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Can essential fatty acids prevent and ameliorate post-Covid-19 long haul manifestations?

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Abstract:

COVID-19, post-COVID and post-mRNA vaccine manifestations can result in "long haul syndrome". I propose that long-haul syndrome is because of deficiency of essential fatty acids (EFAs) and their metabolites. EFAs and their metabolites inactivate SARS-CoV-2 virus, suppress excess cytokine formation and action, are cytoprotective, inhibit NF-kB activation and regulate cGAS-STING pathway, influence gut microbiota and their metabolism, modulate platelet, macrophage, and leukocyte function, regulate neurotransmitters secretion and function, facilitate tissue regeneration and enhance wound healing. In view of their varied actions, it is likely that EFAs are of benefit in the prevention and management of long-haul syndrome

Keywords: long covid; long haul covid syndrome; dietary polyunsaturated lipids; essential fatty acids; efa; diet.

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Introduction

Post-covid manifestations following acute SARS-CoV-2 infection and post-CoVID-19 vaccination especially after mRNA vaccination is no uncommon. These post-Covid-19 infection and/or vaccination manifestations called as "long-haul syndrome". The importance of long-haul syndrome lies in the fact that its manifestations may last from months to years and produce significant morbidity in those who suffer from it. Long-haul manifestations include but are not limited to fatigue, post-exertional malaise, memory loss, and other neurocognitive impairments. It is estimated that about 10-20% of subjects who had SARS-CoV-2 infection and/or COVID vaccination, especially mRNA vaccine (Thaweethai, et al., 2023). The molecular etiology of post-viral syndromes, including Long COVID, remains unclear. Some of the hypotheses proposed to explain the Long-haul syndrome and the persistence of symptoms include: persistence of the virus or viral particles that continuously stimulate the immune system to produce the symptoms experienced by these people; such non-resolving infection and resultant anti-viral responses may result in tissue damage and their dysfunction; auto-antibody development; and persistent production of pro-inflammatory cytokine(s) response that results in chronic inflammation. One significant feature of post-COVID long-haul syndrome is the presence of platelet dysfunction and potential hypercoagulability state. It has also been suggested that there could occur autonomic nervous system dysfunction that may explain the features of post-COVID long-haul syndrome. But it is not clear whether all the mechanisms described occur in different subsets of patients or they occur in all those who have the long-haul syndrome and if so and why.

A recent metabolomics investigation (Wong, et al., 2023) revealed that a deficiency of serotonin occurs in post-COVID-19 long-haul syndrome that results in reduced activity of the vagus nerve, which causes hippocampal dysfunction and memory loss. It was reported that the presence of viral RNA and downstream interferon responses cause a decrease in serotonin. Some of the mechanisms that could account for the deficiency of serotonin include diminished uptake of the serotonin precursor tryptophan in the gastrointestinal tract, reduced storage in platelets due to thrombocytopenia, and enhanced turnover by serotonin-metabolizing enzymes. Peripheral serotonin deficiency can reduce the activity of the vagus nerve, which may induce hippocampal dysfunction and memory loss. These findings led to the suggestion that many of the current hypotheses for the pathophysiology of post-acute sequelae of COVID-19 (PASC-ths term is also applied to those who develop post-mRNA COVID-19 vaccination) might be interconnected. If this is true, it might lead to newer therapeutic strategies.

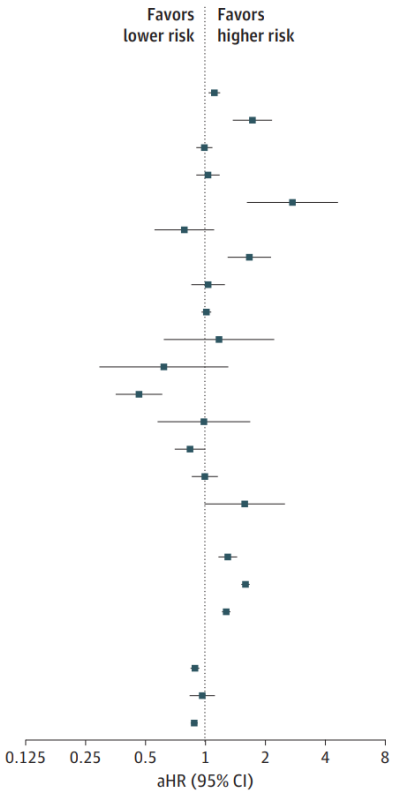
Hypotheses of PASC

Post-viral syndromes and/or post-anti-viral vaccination more particularly post-mRNA COVID-19 vaccination is known to occur in a small but significant number of individuals. Those who develop PASC suffer from a variety of symptoms (see Table 1, Lim, et al., 2023) that persist for months to years after disease onset or following vaccination. The manifestations of PASC are diverse and may include fatigue, post-exertional malaise, memory loss, and other neurocognitive impairments. One of the well recognised PASC include what is called as "*Long COVID"* which are experienced and reported by a subset of individuals after SARS-CoV-2 infection or following mRNA vaccination against COVID-19. The exact cause for these post-vial syndromes, including

Long COVID, is not known. Some of the hypotheses suggested to explain the persistence of symptoms (PASC) include but not limited to (i) the presence of a viral reservoir that is remains in the circulation or in the target issues after the initial infection; (ii) chronic inflammation, partly due to increased formation and circulation of pro-inflammatory cytokines such as IL-6 and TNF-α; (iii) auto-antibody development; and (iv) tissue damage as a result of non-resolving anti-viral responses. One common feature that has been reported with post-viral syndromes is platelet dysfunction and hypercoagulability. The possibility that long COVID or long haul (PASC) and other post-viral syndromes could be due to autonomic nervous system dysfunction has also been proposed (Al-Aly, et al., 2021; Pretorius, et al., 2021; Dani, et al., 2021; Choutka, et al., 2022; Merad, et al., 2022; Wong, et al., 2023; Lim, et al., 2023; Davis, et al., 2023). In view of the different types of conflicting proposals as to the molecular pathophysiology of long COVID and PASC, a deeper understanding of the potential mechanism(s) that underlie this phenomenon is urgently needed so that better diagnostic and therapeutic approaches can be developed.

Table N° 1: Risks of Incident Autoimmune and Autoinflammatory Disease Outcomes in the COVID-19 Cohort Compared with the Control Cohort.

Outcome	Incidence rate, No. events/person-year		aHR (95% CI)
	COVID-19	Control group	
Autoimmune/autoinflammatory disorders			
Alopecia areata	11.79 (135/114 542)	9.48 (1907/2 012 295)	1.12 (1.05-1.19)
Alopecia totalis	1.21 (14/116 054)	0.60 (123/2 036 903)	1.74 (1.39-2.17)
Psoriasis	5.40 (62/114 856)	5.09 (1025/2 013 810)	1.00 (0.91-1.09)
Vitiligo	2.59 (30/115 768)	2.30 (467/2 032 049)	1.04 (0.91-1.19)
ANCA-associated vasculitis	0.26 (3/116 137)	0.10 (21/2 038 149)	2.76 (1.64-4.65)
Behçet disease	0.34 (4/116 008)	0.38 (78/2 036 137)	0.79 (0.56-1.11)
Crohn disease	1.03 (12/116 063)	0.52 (106/2 036 833)	1.68 (1.31-2.15)
Ulcerative colitis	1.12 (13/115 873)	1.07 (21/2 034 322)	1.04 (0.86-1.26)
Rheumatoid arthritis	16.92 (190/112 321)	15.56 (3068/1 971 486)	1.02 (0.97-1.08)
Adult-onset Still disease	0.09 (1/116 137)	0.08 (17/2 038 152)	1.18 (0.63-2.23)
Polymyositis	0.09 (1/116 141)	0.10 (21/2 038 049)	0.63 (0.30-1.31)
Systemic lupus erythematosus	0.52 (6/115 992)	0.92 (188/2 035 386)	0.47 (0.36-0.61)
Systemic sclerosis	0.09 (1/116 119)	0.15 (31/2 037 867)	0.99 (0.58-1.69)
Sjögren syndrome	1.29 (15/115 956)	1.53 (312/2 034 400)	0.85 (0.71-1.00)
Ankylosing spondylitis	1.99 (23/115 821)	1.86 (379/2 032 445)	1.00 (0.87-1.16)
Sarcoidosis	0.26 (3/116 132)	0.14 (29/2 037 948)	1.59 (1.00-2.52)
Positive control outcomes			
Myocardial infarction	4.15 (48/115 684)	3.38 (685/2 029 628)	1.31 (1.18-1.45)
Congestive heart failure	31.10 (352/113 190)	18.02 (3580/1 986 762)	1.60 (1.54-1.68)
Stroke	24.24 (273/112 637)	20.15 (3983/1 976 716)	1.28 (1.23-1.34)
Negative control outcomes			
Epidermal cyst	18.45 (211/114 386)	19.99 (4010/2 005 922)	0.90 (0.86-0.94)
Tympanic membrane perforation	1.99 (23/115 847)	2.06 (418/2 033 487)	0.97 (0.85-1.12)
Trauma of multiple sites	30.47 (346/113 544)	33.65 (6709/1 993 987)	0.89 (0.86-0.92)



Taken from: Lim, S. H., Ju, H. J., Han, J. H., Lee, J. H., Lee, W. S., Bae, J. M. y Lee, S. (2023). Autoimmune and Autoinflammatory Connective Tissue Disorders Following COVID-19. JAMA network open, 6(10), e2336120. https://doi.org/10.1001/jamanetworkopen.2023.36120.

Serotonin deficiency in PASC

In a recent study (Wong, et al., 2023), it was reported that viral infection {SARS-CoV-2 that causes COVID-19 and possibly other similar viruses}, type I interferon-driven inflammation reduce serotonin by diminishing intestinal absorption of tryptophan, the serotonin precursor; platelet hyperactivation and thrombocytopenia that leads to reduced serotonin storage; and enhanced MAO (monoamine oxidase) activity that results in increased serotonin. Peripheral serotonin reduction impedes the activity of the vagus nerve that results in impairment of hippocampal responses and memory (see Figure 13). Thus, reduced synthesis and action of serotonin may be responsible for many of the features of long haul or long COVID (PASC) manifestations. This implies that efforts made to enhance serotonin levels may be of significant benefit in the prevention and management of post-COVID or post mRNA vaccine side effects.

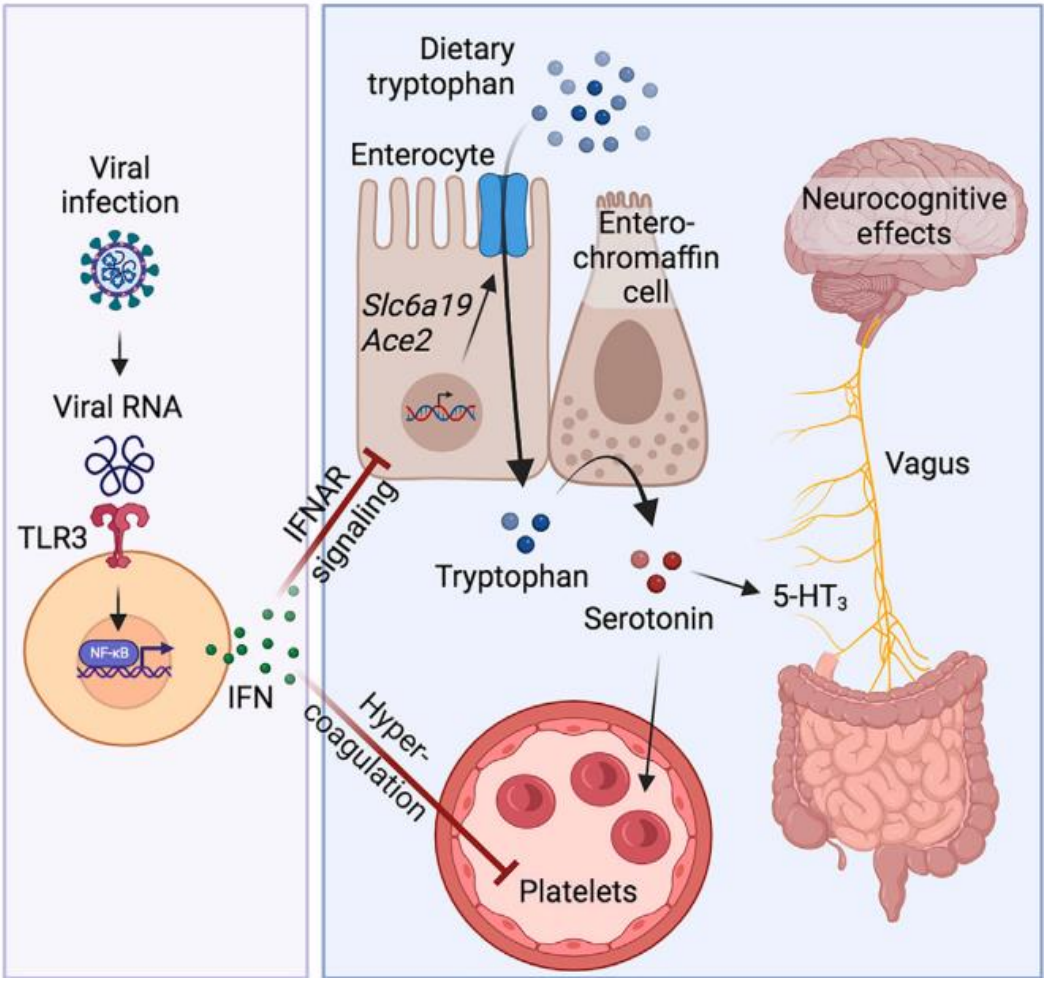


Figure N° 1. Scheme showing potential interaction between EFAs and its metabolites and serotonin.

Serotonin and essential fatty acids (EFAs)

In this context, it is noteworthy that essential fatty acids (EFAs) and their metabolites have a regulatory role in the synthesis and action of serotonin. For instance, it was reported that EFAs supplementation influence central nervous system serotonin and dopamine metabolism and modify impulsive behaviors related to these neurotransmitters (Hibbeln, et al., 1998). Studies employing positron emission tomography (PET) and [^{11}C]DASB ([^{11}C]DASB PET quantified serotonin transporter binding) studies revealed that AA predicted both 5-HTT BP_P and depression severity nonlinearly, suggesting that 5-HTT binding potential mediated the relationship between AA and depression severity (Gopaldas, et al., 2019).

Previously (Patrick and Ames, 2015), it was suggested that EPA increases serotonin release from presynaptic neurons by reducing PGE2, whereas DHA influences serotonin receptor action by increasing cell membrane fluidity in postsynaptic neurons. Thus, it has been proposed that deficiency of EPA, and/or DHA (and possibly, AA) could result in dysfunctional serotonin activation and function and may play a key role in contributing to neuropsychiatric disorders and depression that are common in PASC. This implies that AA/EPA/DHA may help to prevent and modulate brain dysfunction.

Impulsive violence, suicide, and depression are strongly associated with low concentrations of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA). When cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) and homovanillic acid (HVA), and plasma fatty acid concentrations were examined in healthy volunteers, and alcoholics, polyunsaturated fatty acids predicted both CSF 5-HIAA and CSF HVA concentrations suggesting that EFAs influence central nervous system serotonin and dopamine metabolism and thus, modify neuropsychiatric conditions by influencing neurotransmitters synthesis and action (Hibbeln, et al., 1998). These results suggest that AA/EPA/DHA have a regulatory role in the synthesis and action of serotonin and other neurotransmitters. Based on these results, it can be suggested that low concentrations of serotonin reported in those with long-haul or long haul or long COVID (PASC) could be attributed to deficiency of EFAs (such as AA/EPA/DHA and consequently some of their more biologically active metabolites.

EFAs and COVID-19

Previously, I suggested that COVID-19 could be due to a deficiency of EFAs especially AA/EPA/DHA. This proposal is based on the fact that (i) SARS-CoV-2 and other similar enveloped viruses can be inactivated by PUFAs; (ii) EFAS and their metabolites prostaglandin E1, lipoxin A4, resolvins, protectins and maresins have the unique ability to augment phagocytosis of macrophages and leukocytes to enhance wound healing and suppress wound infections; and (iii) regulate vasomotor tone, inflammation, thrombosis, immune response, regulate T cell proliferation and secretion of cytokines, stem cell survival, proliferation and differentiation, and leukocyte and macrophage functions, JAK kinase activity and neutrophil extracellular traps-actions that imply that these bioactive lipids play a critical role in COVID-19 (Das, 2020a; Das, 2020b; Das, 2021a; Das, 2021b). This is further supported by the observation that SARS-CoV, MERS-CoV, SARS-CoV-2, and their variants of concern (VOCs) bind the essential fatty acid linoleic acid (LA), In the SARS-CoV S structure, LA stabilizes the locked conformation, and as a result LA inhibits viral replication (Goc, et al., 2021; Toelzer, et al., 2022). Similar properties were also found to be shown by other PUFAs such as AA and EPA (Yan, et

al., 2019). It was noted that both LA and AA metabolism axis was markedly perturbed on exposure to SARS-CoV-2 virus; supplementation of LA or AA to SARS-CoV-2 and similar viruses infected cells in vitro significantly suppressed the virus replication demonstrating that that host EFAs metabolism has a significant role in human-pathogenic coronavirus infection and could form a therapeutic strategy for various SARS-CoV-2 and similar infections.

EFAs, gut microbiota and serotonin

There is considerable evidence to suggest that there is a pivotal role for gut microbiota in the metabolism of serotonin. The gut microbiota can alter the expression of key serotonin-related genes to promote its (serotonin) biosynthesis. Gut microbiota may produce microbial metabolites that can influence host serotonergic system. The gut microbiota can influence host serotonin through direct and indirect means. Gut bacteria can act (i) directly on enterochromaffin (EC) cells to increase colonic tryptophan hydroxylase 1 (Tph1) expression and promote serotonin synthesis; (ii) alter host by virtue of their metabolites, including short chain fatty acids, tryptophan, tryptamine, and secondary bile acids; (iii) short chain fatty acids can stimulate serotonin synthesis and release by acting on enterochromaffin cells; (iv) since tryptophan is an essential amino acid and its metabolism is regulated by the gut microbiota and thus, by modulating the availability of tryptophan the gut microbiota is able to influence the metabolism of serotonin; (v) tryptamine is a ligand for the 5-HT_4 receptor (5-HT_4R); (vi) secondary bile acids, formed by the gut microbiota promote Tph1 expression and stimulate serotonin synthesis (Legan, et al., 2022).Furthermore, gut microbiota is able to induce maturation of enteric nervous system through the release of serotonin and activation of serotonin-receptors (5-HT_4) demonstrating a strong interaction between the gut microbiota and the enteric nervous system and the potential role of both gut microbiota and serotonin in various gut diseases (De Vadder, et al., 2018).

It is noteworthy that PUFAs influence the gut microbiota proliferation and function. (Wan, et al., 2017; Todorov, et al., 2020; Pinchaud, et al., 2022). Thus, it can be said that gut microbiota, gut serotonin and PUFAs function are closely associated with each other and have a feedback regulatory role among them. These results imply that alterations in the dietary intake of PUFAs alters gut microbiota and that, in turn, modulate maturation of enteric nervous system through serotonin synthesis and action.

Conclusions and therapeutic implications

It is evident from the preceding discussion that dietary PUFAs have a significant role in the pathobiology of COVID-19 both directly and indirectly. It is envisaged that insufficient intake of EFAs (especially LA and ALA that are the precursors of their long-chain metabolites GLA, DGLA, AA and EPA and DHA respectively) may render an individual more susceptible to various infections especially SARS-CoV-2 and other related viruses, alteration in gut microbiota, decreased formation of serotonin and action and deficiency in the maturation of gut enterochromaffin cells and subsequent development of long haul or long CVOID and PASC disorders. It is known that various viruses can interfere with the action of desaturases, enzymes that are needed for the conversion of dietary LA and ALA to their respective long-chain

metabolites AA and EPA and DHA. Based on the current evidence presented above, it is suggested that subclinical or inadequate intake of dietary LA and ALA (EFAs) and their inefficient conversion to AA< EPA and DHA is expected to result in increased susceptibility to various infections including SARS-CoV-2, decreased formation of serotonin, defective immune response and defective wound healing and development of post-COVID long haul or long CVOID and PASC. Hence, it is proposed that administration of AA EPA and DHA could be of benefit in the management of SARSCV-2 infection, and long haul or long CVOID and PASC.

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