Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 6 Issue 4 April 2022

Review Article

Rice Consumption Enhancing Innate Immunity with a Reduced Risk of COVID-19 Infection and Mortality

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DOI: 10.31080/ASNH.2022.06.1028

Received: March 08, 2022

Published: March 21, 2022

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Abstract

Incidence and mortality of COVID-19 varied significantly by country. No clear hypothesis has been proposed to explain such an enormous difference. We found that annual rice consumption by country inversely correlated well to the cumulative number of COVID-19/million by compiling data from 17 major countries of G20. The negative correlation coefficient was 0.74, while wheat consumption showed a positive correlation. It suggested that the nature of staple foods supported primary resistance to SARS-CoV-2 infection. Early resistance to developing COVID-19 pneumonia would be cellular immunity and curable inflammation. Parallel increase of antibodies helped to eradicate pathogenic viruses. Pathologically, two plausible factors were sIgA, which mechanically blocked the virus from binding to the ACE2 receptor. Another factor was suppressing cytokine storm by regulatory T cells expanded by butyrate from intestinal microbiota.

The gut environment based upon the rice eating habit seemed essential to support a stable immune system byT17/Treg balance. Long rice-eating practices contributed to producing a secretary piece of IgA and growing particular microbiota composition, which had produced butyrate and other short-chain fatty acids, influencing various physiological functions. Rice eating would be the "X factor" by building solid innate immunity. However, different cultural habits, such as bowing etiquette, wearing face masks, and handwashing with sanitizing equipment, also suppress SARC-Co-2 infection. The suppressive action of the X-factor continued regardless of the different variants of SARS-Co-2. infection. The recent pandemic of Omicron seems to attenuate to habituate in human society as suggested from the historical aspect.

Keywords: COVID-19; Innate Immunity; Rice Eating; sIgA; Microbiota

Introduction

Infectious disease pandemics have been repeated many times in human history [1,2]. Coronavirus pandemics, such as SARS (severe acute respiratory syndrome), MERS (Middle East Respiratory Syndrome), and COVID-19, seem to reappear every eight years [3]. Incidentally, the mortality rate of SARS was 10%. For MERS, 44% in Saudi Arabia and 18% in Korea among confirmed cases [4]. SARS-CoV-2 is thought to have been transmitted to humans directly from bats or through other animals [5,6].

The case fatality rate of COVID-19 in Japan was constantly around 1.%. Such a low rate was ordinary in many Asian countries compared to Western countries. Also, in the case of SARS-CoV-2, a significant number of asymptomatic infected individuals was present, and the actual case fatality rate may be even lower. SARS-CoV-2 was considered more transmissible from human to human and caused a pandemic than SARS-CoV and MERS-CoV, but less pathogenic. The proportion of patients with pneumonia decreased, and the number of young people complained of cold symptoms such as runny nose, headache, and sore throat. Given that the δ strain and Omicron had a higher affinity for the upper respiratory tract

and were more likely to cause cold symptoms than pneumonia, we could interpret them as attenuated.

Pathogenicity should be grasped from a bird's-eye view while considering various factors. Currently, SARS-CoV-2 seems to follow an evolutionary path from bat coronavirus to human coronavirus by repeated human-to-human transmission. It is estimated that 10 to 15% of colds are caused by a coronavirus (HCoV) [6], and this is the second most common after rhinovirus (30-50%).

While the SARS-CoV-2 epidemic first found in Wuhan has ended, various mutant strains have been identified worldwide, showing multiple pandemics [7]. Currently, it is called the α, b, g, d, and omicron strain [8,9]. The characteristic mutations found in the S protein of the α to δ strains and Omicron are shown in table 1. D614G mutated variant was more transmissive than previous epidemic strains.

WHO Name	First report	Pangolin	K417N	K417t	L454R	T478K	E484K	E484Q	N501Y	D614G	P681H	P681H
a	England	B.1.1.7					○		○	○	○	
b	South Africa	B.1.351	○				○		○	○		
g	Brazil	P.1		○			○		○	○		
d	India	B.1.617.2			○	○		○		○		○
omicron	South Africa	B.1.1.529	○			○	○		○			

Table 1: SARS-Cov-2 variants and points of mutation in S-protein.

Additional mutations in Omicron; G142D, G339D, S371L, S373P, S375F, N440K, G446S, S477N, E484A, Q493K, G496S, N440K, G446S, S477N, E484A, Q493K, G496S.

As of this writing (February 15, 2022), the number of infected people worldwide has exceeded 411.7 million, and the number of death has been approximately 5.8 million (1.4%). In Japan, more than 4 million people have been infected, and 20,770 have died (0.51%). More than 80.0% of patients were discharged, and 0.03% of patients with respirator use remained in hospitals [7,8].

Antiviral drugs and vaccine development are urgently needed for COVID-19, but individuals should keep solid immune defenses in the meantime [4]. The nutritional state was related to the mortality of COVID -19. Fei Zhou., *et al*. described the clinical course of 191 COVID-19 patients, 137 discharged, and 54 died [10]. Undescribed deaths without complications might reflect poor immunity due to malnutrition, as suggested by low serum albumin levels and low lymphocyte count. The Chinese Society of Dieticians and the People's Liberation Army have issued optimal energy and protein intakes recommendations. Daily meals should include 250 - 400g of cereals, and 150 - 200g of meat and fish, containing 30g - 40g of proteins. Adequate nutrition should be among priorities for treatment, as there is no remedy yet.

Low- and middle-income countries should strategize to ensure the population at large has access to optimal nutrition to boost the immune system and should provide specific supplementation for the treatment of COVID-19 patients, especially those with severe disease [11]. Merino., *et al*. reported diet quality and risk and severity of COVID-19 on the 592,571 smartphone-based cohorts [12]. They found healthy plant-based food (fruits, vegetables, and whole-grain) was associated with lower risk and severity of COVID-19. However, the adjusted hazard ratio for COVID-19 was 0.8-0.9 in the high hPDI group and 0.45 for severe COVID-19. Although the study population was mainly white in England, they showed the joint association of diet quality with socioeconomic deprivation.

Bollyky., *et al*. exploratory analyzed infection and fatality rates of COID-19 to find contextual factors associated with preparedness in 177 counties from Jan 1, 2020, to Sep 30, 2021 [12]. They selected many factors, including GDP per capita, population density, the population living below 100m, age distribution, BMI, exposure to air pollution, smoking rate, the prevalence of chronic obstructive pulmonary disease, and cancer. They also assessed the relationship between interpersonal and government trust and corruption, and changes in morbidity patterns and COVID-19 vaccination rates. However, most cross-country variations in cumulative infection rates could not be explained. Only high levels of government and interpersonal trust, associated with higher COVID-19 vaccine coverage among middle-income and high-income countries, were

associated with a more significant reduction in morbidity. Yet, the conditions related to cross-country variation in infection and fatality rates during the COVID-19 pandemic are not well understood.

Futhermore, most research on COVID-19 outcomes has had a regional focus or has focused on a small number of country experiences.

COVID-19 pndemicpandemic in Japan

In Japan, six pandemic peaks were present (Figure 1). Wuhan strain detected in February 2020 were cases on the cruise ship Diamond Princess [13]. In mid-March 2020, an epidemic (first wave) happened due to European strains (B.1.1.114 strain), and Wuhan strains disappeared. The 614th amino acid of the S protein was aspartic in the Wuhan strain, and in contrast, it was mutated to glycine (D614G mutation) in the European strain, advantageous for replication (Table 1).

Figure 1: Corona pandemic in Japan.

Then, in June, when the first wave by SARS-CoV-2 had subsided, European strain suddenly became apparent and formed the second wave of the epidemic. And the outbreak from October, in the third wave, mutant viruses of yet another strain (B.1.1.214 strain) derived from European strains became the main constituents [14].

The fourth and fifth waves occurred by d type. Infection with the d strain in Japan has spread rapidly, and the number of infected people exceeded the past wave. In August 2020, it reached more than 5000 patients a day but suddenly disappeared to less than 50 a month later. We are concerned now that Omicron made the sixth wave. In January 2022 number of new patients became more than 20,000 a day, which was 20 times more than the one week before (Figure 1).

The number of infected people has increased rapidly due to the spread of community-acquired infections like kindergarten and the rapid replacement with Omicron strain. Still, the different prevalence and mortality between Japan and European countries were present. The Omicron variant BA.1 has recently become dominant, and BA.2 is rarely present. Fortunately, we could expect a level off in March, 2022. Among all the coronavirus variations discovered so far, Omicron is thought to be the milder of the bunch.

Low COVID-19 infection and mortality in rice eating countries

It became clear that the number of infected people in Europe and the United States was more than ten times higher than in Asia (Figure 2). Qualitative explanations included differences in lifestyle such as kisses/masks, but none from a macro statistical point of view to explain the global contrast.

We statistically analyzed the correlation between “staple food” and “COVID-19” under the health norm of “medicine and food source.” We had found that the rice-eating countries showed less infectivity and mortality of COVID-19 [15]. The mortality data were independently affected by medical care and other conditions. However, the total number of incident cases and deaths by European and Asian counties showed a dramatic difference in the last two years (Figure 2).

It seems that there has never been a comprehensive model that can answer these questions consistently. We had reported that the high proportion of sIgA deficiency among Caucasians would be one explainable factor of different incidence and mortality by countries [16,17]. However, the relationship showed marginal statistical significance.

Figure 2: Number of COVID-19 patients and deaths in Western and Asia countries by every 6 months.

Then, we observed the relationship between rice consumption by country and COVID-19 incidence and mortality from June 2020 to December 2021. For correlation analysis, we selected 17 representative countries, 16 members of the G20, and additional data from Spain. For the same countries, per capita consumption of rice and wheat (kg/year) were taken as independent variables [15]. We obtained the source of food data of 60 years avaraged between 1960 to 2019 from "world food.apionet" [18]. The two variables were used for regression analysis after common logarithmic transformation. Correlations were calculated by the least square's method by IBM-SPSS ver [24].

We followed up the relationship until Dec 2021 with six-month intervals from Jan 1, 2020 (Figure 3) Corona infections continue to spread, and the number of people infected worldwide has increased about 22 times over the past year. The coefficient of determination R2 between COVID-19 disease and rice consumption showed a strong negative correlation continuously; 0.58 in June 2020, 0,73 in December 2020, 0.68 in June 2021, and 0.69 in December 2021 (total population 2.9 billion, 38% of the world population). Similarly, the coefficient of determination R2 for the number of deaths every six months was 0.58, 0.76, 0.76, and 0.72, respectively.

Despite the pandemic variants that showed the different effects of vaccines, steady negative correlations between Covid-19 death and rice consumption suggested the presence of underlying solid innate resistance against SARS-Cov-2 infection. On the contrary, a positive correlation between COVID-19 and wheat consumption was present. Such an apparent contrast could cover the effects of many other confounding factors and strongly suggested the importance of innate immunity based on rice eating habits [4]. Past rice consumption trends weighed more than 200 kg per person per year in Vietnam and Myanmar, about 100 kg in Thailand and China, and 60-70 kg in South Korea and Japan.

Our previous studies suggested that rice eaters had an excellent intestinal environment related to high innate immunity [19]. It appeared that the Asian-type dietary habit centered on rice provided more resistance to virus infection than the Western-type meal centered on bread and meat.

The missing link between rice-eating habit and SARS-Cov-2 infection

The above-described data suggested that the nature of staple foods strongly influenced resistance to SARS-CoV-2 disease. Our previous findings indicated that rice eaters had a specific composition of intestinal microbiota profile, which could prevent inflammation [20,21].

So, we tried to explain why rice-eating habits protected from Covid-19 death. We had done the intervention study by a brown rice lunch [21]. The results suggested that rice-eating induced stable innate immunity by short-chain fatty acids (SCFA), which stimulated the proliferation of regulatory T cells. In that study, brown rice genmai omusubi (rice cake) was provided five times/week as a business lunch for 12 weeks. Participants practiced the pre-and post-questionnaires, including dietary habits and daily life records, monthly blood pressure, and body composition. Before and after the intervention, the fecal samples' simultaneous measurement of intestinal microbiota and SCFAs was done. We used biochemical data, including IL-6, CRP, and TNFa, as inflammatory markers for correlation analysis with microbiota changes.

After three months of eating brown rice lunch, the bodyweight decreased in about half of the participants, and bowel movements and stool status improved significantly [21]. Brown (genmai) rice favored a gut microbiota with highly prevalent *Firmicutes* and a low prevalence of *Fusobacterium*. Significant microbiotic change was an increase of *Actinobacteria* and a decrease of *Proteobacteria. Blautia wexlerae, Collinsella aerofacience*, and *Eubacterium hallii* significantly increased at the species level. The phytonutrient profile of *genmai* included feruloylated oligosaccharides, γ-oryzanol, and GABA, which corrected to keep this microbiome profile and function [22].

Honda., *et al*. has found 11 rare, low-abundance human microbiome components with potential as broadly effective biotherapeutics [23]. Brown rice eaters have most of these, and the difference between brown and white rice eaters by microbiota profile was in high butyrate production [21]. In particular, *Faecalibacterium prausnitzii* may favor butyrate production and *Blautia wexlerae* seemed to stabilize intestinal immunity [24]. This may contribute to possible differences in susceptibility to Covid-19, where rice rather than wheat was a COVID-19 preventable staple food.

Brown rice lunch also increased microbiota diversity. They were positively or negatively associated with SCFAs. In SCFAs, acetate and propionate tended to decrease, while i-butyrate and i-valerate kept the same level, and caproate was raised by brown rice lunch. The upper tertial of *genmai* eaters tended to show low IL-6 and CRP, while TNFα was high. Butyrate binds the GRP109 receptor of the epithelial surface, and the signal is transferred to the submucosal layer and stimulates the proliferation and maturation of regulatory T cells [25-27]. Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated CD8 (+) T cells.

Hirayama., *et al.* [28]. reported that high *Collinsella* level was associated with low COVID-19 mortality rates by a cross-sectional study on OECD 10 countries. *Collinsella* produced orsodeoxycholate, which inhibits the binding of SARS-CoV-2 to ACE2 and suppresses pro-inflammatory cytokines like TNF-α, IL-1β, IL-2, IL-4, and IL-6. However, *Collinsella* did not directly associate with butyrate and other short-chain fatty acids, so it might be a surrogate marker of *Blautia* or other butyrate-producing bacilli.

Pathological Process of SARC-Cov-2 Infection

Pathologically, the COVID-19 infection could be divided into 5 phases; (a) binding to ACE receptor, (b) viral replication inside the infected cells, (c) initial response of non-specific defense system, (d) acute inflammation, (e) antibody production in subacute/chronic phase leading to cure (Figure 3). The CoV-2 virus has been well studied, but host interaction is still unsatisfactory. The emerging immunopathological determinants for recovery or death were essential [29].

The first phase to bind to the ACE2 receptor could be mechanically blocked by the thick secretory IgA (sIgA) layer. We had found that countries with high sIgA deficiency had high COVID-19 disease in late 2019 when SARC-Cov-2 specific IgA would not be present in Japan. So, we considered the mechanical block would adsorb virus particles to the glycoprotein of the sIgA component and discarded into feces.

Genetic susceptibility to produce the secretory component of IgA was still unclear. However, the sIgA level showed a positive correlation with rice consumption, so long history of rice-eating should contribute to making a secretary piece of IgA in the gut and oropharyngeal epithelia. It should be effective in upper respiratory tract infections. It may explain why omicron infection is so frequent in Europe and the USA, where a high proportion of sIgA deficiency exists.

Figure 3: Relationship between the number of COVID-19 patients (upper) and death (lower) in 2020 (left) and 2021 (right).

Reducing virus-cell interactions at an early stage might be a way to control the onset of the disease [30]. Viral infectivity depended on interactions between the host cell plasma membrane and the virus envelope. Baglivo., *et al*. found that specific molecules can reduce the infectivity of some coronaviruses, possibly by inhibiting viral lipid-dependent attachment to host cells [31].

The second phase was intracellular viral replication, which was interfered with by many antiviral factors [32,33]. MicroRNA might control viral RNA proliferation in situ, and there would be many unknown reactions in this phase *in vivo* state.

Cellular immunity

At 3rd phase of an initial response was cellular immunity. Dendritic cells, NK cells, other immature T-cells nonspecifically responded to SARS-Cov-2 and secreted various cytokines and chemokines. The interferon (IFN) response constituted the primary first line of defense against viruses [32,33]. Recognition of viral infections by innate immune sensors activated type I and type III IFN response. Type I IFNs (IFN-a, IFN-b, IFN-ε, IFN-k, IFN-u in humans) bound to the ubiquitously expressed type I IFN receptor in an autocrine and paracrine manner. This activates a powerful antiviral defense program of hundreds of interferon-stimulated genes, which can interfere with every step of viral replication. Type III IFNs bind to the type III IFN receptor, preferentially expressed on epithelial cells, but the particular de-novo reaction was still insufficiently reported.

We recognized the importance of dendritic cells as the first playmaker because they were tissue-fixed cells and kept intimate communication with T cells. We had studied the maturation and distribution of dendritic cells in the human fetus [34]. They first appeared in the thymus of a two-month-old human fetus and then spread to the peripheral lymphoid tissues with T lymphocytes. This movement was independent of the monocyte-macrophage lineage.

Dendritic cells and macrophages processed viral antigens to T4, T8 lymphocytes, which secreted cytokines and chemokines to cause tissue inflammation. If the secreted cytokines were over-

shooting [35] any suppressive mechanisms to stabilize immune reaction should be present to avoid severe progression. The dysfunctional interferon response in conjunction with other innate and adaptive immune responses may thus decide the path to recovery or advancement to more severe disease.

Cellular immunity seems to work mainly at this early stage of SRC-Cov-2 infection. The history of mandatory BCG vaccination in Japan, Korea, China, India, and the Russian Federation was causally related to reduced COVID-19 mortality [36-39]. These countries have so far a relatively low death rate from COVID-19. This association between BCG vaccination and apparent low COVID-19 incidence has spurred the idea that cellular T cell immunity was a legacy.

Functionally competent cytotoxic T cells seemed to be cross-reactive to SARS-CoV-2 [40]. A recent report of the leukocyte type "HLA-A24" also be a candidate to explain factor X [41]. HLA-A24 positive Japanese was about 60%, and the experimental results showed that immune cells against the common seasonal cold also attack cells infected with the new coronavirus. They found that the killer T cells of humans with HLA-A24 type react with the molecules of the standard part in the seasonal corona and the SARS-Cov-2 simultaneously. Killer T cells have the function of memorizing these characteristics. When a person was infected with a seasonal corona in the past and infected with the new corona, the number of killer T cells sleeping in the body could increase rapidly and eliminate the infected cells. Low COVID-19 Taiwanese also had HLA-A24, but the hypothesis needs further confirmation in other countries.

Humoral immunity and tissue inflammation

In parallel to the cellular immunity, antibody production started in the BALT, GALT, and local lymphoid tissues and produced IgM, IgG, and IgA to eradicate viruses for a cure. Neutralizing antibodies appeared within two weeks after the infection, then viral pneumonitis recovered.

However, neutralizing antibodies and enhancing antibodies were simultaneously produced during SARS-CoV-2 infection. The antibodies against this infectivity-enhancing site were detected at high levels in severe patients. Breakthrough infections among vaccine receivers were problematic [42] and a similar mechanism may be present.

Infiltration of PMN leukocytes, monocytes, and mast cells caused interstitial viral pneumonitis, making acute inflammation. Systemic viremia and microthrombi may occur when local capillaries are affected [43]. Inflammation of the circulatory system led to thrombotic disease and multisystem failure. This cascade of tissue damage may culminate in a "cytokine storm." What is not yet known is the recoverability from these potentially disabling complications of Covid-19, especially as the pathogenesis is unfamiliar territory.

Local inflammation included the central nervous system with hemorrhagic encephalopathy, stroke, and adverse effects on cognition [44]. Loss of taste and smell seemed to have a central nervous system basis rather than or as well as one in the taste or olfactory receptors. The impact of coronavirus on the central, spinal and peripheral nervous system could occur earlier and be more extensive and consequential for disability-adjusted life expectancy (DALYS) than presently appreciated.

Strengthen the innate immunity

Power up of innate immunity is essential to suppress the Covid-19 pandemic. He., *et al*. reported a substantial transmission potential of CoV-2 virus before symptom onset [45]. They observed the highest viral load in throat swabs at symptom onset and inferred that infectiousness peaked on or before symptom onset. Contact tracing/quarantine and isolation were no longer feasible in a rapidly expanding pandemic. Encouragement to change eating habits and social, behavioral change, especially the promotion of brown rice food and rice bran, should be part of the national strategies to counter the COVID-19 pandemic. Recognizing the strong relationship between dietary habit and the Covid-19 infection is especially recommended to developing countries with no funds to buy expensive vaccines and therapeutic drugs.

Rice eaters had a preference for plant-based side dishes [46]. Functional factors of the plant may strengthen innate immunity. Eponymous dietary patterns like the Mediterranean were relatively more biodiversity than their reference diets [47]. Humans are omnivorous, even if a plant or aquatic food orientation conferred biological and environmental advantages. More biodiverse diets were associated with better overall and vascular health and disease-specific survival, especially among older people.

Individual nutrients, such as vitamin D, manganese/magnesium, phytochemicals, etc., may suppress SARS-Cov-2 infection. However, a single element could not stop SARS-Cov-2 disease and clinical manifestation. Integration and balance of foods were more favorable, and a Mediterranean diet would be an example, containing nuts, berries, fermented dairy, green leafy and yellow vegetables, fruits, fish, yeast, wheat germ, whole grains, eggs, herbs, and spices like turmeric, tea, etc.

Conceptually minor dietary contributors like culinary herbs and spices often have potent bioactive profiles and offer palatability and acceptability, enhancing food biodiversity's healthfulness and immunoinflammatory properties. They are now fundamental to international and local Food-Based Dietary Guidelines (FBDGs).

FBDGs inevitably provide adequate energy and macronutrients (protein, carbohydrate, dietary fiber, fat, water) intakes and various sources, which subserves our omnivorous biology with essential components like essential amino and fatty acids.

Figure 4: Pathological changes after virus infection.

No single food has the potentiality to prevent or treat coronavirus like rice [48,49].

Future attenuation

To date, four types of cold coronavirus have been identified, all of which are thought to be derived from animal-based coronaviruses [50]. For example, a report suggests that the origin of the cold coronavirus HCoV-OC43 is a bovine coronavirus, which caused a zoonotic infection in humans around 1890 when it coincided with the "Russian cold" pandemic [3]. A Russian cold arrived in Japan around April 1890 after the epidemic in Europe and the United States. Looking at Japan as a whole, the epidemic seems to have ended in 1890. Although there was no PCR or vaccine, and even the existence of a virus was unknown, people at that time seemed to have successfully overcome the coronavirus. The "end" is actually "convergence," and it may have settled down to coexistence with the cold coronavirus HCoV-OC43. In circumstantial evidence, this story does not seem to be absurd. Other cold coronaviruses have probably reached the zoonotic infection → epidemic of severe respiratory infection → habituation to humans by mutation.

Figure 5: Result of intervention study by brown rice cake lunch for 3 months.

In the case of SARS-CoV-2, it is difficult to predict how it will evolve in the future because it will mutate in the presence of the selection pressure of immunity due to vaccination and habituation to humans. It will be necessary further to improve the analysis system for the viral genome and analyze new mutations and their effects on time.

The number of young people with Omicron is rapidly increasing, and replaced 80% of infections. If it is permissible to think in contrast to the Russian cold, we can see the path to convergence. And it may be recognized as the fifth cold coronavirus. Understand-

ably, every effort has been made to stem the pandemic at the earliest stage through case identification, contact tracing, and isolation. Until vaccination is available or antiviral agents effective and safe, the emphasis must be on reducing transmission and enhancing resistance by innate immunity.

Conclusion

Rice consumption was the "X factor," which explained the noticeable difference of COVID-19 incidence and mortality in the East and West. Brown rice would contribute to an excellent dietary pattern rather than a unique explanator. Different cultural habits, such as bowing etiquette, wearing face masks, and handwashing with sanitizing equipment, may contribute to the lower opportunity of infection. Still, a more explainable factor was rice consumption by countries. Annual consumption of rice by country inversely correlated well to the cumulative number of COVID-19 by compiling data from 17 major countries of G20. The negative correlation coefficient was 0.74, while wheat consumption showed a positive correlation. Two plausible factors were sIgA, which mechanically blocked the virus from binding to the ACE2 receptor. Another was suppressing ability for cytokine storm by regulatory T cells that expanded by butyrate of intestinal microbiota. Early resistance to developing COVID-19 pneumonia would be the cellular immunity and cure-oriented mild inflammation.

Long rice-eating habits contributed to the growing unique composition of the microbiota, which produced butyrate and other short-chain fatty acids, influencing various physiological functions. Early resistance to develop COVID-19 pneumonia would be the cellular immunity, and cure-oriented inflammation proceeded. Parallel increase of antibodies helped to eradicate pathogenic viruses. The gut environment was essential to making a stable immune system, among which T17/Treg balance seemed to be crucial to suppress cytokine storms. Dietary improvement should be most practical for developing innate immunity.

Funding

A part of this research was supported by a grant from the Project of the NARO Bio-oriented Technology Research Advancement Institution (research program on development of innovative technology).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Unnecessary.

Data Availability Statement

Not applicable. We used all public data online.

Acknowledgments

The authors appreciate Mr. Toyohisa Aoyama, Secretary-General, Technical Council, Ministry of Agriculture, Forestry, and Fisheries for discussing rice function and corona pandemic.

Conflicts of Interest

None.

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