***Corresponding author**: Paul Verbanck, Human Waves c/o PsyPluriel, Avenue Jacques Pastur 47A, 1180 Brussels

Methods: 20 patients suffering from chronic COVID syndrome were selected. The symptoms were carefully recorded, and a personal intensity scale was constructed for each patient. They received 10 daily tVNS stimulations using a Parasym device. Clinical assessments and measures of blood inflammatory factors were performed on days 0, 5 and 10. The data were analyzed using non-parametric statistical methods. Results: All the patients completed the study. The clinical manifestations of the disorder were globally similar for each patient: a wax-andwaning syndrome combining fatigue, pain, digestive problems and cognitive difficulties. All the patients improved dramatically during treatment. We did not observe a modification of the blood inflammatory circulating factors, invalidating the hypothesis of an effect of tVNS on a remaining inflammatory state. Conclusions: In this study, we showed that tVNS is an interesting tool for patients with chronic COVID syndrome. Even if this preliminary study did not confirm the hypothesis of protracted inflammation, it helped to propose an alternate explanation, based on the clinical observations supporting COVID-induced dysautonomia. We suggest that tVNS improves chronic COVID syndrome through a “sympathetic reset”

a

At-Home, Supervised taVNS Briefcase Contents



A Tablet for Virtual Supervision

B Heart Rate and Blood Pressure Monitoring System (Caretaker Medical)

C Double-blind taVNS System (Soterix Medical)

D Alcohol Wipes and Electrodes

E Embedded Power Strip and Rechargeable Batteries

F Tablet for Physiology Monitoring

G Electrode Reference Photo

b

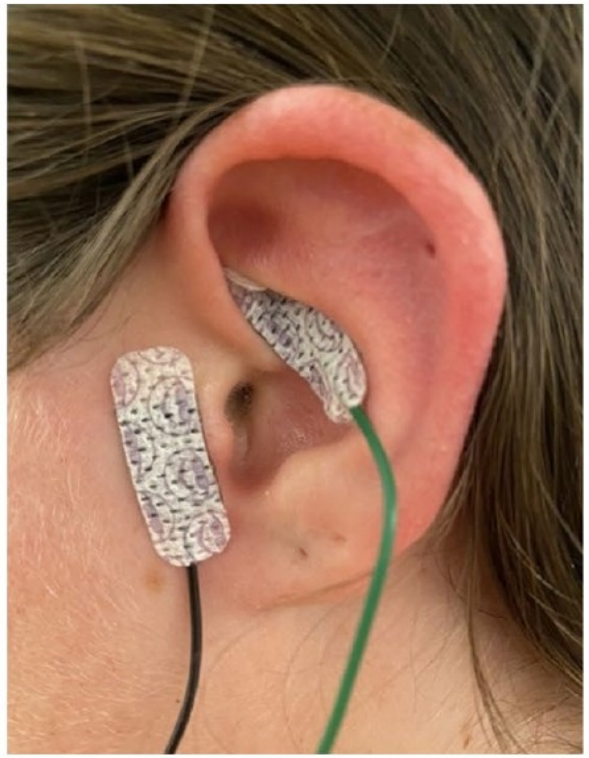


Fig. 2 Overview of Stimulation Methodology. **A** we created an at-home taVNS kit that included all the components required to safely self-administer taVNS, as well as real-time monitor safety via physio monitoring. **B** taVNS was administered to participant's left ear, with the anode placed on the cymba conchae of the ear, and the cathode on the tragus

Vagus Nerve Stimulation

Case Study #2

- 65 year-old-male
- Retired Chiropractor
- Fatigue and low stamina since moderate to severe COVID-19
- Hyperacusis
- Tinnitus
- General body sensitivity – “Feels like nerves are frayed.”
- Can’t drive
- Moving eyes and head feels strange
- Low libido
- Left side of face gets tight
- Hypertension – 6 years
- Anxiety – 25 years
- Klonopin - 25 years, anxiety
- Zyprexa – 15 years, anxiety
- Gabapentin 1 year, anxiety
- Bystolic - BP
- Benicar - BP
- Spironolactone - BP
- Amlodipine – BP
- CPAP machine for sleep apnea
- Mediterranean/Low Carb diet
- 50% of normal exercise
- Sleeps 7 hours – unrefreshing
- Lack of nature exposure

Case Study #2

- Stressful period - 15-year-old dog bladder cancer
- Marriage stress
- Black mold in home in crawl space within the last 6 months
- ACE score = 3

- Cardiologist ordered Spirometry:
- FVC--2.49 (Predicted %- 61%)
- FEV1--1.85 (Predicted % 59%)
- FEF 25-75%--1.4 (Predicted % 42 %)
- The spirometry test results revealed moderately restricted

Case Study #2

- Neurologist opinion:
- Past COVID Infection---->Significant Stress-----> Reactivation of Latent Virus (Herpes 6 and Epstein Barr virus)----->Facial Nerve Dysfunction------>Compromised Stapedial Reflex----->Hyperacusis

Complement C3a

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Complement C3a** [01]	**205.3**	**High**		ng/mL	54.0-202.0

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Tryptase

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Tryptase [01]	6.2			ug/L	2.2-13.2

Complement C4a

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Complement C4a** [01]	**5228.4**	**High**		ng/mL	0.0-650.0

Results verified by repeat testing
Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Cytomegalovirus (CMV) Ab, IgG

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Cytomegalovirus (CMV) Ab, IgG** [01]	**>10.00**	**High**		U/mL	0.00-0.59

Negative	<0.60
Equivocal	0.60 - 0.69
Positive	>0.69

	Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
	LDL Particle Number [01]						
▲	**LDL-P** [A, 01]	**1785**	**High**	**2403**	04/08/2022	nmol/L	<1000
					Low	< 1000	
					Moderate	1000 - 1299	
					Borderline-High	1300 - 1599	
					High	1600 - 2000	
					Very High	> 2000	
	Lipids [01]						
▲	**LDL-C (NIH Calc)** [01]	**134**	**High**	**164**	04/08/2022	mg/dL	0-99
					Optimal	< 100	
					Above optimal	100 - 129	
					Borderline	130 - 159	
					High	160 - 189	
					Very high	> 189	
▼	**HDL-C** [A, 01]	**37**	**Low**	**36**	04/08/2022	mg/dL	>39
▲	**Triglycerides** [A, 01]	**152**	**High**	147	04/08/2022	mg/dL	0-149
	Cholesterol, Total [A, 01]	198		**227**	04/08/2022	mg/dL	100-199
	LDL and HDL Particles [01]						
▼	**HDL-P (Total)** [A, 01]	**25.9**	**Low**	**23.2**	04/08/2022	umol/L	>=30.5
▲	**Small LDL-P** [A, 01]	**771**	**High**	**1402**	04/08/2022	nmol/L	<=527
	LDL Size [A, 01]	21.0		20.7	04/08/2022	nm	>20.5

** INTERPRETATIVE INFORMATION**
PARTICLE CONCENTRATION AND SIZE

	<--Lower CVD Risk		Higher CVD Risk-->	
LDL AND HDL PARTICLES	Percentile in Reference Population			
HDL-P (total)	High	75th	50th	25th	Low
	>34.9	34.9	30.5	26.7	<26.7
Small LDL-P	Low	25th	50th	75th	High
	<117	117	527	839	>839
LDL Size	<-Large (Pattern A)->		<-Small (Pattern B)->	
	23.0	20.6	20.5	19.0	

NMR LipoProfile+Lipids+IR+Gph (Cont.)

▲	**Small LDL-P** [A, 01]	**771**	**High**	**1402**	04/08/2022	nmol/L	<=527
▼	**Large HDL-P** [A, 01]	**<1.3**	**Low**	**<1.3**	04/08/2022	umol/L	>=4.8
	VLDL Size [A, 01]	40.7		45.2	04/08/2022	nm	<=46.6
	LDL Size [A, 01]	21.0		**20.7**	04/08/2022	nm	>=20.8
▼	**HDL Size** [A, 01]	**8.2**	**Low**	**8.3**	04/08/2022	nm	>=9.2
	Insulin Resistance Score [01]						
▲	**LP-IR Score** [A, 01]	**57**	**High**	**55**	04/08/2022		<=45

INSULIN RESISTANCE / DIABETES RISK MARKERS

<--Insulin Sensitive Insulin Resistant-->

Percentile in Reference Population

Large VLDL-P	Low	25th	50th	75th	High
	<0.9	0.9	2.7	6.9	>6.9
Small LDL-P	Low	25th	50th	75th	High
	<117	117	527	839	>839
Large HDL-P	High	75th	50th	25th	Low
	>7.3	7.3	4.8	3.1	<3.1
VLDL Size	Small	25th	50th	75th	Large
	<42.4	42.4	46.6	52.5	>52.5
LDL Size	Large	75th	50th	25th	Small
	>21.2	21.2	20.8	20.4	<20.4
HDL Size	Large	75th	50th	25th	Small
	>9.6	9.6	9.2	8.9	<8.9
Insulin Resistance Score					
LP-IR SCORE	Low	25th	50th	75th	High
	<27	27	45	63	>63

Lipid Panel w/ Chol/HDL Ratio

	Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
	Cholesterol, Total [01]	195		**247**	02/03/2023	mg/dL	100-199
	Triglycerides [01]	144		**168**	02/03/2023	mg/dL	0-149
▼	**HDL Cholesterol** [01]	**37**	**Low**	41	02/03/2023	mg/dL	>39
	VLDL Cholesterol Cal	26		31	02/03/2023	mg/dL	5-40
▲	**LDL Chol Calc (NIH)**	**132**	**High**	**175**	02/03/2023	mg/dL	0-99
▲	**T. Chol/HDL Ratio**	**5.3**	**High**			ratio	0.0-5.0
	Please Note: [01]						

T. Chol/HDL Ratio

	Men	Women

HHV 6 IgG Antibodies **8.85** **High** index 01

Negative	<0.76
Equivocal	0.76 - 0.99
Positive	>0.99

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

OmegaCheck(TM) (EPA+DPA+DHA) (Cont.)

Relative Risk: LOW
Increasing blood levels of long-chain n-3 fatty acids are associated with a lower risk of sudden cardiac death (1). Based on the top (75th percentile) and bottom (25th percentile) quartiles of the CHL reference population, the following risk categories were established for OmegaCheck: A cut-off of >=5.5% by wt defines a population at low relative risk, 3.8-5.4% by wt defines a population at moderate relative risk, and <=3.7% by wt defines a population at high relative risk of sudden cardiac death. The totality of the scientific evidence demonstrates that when consumption of fish oils is limited to 3 g/day or less of EPA and DHA, there is no significant risk for increased bleeding time beyond the normal range. A daily dosage of 1 gram of EPA and DHA lowers the circulating triglycerides by about 7-10% within 2 to 3 weeks. (Reference: 1-Albert et al. NEJM. 2002; 346: 1113-1118).

▼	**Arachidonic Acid/EPA Ratio** 02	**3.3**	**Low**	**3.0**	02/25/2022		3.7-40.7
	Omega-6/Omega-3 Ratio 02	4.0		3.8	02/25/2022		3.7-14.4
	Omega-3 total 02	8.7		9.2	02/25/2022	% by wt	
▲	**EPA** 02	**2.5**	**High**	**2.9**	02/25/2022	% by wt	0.2-2.3
	DPA 02	1.3		1.1	02/25/2022	% by wt	0.8-1.8
	DHA 02	4.9		**5.2**	02/25/2022	% by wt	1.4-5.1
	Omega-6 total 02	34.5		34.8	02/25/2022	% by wt	
	Cleveland HeartLab measures a number of omega-6 fatty acids with AA and LA being the two most abundant forms reported.						
▼	**Arachidonic Acid** 02	**8.2**	**Low**	8.7	02/25/2022	% by wt	8.6-15.6
	Linoleic Acid 02	24.0		24.5	02/25/2022	% by wt	18.6-29.5

EBV Antibody Profile

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
EBV Ab VCA, IgM [01]	<36.0		U/mL	0.0-35.9
			Negative <36.0	
			Equivocal 36.0 - 43.9	
			Positive >43.9	
▲ **EBV Ab VCA, IgG** [01]	**119.0 High**		U/mL	0.0-17.9
			Negative <18.0	
			Equivocal 18.0 - 21.9	
			Positive >21.9	
▲ **EBV Nuclear Antigen Ab, IgG** [01]	**57.4 High**		U/mL	0.0-17.9
			Negative <18.0	
			Equivocal 18.0 - 21.9	
			Positive >21.9	
Interpretation: [01]				

EBV Interpretation Chart

Key: Antibody Present +	Antibody Absent -		
Interpretation	VCA-IgM	VCA-IgG	EBNA-IgG
No previous infection/ Susceptible	-	-	-
Primary infection (new or recent)	+	+	-
Past Infection	+or-	+	+
See comment below*	+	-	-

EBV Early Antigen Ab, IgG

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **EBV Early Antigen Ab, IgG** [01]	**32.7 High**		U/mL	0.0-8.9
			Negative < 9.0	
			Equivocal 9.0 - 10.9	
			Positive >10.9	

Testosterone, Free/Tot Equilib

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Testosterone [01]	348		ng/dL	264-916
	Adult male reference interval is based on a population of healthy nonobese males (BMI <30) between 19 and 39 years old. Travison, et.al. JCEM 2017,102;1161-1173. PMID: 28324103.			
Testosterone,Free	9.29		ng/dL	5.00-21.00
% Free Testosterone [01]	2.67	2.99 07/29/2022	%	1.50-4.20

Apo A1 + B + Ratio

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Apolipoprotein A-1 [01]	117	110 04/08/2022	mg/dL	101-178
▲ **Apolipoprotein B** [01]	**125** **High**	**140** 04/08/2022	mg/dL	<90
		Desirable < 90 Borderline High 90 - 99 High 100 - 130 Very High >130		
		ASCVD RISK CATEGORY / THERAPEUTIC TARGET APO B (mg/dL) Very High Risk: <80 (if extreme risk <70) High Risk: <90 Moderate Risk: <90		
▲ **Apolipo. B/A-1 Ratio**	**1.1** **High**	**1.3** 04/08/2022	ratio	0.0-0.7
		Apolipoprotein B/A-1 Ratio Male / Female Avg.Risk 0.7 / 0.6 2X Avg.Risk 0.9 / 0.9 3X Avg.Risk 1.0 / 1.0		

Prolactin

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Prolactin [01]	8.4		ng/mL	4.0-15.2

Estradiol

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Estradiol [01]	10.5 Roche ECLIA methodology	**<5.0** 07/29/2022	pg/mL	7.6-42.6

Vitamin B6, Plasma

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **Vitamin B6** [A, 01]	**90.4** **High**	**180.7** 07/29/2022 Deficiency: Marginal: Adequate:	ug/L <3.4 3.4 - 5.1 >5.1	3.4-65.2

Reverse T3, Serum

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **Reverse T3, Serum** [B, 01]	**30.9** **High**		ng/dL	9.2-24.1

Lipoprotein (a)

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **Lipoprotein (a)** [01]	**223.8** **High**	**198.2** 04/08/2022	nmol/L	<75.0

	CBC, Platelet Ct, and Diff [01]						
	WBC [01]	4.6		4.3	08/02/2022	x10E3/uL	3.4-10.8
▲	**RBC** [01]	**6.49**	**High**	**6.21**	08/02/2022	x10E6/uL	4.14-5.80
▼	**Hemoglobin** [01]	**12.8**	**Low**	**11.9**	08/02/2022	g/dL	13.0-17.7
	Hematocrit [01]	41.8		41.7	08/02/2022	%	37.5-51.0
▼	**MCV** [01]	**64**	**Low**	**67**	08/02/2022	fL	79-97
▼	**MCH** [01]	**19.7**	**Low**	**19.2**	08/02/2022	pg	26.6-33.0
▼	**MCHC** [01]	**30.6**	**Low**	**28.5**	08/02/2022	g/dL	31.5-35.7
▲	**RDW** [01]	**18.2**	**High**	**18.7**	08/02/2022	%	11.6-15.4
	Platelets [01]	215		210	08/02/2022	x10E3/uL	150-450
	Neutrophils [01]	68		52	08/02/2022	%	Not Estab.
	Lymphs [01]	24		36	08/02/2022	%	Not Estab.
	Monocytes [01]	6		9	08/02/2022	%	Not Estab.
	Eos [01]	1		2	08/02/2022	%	Not Estab.
	Basos [01]	1		1	08/02/2022	%	Not Estab.

TMAO (Trimethylamine N-oxide)

Test	Current Result and Flag	Previous Result and Date		Units	Reference Interval
TMAO (Trimethylamine N-oxide) [A, 01]	<3.3	**25.0**	04/08/2022	uM	<6.2

TMAO Medical Decision Limits

Low	<6.2
Moderate	6.2 - 9.9
High	>9.9

▲	**Glucose** [01]	**102**	**High**	98*	08/02/2022	mg/dL	70-99
	Uric Acid [01]	5.0		4.8	08/02/2022	mg/dL	3.8-8.4
				Therapeutic target for gout patients: <6.0			
	BUN [01]	16		13	08/02/2022	mg/dL	8-27
	Creatinine [01]	0.99		0.88	08/02/2022	mg/dL	0.76-1.27
	eGFR	85		95	08/02/2022	mL/min/1.73	>59
	BUN/Creatinine Ratio	16		15	08/02/2022		10-24
	Sodium [01]	140		142	08/02/2022	mmol/L	134-144
	Potassium [01]	4.0		4.2	08/02/2022	mmol/L	3.5-5.2
	Chloride [01]	97		101	08/02/2022	mmol/L	96-106
	Carbon Dioxide, Total [01]	26		25	08/02/2022	mmol/L	20-29
	Calcium [01]	9.2		9.3	08/02/2022	mg/dL	8.6-10.2
	Phosphorus [01]	3.6		3.3	08/02/2022	mg/dL	2.8-4.1
	Magnesium [01]	2.2		2.1	08/02/2022	mg/dL	1.6-2.3
	Protein, Total [01]	7.4		7.0	08/02/2022	g/dL	6.0-8.5
▲	**Albumin** [01]	**5.1**	**High**	4.8	08/02/2022	g/dL	3.8-4.8
	Globulin, Total	2.3		2.2	08/02/2022	g/dL	1.5-4.5
	A/G Ratio	2.2		2.2	08/02/2022		1.2-2.2
	Bilirubin, Total [01]	0.4		0.5	08/02/2022	mg/dL	0.0-1.2
	Alkaline Phosphatase [01]	67		56	08/02/2022	IU/L	44-121
	LDH [01]	145		136	08/02/2022	IU/L	121-224
	AST (SGOT) [01]	17		20	08/02/2022	IU/L	0-40
	ALT (SGPT) [01]	16		19	08/02/2022	IU/L	0-44
	GGT [01]	18		15	08/02/2022	IU/L	0-65
	Iron Bind.Cap.(TIBC)	412		404	08/02/2022	ug/dL	250-450
	UIBC [01]	297		307	08/02/2022	ug/dL	111-343
	Iron [01]	115		97	08/02/2022	ug/dL	38-169
	Iron Saturation	28		24	08/02/2022	%	15-55
	Ferritin [01]	55		69	08/02/2022	ng/mL	30-400

EXAM: CT-Heart, without contrast, eval of coronary calcium

REASON FOR EXAM: screening

TECHNIQUE: Utilizing a multi-slice CT scanner, EKG-gated spiral acquisitions of the heart were obtained. These generally provide limited views of the lungs and upper abdomen.

FINDINGS: CT coronary calcium score of 240. Contributions from the LM, RCA, LAD, and CX of 7, 107, 107, and 19, respectively.

No significant paracardiac lung findings. Normal heart size.

Calcium Score	Implication	Risk of Coronary Artery Disease
0	No identifiable plaque	Very low, generally less than 5 percent
1-10	Minimal identifiable plaque	Very unlikely, less than 10 percent
11-100	Definite, at least mild atherosclerotic plaque	Mild or minimal coronary narrowings likely.
101-400	Definite, at least moderate atherosclerotic plaque	Mild coronary artery disease highly likely, significant narrowings possible
401 or Higher	Extensive atherosclerotic plaque	High likelihood of at least one significant coronary narrowing

[1] Callister TQ et. al., Coronary Artery Calcium Scores on Electronic Computed Tomography: JACC 1999; 33 (Supl): 415A
[2] Mayo Clinic Proceedings, March 1999, Vol. 74. Findings based E8CT data.
[3] Carr JJ, et. al., Evaluation of Subsecond Gated Helical CT for Quantification of Coronary Artery Calcium and Comparison with Electron Beam CT.: AJR 2000; 174: 915-921

IMPRESSION: Coronary atherosclersis. Calcium score of 240.

Premier Radiology

Study read by DANIEL WUNDER

PROCEDURE: CARDIAC CT FOR CORONARY ARTERY CALCIUM SCORING

TECHNIQUE: Multi-detector computed tomography of the heart was performed during suspended respiration, and without the administration of contrast material. Post-processing was performed on a workstation to measure the amount of coronary vascular calcium. Techniques to minimize radiation exposure, such as automated exposure control, adjustment of mA and/or kV according to patient size, or iterative reconstruction, are utilized, when appropriate, to reduce radiation dose to as low as reasonably achievable. CPT G9637, 75571

HISTORY: Essential (primary) hypertension I10 Essential (primary) hypertension, Z13.6

COMPARISON: None

RESULTS:

Thorax: No significant abnormalities identified in the lungs or mediastinum. Note that the CT examination is limited to the heart and the adjacent lung and mediastinum.

CALCIUM SCORING:

Left main coronary artery (LMCA): 13.83

Left anterior descending artery (LAD): 83.68

Circumflex artery: 24.32

Right coronary artery (RCA): 73.91

TOTAL AGATSTON SCORE: 195.74

EXAM: MR-Brain without contrast

REASON FOR EXAM: tinniitus

ADDITIONAL HISTORY: Tinnitus, hypertension, hyperacusis.

COMPARISON: MRI brain 03/02/2012.

TECHNIQUE: Multiplanar T1-weighted and T2-weighted images of the brain supplemented with more specialized pulse sequences were obtained unenhanced.

FINDINGS:
There are several tiny foci of FLAIR hyperintensity within the periventricular white matterwhich have developed since the previous MRI.

The thalami, brainstem, and cerebellum are unremarkable. 7.5 mm AP by 5.5 mm transverse site of chronic, cystic lacunar infarction within the cephalad aspect of the right putamen(basal ganglia). This was not present on the prior study and has occurred in the interim.

The ventricular system is normal. There are no abnormal extra-axial fluid collections.

There is no evidence of acute infarction, intracranial hemorrhage, mass effect, or midline shift.

Sellar and parasellar areas are normal.

Craniocervical junction is normal.

Normal flow voids at the base of the brain.

Orbits are unremarkable.

7th-8th cranial nerve complexes and cerebellopontine angles are normal. Unremarkable vestibulocochlear structures. No IAC or CP angle tumor. No aberrant ICA. Normal evaluation of the

MRI continued

jugular foramina.

No foci of restricted diffusion.

No otomastoiditis. No acute sinusitis. Mild thickening of the mucosa within the ethmoid air cells.

Unremarkable TMJs.

CONCLUSION: Imaging findings in this age group with high blood pressure are most likely due to chronic microvascular disease/small vessel arteriopathy. No appreciable temporal bone abnormality

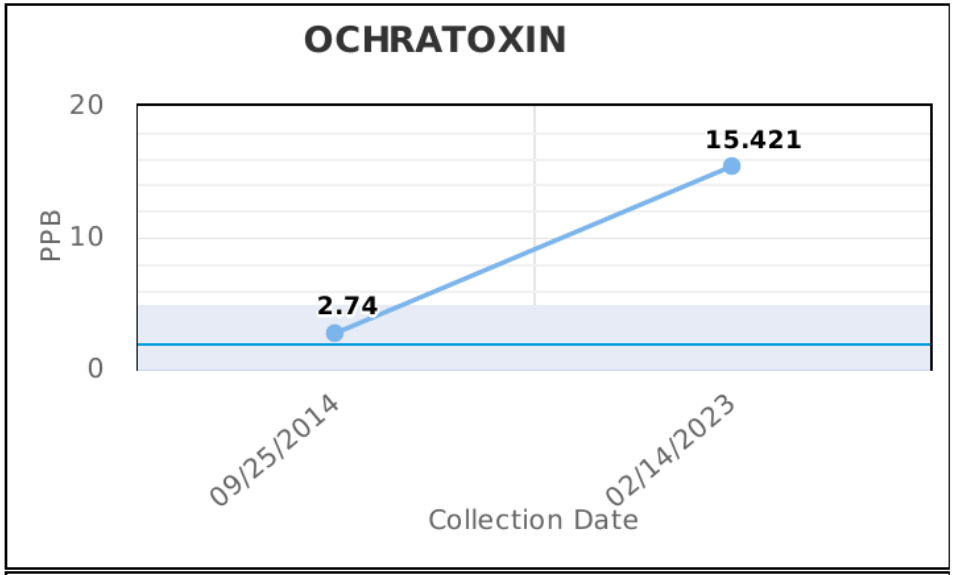
Procedure Type: Semi-quantitative procedure by ELISA

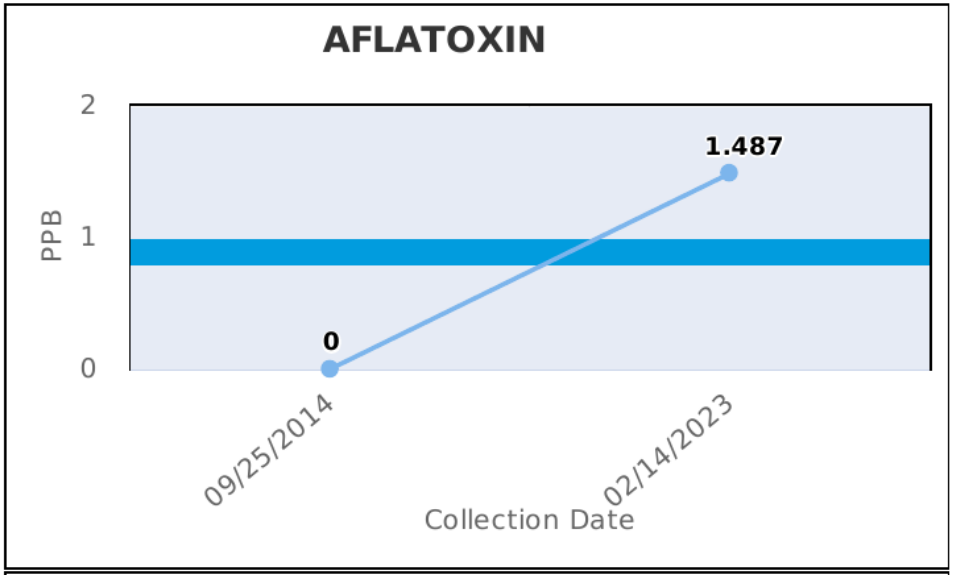
List of Mycotoxins tested in the Panel
Ochratoxin A - Procedure by ELISA
Aflatoxin Group: (B1, B2, G1, G2) - Procedure by ELISA
Trichothecene Group (Macrocyclic): Roridin A, Roridin E, Roridin H, Roridin L-2, Verrucarin A, Verrucarin J, Satratoxin G, Satratoxin H, Isosatratoxin F - Procedure by ELISA
Gliotoxin Derivative - Procedure by ELISA
Zearalenone - Procedure by ELISA

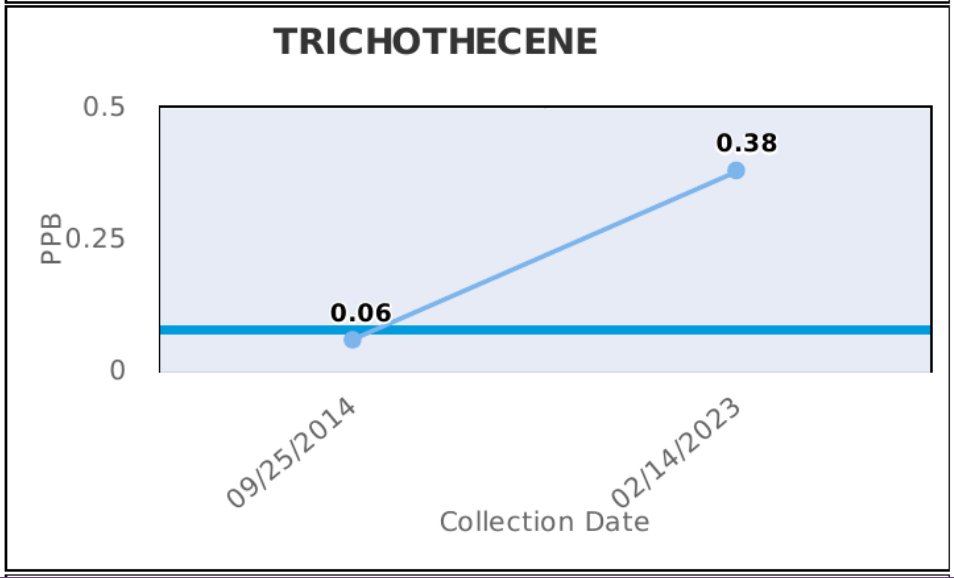
Results:

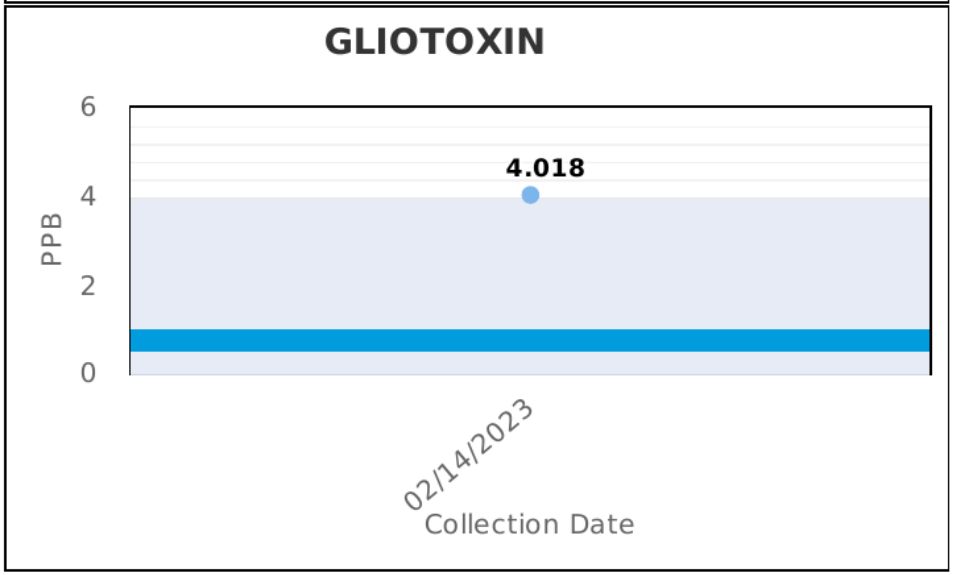
Code	Test	Specimen	Value	Result	Not Present if less than	Equivocal if between	Present if greater or equal
E8501	Ochratoxin A	Urine	15.42100 ppb	Present	1.8 ppb	1.8-2 ppb	2 ppb
E8502	Aflatoxin Group: (B1, B2, G1, G2)	Urine	1.48700 ppb	Present	0.8 ppb	0.8-1 ppb	1 ppb
E8503	Trichothecene Group (Macrocyclic): Roridin A, Roridin E, Roridin H, Roridin L-2, Verrucarin A, Verrucarin J, Satratoxin G, Satratoxin H, Isosatratoxin F	Urine	0.38000 ppb	Present	0.07 ppb	0.07-0.09 ppb	0.09 ppb
E8510	Gliotoxin Derivative	Urine	4.01800 ppb	Present	0.5 ppb	0.5-1.0 ppb	1.0 ppb
E8512	Zearalenone	Urine	2.95600 ppb	Present	0.5 ppb	0.5-0.7 ppb	0.7 ppb

Historical Results:









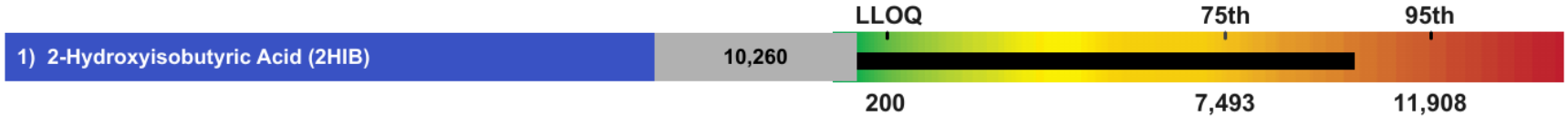
Mycotox Profile

Creatinine Value: 110.73 mg/dl

Metabolite	Results (ng/g creatinine)	Normal Range *	Abnormal Range
Aspergillus			
Aflatoxin-M1	11.48	< 0.5	▲ 0.5
Ochratoxin A	0.00	< 7.5	▲ 7.5
Gliotoxin	0.00	< 200	▲ 200

Metabolite	Result µg/g creatinine	Percentile

Industrial Toxicants



Parent: MTBE/ETBE

MTBE and ETBE are gasoline additives used to improve octane ratings. Exposure to these compounds is most likely due to groundwater contamination, inhalation or skin exposure to gasoline or its vapors, and exhaust fumes. MTBE has been demonstrated to cause hepatic, kidney, and central nervous system toxicity, peripheral neurotoxicity, and cancer in animals. Very high values have been reported in genetic disorders. Because the metabolites of these compounds are the same, ETBE may be similarly toxic.

Parent: Diethylphthalates

Phthalates may be the most widespread group of toxins in our environment, commonly found in many bath and beauty products, cosmetics, perfumes, oral pharmaceuticals, insect repellants, adhesives, inks, and varnishes. Phthalates have been implicated in reproductive damage, depressed leukocyte function, and cancer. Phthalates have also been found to impede blood coagulation, lower testosterone, and alter sexual development in children. Low levels of phthalates can feminize the male brain of the fetus, while high levels can hyper-masculinize the developing male brain.

Parent: Xylene

Xylenes (dimethylbenzenes) are found not only in common products such as paints, lacquers, pesticides, cleaning fluids, fuel and exhaust fumes, but also in perfumes and insect repellents. Xylenes are oxidized in the liver and bound to glycine before eliminated in urine. High exposures to xylene create an increase in oxidative stress, causing symptoms such as nausea, vomiting, dizziness, central nervous system depression, and death. Occupational exposure is often found in pathology laboratories where xylene is used for tissue processing.

Digestion / Absorption	Result	Unit	Reference Interval
Elastase	148	µg/mL	> 200
Fat Stain	Few		None – Moderate
Carbohydrates†	Negative		Negative – Intermediate

Inflammation	Result	Unit	Reference Interval
Lactoferrin	1.0	µg/mL	< 7.3
Calprotectin	<5	µg/g	≤ 50
Lysozyme*	244	ng/mL	≤ 500

Immunology	Result	Unit	Reference Interval
Secretory IgA*	44.2	mg/dL	30 – 275

Short Chain Fatty Acids	Result	Unit	Reference Interval
% Acetate‡	48	%	50 – 72
% Propionate‡	30	%	11 – 25
% Butyrate‡	17	%	11 – 32
% Valerate‡	5.0	%	0.8 – 5.0
Butyrate‡	1.6	mg/mL	0.8 – 4.0
Total SCFA's‡	9.4	mg/mL	5.0 – 16.0

Intestinal Health Markers	Result	Unit	Reference Interval
pH	6.7		5.8 – 7.0
Occult Blood	Negative		Negative – Intermediate

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS

Lyme ImmunoBlot IgM Serum
IGX Criteria: **Positive**
CDC/NYS Criteria: Negative
***
[REVISED REPORT: EFFECTIVE APRIL 10, 2019]

Lyme ImmunoBlot IgM detects antibodies to B. burgdorferi strains and species

Band (kDa)	**23***	**31***	**34***	**39***	**41***	**93**
Intensity	**+**	**+**	**+**	**-**	**IND**	**-**

Band Intensity: Positive: + to ++++, Indeterminate: Ind, Negative: (-)

INTERPRETATION	**IGX CRITERIA**	**CDC/NYS CRITERIA**
Positive	2 or more of the starred bands are present (+): 23*, 31*, 34*, 39*, 41* kDa	2 or more of the following bands are present (+): 23*, 39*, 41* kDa
Negative	Does not meet IGX criteria for a positive.	Does not meet CDC/NYS criteria for a positive.

LIMITATION: Bands 31* and 34* kDa are present in Lyme vaccinated patients. Viral antibodies cross react with the 93 kDa antigen.

Supplements – Self + Cardiologist

- CoQ10
- ALA
- Garlic
- Mixed tocopherols and tocotrienols
- Astaxanthin
- Bergamot
- Silymarin
- Pantethine
- Pomegranate
- Lycopene
- Quercetin
- Resveratrol
- EPA/DHA
- DHEA 25 mg
- Metal detox product
- Shilajit + LongJax
- Inositol
- TMG
- B12/folate
- Pycnogenol
- Acetyl-l-carnitine, carnitine
- Carnosine
- Magnesium
- Pro-resolving mediators
- Curcumin
- Niacin
- Plant sterols
- Olive leaf extract
- Lumbrokinase/Nattokinase/Serrapeptase
- Berberine
- Green tea
- Vitamin D
- Grape seed extract
- Bonito peptide powder
- Gut repair blend
- L-proline
- L-lysine
- Phosphatidylcholine

Supplementation - Hedberg

- Magnesium-l-threonate 144 mg/day
- NAC 700 mg tid
- Liposomal Glutathione 2 tsp/day
- Probiotics – Bacillus species
- Gingko biloba 120 mg bid
- Korean ginseng tincture
- PEA 600 mg bid + Luteolin 100 mg bid
- Monolaurin protocol

Treatment Plan

- Limbic System Retraining – Gupta Program
- Vagus nerve stimulation - GammaCore
- Microcirculation strategies
- Local Table Tennis Club
- Increase nature exposure
- Hyperbaric Oxygen Therapy

frontiers in Nutrition

ORIGINAL RESEARCH
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Oral Bacteriotherapy Reduces the Occurrence of Chronic Fatigue in COVID-19 Patients

Letizia Santinelli[1], Luca Laghi[2,3], Giuseppe Pietro Innocenti[1], Claudia Pinacchio[1],

On a total of 58 patients hospitalized for COVID-19, 24 (41.4%) received OB during hospitalization (OB+) while 34 (58.6%) taken only the standard treatment (OB–). Serum metabolomic profiling of patients has been performed at both hospital acceptance (T0) and discharge (T1). 70.7% of participants reported fatigue while 29.3% were negative for such condition. The OB+ group showed a significantly lower proportion of subjects reporting fatigue than the OB– one ($p < 0.01$). Furthermore, OB+ subjects were characterized by significantly increased concentrations of serum Arginine, Asparagine, Lactate opposite to lower levels of 3-Hydroxyisobutirate than those not treated with probiotics. Our results strongly suggest that in COVID-19, the administration of probiotics during hospitalization may prevent the development of chronic fatigue by impacting key metabolites involved in the utilization of glucose as well as in energy pathways.

Chronic Virus (EBV, CMV, HHV-6 etc.)

- Monolaurin 600 mg protocol
- Cs-4 Cordyceps: 1,000 mg tid
- Liposomal Glutathione 500 mg qd or NAC 700 mg tid
- Black Cumin Seed Oil 500 mg bid Curcumin 500 mg bid
- Resveratrol + Quercetin 225 mg bid
- Probiotic – Bacillus, Lacto/bifido blend 1 bid

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Alleviation of Post-COVID-19 Cognitive Deficits by Treatment with EGb 761®: A Case Series

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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In many studies, EGb 761(Gingko biloba) has been demonstrated to protect endothelial cells, to have potent anti-inflammatory effects, and to enhance neuroplasticity. CASE REPORT Here, we report for the first time the application of EGb 761 in the therapy of post-COVID-19-related cognitive deficits. Three women and 2 men, aged 26 to 59 years (average age 34.6 years), presented with concentration and attention deficits, cognitive deficiencies, and/or fatigue 9-35 weeks after infection. A daily dose of 2×80 mg of EGb 761 did not cause any detectable adverse effects, and it substantially improved or completely restored cognitive deficits and, when initially present, also other symptoms, such as fatigue and hyposmia, within an observation period of up to 6 months.

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Hindawi

Research Article

Ginkgo Biloba Ameliorates Subfertility Induced by Testicular Ischemia/Reperfusion Injury in Adult Wistar Rats: A Possible New Mitochondrial Mechanism

This study demonstrates histopathological and physiological effects of testicular ischemia/perfusion (I/R) injury and the possible protective effects of Ginkgo biloba treatment. Plasma-free testosterone was significantly decreased, while plasma FSH, TNF-α, IL-1β, and testicular mitochondrial NAD+ were significantly increased in I/R group compared to control group. These parameters were reversed in Gingko biloba treated I/R group compared to I/R group. I/R caused marked testicular damage and increased APAF-1 in the apoptotic cells which were reversed by Ginkgo biloba treatment. Also, testicular injury could be reduced by Gingko biloba administration alone.

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Co-ultramicronized palmitoylethanolamide/luteolin normalizes $GABA_B$-ergic activity and cortical plasticity in long COVID-19 syndrome

Transcranial magnetic stimulation (TMS) studies showed that patients with cognitive dysfunction and fatigue after COVID-19 exhibit impaired cortical GABAB-ergic activity, as revealed by reduced long-interval intracortical inhibition (LICI). Aim of this study was to test the effects of co-ultramicronized palmitoylethanolamide/luteolin (PEA-LUT), an endocannabinoid-like mediator able to enhance GABA-ergic transmission and to reduce neuroinflammation, on LICI.

Methods: Thirty-nine patients (26 females, mean age 49.9 ± 11.4 years, mean time from infection 296.7 ± 112.3 days) suffering from persistent cognitive difficulties and fatigue after mild COVID-19 were randomly assigned to receive either PEA-LUT 700 mg + 70 mg or PLACEBO, administered orally bid for eight weeks.

Conclusions: Eight weeks of treatment with PEA-LUT restore GABAB activity and cortical plasticity in long Covid patients.

Significance: This study confirms altered physiology of the motor cortex in long COVID-19 syndrome and indicates PEA-LUT as a candidate for the treatment of this post-viral condition.

medical sciences

MDPI

Article

The Use of Palmitoylethanolamide in the Treatment of Long COVID: A Real-Life Retrospective Cohort Study

Loredana Raciti [1], Rosaria De Luca [2], Gianfranco Raciti [1], Francesca Antonia Arcadi [2] and Rocco Salvatore Calabrò [2,*]

Palmitoylethanolamide (PEA) is a naturally occurring lipid mediator that has an entourage effect on the endocannabinoid system mitigating the cytokine storm. The aim of this retrospective study is to evaluate the potential efficacy of PEA in the treatment of long COVID. We included only long COVID patients who were treated with PEA 600 mg two times daily for about 3 months. A substantial difference in the PCFS score between the two groups at baseline and after treatment with PEA were found. Our findings encourage the use of PEA as a potentially effective therapy in patients with long COVID.

cells

MDPI

Article

Effect of Ultra-Micronized Palmitoylethanolamide and Luteolin on Olfaction and Memory in Patients with Long COVID: Results of a Longitudinal Study

Pietro De Luca [1,2], Angelo Camaioni [2], Pasquale Marra [1], Giovanni Salzano [3], Giovanni Carriere [4], Luca Ricciardi [5], Resi Pucci [6,7], Nicola Montemurro [8], Michael J. Brenner [9] and Arianna Di Stadio [10,11,*]

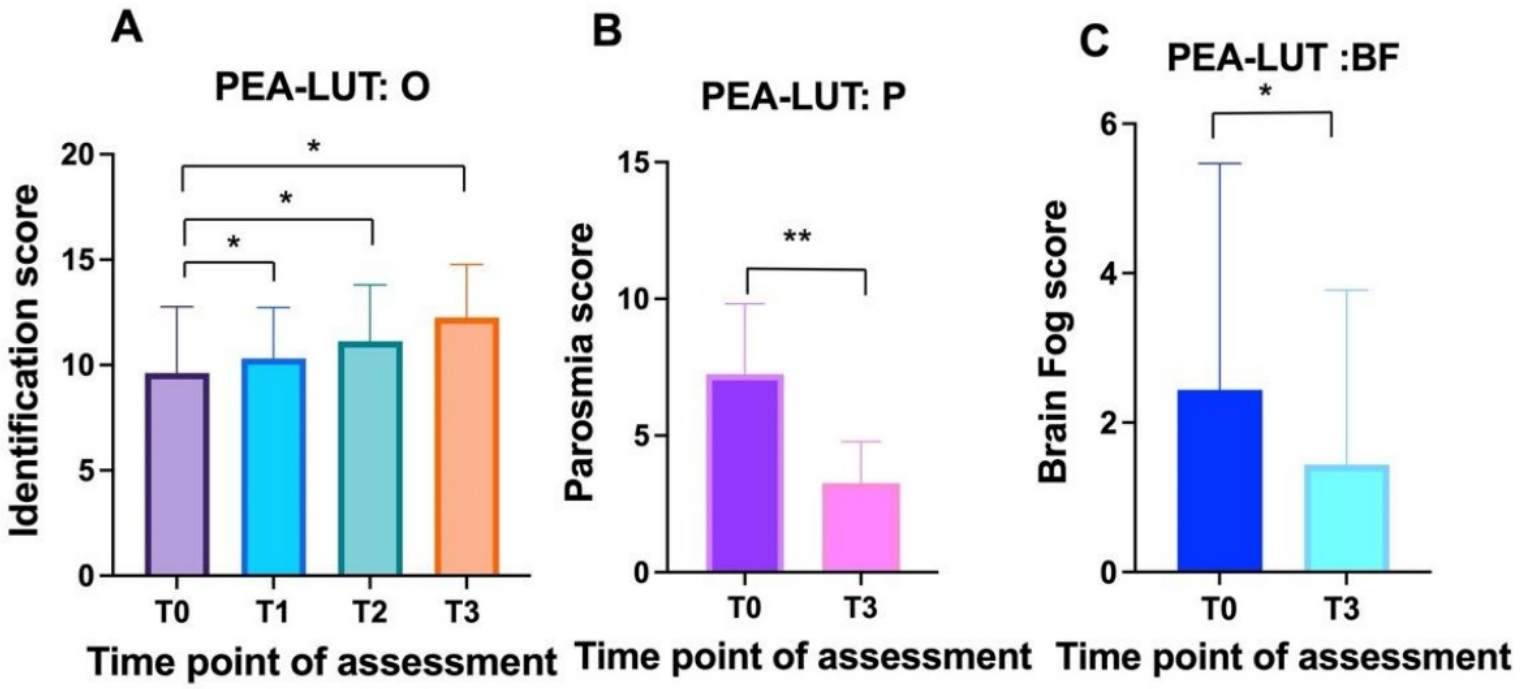

Figure 5. Effect of PEA-LUT treatment without olfactory training on olfaction, parosmia, and mental clouding in patients without prior olfactory training (Naïve 2 group): (**A**) O (olfaction) results of identification test at T0 (baseline), T1 (1 month), T2 (2 months), and T3 (3 months); (**B**) P (parosmia) before (T0) and after three months (T3) of treatment; (**C**) BF (brain fog/mental clouding) before (T0) and after three months (T3) of treatment. **: $p < 0.01$; *: $p < 0.05$.

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Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial

Seventy-three patients were randomized to receive daily 40 session of HBOT (n = 37) or sham (n = 36). Following HBOT, there was a significant group-by-time interaction in global cognitive function, attention and executive function. Significant improvement was also demonstrated in the energy domain, sleep, psychiatric symptoms, and pain interference. Clinical outcomes were associated with significant improvement in brain MRI perfusion and microstructural changes in the supramarginal gyrus, left supplementary motor area, right insula, left frontal precentral gyrus, right middle frontal gyrus, and superior corona radiate. These results indicate that HBOT can induce neuroplasticity and improve cognitive, psychiatric, fatigue, sleep and pain symptoms of patients suffering from post-COVID-19 condition. HBOT's beneficial effect may be attributed to increased brain perfusion and neuroplasticity in regions associated with

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IOS Press

Non-invasive brain microcurrent stimulation therapy of long-COVID-19 reduces vascular

Two female long-COVID patients were treated for 10-13 days with alternating current stimulation of the eyes and brain. While one patient (age 40) was infected with the SARS CoV-2 virus, the other (age 72) developed symptoms following AstraZeneca vaccination. One patient was also tested with a cognitive test battery and with a retinal dynamic vascular analyser (DVA), a surrogate marker of vascular dysregulation in the brain.

Results: In both patients NIBS markedly improved cognition and partially reversed visual field loss within 3-4 days. Cognitive tests in one patient confirmed recovery of up to 40-60% in cognitive subfunctions with perimetry results showing stable and visual field recovery even during follow-up. DVA showed that NIBS reduced vascular dysregulation by normalizing vessel dynamics (dilation/constriction), with particularly noticeable changes in the peripheral veins and arteries.

Conclusions: NIBS was effective in improving visual and cognitive deficits in two confirmed SARS-COV-2 patients. Because recovery of function was associated with restoration of vascular autoregulation, we propose that (i) hypometabolic, "silent" neurons are the likely biological cause of long-COVID associated visual and cognitive deficits, and (ii) reoxygenation of these "silent" neurons provides the basis for neural reactivation and neurological recovery. Controlled trials are now needed to confirm these observations.

PMID: 36700201

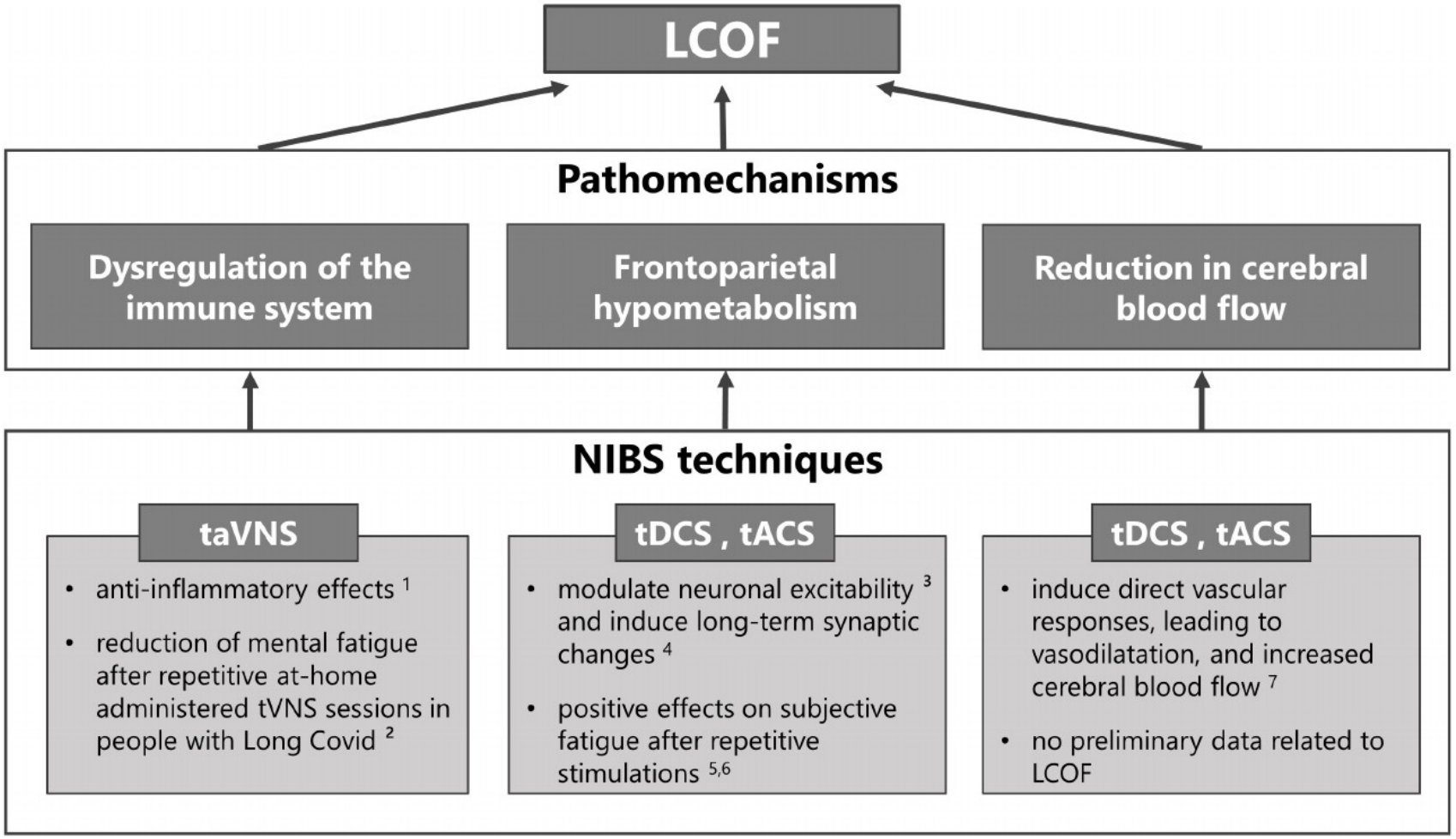

FIGURE 1
Non-invasive brain stimulation (NIBS) techniques for the treatment of individual pathomechanisms of Long-COVID-related fatigue (LCOF).

Complementary Therapies in Medicine 67 (2022) 102823

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Complementary Therapies in Medicine

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Aromatherapy blend of thyme, orange, clove bud, and frankincense boosts energy levels in post-COVID-19 female patients: A randomized, double-blinded, placebo controlled clinical trial

Jessie Hawkins *, Christy Hires, Lindsey Keenan, Elizabeth Dunne

Franklin Health Research Center, 1650 Murfreesboro Rd., Ste 245, Franklin, TN 37067, United States

Forty women were randomized to two groups: intervention and placebo. Both groups inhaled the assigned product twice daily for fourteen consecutive days.

Results: Individuals who inhaled the essential oil blend for 2 weeks had significantly lower fatigue scores after controlling for baseline scores, employment status, BMI, olfactory function, and time since diagnosis, with a large effect size. Subscale analysis identified subscales of vigor, as well as global, behavioral, general, and mental fatigue as benefiting from the intervention. This study provides evidence that a proprietary aromatherapy blend can significantly improve energy levels among women who are experiencing fatigue after recovering from COVID-19.

Long COVID Protocol

- Vitamin D+K 5-10,000 IU/day
- Resveratrol + Quercetin 225 mg bid
- Buffered C 1,000 mg bid
- NAC 700 mg tid
- L-arginine or L-citrulline 1,500 mg bid
- Black Cumin Seed Oil Softgels 1,000-3,000 mg/day or Curcumin 500 mg bid
- Melatonin .3-3 mg
- Nattokinase 100 mg bid or Bromelain 500 mg bid
- Gingko Biloba 120 mg bid
- Probiotics
- Magnesium-l-threonate 144 mg/day
- Berberine 500 mg bid
- Cod Liver Oil 1 tsp or 3 softgels/day
- Cordyceps 1,000 mg tid or Adrenal adaptogens (Panax, eleuthero, rhodiola, ashwagandha)
- PEA 600 mg bid + Luteolin 100 mg bid
- Reginator Amino Acid Blend + HMB
- Aspirin 81 mg/day

Long COVID Protocol

- Low-Histamine, anti-inflammatory diet
- Intermittent fasting
- NIBS
- Vagus Nerve Stimulation
- Limbic System Retraining – Gupta Program
- Tai Chi or Yoga
- Mindfulness meditation
- Whole body vibration therapy
- Hyperbaric Oxygen Therapy
- Microcirculation strategies

Questions?

Send email for detailed Long COVID Protocol:

drhedberg@hedberginstitute.com