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SHORT COMMUNICATIONS

Restoring Good Health in Elderly with Diverse Gut Microbiome and Food Intake Restriction to Combat COVID-19

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Abstract COVID-19 continues to be an ongoing global threat. The elderly with underlying health conditions like cardiovascular and lung diseases, diabetes, obesity, are the most vulnerable to this disease. Curing the pre-existing health conditions will greatly increase a person's resilience to COVID-19 and lower the death rate of the old people. Digestion and immunity form an integrated nutrition acquisition process, especially in obtaining essential amino acids and essential fatty acids from living microbial cells. A mature strong immunity coupled with gut dysbiosis in adults is the main cause of nutritional disorders like morbid obesity, diabetes mellitus, cardiovascular and pulmonary diseases. Nutrition disorders in return worsen dysbiosis. Human microbiome has an intrinsic duality. While a diverse microbiome provides a full spectrum of essential nutrients to our body, nutrition disorders fuel overgrowth of microbiota (dysbiosis) at many sites on or inside our body, and are the main causes of chronic inflammation at these sites. In the case of COVID-19, nutritional disorder impairs the immunity, causes hyperinflammation, and leads to the protracted overload of cytokines by the immune system, i.e., the cytokine storm. Autophagy induced by restrictive eating is an ideal inhibitor of microbiota overgrowth, as autophagy deprives microbiota of excessive nutrition for replication. Autophagy also attenuates inflammation. Therefore, as a precaution, the author suggests restoring good health in the elderly with the support from a diverse gut microbiome and daily regular food intake restriction, so as to lower the risk of developing into severe case even if they are infected by COVID-19.

Keywords COVID-19 · Metabolic syndromes · Digestive immunity · Gut microbiome · Restrictive eating

Introduction

The current COVID-19 pandemic caused by coronavirus SARS-CoV-2 turns out to be a huge threat to the whole of humanity. As of today (23 November 2020), over 59 million people are infected, and more than 1,394,000 people died across the world (https://www.worldometers.info/coronavirus/). The symptoms for COVID-19 can range from asymptomatic through mild to severe fatal cases (https://www.cdc.gov/coronavirus/2019-ncov/). As there is no effective medicine or vaccine for COVID-19, nonpharmacological interventions like travel restriction, social-distancing and lock-down are employed to mitigate the spread of SARS-CoV-2 virus [1, 2], and conventional or traditional medicines are employed to alleviate mild cases of COVID-19 [2]. While COVID-19 primarily exhibits as an acute respiratory disease with lung failure due to microvascular damage followed by necrosis and haemorrhage, it also affects the heart, intestine, lymphatic tissue, liver and kidneys, and cause damage to these organs [3]. Multiple-organ failure including renal and cardiac failure due to overreaction of the immunity (cytokine storm) is the major cause of mortality among the 5% critically ill patients [1, 3, 4]. Elderly aged 65 years above, especially those with pre-existing illnesses like cardiovascular and pulmonary diseases, diabetes mellitus, are in the high-risk group, and the proportion of fatalities is particularly high in the group of patients older than 80 years [https://www.

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worldometers.info/coronavirus/coronavirus-age-sex-demographics/]. Chronic metabolic disorders (such as morbid obesity, type 2 diabetes mellitus, and cardiovascular diseases) are associated with immunometabolism dysregulation and chronic systemic inflammation [1, 4]. The malfunction of immune system and chronic inflammation escalates and prolongs the hyperinflammation in COVID-19 disease, promoting pulmonary fibrosis in the lungs and damages in other organs, causing lung and multiple-organ functional failure, and leading to fatality [4]. These key features of severe COVID-19 cases clearly indicate that, the mortality of old people in COVID-19 is attributed more to the metabolic syndromes than the virus itself. In view of this, the author proposes that, curing the pre-existing health conditions such as cardiovascular and pulmonary diseases, and diabetes should greatly lower the mortality of the elderly and the overall death rate of COVID-19. Yet, the curing of pre-existing diseases is not achievable without the help from a diverse gut microbiome.

The Importance of Gut Microbiome to Good Health

The importance of gut microbiome to health is well-documented [1, 5, 6]. For example, research shows that short-chain fatty acid produced by gut microbiota fermentation alleviates type 2 diabetes mellitus [1, 6]. Gut microbiota also has positive contribution to the host defence against pneumonia [6], and may contribute to super longevity [1]. The preservation of host-microbes homeostasis can counteract inflammation, intestinal permeability, and decline in bone and cognitive health [1, 5, 6]. Gut dysbiosis becomes the main contributing factor to numerous diseases like infection, morbid obesity, diabetes, hepatic diseases, allergies, and more [1, 5, 6]. An abnormal gut microbiota induces disturbances to immune system and metabolism, impairs the barrier ability of gut mucosa, leading to systematic low-grade inflammation, which is causally linked to insulin resistance [6]. The research by Rishi et al. [1] also suggests that the beneficial microbes from plant-based diet may contribute to the better prognosis of COVID-19 patients in India compared to that of the COVID-19 patients in the western countries. Also, as potential pathogens, gut microbiome foster the innate and adaptative immune system of human body [7]. Furthermore, the enormous microbiota species are the vital providers of essential nutrition to the human body [5]. Without the support from a diverse microbiome, malnutrition and nutrition imbalance are inevitable, resulting all the metabolic syndromes like morbid obesity, and impairing the immune system.

A balanced nutrition supply is crucial to our immunity in fighting infectious diseases [8]. Lack or excess of any one of the essential nutrients will weaken our immunity [8]. On the other hand, immunity is also pivotal to human's nutrition acquisition. For example, the digestive gastric acid as an important component of innate immunity kills most of the foodborne microorganisms [8]. The proteolysis of these microorganisms by gastric acid provides a full spectrum of amino acids and fatty acids, which can be used by our body as nutrients. In certain mammals like the ruminants, microbial protein contributes to 60 to 85% amino acids reaching the small intestine [9]. Such microbial protein guarantees the ruminants sufficient balanced nutrition even though they are fed on a simple nutrient-poor diet like grass. In addition, the mammalian gastrointestinal tract mucosa is constantly exposed to dietetic and invasive microbial antigens [8]. The gastrointestinal epithelial cells thus form the first line immune barrier against these antigens [5, 8]. As a regulator and effector in innate immunity, autophagy (xenophagy) is pivotal in initiating relevant gastrointestinal immune responses and degrading invasive microbial antigens [5, 10, 11]. The microbial proteins degraded by autophagy also contributes to the cellular nutritional and energy homeostasis [5, 11]. Thus, in mammals like the ruminants, protein synthesis may be sustained even in the absence of amino acids from dietary. This indicates that immunity and digestion for nutrient acquisition is an integrated process in mammalian physiology, and microbiota as prey of mammalian immunity and source of metabolites plays an indispensable role in mammalian nutrition supply. As monogastric mammals like human beings don't have an organ like the rumen for microbial fermentation, it would be beneficial for human beings to consume raw fermented food daily to fulfil the essential nutrition demand of our body [5]. Yet such integration between immunity against microbiota and nutrition acquisition from microbiota is largely ignored in human health, and lead to all kinds of nutrition disorders like obesity and metabolic syndromes, even though human beings are feed on a vast variety of dietary sources.

The Neglect of Gut Microbiome, Malnutrition and the Cytokine Storm in COVID-19

As some microorganisms can cause infectious diseases, our society tends to eliminate bacteria indiscriminately [12]. For centuries, cleanliness as the central concept of hygiene is deeply rooted in the public knowledge as well as in the medical community [12]. We make all effort to get rid of microorganisms from every surface in the environment, outside our body and inside our body. As a result, the important contribution of microbiome to the development

of our immune system and the innumerable bacteria genes as indispensable source of essential nutrition have long been neglected. Because of this, most of the people have the problem of gut dysbiosis and malnutrition when they grow old, and they have impaired immunity. In people with obesity and metabolic syndromes, lipotoxicity [13] further damage the impaired immunity, and makes the gut dysbiosis even worse. Lipotoxicity is the deposition of lipid intermediates in non-adipose tissue, leading to cellular dysfunction and death [13].

People tend to think that elderly have a weaker immunity than younger people do. This is a misinterpretation about aging. Actually, when people are aging, they have greater opportunity to expose themselves to diverse pathogens. Therefore, the immunities of old people are much robust than their immunities at their younger time. If Elderly were physically fit, they would have great resilience to most of the common diseases, and enjoy "the most beautiful period of life" (Luigi Cornaro, The Art of Living Long. Milwaukee. Butler WF. 1905, http://hdl.handle.net/2027/nnc2.ark:/13960/t1sf3j34q). However, most of the elderly have developed metabolic syndromes when they grow old. Surprisingly, these metabolic syndromes might be the results of the strong immune system of the old people, coupled with malnutrition. The close integration of digestion and immunity for nutrition acquisition clearly shows that a normal or strong immunity is a prerequisite for nutrition supply in our body. Patients with immunodeficiency would more likely have malabsorption in the small intestine, resulting in involuntarily weight-loss, and would not develop into metabolic syndromes like morbid obesity and related complications. The strong immune system of old people captures and degrades the microorganisms (bacteria, viruses, fungi, …) in their body and turns them into nutrients (immunonutrition). Yet, the gut dysbiosis in old people limits the available source of microbiome. Overeating is inevitable, which leads to the accumulation of lipids in non-adipose tissue and lipotoxicity. Human microbiome has an intrinsic duality on our health. While a diverse microbiome provides a full spectrum of essential nutrients to our body, overgrowth of microbiota (dysbiosis) at any site on or inside our body (like in the respiratory tract or gastrointestinal tract) may fuels inflammation [1, 5, 6]. So, the abundance of microbiota in our body should be restricted by the deprivation of available nutrition (dead cells, dysfunctional organelles, metabolic waste, …) for their replication. Autophagy as a cellular quality control pathway is an ideal candidate for clearing dead cells, dysfunctional organelles and redundant large protein platforms such as inflammasomes in the cell [5, 10].

In severe cases of the COVID-19 disease, the SARS-COV-2 virus infection does not account for the severity of the disease. It is the cytokine storm, or the uncontrolled releasing of cytokines to the infected cells by the immune system of the patients, which causes hyperinflammation [1–4], collapses the respiratory systems and kills the patients. Cytokine storm reflects a strong yet malfunctioning immunity. Reported data from China show that there is no death for children under 9 years old (https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/), although it is well-known that children have immature innate and adaptive immunity. This means that, with an immature immune system in young children, cytokine storm will not be triggered, even though infants can be severely infected by the SARS-COV-2 virus [2].

Gut Microbiome as the Only Nutrition Source in Severe Illness: They can Help to Stop the Protein-Energy Malnutrition (PEM) and Involuntary Weight-Loss (IWL)

The role of diverse microbes is most decisive in severe illness, because microbiota will be the only nutrition source targeted by our immune system in critical illness. As a common symptom of acute illness and trauma, loss of appetite can be found in infectious diseases [11] as well as in physical injury and in chronic diseases like the pulmonary, cardiovascular, nervous system, musculoskeletal, renal and articular diseases (https://www.medscape.org/viewarticle/432384_2). This illness-induced anorexia (IIA) is an adaptive, protective response for pathogen and injury elimination (https://www.researchgate.net/publication/329915614). Unlike the occasional inadequate nutrition intake (like starvation) invokes regulatory mechanisms aimed to conserve energy and preserve lean mass in physically fit persons, hypermetabolism and escalated lean mass breakdown are triggered in sick persons with IIA (https://www.medscape.org/viewarticle/432384_2). Even nutrient intake will not reverse this process, and it will only stop when the insult, like the infection or injury has resolved (https://www.medscape.org/viewarticle/432384_2). Furthermore, aggressive nutritional support does not benefit patients but may be detrimental [14]. Yet, research shows that probiotics can dramatically improve the intestinal function of a critically ill infant patient [15], which indicates that microbiota is the only nutrition source targeted by our immune system in critical illness when patients have IIA. During infection and injury, IIA systematically upregulates autophagy to degrade pathogens and reuse the degraded macromolecules and organelles to reinstall body homeostasis and health [11]. In the 16th Century, Luigi Cornaro had already noticed the health benefit of IIA (Luigi Cornaro, The Art of Living Long. Milwaukee. Butler WF. 1905, http://hdl.handle.net/2027/

nnc2.ark:/13960/t1sf3j34q). However, if anorexia turns out to be chronic, hypermetabolism coupled with long time decreased food consumption will inevitably results in malnutrition featured by severe decrease in lean mass and body lipid storage, a situation termed as cachexia (https://www.medscape.org/viewarticle/432384_2). In such condition, gut microbiome will be the only source of nutrition outside our body degraded by the immune system to provide extra immunonutrition to our body to resolve the insults in short time, and prevent the protein-energy malnutrition (PEM) and involuntary weight loss (IWL).

Eat-but-Little (Restrictive Eating) to Support the Gut Microbiome and Gastrointestinal Tract Homeostasis and Restore Good Health

As discussed in the previous sections, although a diverse microbiome is crucial in providing essential nutrients to our body, the overgrowth of microbiome on or inside our body is the source of inflammation for patients with metabolic syndromes, and need to be tightly checked by autophagy, an important component of our innate immunity [5, 10, 11]. As upregulation of autophagy requires serum starvation [10, 11], restrictive eating is now a prerequisite for a person with metabolic syndromes to restore good health. As a preventative measure, one may consume some local fermented food in raw as a source of microorganisms, and stop eating 5 hours before going to bed (https://www.researchgate.net/publication/329915614). In this way, the metabolic syndromes may be reduced or eliminated, a person can regain his good health. He then can reduce the severity of the disease by avoiding the cytokine storm, even if the person is infected by COVID-19, and promotes speed recovery from the possible infection.

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