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Mediterranean Diet: A Nutritional Suggestion for Long Covid Management Strategies – A Literature Review

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ABSTRACT

Long COVID (LC) refers to continuing conditions following acute COVID-19 infection, lasting for weeks to months. It affects a wide range of people's lives, including physical, physiological, and social-economic aspects. Hence, leads to lowering quality of life and other future health challenges worldwide. Health problems following the acute phase of COVID-19 may persist or appear for days to months after the acute infection is resolved. The phenotype of long COVID-19 commonly manifests as a collection of symptoms such as muscle weakness, neuro-cognitive alteration, and respiratory disturbances. Mechanisms underpinning long COVID-19 are still not fully understood. It is hypothesized that inflammation plays a crucial role in LC development through several complex pathways. Recently, effective treatments for long COVID-19 have not been established. Its management depends on the patient's symptoms and needs. Nutritional modulation and physical rehabilitation are advised for long-COVID-19 improvement and increased quality of life. The Mediterranean diet (Med-diet) has been acknowledged for its impact on health through its antioxidant and anti-inflammatory effects. Bioactive compounds in Med-diet have been widely studied to reduce oxidative stress and inflammation in cells. Adherence to Med-diet food intake is linked to a lower incidence of obesity, cancer, cardiovascular disease, and metabolic disease. Therefore, the potential effect of Med-diet as a nutritional approach for long-COVID-19 treatment and prevention will be summarized.

KEYWORDS: Inflammation, Long COVID, Mediterranean Diet, Review

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INTRODUCTION

COVID-19 has caused an increase in morbidity and mortality worldwide. Nowadays, COVID-19 survivors also have to deal with symptoms that may appear after COVID-19 infection. Those post-COVID symptoms may decrease quality of life (QoL) and become a new global health burden in the future. Persistent symptoms after the post-acute phase of COVID-19 are known as long COVID (LC), post-COVID syndrome (PCS), post-COVID conditions, or post-acute sequelae of SARS-COVID (PASC)(1).

SARS-COVID-19 infection may affect the multiorgan system in the body by inducing inflammatory agent release. Concerning the health-related impact of LC, it needs interventions that must be considered on patient needs. Some studies reported that nutritional supplementation, physical training, breathing exercises, and multidisciplinary treatment may effectively improve symptoms and the QoL of patients with LC(2)(3).

Mediterranean diet (Med-diet) term is used for traditional dietary patterns in Mediterranean areas characterized by a low glycemic index, healthy fat, and high fibre nutrient profiles, including intake of plant-based foods, minimally processed whole grains, low-fat dairy products, fresh fruits, and olive oil, moderate red wine intake, and monthly consumption of red meat(4). Med-diet consists of rich antioxidant compounds and their anti-inflammatory effects may reduce the risk of several diseases such as cancer, metabolic disease, and cardiovascular disease(5). The role of the Med-diet in health has been widely observed by researchers. Therefore, this study will summarize the potential of the Mediterranean diet in long COVID-19 treatment and prevention.

LONG COVID AND DISEASES

Long covid (LC) refers to persistent symptoms, lasting for weeks to months, after the initial infection of SARS-COVID-19(6). It can also be defined either as health problems continuing or new symptoms developing post-SARS-COVID infection(1). Long-term manifestations following the acute phase may vary among people, such as headache, memory and concentration disturbances, shortness of breath, and autonomic dysfunction(7)(8)(9). However, respiratory and neuropsychiatric symptoms were commonly experienced by COVID-19 survivors(10).

Huang, *et al* reported in their study that SARS-COVID-19 survivors suffered from fatigue, difficulty sleeping, and depression for 6 months after hospital discharge(11). In an observational study, symptoms like smell and taste disturbance, fever, sore throat, and pneumonia were associated with post-infection SARS-COVID-19(12). Similarly, Steinmetz, *et al* also reported that fatigue, tiredness, poor concentration, psychological alterations (anxiety, post-traumatic stress disorder, and depression), difficulty sleeping, and decreased physical function were commonly complained about by post-COVID-19 outpatients after 3 to 6 months of follow-up(13). LC patients were also predicted to have a higher risk of brain fog incidence that was related to sleep disorder, activity restriction, and breath shortness(14). Persistent symptoms were experienced by 37% of patients post-COVID-19 infection and 51% had brain fog that lasted up to 240 days(15). Numerous manifestations of LC profiling are illustrated in Figure 1.

Few studies have also been carried out to analyse prolonged manifestations following COVID-19 infection and its effect on life. COVID-19 was related to psychological distress and physical disturbances after days to months of hospital discharge(16). Other risk factors such as sociodemographics and pre-existing comorbidity were associated with higher risk of LC development. In addition, the severity of COVID-19 during the acute phase is also associated with an increased risk of LC incidence(17). Sudre, *et al* in their cohort study reported that LC incidence was significantly associated with age, gender, and pre-existing diseases. It described that the elderly and women might escalate potential LC development in people with a history of COVID-19. The potential rate of developing LC increased by 9,9% in 18-49 years old, and 21,9% in ≥70 years old. Intermittent headache, fatigue, and respiratory symptoms (for instance: anosmia, breath shortness, and chronic cough) were mostly complained at 28 days to 56 days after testing positive for COVID-19(9). A recent study conducted on severe COVID-19 patients reported that 76% of hospitalized COVID-19 patients developed PCS and activity disturbances(18). Similarly, a retrospective study also reported that 526 of 801 COVID-19 survivors experienced at least one symptom of LC after 12 months(19). A cross-sectional study reported that the incidence rate of LC was higher in females than males. People with a history of hospitalisation during the acute phase of COVID-19 infection also complained of at least one symptom of LC such as hair loss, fatigue, hyposmia, and cough(20).

Kisiel, *et al* clustering LC phenotypes using post covid syndrome (PCS) score into mild, moderate, and severe. The higher phenotype was related to a higher risk of persistent symptoms and work ability disturbances(21). Similarly, in a cohort study, people troubled with persistent symptoms of LC also showed decreasing quality of life for 3 to 6 months after the onset of the acute phase(22).

Pathobiology of long COVID

COVID-19 has been suggested for its persistence and spreadability in tissue organs for weeks to months after acute infection, even in mild or asymptomatic patients(23). Shortness of breath, fatigue, brain fog, sleep disorder, and anxiety were mainly found in patients after SARS-COVID-19 infection. The biological pathomechanism underlying LC has not been widely studied. Currently, viral persistence, autoimmunity, re-infection, epigenetic modification, and chronic inflammation are hypothesized underlying LC pathomechanisms(24)(25). However, viral persistence and system immune response were suggested to be the main causes of long-COVID-19 development through several pathways such as dysbiosis, mast cell activation, microvascular thrombosis, autoimmunity, autonomic and metabolic disruption, neuroinflammation and dysregulation (26).

Viral Persistence

COVID-19 virus can potentially persist after acute infection and may manifest either as short-term or long-term effects in certain organs' bodies by binding to angiotensin-converting enzyme 2 (ACE-2)(27). ACE-2 can be found in numerous organs, such as the heart, renal, brain, and lung. Spike protein binding to the ACE-2 receptor will result in a downregulation of ACE-2 expression and upregulation of bradykinin, thus promoting pro-inflammatory cytokines release(10). In addition, spike protein-ACE-2 binding induces syncytia formations and leads to cell death due to severe system immune responses(7). A recent animal study found out that spike protein of the COVID-19 virus might induce alteration of mitochondria function, thus leading to systemic chronic inflammation and fibrosis. It was also suggested to be correlated to lipid and glucose metabolic impairment, which could increase the organ's viral deposit as a result(28).

COVID-19 virus might replicate and be deposited both in respiratory and non-respiratory tissues. The abundance of SARS-Cov-19 RNA was found highest in the lung parenchyma, followed by the pericardium and hypothalamus at 2 weeks to a month following symptoms in

the post-mortem study(29). Chronic SARS-Cov-19 presence might cause exhaustion of adaptive and innate immune cells, thus leading to further viral deposits(30). A cohort study performed by Tejerina, *et al*, has indicated the systemic viral persistent possibility in patients with long-lasting symptoms. At least, one positive PCR were detected in 51% of 4-week persistent symptoms patients during extra pulmonary sample evaluation(31). Similarly, the persistence of SARS-COVID-19 still could be identified on faecal specimens or intestinal biopsies in patients with negative nasopharyngeal swab tests more than 6 months after acute infection(25).

System Immune-response

Long COVID-19 infection occurs as the consequence of immune system dysregulation, resulting in stress reaction. Stress induced by COVID-19 might cause alteration of the microbiome, neurotransmitter, and cell metabolism, thus increasing mast cell degranulation and excessive cytokine inflammatory production. Furthermore, leads to chronic systemic inflammation(32). COVID components such as Nucleocapsid (N), Spikes (S), and non-structural and accessory proteins disturb the cell's function through nucleocytoplasmic transport blocking, thus inducing inflammatory agent release. Furthermore, it leads to viral-induced autoimmunity and multiple organ damage(33). Autoimmunity has been demonstrated to contribute to LC development by mimicking peptides of SAR-Cov-19 S glycoprotein and host antigens, especially expressed by the endocrine system, such as the adrenal gland, thyroid gland, beta cells of the pancreatic gland, and pituitary gland(25)

Dysfunction of the immune system has been correlated with hypocortisolemia due to hypothalamus-pituitary-adrenal axis (HPA axis) impairment and insufficiency of the adrenal gland. Multi-omic study of COVID-19 patients showed a downregulation of cortisone and cortisol at 2-3 months following initial onset(34). Those biomarkers cause biological wake-sleep cycle disruption, furthermore contribute to immune system dysregulation worsening and provoke inflammatory processes(35)(36). Additionally, plasma proteomic analyses also indicate heterogeneity of chronic inflammation signatures in LC conditions. Enrichment of type II interferon (IFN) signalling, nuclear factor kappa-light (NF-κB) signalling, and neutrophil activation were discovered in 55 LC patients(37). Plasma proteome examination in people suffering from LC also exhibits natural killer cells (NK-cells) phenotype shifting to inactive, higher levels of memory B cells, activated $CD4^+$ memory cells, TNF-α, IFNγ, and angiopoietin 1 (ANGPT1) expression that was associated with vasculo-proliferative disease(38).

A recent study reported that people with neurocognitive symptoms of LC showed elevated $CD4^+$ T cell response, $CD8^+$ memory T cell downregulation, and increased IL-6 production(39). Another study also reported significantly elevated IFNγ-producing $CD4^+$ and cytotoxic $CD8^+$ T cells(40). A systematic review study resumes immunology factors alteration, such as an increase of cytokine production (IL-1β, IL-6, and TNF-α) through microglial cells, an increase in cytotoxic $CD8^+$ production, dysbiosis gut and oral microbiomes, alteration of gene-linked cell cycle and leukocyte transcriptome(41). Chronically increased C-reactive protein (CRP) and cytokines such as IL-6 could lower senescence cell removal attempts, then lead to the accumulation of necrotic cells and homeostasis dysfunction(42). Immune system activation and the consistent inflammation process could manifest as numerous sequelae depending on where it happens(43).

Alteration of the microbiome is also linked to LC through the gut-lung axis. COVID-19 infection changes the abundance of intestinal and lung microbiota. Propionate-butyrate-produced bacteria (*Firmicutes, Bacteriodetes, and Verrucomicrobia*) and anti-inflammatory TAXA bacteria (*Actinobacteria class Bifidobacteriales*) were found lower in LC patients. Contrary, facultatively anaerobic bacteria (*Firmicutes class Bacili*, and *Gammaproteobacteria class Enterobacteriales*) were found higher. Dysbiosis promotes chronic low-grade inflammation by inducing cytokine inflammatory release(44). A growing body of a study reported that LC condition was characterized by decreased anti-inflammatory bacteria like *Faecalibacterium* and *Bifidobacterium*, and increased pro-inflammatory bacteria like *Actinomyces* and *Steptococcus*. Additionally, SARS-Cov-19 infection inflicts leaky gut by affecting cell tight junction. Intestinal permeability disruption may increase lipopolysaccharides-produced (LPSs-produced) bacteria such as *Salmonella sp.*, and *E. coli*, leading to further epithelial barrier dysfunction and triggering immune response activation(45)(46).

MEDITERRANEAN DIET AND HEALTH

The Mediterranean diet (Med-diet) refers to a dietary pattern emphasized by high intakes of plant-based foods such as vegetables, fruits, and whole grains, and low saturated fats such as olive oil, and fish(47). Those foods possess rich polyphenol-flavonoid, the most abundant antioxidant, such as ellagenic acid, naringenin, kaempferol, and apigenin(48). Mediterranean diet has been widely studied for its role in health. The mechanisms underpinning the health benefits of Med-diet consumption are as follows improving gut dysbiosis, increasing insulin sensitivity and stress resilience, and reducing inflammation, oxidative stress, growth factor, lipid profile, and platelet aggregation(49).

High consumption of the Mediterranean diet is suggested to be associated with lower morbidity and mortality of non-communicable diseases worldwide. A review by Antonino *et al.* reported that the Mediterranean diet could reduce the risk of metabolic and vascular disease

through anti-inflammatory effects, microbiome modification, and gene modulation(50). Contrary to Western foods, med-diet tends to be lower in salt. High sodium intake has been studied to be associated with inflammatory reactions by triggering pro-inflammatory cytokines caused by hyperosmotic stress(51). In a randomized control trial study, the incidence rate of hypertension-induced pregnancy, preeclampsia, and macrosomia was found lower in an intervention obesity pregnant group than control(52). Similarly, dietary intervention affects the microbiome, immune response, and cardiometabolic profile of the pre-diabetic group(53). Adherence to the Med diet has also been studied to be allied with better sleep quality, and the prevention of non-communicable diseases(54)(55). A randomized control trial (RCT) study also reported that the consumption of Mediterranean foods for the long term preserves renal function in patients with coronary heart disease by lowering the decline in glomerular filtration rate (eGFR) compared to a low-fat diet(56).

Numerous epidemiological and clinical findings suggest that dietary patterns, the Mediterranean diet, in particular, are linked to human illness development by contributing to the epigenetic process such as alteration of DNA methylation, non-coding RNA, and histone modification. Alteration of epigenetics might influence gene expression which plays an important role in host immune response. Undesired epigenome changes could also affect the micro-environment of the microbiome balance and immune modulation, thus various non-communicable diseases develop as a result(57)(58).

Bioflavonoids contained in the Mediterranean diet are suggested can improve oxidative stress status by reducing cytokine inflammatory release and stimulating mitochondrial biogenesis, thus preventing cell injury(59). A recent study indicated that plasma IL-6 and LDL were significantly reduced after an intervention of Med-diet for 12 weeks(60). Similarly, Levi *et al.* in their study also reported significant improvement in plasma oxidative stress biomarkers after regular intake of flavonoid-rich cocoa for 8 weeks in the elderly(61). Other flavonoids such as anthocyanins and berberine also have beneficial effects, particularly in cardiometabolic factors. It was shown in a study that 10g of purple-black barberry intake per day could reduce CRP and lipids plasma levels such as triglycerides and LDL(62).

Flavonoid-rich foods were known to be anti-viral agents. Flavonoids such as luteolin, quercetin, penduletin, and baicalin were studied to be used against *Enterovirus*. Luteolin can be found in vegetables like red leaf lettuce, spinach, and radicchio. Luteoin exhibits viral attachment and reduces its replication. Penduletin and quercetin might disrupt viral RNA replication, inhibit protein synthesis, and prevent viral spread(63).

Polyphenol dietary intake is also suggested to have a role in microbiome change and gut permeability repair. Alteration of the microbiome has been suggested to be associated with the activation of immune response and cytokine release through intestinal permeability disruption. A recent study reported that zonulin serum level, an indirect marker of permeability of the intestinal, was significantly reduced after a polyphenol-rich diet lasted for 8 weeks(64). In addition, the abundance of fibre-fermenting bacteria and butyrate-producing bacteria increased significantly. *Roseburia*, *Eubacterium*, *Bifidobacterium* and *Bacteroides were found higher in flavonoid-rich intake(65). Contrary, the high consumption of meat disrupts microbiomes' ecosystem and increases the abundance of Bacteroides thetaiotaomicron, Akkermansia muciniphila, and Desulfovibrio piger bacteria that are related to type II diabetic development(58).*

Other than polyphenols, Mediterranean diet foods also contain other bioactive components such as vitamins (vitamin-A, -B, -C, -E, -K), minerals (copper, potassium, folate, magnesium), Omega-3 fatty acids, and monosaturated fatty acids (MUFA)(49). Omega-3 fatty acids have a role as anti-inflammatory and immunomodulatory agents. Vitamins, minerals, and healthy fats have an essential role as protective agents against pathogens by maintaining cell barrier integrity and regulating immune responses (maturation and development of adaptive and innate immune response) and inflammation(66).

Previous studies have demonstrated the correlation of a high Mediterranean diet could increase essential trace elements absorption. Trace elements (Fe, Cu, Zn, Na, K, Mo, Mg, Ca) protect the body by decreasing cell adhesion and modulating immune cells(67)(68). Zinc (Zn) contained in Med-diet also has a pivotal effect on anti-viral activity. Zn plays a role as an anti-oxidant agent by defending against negative effects from the reactive oxygen species (ROS) process through NF-κB signalling pathway inhibition, IFN-α production up-regulation, lipid peroxidase reduction, and T-cell function regulation. Zn also acts as an enzyme cofactor for RNA and DNA polymerases, thymidine kinase, and ribonuclease which are essential for cell growth, development, and maturation(69).

MUFA contained in Med-diet may improve microvascular endothelial impairment and lower cardiovascular disease (CVD) risk, particularly in the elderly(70). Increasing MUFA intakes as the nutritional intervention was associated with insulin sensitivity improvement in dietary intervention for a 6-month randomized control trial (RCT) study(71). Substitution of saturated fat diet (SFA) with unsaturated fat (UFA) diet associated with better lipidome profile. A high unsaturated fatty acids diet for 16 weeks was beneficial to lower plasma fatty acids (FA) related to CVD(72). Enrichment of the MUFA diet is responsible for lowering LDL and its

fractions. Consumption of MUFA-rich foods contained in the Mediterranean diet for 8 weeks changed metabolite profiles such as decreased serum triglyceride level, free cholesterol level, and very low-density lipoprotein (VRDL) and its fractions in people with high risk of metabolic syndrome(73). Dietary intervention using foods rich in protein and UFAs in people at high risk of unwell ageing for a year induces a better long-term profile of intra-hepatic lipid, as well as glucose and lipid metabolisms(74).

LONG COVID AND MEDITERRANEAN DIET

Long COVID syndromes were mainly characterized by multi-organ inflammation response and inadequate nutritional status(75). Nevertheless, the relationship between nutrition and inflammation is quite complex. However, the effect of micro- and macro-nutrients has been describe in many scientific studies. Natural bioactive contained in the Mediterranean diet is suggested to reduce LC burden through increased protective cytokines production, downregulation of cytokines inflammatory secretion, and inhibition of RAAS(76).

Dietary patterns can also influence immune responses through gut microbiome composition(66). Eubiosis, a favourable diversity of gut microbiome condition, might help short-chain fatty acids (SCFAs) production such as butyrate, acetate, and propionate. Furthermore, those metabolite products could impact the immune system through gut-associated lymphoid tissue (GLAT) modulation. SCFAs also promote anti-inflammatory responses by hindering nuclear factor kappa-β (NF-kβ) and inhibiting intestinal wall leaking(77)(78). A recent study showed that omega-3 fatty acids contained in Med-diet could improve inflammation status and inhibit enveloped virus replication. Low glycaemic index food in Med-diet is also tremendously helpful in decreasing oxidative stress(75).

Intakes of fibre- and antioxidant abundance foods could help alleviate LC symptoms. A high-fibre (roughage) diet consists of plant-based foods. It contributes to few calories and is correlated with better metabolic function profiles and diverse gut microbiomes(79). Fibre intake recommendations may differ for each person. However, intakes of 25 to 30 g daily are globally recommended for adults(80). High-antioxidant foods can help tackle chronic inflammation that is commonly found in LC by neutralizing free radicals(79).

Flavonoids contained in the Mediterranean diet not only play a role as an anti-inflammatory agent but also act on anti-viral activity by disrupting viral infection stages such as viral attachment, translation, and replication(81). A multicenter study performed by Di Stadio, *et al* reported that people with olfactory impairment post-COVID-19 infection showed magnitude recovered after being given ultra-micronized palmitoylethanolamide and luteolin during olfactory training compared to the control group(82).

SUMMARY

In conclusion, people with a history of COVID-19 infection may experience continuing symptoms called long COVID-19 for days to months after the acute phase through several mechanism pathways. Therefore, nutritional modulation may be a potential therapeutic approach for long COVID management strategies.

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Conflict of Interest
The authors declare that there are no competing interests related to the study.

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Authors' Contribution
The idea, study design, and writing of the original manuscript: RWYP, AN. Collecting data: RWYP, AN. Analysis data, data interpretation: RWYP, AN, MAH. Made Figure: RWYP. Reviewing: AN, MAH. Revising: RWYP, AN, MAH. All authors contributed and approved the final version of the manuscript.

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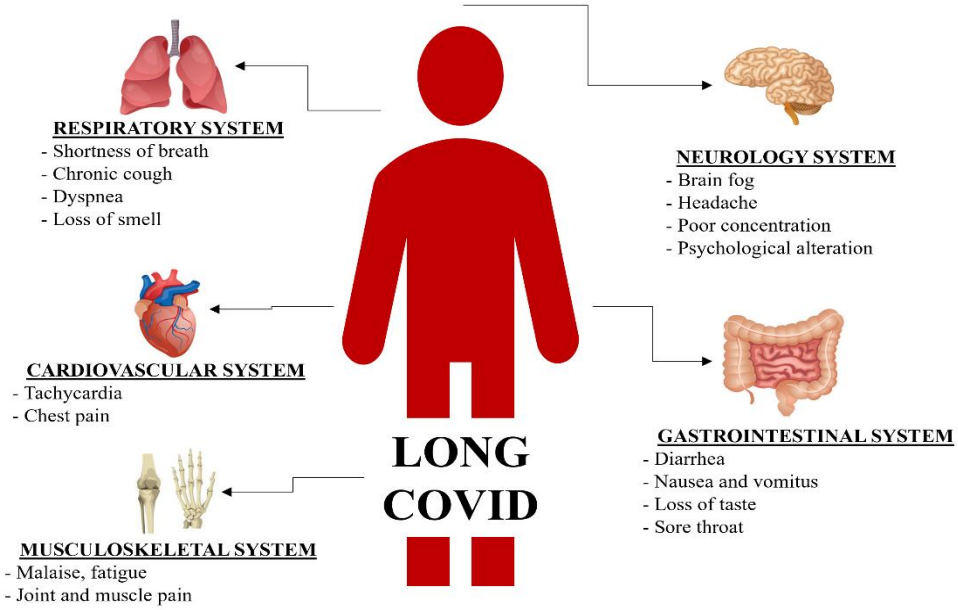

Figure 1. Long covid manifestations on several systems.