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Medical nutrition therapy (MNT) in viral infections with special reference to covid-19

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Abstract
Viral infections refer to the entry and multiplication of harmful viruses in the body of a host thereby causing various damages. Such infections are a major cause of morbidity and mortality. Prevention and treatment of these infections are a challenging task. The current COVID-19 pandemic has made us more concern about the management of such viral infections than before. Medical Nutrition Therapy (MNT) plays a vital role in the treatment of these infections. Macronutrients and micronutrients present in a diet are crucial for the optimal immune response of the host. Each and every viral infection has its own specific set of characteristics which contribute to the complexity of dietary management of these conditions. The current article targets to highlight the overall nutrition care process in viral infections with special reference to COVID-19. An evidence based dietary approach will be helpful for getting optimal outcomes in patients suffering from such infections.

Keywords: virus, infection, diet, functional food, immunity

Introduction
Infectious diseases affect a large number of people worldwide. Viral infections and diseases refer to the entry and proliferation of harmful viruses in the body of a host. Such diseases are an alarming public health problem and an important cause of mortality. A majority of viruses are present in the immediate environment surrounding human beings. They are often present within other species and do not cause human disease. However, these viruses can emerge or re-emerge in human populations due to disturbances in ecological balance. This may lead to sporadic diseases, epidemics and pandemics. Factors like human behaviour, economic development, changing social practices, industrialisation, expanding urban slums, travel, migration, geographical disasters, global warming and deforestation may also lead to an increase in viral infections over time.

Each virus has its own set of characteristics and creates its own set of complications. The enormous variations in the viruses and their epidemiology pose a great challenge to the control and management of such diseases. However there are many similarities in the physiological changes caused by different viruses and for this reason some generalizations can be made. There are several approaches commonly used for the control of viral infections namely immuno prophylaxis, active prophylaxis (vaccination), passive prophylaxis, sanitation and vector control, antiviral chemotherapy, inter ferons etc. [1] Typically no single approach is found to prevent or cure viral infections solely.

The risk of a viral infection depends both on the characteristics of the virus and the host. [2] The response to a virus depends largely on the innate and acquired immunity of the individual. It is well established that diet and nutrition play a huge role in the regulation of the immune system and thus a nutritious diet is highly necessary for an appropriate immune response.

A proper diet not only helps in the prevention and reducing susceptibility to certain infections but also helps in the treatment of various infectious diseases. The current outbreak of 'Coronavirus Disease 2019' (COVID-19) caused by 'Severe Acute Respiratory Syndrome Coronavirus 2' (SARS-CoV-2) is declared to be a pandemic by World Health Organisation (WHO) on March 11, 2020. No specific antiviral therapy is developed yet for COVID-19. [3] Vaccines are under clinical trial. Prevention and management of COVID-19 is thus a great challenge. The target of the present article is to highlight the role of nutrition and therapeutic diet in the management of viral infections with special reference to COVID-19.

2. Viral Infection- An Overview
A virus is a small infectious organism which enters a living cell to reproduce or replicate. Depending on the type of genetic material they can be classified as Deoxyribonucleic acid (DNA) virus and Ribonucleic acid (RNA) virus. The nucleic acid may be single stranded (ss) or double stranded (ds), circular or linear. In the entire genome either single nucleic acid (monopartite genome) or multiple nucleic acid segments (multipartite genome) may be present. [4] The pathogenesis of viral infection involves implantation of the virus at the portal of entry, release of genetic material (DNA and RNA) within the cell, local replication, spread to the target organs or disease sites and spread to the sites of shedding of virus into the environment. The major factors which affect the pathogenesis are virus accessibility to the tissue, susceptibility of cell to the virus multiplication and susceptibility of the virus to host defenses. [5] Viral infections are mostly subclinical. Diseases occur only when a virus sufficiently replicates in order to damage the cells, release toxins and impair organ functions. The different types of viral infections based on the physiological systems and organs affected by them are as mentioned in Table-1.

Table 1: Types of Viral Infections based on Physiological Systems an Organs Affected [6, 7]

Physiological Systems & Organs	Details
Respiratory System	Infections are caused by influenza virus, adenovirus, human respiratory syncytial virus, human bocavirus, coronaviruses, human metapneumovirus, human parainfluenza virus, human rhinovirus, varicella-zoster virus, myxovirus, paramyxovirus, togaviruses etc. Principle syndromes include upper respiratory infection, pneumonia, bronchitis, bronchiolitis, croup, asthma, severe acute respiratory syndrome, chicken pox, measles, mumps, rubella etc.
Gastrointestinal Tract	Infections are caused by rotaviruses, astroviruses, adenoviruses, calciviruses, coronaviruses, Norwalk group viruses, enteroviruses, cytomegalovirus etc. Gastroenteritis and diarrhoeal diseases are common.
Liver	Viral hepatitis is caused by Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis D Virus (HDV) and Hepatitis E Virus (HEV).
Nervous system	Damages are caused by rabies virus, West Nile virus, poliovirus etc.
Immune System	Damaged by Human Immunodeficiency Virus (HIV) leading to Acquired Immunodeficiency Syndrome (AIDS).
Kidney	Damages are caused by Dengue Virus, Hantavirus, Varicella-zoster, Cytomegalovirus, Epstein - Barr virus, HIV, HAV, HBV, HCV, Parvovirus etc.
Placenta and foetus	Affected by Zika virus, rubella, cytomegalovirus etc.

Some zoonotic viral infections include Rabies (Lyssavirus type 1), Yellow fever (Flavivirus fibricus), Dengue (Dengue virus), Japanese encephalitis (Flavivirus), Kyasanur Forest Disease (Flavivirus) and Chikungunya fever (Chikungunya virus). [6] Other emerging or re-emerging viral infections include Hantavirus, Chandipura virus, Nipah virus, Novel H1N1 Influenza Virus etc. [8] The viruses can be transmitted through direct transmission (e.g., direct contact, droplet infection, inoculation into skin or mucosa, transplacental) or indirect transmission (e.g., vehicle-borne, vector-borne, fomite-borne, unclean hands and fingers).

The SARS-CoV-2 is a positive single stranded RNA (+ssRNA) virus with a crown like appearance under the microscope due to the presence of spike glycoproteins on the envelope. It belongs to the beta coronavirus category. SARS-CoV-2 binds to its specific human Angiotensin Converting Enzyme 2 (hACE2) receptors through its Receptor Binding Domain (RBD) present on the spike proteins and is proteolytically activated by cell surface proteases and lysosomal proteases leading cellular entry. [9] The S1 domain of SARS-CoV-2's spike glycoprotein can also interact with the human CD26, an immunoregulatory factor for hijacking and virulence. [10] The first cases of the SARS-CoV-2 infection or COVID-19 are found to be associated with the direct exposure to the Huanan Seafood Wholesale Market of Wuhan, China. The animal-to-human transmission is suspected as the main mechanism. The virus is transmitted from human-to-human mainly via droplets. The symptomatic people are the most frequent source of COVID-19 spread. [9]

3. Physiological and Biochemical Changes in Viral Infections

Viral infection is a hyper metabolic state. It is commonly associated with the wasting of body tissues as a result of increased catabolic processes. There is loss of muscle proteins and redistribution of amino acids leading to negative nitrogen balance. Fever acts as a major stimulus for the initiation of such catabolic processes. Gastrointestinal symptoms like anorexia, nausea, vomiting, abdominal pain and diarrhoea are frequently encountered in viral infections. [6] The occurrence of such gastro-intestinal symptoms is quite high in COVID-19 patients. [11] Viral infections commonly increase insulin resistance (IR) and cause hyperglycaemia. A study conducted on 17 patients suffering from viral infection observed a 33% and 28% increase in IR during infection and convalescence respectively along with hyperglycaemia. [12] Viruses induce the production of Interferon-γ (INF- γ) which in turn downregulates the production of insulin receptors in skeletal muscles. This causes a rapid increase in insulin production to maintain blood glucose levels in human subjects. Insulin also helps in anti-viral immunity by boosting effector $CD8^+$ T Cells directly. But in obese pre-diabetic mice with hepatic insulin resistance this leads to glucose intolerance. [13] It indicates that viral infections act as an important risk factor for the progression of type 2 diabetes mellitus especially in patients with pre-diabetes. There is fall in total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) levels in viral infections whereas plasma triglyceride levels may be elevated or inappropriately normal. [14] Hypolipidaemia can be observed in COVID-19 patients and it increases with disease severity. [15] The level of C-Reactive Protein (CRP), an inflammatory marker, is increased in various acute and chronic conditions including infections like viral hepatitis, [16] dengue, [17] HIV, [18] H1N1 Influenza, [19] COVID-19 [20] etc. Viral infections are known to cause a wide range of kidney diseases namely acute tubular necrosis, immune-complex glomerulonephritis, mesangial proliferative glomerulonephritis, diffuse proliferative glomerulonephritis, polyarteritis nodosa, membranous glomerulopathy, HIV-associated nephropathy etc. Acute Kidney Injury (AKI) is related to dengue haemorrhagic fever and dengue shock syndrome. [7] AKI is also found to be associated with COVID-19. [21] Liver functions Tests (LFTs) are often impaired in viral infections. The Hepatitis A, B, C, D, E and G viruses are commonly known as hepatotropic viruses and cause liver injury. [22] Other viruses like Epstein-Barr virus, cytomegalovirus, human herpes virus cause acute liver injury. [23] The levels of Aspartate transaminase (AST), alanine transaminase (ALT) and gamma glutamyl transferase (GGT) are found to be elevated in patients with dengue infection. Liver injury associated with dengue peaks around day six and seven. [24] Abnormal LFTs are found to be associated with patients suffering from COVID-19. Such patients are at higher risk of developing severe disease. [25] Liver injuries are more prevalent in severe patients of COVID-19 than in mild patients. These damages may be due to direct infection of the hepatocytes or due to certain drugs. Cytokine-storm and pneumonia-associated hypoxia may also be responsible and lead to liver failure in critically ill patients. [26] Viral infections, including HIV, HBV/HCV, influenza, norovirus infections may lead to dysbiosis. The integrity of gut micro-organisms can be disrupted by the invading viruses.

4. Nutrition, Diet and Immunity

We are constantly being exposed to different types of viruses and other microbes on a daily basis. The immune system which involves various cells, organs and complex pathways provides resistance against such invading micro-organisms. A healthy diet balanced in all essential nutrients is required for the proper functioning of all cells including the immune cells. Several macronutrients and micronutrients play an important role in the maintenance of optimum immune responses. A diet which is quantitatively and/or qualitatively poor leads to the development of malnutrition. Malnourished individuals are at higher risk of developing immune dysfunction. Immunodeficiency is not only a consequence but also a cause of malnutrition. The immunometabolic changes act as an important mechanistic pathway of immune dysfunction in malnutrition. [27] Thymic development is found to be influenced by early life nutritional and environmental factors. [28] Significant impairment of several components of immunity, including cell-mediated immune responses, antibody production, antibody affinity, complement system, phagocyte function and cytokine production are associated with protein energy malnutrition (PEM). [29] PEM increases susceptibility to viral infections. Mice fed on a very low protein diet were found to experience higher mortality and morbidity induced by H1N1 influenza virus. They had reduced INF-γ levels, increased viral load and increased inflammatory cells in lung tissue as compared to those fed with higher protein diets. [30] Gut microbial balance has a huge impact on the host immune response. Microbiota influences the transcriptional programming of innate immune cells. Specific species of bacteria are also found to influence the development and differentiation of adaptive immune cells directly. Gut micro-organisms regulate the accumulation of intestinal plasma cells and secretion of immunoglobulin A (IgA). Dysbiosis leads to immune dysfunction through various mechanisms including modulation of Toll-like Receptors (TLRs), modulation of inflammasome signalling pathway and degradation of secretory IgA. [31] The components of a diet determine the composition of microbial population in gut which in turn regulate health and wellbeing. A change in dietary pattern alters the nutrients which are available to microbiota and promote the growth of select species there by altering the composition. A balanced diet is thus highly essential for maintaining the proper balance of beneficial and harmful micro-organisms in the gut. [32]

5. Nutritional Requirements in Viral Infections

Macronutrients and micronutrients present in a diet play a significant role in the optimal immune response of the host. Deficiency, excess and imbalance of certain nutrients have negative impact on the immune system and may increase susceptibility to various viral infections. The role of these nutrients are discussed below,

5.1 Protein and Energy

Hyper-metabolism and negative nitrogen balance are the characteristic features of viral infections leading to an increased calorie and protein requirement. These conditions are modulated by various hormones, cytokines and pro-inflammatory mediators. Reduced food intake due to anorexia further increases the loss of body tissues. There is about 13% rise in basal metabolic rate for every degree centigrade rise in temperature. This increase may be as much as 30-40% or above in sick patients. [33] There is about 20-25% increase in protein requirement over the recommended allowances for most of the infections. [34] The requirements of individual amino acids are not well established yet. Glutamine, arginine, aspartate are beneficial for lymphocyte proliferation and cysteine, glutamine, glycine are required for glutathione synthesis there by improving immune response. [35] Increased protein energy intake (n=8, 3.1 ± 0.3 g protein/kg/day and 119 ± 25 kcal/kg/day) is found to improve protein anabolism in critically ill children suffering from viral bronchiolitis as compared to those receiving a standard diet (n=10; 1.7 ± 0.2 g protein/kg/day, 84 ± 15 kcal/kg/day). [36] Excess intake of dietary protein and L-lysine increases the risk of high HIV replication, immunosuppression and disease progression. [37] So a proper balance of dietary protein and energy should be maintained.

5.2 Lipids

Lipids constitute an essential part of the diet. It is necessary for meeting daily energy needs, structure of cell membranes, cell signalling and maintaining metabolic processes. Polyunsaturated fatty acids (PUFAs) have immunomodulatory properties. Supplementation of high amounts Eicosapentaenoic acid/EPA and Docosahexaenoic acid/DHA (>10% of total fat) may show immunosuppressive properties in healthy human or animal subjects. Few studies have found no effect of EPA and DHA supplementation in infection. Conversely supplementation of moderate amount of EPA+DHA (<1g/day) is found to improve immune response in human subjects via lymphocyte proliferation, Natural Killer (NK) cell activity, macrophage activation and cytokine production (Interleukin-1, Interleukin-2, Tumor Necrosis Factor-α) after mitogen activation. [38] In human subjects mono-unsaturated fatty acids (MUFAs) do not appear to suppress the immune cells. [39] In general a proper ratio of saturated fatty acids (SFAs), MUFAs and PUFAs should be maintained in the diet. An SFA: MUFA: PUFA ratio of 1:1.3:1 is found to be superior for maintaining optimal health. [40]

5.3 Vitamins

Vitamins are popularly known as body protective nutrients. They are involved in various physiological and metabolic processes including immune response. Adequate provision of essential vitamins is required for the prevention of viral infections and reduces its negative impacts.

5.3.1 Fat Soluble Vitamins

Vitamin A, D, E and K are the major fat-soluble vitamins. Vitamin A (VA) and related retinoids can modulate many different elements of immune system, including expression of mucin and keratin, lymphopoiesis, function of neutrophils, T lymphocytes and B lymphocytes, natural killer cells, monocytes or macrophages, cytokine production, apoptosis and production of immunoglobulins. It reduces mortality and morbidity in viral infections like measles, measles related-pneumonia, diarrhoeal diseases, respiratory diseases, HIV etc. [41] The effects of infectious bronchitis virus (IBV), a type of coronavirus, is found to be more prominent in chickens fed on a marginally deficit VA containing diet as compared to those fed on an adequate VA

containing diet. [42] Vitamin D (VD) has potent immunomodulatory properties. Although the active form of VD can activate innate immune response, it may also inhibit the adaptive immune response. VD influences the susceptibility and severity of viral infections. The VD receptors (VDRs) are expressed on the immune cells and these cells are capable of converting circulating calcidiol (25-(OH) $_2$-D_3) to its active form calcitriol (1, 25-(OH) $_2$-D_3). [43] Lung epithelial cells are able to convert inactive VD to its active form in presence of viral infections thereby increasing cathelicidin production. [44] Cathelicidin is an anti-microbial peptide effective against various viruses. VD also influences cytokine profiles during infections and leads to an anti-inflammatory state. [45] VD may be associated with influenza, [46] HIV infection, [47] viral hepatitis (HBV, HCV), [48] dengue viral infection [49] etc. Vitamin E improves immune response via various mechanisms like protection of immune cells against oxidative damage, reduction of prostaglandin E_2 (PGE2) production from macrophages by inhibiting cyclooxygenase 2 (COX2), regulation of maturation and function of dendritic cells, promotion of T cell proliferation, immune synapse formation, increased antibody responses and NK cell activity. [38, 50] Vitamin K acts as a cofactor of various plasma proteins and thereby can regulate immune responses mediated by T cells. [51]

5.3.2 Water Soluble Vitamins

The B-vitamins play significant role in metabolic processes as well as immunity and inflammation. Thiamine deficiency leads to abnormal antibody responses. It also triggers pro-inflammatory responses, disturbance of antioxidant enzymes, tight junction proteins and increase in Nuclear Factor-κB (NF- κB). Thiamine supplementation improves lymphocyte count and its function and helps in immune homeostasis. Riboflavin possesses antioxidant and anti-inflammatory properties. It promotes phagocytic activities of macrophages and protects intestinal tight-junction protein damage. Anti-inflammatory properties are also shown by niacin, pantothenic acid and pyridoxine. Pyridoxine deficiency may reduce antibody production and alter T-cell responses. Folic acid (FA) and Vitamin B12 (VB12) are highly essential for optimal immune responses. Deficiency of FA and VB12 impairs various metabolic processes like serine/glycine cycle and DNA methylation leading to immune dysfunction. Hyperhomocysteinaemia and associated oxidative stress may also cause immune dysfunction. FA and VB12 deficiency compromise both humoral and cell mediated immunity. Such deficiencies alter the function of macrophages, NK cells, decrease circulating T-cells and impair the balance of CD4+/CD8+ ratio. [51] The deficiency of these vitamins may increase susceptibility to various infections. FA and VB12 deficiency is found in patients suffering from HIV. [52,53] VB12 deficiency may also cause severe thrombocytopenia, slow recovery of platelet counts and prolonged hospital stay in dengue fever patients. [54] Vitamin C (VC) is another important vitamin popular for its antioxidant effects. It acts as a cofactor in several biochemical pathways. VC promotes epithelial barrier function by increasing collagen synthesis, stabilization, protecting against oxidative stress, keratinocyte differentiation and fibroblast proliferation. VC enhances chemotaxis, phagocytic activities and antimicrobial activities of neutrophils and macrophages. It also helps in neutrophil clearance and decrease neutrophil necrosis. VC increases lymphocyte (T-cell and B-cell) proliferation and differentiation, enhances antibody levels, modulate cytokine levels and decrease histamine levels. [55] Additionally VC may decrease T-cell death [56] and increase NK cell activity via upregulation of protein kinase C. [57]

5.4 Minerals

Minerals also play a vital role in immune response. Calcium (Ca) acts as a secondary messenger in lymphocytes. Antigen binding to the specific receptors of lymphocytes leads to an increased intracellular Ca concentration due to increased influx of extracellular Ca2+ and increased mobilisation of Ca from intracellular membrane-bound compartments. [58] Magnesium (Mg) acts as a cofactor for immunoglobulin (Ig) synthesis, C'3 convertase, antibody-dependent cytolysis, immune cell adherence, macrophage response to lymphokines, IgM lymphocyte binding, binding of substance P to lymphoblasts, T helper-B cell adherence and antigen binding to macrophage RNA. [59] Mg shows anti-inflammatory properties. Magnesium deficiency may also cause thymus involution. Higher level of apoptosis is observed in the thymuses of Mg2+-deficient rats. [60] Manganese (Mn) is able to activate anti-viral innate immunity via cGAS-STING pathway, required for host defense against DNA viruses. Mice deficient in Mn have higher susceptibility to DNA viruses. [61] Iron (Fe) influences both innate and adaptive immunity. The functions of neutrophils and NK cells are impaired by iron deficiency. The bactericidal activity of macrophages is also reduced. Fe deficiency impairs lymphocyte proliferation, maturation and differentiation. The T-cells can sequester iron better than any other cell during mild to moderate iron deficiency. But in severe deficiency problems may set in. [38] Iron salt ferric ammonium citrate (FAC) is found to inhibit the infection of Influenza A virus, Zika virus, HIV and Enterovirus 71. It suggests that iron is involved in antiviral immunity. [62] Iron toxicity or overload may also impair immune response by decreased mitogen-stimulated and antibody-mediated phagocytosis by macrophages and monocytes, reduced migration of neutrophils, alterations of the subsets of T-lymphocytes, suppression of complement system, modification of lymphocyte distribution and increased rate of infections. [38] Selenium (Se) is required for the effective functions of neutrophils, macrophages, NK cells, T –cells and antibody production. It is a component of glutathione peroxidase (GPx) and thereby involved in the crosstalk from oxidative stress to immune response. Viral infections are often associated with oxidative stress and Se deficiency. Infection with Coxsackievirus is found to be associated with Keshan Disease. Serum Se level and GPx activity is lower in patients suffering from AIDS than in asymptomatic HIV patients and healthy persons. Marginal Se deficiency may also be associated with increased HIV shedding in genital tract. Se supplementation increases GPx activity in dormant infected T-cells, protect against oxidative stress and decrease NF-kB activation. [51] Zinc (Zn) modulates multiple aspects of the immune response. Zn is necessary for normal development and function of cells mediating innate immunity, neutrophils, dendritic cells and NK cells. Zinc deficiency also affects macrophages, phagocytosis, intracellular killing and cytokine production. Zn regulates the structure, integrity and function of membrane barriers. Deficiency of Zn leads to the disruption

of tight junctions and adhesion junctions. Degradation of E-cadherin and β-catenin is also enhanced. The growth and function of T-cells and B-cells are also impaired by Zn deficiency. [51, 63] Zn exerts antioxidant and anti-inflammatory effects via activation of certain antioxidant enzymes and proteins and inhibition of NF-κB pathway. [64] Zn deficiency may cause a decline in antibody production, reduced killing activity, decreased phagocytosis, reduced Fc-receptors-dependent mast cell activation, fall in neutrophil number and recruitment and decline in LPS-induced DC activation. Zn supplementation is found to be beneficial in many viral infections like HIV/AIDS, HCV, common cold, respiratory tract infection, diarrhoea etc. [51] Zn may also be beneficial in COVID-19 due to its immunomodulatory, anti-inflammatory and anti-viral properties. It can thus be used effectively as a preventive and adjuvant therapy in COVID-19. [65] Copper (Cu) is also involved in the optimal functioning of various immune cells like T-cells, B-cells, NK cells, neutrophils and macrophages. Cu can kill several infectious viruses such as HIV-1, poliovirus, bronchitis virus and other enveloped and non-enveloped viruses, single and double-stranded viruses, DNA and RNA viruses. Dietary or therapeutic supplementation of Cu and correction of mineral deficits may boost host immune response and is recently hypothesised to be beneficial in COVID-19. Zn competes with Cu for absorption in the jejunum via metallothionein. Supplementation with high doses of Zn (>150mg/day) may thus impair Cu absorption in COVID-19 patients. So intake of Cu should be properly monitored. [66]

Adequate supplementation of these vitamins and minerals is found to restore the adverse effects. The target should be to maintain the optimal physiological levels of these vitamins and minerals. However excess supplementation over the normal levels does not show any beneficial effect and may even show adverse effects.

6. Dietary Management of Viral Infection

The nutritional requirements during viral infections including COVID-19 are already discussed. Based on these requirements diets should be modified. The hospitalized patients can be broadly classified as Non-ICU patients and ICU patients. The persons who are in quarantine and mild cases who are receiving treatment at home should also be taken into consideration. Oral feeding may be tolerated by mild and moderate cases. The severe cases do not always tolerate oral feeding. If nutritional requirements cannot be met with oral feeding especially for ICU patients relevant guidelines for enteral feeding and parenteral nutrition should be followed. The overall target is to minimize catabolism by providing adequate nutrition through oral feeding, enteral feeding and/or parenteral nutrition.

For the patients suffering from COVID-19, 1-1.5 g/kg/day protein can be recommended in the absence of chronic renal insufficiency. Energy requirements may be calculated based on indirect calorimetry, predictive equations or oxygen consumption data whichever is feasible. Energy intake should be around 27-30 kcal/kg/day based on individual nutritional status, physical condition and comorbidities. Non-protein energy comes from carbohydrates and lipids. For patients having COVID-19, dietary energy ratio from lipids and carbohydrates should be between 30:70 (without respiratory insufficiency) to 50:50 (with respiratory insufficiency). [67]

6.1 Oral Feeding

If oral feeding is indicated in patients having viral infections it should be preferred. A healthy balanced diet with higher energy and higher protein should be recommended. For severely underweight patients and those who have not consumed food properly for many days, the target of 30kcal/kg/day should be achieved slowly to avoid refeeding syndrome. At least 50% of total protein intake should come from animal sources having higher biological value. Correction of vitamin and mineral deficiencies is highly essential and proper supplementation should be done. Hydration status and electrolyte balance should be properly monitored. Oral Rehydration Solution (ORS) is vital for patients having diarrhoea and vomiting. Fresh coconut water, rice water, barley water, pulse water are ideal for rehydration during viral infections. Nausea can be alleviated by light carbohydrate rich foods like puffed rice, toast, bread sticks, thin biscuits etc. Warm ginger tea may be helpful in reducing headaches. The food items prescribed should be easily digestible, tolerable and locally available. Small and frequent meals should be encouraged as anorexia is common. A variety of foods including cereals, pulses, legumes, milk, egg, meat, fish, whole fruits, vegetables and other energy rich foods should be included in the diet. Soothing foods such as warm water, warm liquids, chicken soup, vegetable soup, liquor tea etc. are beneficial for cough and sore throat. Persons with chewing and swallowing difficulties may consume a soft diet which may include boiled rice, boiled oatmeal, mashed potato, light pudding, custard, banana/fruit smoothie, soup, yoghurt, boiled papaya, etc. Bland diet can be recommended with persons having gastric discomfort. Cooking methods should include boiling, poaching, simmering, stewing, steaming, pressure cooking, toasting etc. Some baked and sauteed items can be included like baked fish, sautéed vegetables, chicken, mushrooms etc. Deep fried foods should be avoided.

Some functional foods are found to be effective against many viral infections. Curcumin present in turmeric is effective against Influenza virus, Zika virus, HCV, HIV, Chikungunya virus, Herpes simplex virus 2 and Human papillomavirus (HPV). Quercetin present in onion, chives, capers protects against Influenza A virus and SARS. Epigallocatechin gallate present in green tea is beneficial against Herpes simplex virus, adenovirus, HIV, HPV, HBV, HCV, Zika virus, Dengue virus, Chikungunya virus and West Nile virus. Phloretin present in apples, pears and strawberries is effective against Zika virus. Berberine found in barberry, turmeric is beneficial against H1N1 and Chikungunya virus. Broccoli contains sulforaphane effective against Live attenuated influenza virus (LAIV) and Epstein Bar Virus (EBV). Thymoquinone present in *Nigella sativa* (Black seed oil) is protective against Avian influenza virus (H9N2). Polyphenols present in sage is effective against herpes simplex virus 1, HIV and SARS-CoV. [68] Honey contains various nutrients, health promoting substances and shows antiviral properties. Cu, ascorbic acid, flavonoids and H_2O_2 present in honey inhibits viral transcription and translation. Nitric oxide (NO) present in honey inhibits viral polymerase, nucleic acids and capsid proteins. [69] Fresh ginger is found to show antiviral properties against Human Respiratory Syncytial Virus by decreasing plaque formation on airway epithelium by blocking the attachment and internalization of virus. [70] Daily supplementation of *Spirulina platensis* (10 gm/day)

along with standard care has been found to improve CD4 cell count and decrease viral load in HIV-1 patients after six months. [71] Probiotics are also highly beneficial in viral infections and respiratory tract infections due to their immunomodulatory properties and promotion of gut microbial balance. [72, 73] Probiotics (*Lactobacillus* and *Bifidobacteria*) may be useful in COVID-19 but a more targeted approach is required for preventing dysbiosis. [74] Papaya leaf is popularly used for the management of dengue patients. Papaya leaf extract may be useful for increasing platelet count and may show antiviral properties [75, 76].
Oral Nutritional Supplements (ONS) are recommended whenever necessary. For COVID-19 patients ONS should provide at least 400 kcal and 30 g protein per day. [77]

6.2 Enteral and Parenteral Nutrition

The general protocols for medical nutrition therapy (MNT) in critically ill patients should be followed. When oral feeding is not indicated and/or cannot meet the nutritional requirements enteral nutrition (EN) should be initiated. When enteral feeding is also not indicated and/or able to meet nutritional requirements parenteral nutrition (PN) should be initiated within three to seven days. In case of contraindications for EN in high risk patients early and progressive PN can be initiated. Continuous rather than bolus EN is recommended. Gastric access should be ideally used for EN. If gastric intolerance or high risk of aspiration is present then post pyloric feeding is recommended. Necessary prokinetic therapy (erythromycin, metoclopramaide) should be performed. EN should be delayed in patients having uncontrolled shock, uncontrolled hypoxemia, uncontrolled upper GI bleeding, bowel ischemia, bowel obstruction, gastric residual volume (GRV) >500 ml/6 hour and other life-threating conditions. Hypocaloric nutrition (not exceeding 70% of calculated energy requirement) should be administered during early acute phase of illness and then gradually increased (up to 80-100% of energy requirement) by following necessary protocols. Overfeeding should be avoided. 1.3 gm/kg/day protein can be delivered progressively to critically ill patients. For obese patients adjusted body weights should be used. Omega-3-fatty acids can be added to enteral feeds within nutritional range. High dose monotherapy with antioxidants is not recommended if deficiency is not present. If full EN is not tolerated by the critically ill patients during the first week of ICU admission, then the benefits and safety of PN should be judged on a case by case basis. All strategies to optimize EN should be performed. In extubated or non-intubated ICU patients with dysphagia texture-adapted foods are recommended. If swallowing is unsafe then EN or temporary PN can be used. The levels of blood glucose, vitamins, minerals and electrolytes (potassium, magnesium, phosphate) should be properly monitored. [78, 79] The overall process is summarized in Figure-1.

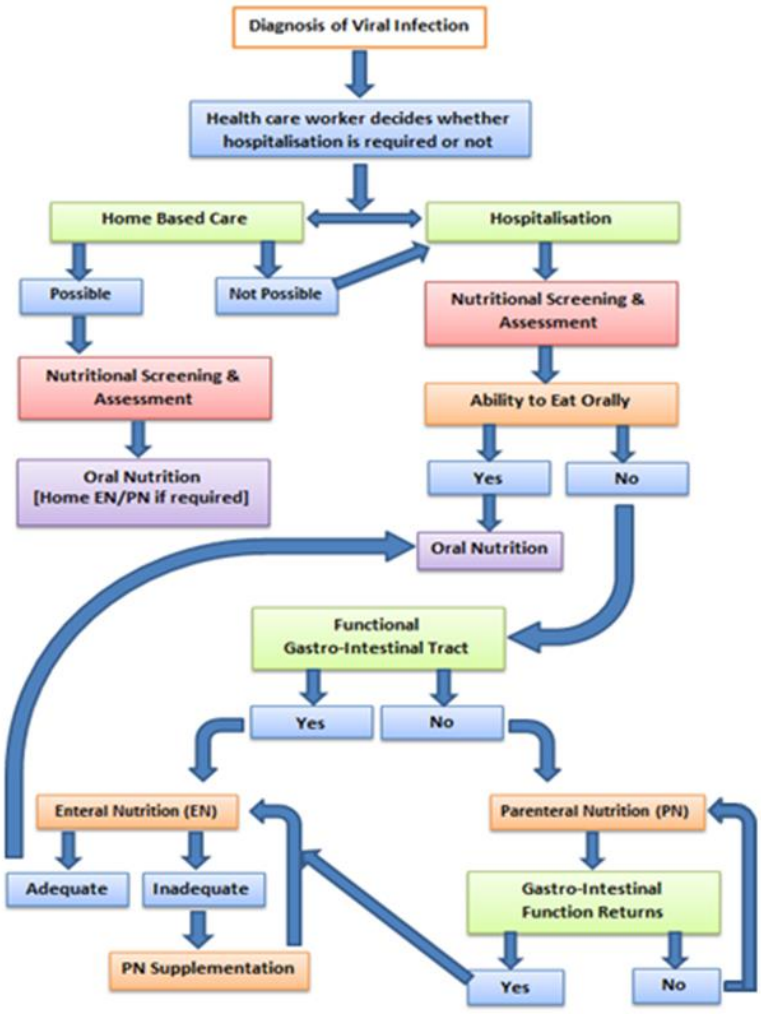

Fig 1: Protocol for Medical Nutrition Therapy (MNT) in Viral Infections

7. Conclusion

Nutrition and diet therapy play vital role in the prevention and management of viral infections. Nutrients and functional foods possess immunomodulatory properties which are beneficial to fight against viruses. Several physiological and biochemical changes induced by viruses can also be reversed with the help of a proper diet. Medical Nutrition Therapy (MNT) has a significant role in the management of COVID-19 patients. It is necessary to focus more on improving immune response with the help of a nutritious diet. Although further research work is necessary to optimize nutrition care processes in viral infections.

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