Potential Effects of Fasting in SARS-CoV-2 Infection

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Intermittent fasting is a potential complementary therapy to vaccination and antiviral therapies that not only impacts chronic disease risk but also has good evidence of an impact on infectious diseases such as COVID-19. Intermittent fasting should improve the immune response of and reduce acute hyperinflammation for unvaccinated people, strengthen immunity between vaccinations for vaccinated people, and prolong the length of time a vaccinated person can go before receiving a subsequent booster dose of the SARS-CoV-2 vaccine. A set of at least 10 biological mechanisms may be impacted by intermittent fasting in the human physiological response to SARS-CoV-2 that may reduce the severity of COVID-19 outcomes. For example, by boosting autophagy, fasting may aid the immune system to identify silently infected cells via increased degradation of viral proteins and through antigen presentation to natural killer cells and cytotoxic T cells. Intermittent fasting may also provide a constellation of mechanisms that empower a damaged human immune system to repair itself and to hunt down residual SARS-CoV-2 virus that is hiding from it in the context of both acute infection and post-acute sequelae of COVID-19. Furthermore, fasting adds no financial cost to a care plan and, when practiced safely, is available to most adults regardless of education, income, location, or ancestry. Clinical trials of intermittent fasting for reduction of COVID-19 severity are needed.

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1. Introduction

Mark Twain, an astute observer, noted in an 1866 story that he, “has a surprise in it for those dull people who think that nothing but medicines and doctors can cure the sick. A little starvation can really do more for the average sick man than can the best medicines and the best doctors. I do not mean a restricted diet, I mean *total abstention from food for one or two days*. I speak from experience; starvation has been my cold and fever doctor for fifteen years, and has accomplished a cure in all instances” [1]. More than 150 years later, the best medicines and doctors are much more advanced, including that we have access to many more safe and effective treatments, including vaccines, antivirals, and antibiotics. Despite these important advancements, intermittent fasting (or “starvation” as Twain called it) may become a complementary therapy (note that fasting does not result in the break-down of vital organs like real starvation does). Importantly, fasting is available for free to all people regardless of location, ancestry, income, or education. Widespread individual experimentation with intermittent fasting began about 2018 when the practice moved from diet and nutrition circles into the consciousness of the general public. While the

proportion of people throughout the world who have tried some form of health-related fasting is unclear, it continues to be a popular topic in the lay press, in health and research communities, and in friendly conversations.

Conceptually, the benefits of fasting occur due to the triggering by fasting of molecular, cellular, and tissue-level mechanisms that are encoded in human DNA. These mechanisms are anticipated to have accumulated widely in the collective human genetic code historically as fasting preserved the lives of distant ancestors who were sufficiently fit to resist conditions in which a combination of low food availability and other environmental factors such as infectious diseases were present. The effect of the adverse conditions had to be just enough to induce hormesis for some individuals—a situation in which protective physiologies are triggered at low to moderate dose of fasting, while other people deficient in the protective mechanisms triggered by fasting did not have a sufficient shield from the environmental conditions and died without producing offspring. The adverse conditions could not be of a high dose that caused a profound impact in which all people experienced death or a reproduction-inhibiting harm.

Intermittent fasting (i.e., daily or weekly patterns of energy restriction) and periodic fasting (i.e., monthly patterns of energy restriction) may strengthen the body against infectious diseases and their consequences, including COVID-19. Fasting may reduce inflammation, activate pathways that destroy pathogens, support a healthy microbiome, and trigger the innate immune system to respond to infectious disease even if the pathogen tries to shut down or evade human immunity. For example, during a fasting period while energy intake is restricted, fasting may boost physiological mechanisms of human immunity specifically related to the spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2][3], activate other mechanisms related to general human immune responses [4][5][6][7], reduce the hyperinflammatory response to SARS-CoV-2 infection [8][9][10][11][12][13], and strongly induce the cellular “housecleaning” of autophagy [6][14][15][16]. The diet and gut-microbiota play an important role in health generally [5][17], and SARS-CoV-2 can cause major adverse effects on the microbiome [18], but fasting may support a healthy microbiome and increase resistance to gut dysbiosis [3][19][20]. In the long-term, fasting may improve basal levels of factors related to the response to infectious disease and to inflammation modulation [4][10][21][22][23], and generally reduce the risk and the prevalence of morbidities that are associated with worse prognosis after COVID-19 diagnosis, such as coronary artery disease, myocardial infarction, heart failure, and diabetes [7][24][25][26][27][28][29][30][31][32][33][34][35][36].

2. Mechanisms of SARS-CoV-2 and Potential Opposing Effects of Fasting

2.1. A Spike Protein Fatty Acid Binding Pocket

The SARS-CoV-2 virus is distinguished from other coronaviruses including SARS-CoV-1 in part by its unique polybasic furin cleavage site on its spike protein [2]. This aspect of the spike protein endows SARS-CoV-2 with a greater affinity for attachment and entry into human cells than other coronaviruses [2]. Further, most therapeutics for COVID-19 such as monoclonal antibody antiviral medications and the various vaccines target the spike protein to neutralize the effect of SARS-CoV-2 because the spike is specific for this virus. SARS-CoV-2 contains a fatty

acid binding pocket on the pathogen's spike protein that, when linoleic acid becomes attached to it, locks the spike protein in a conformation that is not conducive to binding the angiotensin converting enzyme 2 (ACE2) [2]. ACE2 is the primary protein that SARS-CoV-2 hijacks to infect human cells. The SARS-CoV-2 fatty acid binding pocket was recognized early in the pandemic and was determined to be a potential drug target for reducing or inhibiting the ability of SARS-CoV-2 to spread into host cells [2]. Subsequently, additional ligands were identified through functional simulations as having the potential to bind to the pocket to decrease the ability of the spike protein to adhere to ACE2, including steroids such as dexamethasone, fat-soluble vitamins including vitamins A, D, and K, and retinoids such as tretinoin, acitretin, and tazarotene [37].

Notably during fasting, fatty acids including the essential fatty acid linoleic acid are increased in the circulation as the metabolic switch is thrown [3][38]. This well-established mechanism of fasting minimizes the use of glucose for energy and triggers the extraction of fatty acids from adipose cells [3][38][39]. Ketogenic diets also function by activating this switch to extract fatty acids that, in the presence of low insulin, are converted to ketone bodies such as β-hydroxybutyrate and used for energy production [39]. Both intermittent fasting and ketogenic diets may produce a benefit in the context of SARS-CoV-2 by providing elevated fatty acids that will bind to the spike protein and, to some extent, inhibit host infection. The degree to which a SARS-CoV-2 infection is minimized via this mechanism likely depends on the amount of fatty acids that are available in storage, especially since linoleic acid is an essential fatty acid that would only be available through storage capabilities during fasting.

2.2. T Cells and Deactivation of Ketosis

In a recent comparative study of influenza infection versus SARS-CoV-2 infection, human and mouse data revealed that infection by influenza induced ketogenesis, including an increased production of β-hydroxybutyrate [40]. In contrast, ketogenesis was impaired in moderate to severe COVID-19 and a deficit in the production of interferon-γ and other interferon-related cytokines by $CD4^+$ T cells was found. However, addition of β-hydroxybutyrate to human and mouse T cells resulted in increased production of interferon-γ by $CD4^+$ and $CD8^+$ T cells, aided in the generation of energy and bioenergetic amino acids and in the function of mitochondria in activated T cells, and generally supported T cell survival [40].

2.3. Adipocyte Infection and Non-ACE2 Entry into Host Adipose Cells

A study documented a potential non-ACE2 mechanism through which SARS-CoV-2 infects human adipocytes and adipose tissue-resident macrophages [41]. Other potential SARS-CoV-2 entry points include receptors at CD147, dipeptidyl peptidase 4, and neuropilin-1 in adipose cells [42]. While chronic inflammation is a hallmark of obesity, SARS-CoV-2 is known to cause a strong inflammatory response in adipose tissue [42]. Presumably, people with a greater amount of adipose tissue will experience substantially greater localized and systemic inflammation. This may be one reason that people with obesity are subjected to more severe COVID-19 and its associated poor health outcomes [7][33][43].

To the obverse, while a person is fasting, adipocyte contents such as fatty acids are scavenged for energy and this should lead to acutely reduced levels of inflammation in those cells [8][9][27]. Further, in the long-term, the use of repeated intermittent fasting results in the decrease of the volume of adipose tissue and a decline in levels of insulin resistance and chronic inflammation associated with obesity [24][25][28]. These acute and chronic benefits of fasting should ameliorate adiposity-related concerns of COVID-19 [7], although this requires direct testing in people with acute or post-acute COVID-19. Standard weight loss diets should also produce similar COVID-19-targeted benefits related to decreased adiposity, reduced obesity-associated inflammation, and lower the risk of poor COVID-19 outcomes, but this also requires evaluation.

2.4. Infection of Activated T Cells and Non-ACE2 Entry into Host T Cells

A study that documented a potential non-ACE2 method of SARS-CoV-2 transport into host cells reported that the virus preferentially infects activated T cells [13]. The proposed mechanism for viral spread into activated T cells was through lymphocyte function-associated antigen 1 (LFA-1). Naturally, destruction of T cells by an infectious agent is a powerful action that facilitates its goal of invasive control of host resources so that the pathogen can turn those resources to its own ends, including viral replication and propagation. It may be in part that the hyperinflammation that some people experience in COVID-19 is a response to the destruction of activated T cells that results in dysregulation of the immune response as other components of the immune system attempt to compensate.

2.5. T Cells, the Inflammasome, and Hyperinflammation

As noted above, the $CD4^+$ T cell activation of the human inflammatory cytokine cascade in response to the major histocompatibility complex binding of pathogen protein fragments (e.g., SARS-CoV-2) contributes to the characteristic hyperinflammation frequently observed in severe COVID-19 [44]. Additionally, as discussed above, during fasting the $CD4^+$ T cell response is blunted and circulating inflammatory cytokines are reduced due to fasting [6][8][9][12].

2.6. Targeted Impairment of Autophagy

Autophagy is the selective degradation of damaged cellular components [6][14]. It results in the recycling of those components and the regeneration of healthy mitochondria, peroxisomes, ribosomes, and other cellular constituents that function effectively and efficiently. This rejuvenates cells, tissues, and the human body generally, returning it to homeostasis. Autophagy may also aid cells in adapting to new physiological conditions through the selective degradation of proteins necessary for living in the recent past and stimulation of transcription and translation of proteins composing a milieu tailored to the new environment.

Remarkably, or perhaps not so remarkably for this well-adapted virus, SARS-CoV-2 inhibits autophagy of infected human cells [45][46][47]. At least five SARS-CoV-2 proteins alter or block key steps in the autophagy pathway, including raising the pH of the lysosome and blocking autophagosome fusion with the lysosome [45][47]. This targeted corruption of human homeostasis is potentially critically damaging in shutting down a key physiological process that is especially important for the maintenance of cellular health and the reduction of oxidative stress.

Because of the potential previous accumulation of oxidative damage in cells and tissues of people with certain conditions, such as obesity, diabetes, coronary artery disease, and chronic obstructive pulmonary disease, those individuals may be less able to adapt to the additional oxidative stress caused by SARS-CoV-2. Therapies that strengthen autophagy could provide important treatment effects to reduce severity of COVID-19 and a variety of anti-coronavirus pharmaceuticals are under study that appear to do just that [46].

Similarly and remarkably, fasting activates and enhances autophagy [6][14][15][16][34], potentially directly counteracting a major effect of SARS-CoV-2 infection [45][46][47]. Fasting strengthens the ability of the body to degrade damaged proteins and dysfunctional cells, including infected cells, and may thus directly trigger the destruction of a percentage of SARS-CoV-2 virions if the pathogen has gained entry into host cells. This action of fasting is non-specific, activating autophagy to the benefit of various organ systems and physiologic processes, including having effects on cognitive and metabolic pathophysiologies [15][16]. Thus, this canonical function of fasting would be expected to counteract SARS-CoV-2 even if the virus did not attempt to disable autophagy, since fasting's trigger to enable autophagy is related to optimizing human physiological function through multiple pathways and is not solely an anti-pathogen effect [12].

2.7. Viral Suppression of Innate Immunity and Antigen Presentation

Analysis of SARS-CoV-2 viral proteins and their effects within cells have revealed that at least 18 of the 29 viral proteins actively block or suppress human cellular pathways that lead to the production of type I interferon and the activation of hundreds of interferon stimulated genes [48][49]. Within cells, retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) sense viral mRNAs and utilize an adaptor protein called the mitochondrial antiviral signaling protein (MAVS) [48][49][50]. MAVS initiates a signal transduction pathway causing the cell to produce interferon-β, that is then exported and stimulates a signaling pathway in neighboring cells causing the induction of interferon stimulated genes. One of these is 2′-5′-oligoadenylate synthetase 1 (OAS1), whose gene product leads to the activation of RNAse L. RNAse L can directly destroy viral mRNAs in the cytoplasm or, even better, in membrane-bound viral replication compartments [51][52]. Unfortunately, new viral variants are evolving to become more resistant to the various types of interferons that human cells produce [53]. It is well known that the innate antiviral immune response is necessary to trigger adaptive immunity, thus it is possible that by suppressing innate immunity that SARS-CoV-2 can replicate to higher levels before triggering strong T and B cell responses. Indeed, this may account for asymptomatic transmission which is common with COVID-19 [54]. SARS-CoV-2 also suppresses antigen presentation in infected cells wherein a viral protein ORF6 decreases the expression of major histocompatibility complex class I on the surface of epithelial cells [47]. This likely reduces the effectiveness of antiviral immune surveillance and results in decreased immune surveillance by Cytotoxic T Cells. While speculative, because of the impact of fasting on autophagy and related pathways [6][47][55][56], it may be that early in a SARS-CoV-2 infection that some of the mechanisms mentioned above for fasting boost viral antigen presentation on cell surfaces or more quickly stimulate innate immunity to speed the development of adaptive immunity, leading to a less complicated or even asymptomatic course of infection with lower incidence of post-acute sequelae. The timing for this response would either require someone to be fasting frequently so that when they were first infected that the effects that occur during total energy restriction were present [3][27], or that routine

repetitions of fasting had caused physiological adaptations over the long-term as is likely occurring in long-term periodic fasting [4][30][31].

2.8. Long-Term Modulation of Inflammation

Galectin-3 is a multi-role protein that was originally identified in the response to infection [21][22][23]. Galectin-3 responds directly and indirectly to infection (e.g., binds pathogens and activates the innate immune system), and reduces inflammation arising from NF-κB and the NLRP3 inflammasome [21][22][23]. Galectin-3 was also found to be involved in various other pathways, including in key capacities but complex relationships in the metabolism, heart failure, and fibrosis [4][10][57][58]. Of particular interest, it functions in a protective capacity related to type 2 diabetes onset, maintaining glucose homeostasis and having an inverse relationship with hemoglobin A1c levels [4][10]. As a widely-acting factor whose basal level is increased by repeated fasting over a period of months to years, a long-term elevation in galectin-3 may provide an adaptation that allows someone who chronically engages in fasting to potentially respond more quickly or effectively to conditions such as infection (e.g., by SARS-CoV-2) or chronic diseases that require modulation of inflammation to maintain homeostasis.

2.9. Gut Microbiome and Secondary Infections

The gut microbiome, including the appendix that is now recognized as a non-vestigial well that maintains the microbiome [59], is recognized today for substantial influences on human health [18][19][20][60][61][62][63]. The microbiome impacts human health, both in the prevention of or acceleration of chronic diseases and in limiting or enhancing infectious diseases [3][18][19][20][60][61][62][63]. This includes the potential for acute infections in the intestine or in the appendix to radically alter organ-level health [60][61][62][63]. SARS-CoV-2 may be one of such infections, inducing gut microbiome dysbiosis that leads to enhanced proliferation of pathogenic microbial species, including anti-microbial resistant strains, and to the movement of harmful secondary pathogens into the bloodstream from the gut [18][60].

2.10. Chronic Diseases and Risk of Poor COVID-19 Outcomes

Risk factors for and the risk of diagnosis of those chronic disease diagnoses are lower among people who engage in intermediate- or long-term intermittent fasting [7][24][25][26][27][28][29][34]. This includes a lower risk of the metabolic syndrome and the cardiometabolic risk factors that lead to the diagnoses [24][25][26][27][28][64][65]. Further, the risk of mortality, hospitalization, and a new diagnosis of heart failure are also lower for people engaging in periodic fasting [30][31]. In particular, fasting reduces glucose levels acutely and substantially during a fasting period and it reduces the basal level of glucose over the long-term [24][26][27][28], which in both cases will make glucose less available for use during infection and, thus, should counteract the stimulation of glycolysis performed by SARS-CoV-2 [66]. Because they are known to reduce the risk of the onset of those chronic diseases, standard weight loss diets should also produce some of these benefits over the long-term, including reduced risk of chronic disease and improved glucose control. From a practical perspective, sustainable intermittent fasting regimens and weight loss diets should be utilized to ensure that people continue with the dietary practices for as long as their health requires it.

3. Safety Considerations

Intermittent fasting is a generally safe [67], inexpensive, and well-tolerated dietary energy restriction practice that reduces weight [24][25][64][65], and is effective in improving metabolic and cardiovascular health primarily in people with elevated cardiometabolic risks [24][25][26][27][28]. Safety outcomes have been largely ignored in intermittent fasting studies and some populations are at considerable risk if they participate in fasting, such as people with diabetes and especially children with juvenile or type 1 diabetes [67]. Safety concerns with fasting include mild potential side effects, such as hunger, fatigue, dizziness, constipation, headache, lightheadedness, syncope, and falls that make fasting generally safe for people who are apparently healthy. For some people, though, fasting can cause more serious safety issues, including for people with diagnosed chronic diseases (including people with prior heart attack or stroke and especially those with lingering symptoms of those events). In particular, fasting reduces blood sugar and can result in hypoglycemia. It can also result in dehydration. People with type 2 diabetes should be cautious about fasting and talk with their physician before initiating a fasting regimen because many anti-diabetes medications can also cause dehydration and hypoglycemia; dehydration is a risk factor for stroke and general thromboembolism while hypoglycemia can be fatal [67]. People with pre-diabetes or who are being treated for insulin resistance or metabolic syndrome using anti-diabetic medications should consult with their physician about safe dietary and medication practices before engaging in a fasting regimen [67]. Adults with type 1 diabetes should not fast unless it is prescribed and monitored by a physician [67]. Other safety concerns may include excessive stressors and nutritional deprivations on the body that generally can cause severe adverse events in people who are older and frail and those who are pregnant, lactating, have significant kidney disease, have had an organ transplant, are receiving active cancer treatment, have an eating disorder, are malnourished, have type 1 diabetes, or have dementia. Additionally, people with inflammatory bowel disease, Celiac disease, irritable bowel syndrome, diabetes, and cancer often require a specific diet that may not accommodate introduction of a fasting regimen. Malnutrition in particular should be paid attention to, and individuals with nutrition concerns may exhibit oral markers of this condition that would indicate that someone is not a candidate for fasting [68]. Children also should not fast for health purposes unless it is prescribed by their physician or another medical professional trained in pediatrics, and children with a diagnosis of diabetes (type 1 or 2) or who are being treated for diabetes should not fast.

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