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The impact of dawn to sunset fasting on immune system and its clinical significance in COVID-19 pandemic

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ABSTRACT

Dawn to sunset fasting, a type of intermittent fasting commonly practiced in the month of Ramadan, requires abstinence from food and drink from dawn to sunset. Dawn and dusk are two transition time zones of the day that play a critical role in the human circadian rhythm. Practicing dawn to sunset fasting requires the alignment of mealtimes and wake-sleep times with the human biological dawn and dusk.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impairs immune cell responses at multiple levels and leads to severe Coronavirus Disease 2019 (COVID-19). It generates high levels of pro-inflammatory cytokines and chemokines, also known as a cytokine storm, leads to mitochondrial dysfunction and generation of excessive amounts of mitochondrial reactive oxygen species, downregulates autophagy to escape detection for unchecked replication, and alters gut microbiome composition. Severe cases of COVID-19 have been associated with several comorbidities that impair immune responses (e.g., obesity, diabetes, malignancy) and blood laboratory abnormalities (e.g., elevated procalcitonin, C-reactive protein, interleukin-6, leukocytosis, lymphopenia).

Several studies of dawn to sunset fasting showed anti-inflammatory effect by suppressing several pro-inflammatory cytokines, reducing oxidative stress, inducing a proteome response associated with increased autophagy, remodeling the gut microbiome, and improving the components of metabolic syndrome (e.g., obesity, blood glucose levels, blood pressure, lipids).

In conclusion, dawn to sunset fasting has the potential to optimize the immune system function against SARS-CoV-2 during the COVID-19 pandemic as it suppresses chronic inflammation and oxidative stress, improves metabolic profile, and remodels the gut microbiome. This review presents scientific literature related to the effects of dawn to sunset fasting on the immune system. Studies are needed to assess and confirm the potential benefits of dawn to sunset fasting against SARS-CoV-2.

1. Introduction

According to World Health Organization (WHO), as of December 21, 2021, the Coronavirus Disease 2019 (COVID-19) pandemic has a death toll of over 5 million [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has raised great interest in human immunology. There is a lot that remains unknown about SARS-CoV-2. More importantly, there is an urgency towards understanding the lifestyle and pharmacologic measures to help prevent and decrease the acuity of the infection. As we learn more about the SARS-CoV-2, several comorbidities (e.g., advanced age, male sex, obesity, diabetes, hypertension, malignancy, thromboembolism, chronic obstructive pulmonary disease, interstitial lung disease, chronic liver disease, acute kidney injury, and chronic kidney disease) and blood laboratory abnormalities (e.g., elevated procalcitonin, basal urea nitrogen, creatinine, C-reactive protein, interleukin-6, cardiac troponin I, leukocytosis, lymphopenia, thrombocytopenia, ferritin, D-dimer levels) have been associated with increased risk of severe COVID-19 infection [2–5].

Despite the roll-out of vaccines, there is no end in sight as the SARS-CoV-2 mutates and increases virulence. A spectrum of therapeutic drugs has evolved since the beginning of the pandemic, with current treatments including, but are not limited to, antivirals, immunomodulators

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(e.g., corticosteroids, biologics), anticoagulants, and complement inhibitors [6]. Thus far, preventative measures include social distancing, wearing proper-fitting medical masks, eye protection, frequent hand washing, and vaccination [7,8]. In addition to these preventative measures, intermittent fasting and time-restricted eating were proposed as a potential lifestyle modification to strengthen the immune system during the COVID-19 pandemic [3,9–14]. Although there are no randomized controlled studies conducted to assess the effects of intermittent fasting and time-restricted eating on the immune system during the COVID-19 pandemic, there has since been an avid interest in the physiology of intermittent fasting and time-restricted eating as a means of modulating the immune system to viral infections, including SARS-CoV-2 [3,9–14].

2. Dawn to sunset fasting and its difference from other types of intermittent fasting

Two major types of intermittent fasting have been adopted to pursue a healthier lifestyle based on the starting and ending times of the fasting period. The most popular type of intermittent fasting is dawn to sunset/dawn to dusk fasting that has one fasting and one eating/drinking period within a day. Dawn to sunset fasting is a type of intermittent fasting commonly practiced in the month of Ramadan [15]. Although the term "time-restricted eating" can be used interchangeably with "intermittent fasting," time-restricted eating has a broader meaning. In general, while intermittent fasting has one fasting and one eating/drinking period within a day, time-restricted eating may have more than one fasting and one eating/drinking period within a day (e.g., breakfast between 7 a.m. and 8 a.m. followed by fasting from 8 a.m. until 1 p.m., lunch between 1 p.m. and 2 p.m. followed by fasting from 2 p.m. until 7 p.m., and dinner between 7 p.m. and 8 p.m. followed by fasting from 8 p.m. until 7 a.m. next day).

In dawn to sunset fasting, the daily fast starts at dawn after having a pre-dawn breakfast and ends at dusk with dinner [16,17]. Dawn and dusk are two transition time zones of the day and play a critical role in the function of the human circadian pacemaker [18,19]. Morning and evening oscillators, the two components of the circadian pacemaker, were shown to be entrained to dawn and dusk, respectively [18,19]. Therefore, starting the fast at dawn and ending it at sunset/dusk appears to be compliant with the function of these two components of the circadian pacemaker and act as a robust Zeitgeber (a time giver) [16], entraining peripheral oscillators to dawn and dusk.

Mealtimes during intermittent fasting play a critical role in maintaining a healthy circadian rhythm. During dawn to sunset fasting, mealtimes should be scheduled at the transition zones of the day, including a pre-dawn breakfast just before dawn and dinner at sunset. Pre-dawn breakfast should not be skipped as skipping breakfast was shown to cause a disrupted cortisol circadian rhythm and elevate blood pressure [20]. Skipping breakfast or delaying it to a later hour in the morning during intermittent fasting can exert additional cardiometabolic stress, specifically in individuals with metabolic syndrome [20]. Likewise, eating meals or having snacks in the middle of the night or throughout the night would likely disrupt the circadian rhythm and blunt the effects of dawn to sunset fasting. A randomized controlled study conducted on late dinner (11 p.m.) and routine dinner (6 p.m.) eaters showed that the late dinner eaters had higher glucose and lower free fatty acid levels in the postprandial period compared with routine dinner eaters, likely due to altered cortisol rhythm [21].

Healthy sleep patterns are as important as circadian compliant meal timing. Dawn to sunset fasting requires wake-up before dawn to have a pre-dawn breakfast [22]. An average of seven or more hours of daily sleep at night is recommended for adults [23]. Therefore, individuals who practice dawn to sunset fasting should ensure a minimum of 7 h of sleep at night to prevent sleep deprivation. Taken altogether, practicing dawn to sunset fasting requires self-discipline to perfectly align the mealtimes and wake-up and sleep times with human biological dawn and dusk.

Ramadan fasting [15] is dawn to sunset fasting that is practiced in the holy month of Ramadan (the month of Ramadan is based on the lunar calendar, and therefore it varies every year) for 12 h to 20 h a day, varying based on geographic location and season for 29 to 30 consecutive days. In contrast to dawn to sunset fasting, the other types of intermittent fasting (e.g., 16:8 intermittent fasting with 16 h fasting and 8 h eating) start and end at a self-determined/predetermined time during the day without taking human biological dawn and dusk into account [24,25]. There are no randomized controlled clinical trials that compared the metabolic effects of dawn to sunset fasting with the effects of other types of intermittent fasting that starts and ends at a self-determined (or predetermined time) without taking biological dawn and dusk into account. A small non-randomized study of time-restricted eating with a fasting period that started and ended at a self-determined time during the day (approximately 14 h fasting and 10 h eating) for 12 weeks showed significant improvement in the components of metabolic syndrome [26]. In contrast with the findings of this non-randomized study, a large randomized controlled trial conducted in subjects with body mass index between 27 and 43 kg/m^2 showed that time-restricted eating with a fasting period that started and ended at a predetermined time (fasting for 16 h from 8 p.m. until 12 p.m. next day by skipping breakfast and allowing water, tea, coffee during fasting period) for 12 weeks showed no significant changes in the body weight, fat mass, insulin resistance estimated by homeostatic model assessment for insulin resistance (HOMA-IR), hemoglobin A1c, and lipids compared with eating three structured meals a day and also snacking between the meals [25].

Another unique feature of dawn to sunset fasting is strict fasting without food or fluid intake during the fasting period and no dietary or calorie restriction during the eating period. In several studies of intermittent fasting other than the dawn to sunset fasting, subjects were reported to perform intermittent fasting or time-restricted eating; however, they did not strictly fast during the fasting period, but instead, they consumed low or no-calorie containing food or drinks [24,25,27]. In these studies, the effect of intermittent fasting might be limited to caloric restriction rather than the circadian rhythm reset as the subjects were allowed to have low or no-calorie containing food and drinks during the fasting period, likely blunting the effect of mealtime to function as a dominant Zeitgeber (a time giver, rhythmic environmental cue) [28] on peripheral circadian oscillators. Randomized controlled trials are needed to compare the metabolic effects of dawn to sunset fasting with and without no-calorie drink intake during the fasting period.

Fasting from dawn to sunset during activity hours may have more potent anti-cancer and immune function enhancing effects than fasting during inactivity or both inactivity and activity hours. Food restriction in mice during the activity hours (i.e., 12-h dark phase in nocturnal animals corresponding to dawn to dusk in humans) was shown to have a more potent anti-cancer effect compared with food restriction during inactivity hours (12-h light phase) and ad libitum eating [29], suggesting the presence of an optimized immune response associated with fasting during activity hours. The results of intermittent fasting studies conducted on rodents need to be interpreted in the context that rodents are nocturnal animals, and their activity period is nighttime, corresponding to the period from dawn to sunset in humans [17]. Two human studies showed that dawn to sunset fasting for 4 weeks induced an anti-cancer proteome in healthy subjects and subjects with metabolic syndrome [16,17]. Randomized, controlled studies are needed to evaluate the effect of dawn to sunset fasting and other types of intermittent fasting on the immune system and cancer prevention.

This review presents scientific literature on the effects of dawn to sunset fasting, a specific type of intermittent fasting commonly practiced during the month of Ramadan, on immune system and how it may mediate physiologic responses against SARS-CoV-2 (Table 1).

Table 1
Representative studies showing the impact of dawn to sunset fasting on inflammation, oxidative stress, autophagy, immune function, obesity, metabolic syndrome, components of metabolic syndrome, and gut microbiome.

	Study	Study design	Study population	Duration of dawn to sunset fasting	Summary of study outcome
Inflammation	Faris et al. (2012) [44]	A non-randomized, within-subject design	50 Healthy subjects, 21 men and 29 women, mean (SD) age: 32.7 (9.5) years	Men: 30 days, women: 23–25 days during the month of Ramadan	The levels of IL-6, IL-1β, TNF-α were significantly decreased after 3 weeks of dawn to sunset fasting compared with the baseline levels.
	Almeneessier et al. (2019) [45]	A non-randomized, within-subject design	12 Healthy male subjects, mean (SD) age: 25.1 (2.5) years	One week outside the month of Ramadan and the first 2 weeks in the month of Ramadan	The plasma levels of IL-6, IL-8, IL-1β were significantly reduced after one week of dawn to sunset fasting outside the month of Ramadan and after two weeks of dawn to sunset fasting during the month of Ramadan compared with the plasma levels before the weeks of fasting (there was a washout period between dawn to sunset fasting weeks outside the month of Ramadan and during the month of Ramadan).
	Faris et al. (2019) [48]	A non-randomized, within-subject design	57 Subjects with body mass index (BMI) greater than 25 kg/m^2, 35 men and 22 women, mean (SD) age: 36.2 (12.5) years	Men: 28–30 days, women: 23–25 days during the month of Ramadan	There was a significant reduction in the serum levels of pro-inflammatory cytokines including IL-6, and TNF-α, along with a significant increase in the anti-inflammatory cytokine IL-10 and IL-10/IL-6 ratio at the end of 23–30 days of dawn to sunset fasting compared with the baseline levels. There was also a reduction in IGF-1 levels at the end of 23–30 days of dawn to sunset fasting compared with the baseline levels.
	Rahbar et al. (2019) [51]	A non-randomized, within-subject design	34 Healthy male subjects (exclusion criteria included smoking, being on thyroid and hypertension medications, being on estrogens, clinical dyslipidemia, diabetes mellitus, and hypothyroidism), mean age (SD): 35 (11) years	One month during the month of Ramadan	There was a significant decrease in circulating IGF-1 and IL-2 levels at the end of one month of dawn to sunset fasting compared with the levels before one-month dawn to sunset fasting.
	Madkour et al. (2019) [52]	A non-randomized, within-subject design	56 Subjects with BMI greater than 25 kg/m^2, 34 men and 22 women, 6 control subjects with healthy body weight, mean (SD) age: 35.72 (12.35) years in the overweight/obese subjects, 29.8 (14.0) years in the control subjects	28 to 30 days during the month of Ramadan	There was a significant reduction in IGF-1 levels at the end of 28 to 30 days of dawn to sunset fasting compared with the baseline levels..
	Aliasghari et al. (2017) [46]	Non-randomized, controlled, within-subject, and between-subject design	83 Subjects with nonalcoholic fatty liver disease (NAFLD), 42 subjects who fasted, 41 subjects who did not, 57 men and 26 women, mean (SD) age: 37.59 (7.06) years in the fasting group, 35.80 (7.33) years in the non-fasting group	One month during the month of Ramadan	The reduction in serum levels of IL-6 and high-sensitivity C-reactive protein was significantly higher in subjects who fasted from dawn to sunset for a month than the reduction in the levels of these pro-inflammatory markers in subjects who did not fast.
	Akrami Mohajeri et al. (2013) [53]	A non-randomized, within-subject design	58 Healthy male subjects, age: 20–40 years	One month during the month of Ramadan	There was a significant decrease in serum levels of CXCL1, CXCL10, and CXCL12 at the end of one month of dawn to sunset fasting compared with the levels collected on the first day of one-month fasting.
	Mari et al. (2021) [54]	A non-randomized, controlled, within-subject design/ retrospective, case-control study	155 Subjects with NAFLD, 74 subjects (39 men and 35 women) who fasted and 81 subjects (42 men and 39 women) who did not fast, mean age (SD): 51.8 (20.9) years in the fasting group, 52.6 (19.3) years in the non-fasting group	One month during the month of Ramadan	In subjects who fasted, there was a significant reduction in C-reactive protein levels after dawn to sunset fasting compared with the levels before dawn to sunset fasting. In subjects who did not fast, there was no significant change in C-reactive protein levels.
	Zouhal et al. (2020) [47]	A randomized controlled, within-subject, and between-subject design	28 Male subjects, 14 in the fasting group, 14 in the non-fasting group, with obesity with BMI between 30 and 40 kg/m^2, mean (SD) age: 24 (3.4) years in the intervention group, 23.8 (3.8) years in the control group	One month during the month of Ramadan	Subjects who fasted from dawn to sunset for one month had a significantly lower plasma IL-6 level on the 15th day of one-month dawn to sunset fasting, the day after the end of one-month dawn to sunset fasting, and 21 days after the end of one-month dawn to sunset fasting compared with the plasma levels before one-month dawn to sunset fasting. In contrast to these findings, there was no significant change in IL-6 levels in control subjects who did not fast.

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Table 1 (*continued*)

	Study	Study design	Study population	Duration of dawn to sunset fasting	Summary of study outcome
	Mindikoglu et al. (2020) [16]	A non-randomized, within-subject design	14 Healthy subjects, 13 men and 1 woman, mean age: 32 years	Men: 30 days, woman: 26 days during the month of Ramadan	The study showed findings suggestive of upregulation of nuclear receptor subfamily 1 group D member 1 (NR1D1) which is the inhibitor of NLRP3 inflammasome, with an average of 11 fold increase in the NR1D1 protein level at the end of 4th week of 30-day dawn to sunset fasting compared with the level before 30-day dawn to sunset fasting.
Oxidative stress	Madkour et al. (2019) [52]	A non-randomized, within-subject design	56 Subjects with BMI greater than 25 kg/m^2, 6 control subjects with healthy body weight, 34 men and 22 women, 6 control subjects, mean (SD) age: 35.72 (12.35) years in the overweight/obese subjects, 29.8 (14.0) years in the control subjects	One month during the month of Ramadan	There was a significant increase in the relative expression of the antioxidant genes, including transcription factor A, mitochondrial (TFAM), superoxide dismutase 2, mitochondrial (SOD2), and nuclear factor erythroid 2-related factor 2 (Nrf2) compared with the expression of the antioxidant genes in the controls at the end of 28 to 30 days of dawn to sunset fasting in subjects who fasted.
	Al-Shafei (2014) [63]	A non-randomized, controlled, within-subject design	40 Subjects with hypertension and 40 control subjects, mean age (SD): 55 (5) years, both men and women in equal proportions	One month during the month of Ramadan	In both groups, there was a significant improvement in both groups in oxidative stress parameters, including an increase in blood glutathione and decrease malondialdehyde levels during the 4th week of dawn to sunset fasting and six weeks after the completion of 4-week dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting.
	Al-Shafei (2014) [64]	A non-randomized, controlled, within-subject design	40 Subjects with diabetes and 40 subjects without diabetes, mean age (SD): 55 (5) years, both men and women in equal proportions	One month during the month of Ramadan	In both groups, there was a significant improvement in both groups in oxidative stress parameters, including an increase in blood glutathione and decrease malondialdehyde levels during the 4th week of dawn to sunset fasting and six weeks after the completion of 4-week dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting.
Autophagy	Mindikoglu et al. (2020) [17]	A non-randomized, within-subject design	14 subjects with metabolic syndrome, 8 men and 6 women, mean age (SD): 59 (16) years	29 days during the month of Ramadan	Four-week dawn to sunset fasting induced a proteome response associated with increased autophagy simultaneous to the reduction in oxidative stress and inflammation biomarkers in subjects with metabolic syndrome. The decrease in protein kinase C substrate 80K-H (PRKCSH) gene protein products during 4-week dawn to sunset fasting and an average of a 73-fold increase in its level one week after 4-week dawn to sunset fasting suggests increased autophagy during 4-week dawn to sunset fasting, and decreased autophagy with ad libitum eating after the completion of 4-week dawn to sunset fasting.
Immune function	Faris et al. (2012) [44]	A non-randomized, within-subject design	50 Healthy subjects, 21 men and 29 women, mean (SD) age: 32.7 (9.5) years	Men: 30 days, women: 23–25 days during the month of Ramadan	There was a significant reduction in total leukocytes, granulocytes, lymphocytes, and monocytes after 3 weeks of dawn to sunset fasting compared with baseline levels. The same study showed a significant increase in monocyte count and no significant change in other immune cells one month after the completion of the fasting month compared with baseline levels.
	Mindikoglu et al. (2020) [17]	A non-randomized, within-subject design	14 subjects with metabolic syndrome, 8 men and 6 women, mean age (SD): 59 (16) years	29 days during the month of Ramadan	There was 16-fold increase in the mean level of calreticulin (CALR) gene protein products one week after the cessation of 4-week dawn to sunset fasting compared with the level before 4-week dawn to sunset fasting.

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Table 1 (*continued*)

	Study	Study design	Study population	Duration of dawn to sunset fasting	Summary of study outcome
Obesity, metabolic syndrome, components of metabolic syndrome	Mindikoglu et al. (2020) [17]	A non-randomized, within-subject design	14 subjects with metabolic syndrome, 8 men and 6 women, mean age (SD): 59 (16) years	29 days during the month of Ramadan	There was a significant reduction in body weight, body mass index, waist circumference both at the end of the 4th week during 4-week dawn to sunset fasting and one week after the completion of 4-week dawn to sunset fasting. This study also showed significant improvement in systolic, diastolic, and mean arterial blood pressures at the end of the 4th week during 4-week dawn to sunset fasting and a significant reduction in homeostatic model assessment for insulin resistance one week after 4-week dawn to sunset fasting compared with baseline levels.
	Faris et al. (2019) [48]	A non-randomized, within-subject design	57 Subjects with BMI greater than 25 kg/m^2, 35 men and 22 women, mean (SD) age: 36.2 (12.5) years	Men: 28–30 days, women: 23–25 days during the month of Ramadan	There was a significant reduction in total cholesterol, triacylglycerol, visceral fat surface area, BMI, fat mass, body weight, and systolic blood pressure after 3 weeks of dawn to sunset fasting compared with the baseline levels.
	Al-Shafei (2014) [63]	A non-randomized, controlled, within-subject design	40 Subjects with hypertension and 40 control subjects, mean age (SD): 55 (5) years, both men and women in equal proportions	One month during the month of Ramadan	In subjects with hypertension, there was a significant reduction in systolic blood and pulse pressure, triglyceride, and low-density lipoprotein levels and a significant increase in high-density lipoprotein levels during the 4th week of dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting. In control subjects, there was a significant decrease in triglyceride levels during the 4th week of dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting.
	Al-Shafei (2014) [64]	A non-randomized, controlled, within-subject design	40 Subjects with diabetes and 40 subjects without diabetes, mean age (SD): 55 (5) years, both men and women in equal proportions	One month during the month of Ramadan	In subjects with diabetes, there was a significant improvement in fasting blood glucose and triglyceride levels during the 4th week of dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting. In subjects without diabetes, there was a significant decrease in triglyceride levels during the 4th week of dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting.
	Tahapary et al. (2020) [98]	Meta-analysis (28 observational studies)	Subjects with type 2 diabetes mellitus, age (SD): 48.0 (10.9) to 60.1 (10.7) years	10 to 29–30 days during the month of Ramadan	There was a significant decrease in fasting glucose level (11 studies), hemoglobin A1c (15 studies), decrease in total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels (11 studies), body weight (10 studies), and waist circumference (6 studies) at the end of dawn to sunset fasting period compared with baseline levels.
	Nematy et al. (2012) [101]	A non-randomized, within-subject design	82 subjects with metabolic syndrome, coronary artery disease, or cerebrovascular disease, 38 men and 44 women, age (SD): 54 (10) years	10 to 35 days during the month of Ramadan	There was a significant reduction in body weight, BMI, waist circumference, total cholesterol, triglycerides, low-density lipoprotein, systolic blood pressure, and a significant increase in high-density lipoprotein levels at the end of dawn to sunset fasting (from 27th day of dawn to sunset fasting month until 6 days after the end of fasting month) compared with the levels before the fasting month (from 7 days prior to the start of fasting month until two first days of the fasting month).
Gut microbiome	Su et al. (2021) [109]	A non-randomized, controlled, within-subject design	30 healthy young male adult cohort who fasted, age (SD): 18.63 (1.75) years, 27 healthy middle-aged cohort who fasted, age (SD): 39.9 (6.4) years,	One month during the month of Ramadan	In the young cohort, there was a significantly increased gut microbiome diversity and remodeling of the gut microbiome at the end of dawn to sunset fasting month compared with

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Table 1 (*continued*)

	Study	Study design	Study population	Duration of dawn to sunset fasting	Summary of study outcome
			10 healthy middle-aged cohort who did not fast, age (SD): 42.6 (7.9) years		baseline levels. In the middle-aged cohort, there was a significant remodeling of the gut microbiome induced by dawn to sunset fasting, upregulation of Lachnospiraceae at the end of dawn to sunset fasting month and upregulation of Ruminococcacea one month after the completion of dawn to sunset fasting month compared with baseline levels. The subjects in the middle-aged cohort who did not fast had no significant change in microbiome composition and taxa during the study period.
	Ozkul et al. (2020) [110]	A non-randomized, within-subject design	9 healthy subjects, 2 men and 7 women, age (SD): 45 (9.7) years	29 days during the month of Ramadan	There was a significant beta diversity and enrichment in the Bacteroidetes phylum after 29 days of dawn to sunset fasting.
	Ali et al. (2021) [111]	A non-randomized, within-subject design	34 healthy subjects (16 Chinese and 18 Pakistani subjects), age range 18–40 years	One month during the month of Ramadan	There was a significant increase in Bacteroidetes and a decrease in Firmicutes in the Pakistani cohort, and a significant increase in Proteobacteria and a decrease in Bacteroidetes in the Chinese cohort after dawn to sunset fasting month compared to the levels before fasting month.

3. Effect of dawn to sunset fasting on immune system

3.1. Effect of dawn to sunset fasting on inflammation

SARS-CoV-2 enters host cells via interaction with the angiotensin-converting enzyme 2 (ACE2) protein, markedly expressed in the alveolar epithelium of the lungs and enterocytes of the small intestine [30–32]. The immune response to SARS-CoV-2 is similar to other coronaviruses and involves both the innate and adaptive arms of immunity [33]. It has been proposed that in mild cases of COVID-19, the inflammatory response generated by the immune system is self-limited as the innate and adaptive immune responses are quick [33]. In contrast to mild cases, severe cases of COVID-19 result from delayed and dysregulated innate and adaptive immune responses, which involve recruitment of a massive number of inflammatory cells and generation of high levels of pro-inflammatory cytokines and chemokines, also known as a cytokine storm [33]. This impaired immune response leads to severe damage, including acute respiratory distress syndrome, multisystem organ failure, and death [34,35].

Type I interferon deficiency, mitochondrial dysfunction, and virus-induced senescence were shown to be the driving force of this cytokine storm that leads to severe COVID-19 [36–39]. Although circulating interferon-beta levels were undetectable in all patients with COVID-19 regardless of the severity of the infection, interferon-alpha 2 levels were significantly reduced in patients with critical COVID-19 compared with the levels in patients with mild to moderate infection [36]. Additionally, low interferon-alpha 2 plasma level was an independent risk factor for progression to critical COVID-19 [36].

Persistent elevation of interleukin (IL)-6 and IL-1 levels have been associated with non-survival in COVID-19 [40]. Increased IL-6 was shown to be associated with cytokine release syndrome and severe pneumonia [41,42]. These results are in line with the findings of another study that showed that IL-6-induced genes, including IL6R, SOCS3, and STAT3, were significantly expressed in patients stratified as having severe and critical COVID-19 than healthy controls [36]. A study conducted in 41 patients with COVID-19 in Wuhan, China, showed that patients admitted to intensive care unit (ICU) had significantly higher plasma IL-2, IL-7, IL-10, interferon gamma-induced protein 10 (IP-10), which is also known as C-X-C motif chemokine ligand (CXCL)-10, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1A (MIP-1A), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) levels compared with patients who were not admitted to ICU [43]. A larger study conducted in Wuhan, China, among 452 patients with COVID-19 showed that patients with severe infection had significantly higher IL-2R, IL-6, IL-8, IL-10, and TNF-α than those without severe infection [35].

Several studies of dawn to sunset fasting showed anti-inflammatory effect by suppressing pro-inflammatory cytokines in various populations, including healthy subjects, subjects with at least one component of metabolic syndrome, and subjects with nonalcoholic fatty liver disease (NAFLD) (Table 1). A study conducted on 50 healthy subjects who fasted from dawn to sunset for 23 to 30 consecutive days during the month of Ramadan showed that the levels of circulating cytokines including IL-6, IL-1β, TNF-α were significantly decreased after three weeks of dawn to sunset fasting compared with the baseline levels [44]. Likewise, another study of dawn to sunset fasting conducted among healthy subjects showed that plasma levels of cytokines including IL-6, IL-8, IL-1β were significantly reduced after one week of dawn to sunset fasting outside the month of Ramadan and after two weeks of dawn to sunset fasting during the month of Ramadan compared with baseline plasma levels before the weeks of fasting [45]. Additionally, the cosinor analysis of cytokines assessing the circadian rhythms of IL-6, IL-8, IL-1β at five different time points during the day (at 10 p.m., 2 a.m., 4 a.m., 6 a.m., and 11 a.m.) showed no significant variation in the acrophase of these cytokines during different times of the day [45]. The strength of this study was the control of the confounders that could affect the circulating cytokine levels, including sleep duration and timing, food composition, calories consumed, energy expenditure, and exposure to light [45]. More importantly, this study demonstrated that pro-inflammatory cytokines would decrease even after one or two weeks of dawn to sunset fasting [45].

The beneficial effect of dawn to sunset fasting on cytokines also was shown in overweight and obese subjects and subjects with NAFLD. A study that included 83 patients with NAFLD showed that the reduction in serum levels of IL-6 was significantly higher in subjects who fasted from dawn to sunset for a month than the reduction in the IL-6 levels in subjects who did not fast [46]. A randomized controlled study conducted in 28 male subjects with obesity showed that 14 subjects who

fasted from dawn to sunset for one month had a significantly lower plasma IL-6 level on the 15th day of one-month dawn to sunset fasting, the day after the end of one-month dawn to sunset fasting, and 21 days after the end of one-month dawn to sunset fasting compared with the plasma levels before one-month dawn to sunset fasting [47]. In contrast to these findings, there was no significant change in IL-6 levels in control subjects who did not fast [47]. A study of 57 overweight and obese subjects who performed dawn to sunset fasting showed a significant reduction in the serum levels of pro-inflammatory cytokines including IL-6 and TNF-α, along with a significant increase in the anti-inflammatory cytokine IL-10 and IL-10/IL-6 ratio at the end of 23–30 days of dawn to sunset fasting compared with the baseline values [48]. This study also showed reduction in insulin-like growth factor-1 (IGF-1) levels at the end of 23–30 days of dawn to sunset fasting compared with the baseline values [48]. IGF-1 promotes inflammation in peripheral mononuclear and endothelial cells [49,50], and several other studies of dawn to sunset fasting reported reduction of IGF-1 with fasting [51,52].

Regarding the effect of dawn to sunset fasting on chemokines and inflammatory biomarkers, a study of 58 healthy individuals between the ages of 20 and 40 years showed a significant decrease in serum levels of CXCL1, CXCL10, and CXCL12 at the end of one month dawn to sunset fasting compared with the levels collected on the first day of one-month fasting [53]. Although most dawn to sunset fasting studies showed a significant reduction in C-reactive protein levels [46,54–56], a small study showed no significant change in the C-reactive protein levels [57].

In mice, SARS-CoV-2 causes cytokine storm and lung injury by activating the inflammasome called NLR family pyrin domain containing 3 (NLRP3) through the structural nucleocapsid protein (N protein) [58]. The inhibition of NLRP3 inflammasome alleviates cytokine storm and lung injury [58]. Two significant mechanisms likely play a role in inhibiting NLRP3 inflammasome during intermittent fasting. The first mechanism appears to be the production of beta-hydroxybutyric acid, a ketone metabolite that was shown to alleviate IL-1β and IL-18 production and inhibit the caspase-1 activation induced by NLRP3 inflammasome [59]. A second mechanism works by activating nuclear receptor subfamily 1 group D member 1 (NR1D1), a core clock component that was shown to inhibit the NLRP3 inflammasome signaling pathway [60]. A study of dawn to sunset fasting for 30 days in humans showed findings suggestive of upregulation of NR1D1, the inhibitor of NLRP3 inflammasome [16]. Further human studies of dawn to sunset fasting are needed to replicate these findings in patients with COVID-19.

Altogether, these studies highlight the role of dawn to sunset fasting in promoting an anti-inflammatory milieu by suppressing circulating cytokine, chemokine, pro-inflammatory biomarker levels, and NLRP3 inflammasome. Additionally, the anti-inflammatory effect of dawn to sunset fasting appears to be independent of caloric intake, sleep/wake patterns, and blood collection timing [45]. However, larger studies of dawn to sunset fasting need to be conducted controlling for caloric intake and circadian rhythm variations.

3.2. Effect of dawn to sunset fasting on oxidative stress

SARS-CoV-2 can lead to mitochondrial dysfunction and the generation of excessive amounts of mitochondrial reactive oxygen species, leading to endothelial dysfunction associated with complications of severe COVID-19 infection (e.g., thrombosis, acute respiratory distress syndrome, and cardiovascular disease) [38,61,62]. Multiple studies showed that dawn to sunset fasting reduces the generation of reactive oxygen species, which mediate damage to host tissue [52,63–65]. It appears that dawn to sunset fasting reduces oxidative stress by upregulating the expression of antioxidant genes, including transcription factor A, mitochondrial (TFAM), superoxide dismutase 2 (SOD2), and nuclear factor erythroid 2-related factor 2 (Nrf2) [52]. A study conducted in 40 subjects with hypertension and 40 controls showed significant improvement in both groups in oxidative stress parameters, including an increase in blood glutathione and decrease malondialdehyde levels at the end of 4-week dawn to sunset fasting and six weeks after completion of 4-week dawn to sunset fasting compared with the levels before 4-week dawn to sunset fasting [63]. A similar study conducted in 40 subjects with diabetes and 40 subjects without diabetes showed similar improvement in oxidative stress parameters with 4-week dawn to sunset fasting [64]. In contrast to the findings of these two large studies, a small study of dawn to sunset fasting that controlled for sleep patterns and caloric intake and conducted in only eight healthy subjects showed no significant change in malondialdehyde levels and weight [66]. These findings could be related to the early measurement of oxidative stress parameters only after two weeks of dawn to sunset fasting instead of 4 weeks of dawn to sunset fasting, inadequate washout time between fasting periods in the month preceding the month of Ramadan and in the month of Ramadan, and lack of weight loss [66] as one study linked alterations in oxidative stress parameters to changes in body weight after fasting [67]. Additionally, demonstration of a substantial difference between before and after Ramadan fasting values of metabolic parameters in healthy subjects can be more difficult compared with subjects with chronic metabolic problems as healthy subjects may have normal or near-normal values of these parameters as the baseline.

3.3. Effect of dawn to sunset fasting on autophagy

Autophagy, a lysosome-dependent cellular process, is crucial for innate and adaptive immunity [68–72]. Specifically, autophagy is necessary for the proliferation, differentiation, and function of T cells, B cells, dendritic cells, macrophages, natural killer cells, and generation of chemokines, cytokines, and antibodies [68–72]. Downregulation of autophagy is a key mechanism adopted by SARS-CoV-2, to escape detection and have unchecked replication [73]. On the other hand, increased autophagy is reported by downregulation of the protein kinase C substrate 80K-H (PRKCSH) gene [74] that encodes for hepatocystin [75]. It was shown that dawn to sunset fasting for 4 weeks induced a proteome response associated with increased autophagy that was simultaneous to the reduction of oxidative stress and inflammatory biomarkers in subjects with metabolic syndrome [17]. The decrease in PRKCSH gene protein products during 4-week dawn to sunset fasting and an average of a 73-fold increase in its level one week after the completion of 4-week dawn to sunset fasting suggests increased autophagy during 4-week dawn to sunset fasting, and decreased autophagy with ad libitum eating after 4-week dawn to sunset fasting [17].

3.4. Effect of dawn to sunset fasting on immune function

Studies showed that patients with COVID-19 had increased leukocyte and neutrophil counts along with decreased lymphocyte and monocyte counts [5,76–79]. Additionally, leukocytosis and lymphopenia were more severe in critically ill patients than those with mild infection [3,5,76–79]. Specifically, lymphopenia was shown to be an independent predictor of poor prognosis in patients with COVID-19 [42,79]. A study conducted among 452 patients with COVID-19 in Wuhan, China, showed a significant increase in leukocyte numbers, neutrophil to lymphocyte ratio, neutrophil percentage, and a decrease in lymphocyte and monocyte percentages [35]. The mean combined number of T, B, and natural killer cells was below the normal range, and this decrease was more profound in severe cases than non-severe cases [35]. The mean number of T helper and T suppressor cells was below the normal range in all patients with COVID-19 [35]. However, T helper cells were significantly lower in severe cases than in non-severe cases [35]. Most importantly, patients with severe COVID-19 infection had a higher naive to memory T helper cell ratio than those without severe infection, suggesting that the naive T helper cells in patients with severe COVID-19 infection failed to differentiate into memory T helper cells [35].

Few studies of dawn to sunset fasting investigated the impact of

fasting on peripheral blood cells. A study conducted on 50 healthy subjects who fasted from dawn to sunset for a month had a significant reduction in total leukocytes, granulocytes, lymphocytes, and monocytes after 3 weeks of dawn to sunset fasting compared with baseline levels [44]. The same study showed a significant increase in monocyte count and no significant change in other immune cells one month after the completion of the fasting month compared with baseline levels [44]. Other studies of dawn to sunset fasting showed a similar significant increase in monocyte count [55] and no change in leukocyte counts after the completion of one month dawn to sunset fasting month [55,80]. Collectively, the lack of data on the effect of dawn to sunset on the percentage of T cell subsets and T cell function were the significant limitations of these studies. A proteomic analysis of dawn to sunset fasting conducted on subjects with metabolic syndrome showed a16-fold increase in the mean level of calreticulin (CALR) gene protein products one week after the cessation of 4-week dawn to sunset fasting compared with the level before 4-week dawn to sunset fasting [17]. Calreticulin [74], a phagocytosis-promoter protein [81] fused with severe acute respiratory syndrome coronavirus (SARS-CoV) recombinant S protein 450–650 fragment, was shown to enhance IgG-mediated immune response and result in much higher immunogenicity than SARS-CoV recombinant S protein 450–650 fragment alone [82]. Although these findings suggest that dawn to sunset fasting can play an essential role in adaptive humoral defense against SARS-CoV-2 [17], they need to be replicated in SARS-CoV-2.

3.5. Effect of dawn to sunset fasting on obesity and metabolic syndrome

Obesity and metabolic dysfunction are major risk factors for severe COVID-19 infection [83–86]. Obesity and metabolic syndrome impair adaptive and innate immune responses [87,88]. The excess adipocytes lead to increased leptin levels and pro-inflammatory cytokines including IL-6 and TNF-α, and decreased adiponectin level and anti-inflammatory cytokines including IL-10 and IL-1 receptor antagonist (IL-1 RA) [48, 89–91]. A study conducted on 417 patients with COVID-19 showed that even a minor elevation within the normal fasting blood glucose range was a risk factor for admission to the intensive care unit [92]. Another study conducted on 941 patients with COVID-19 reported that patients with diabetes had higher mortality compared with those without diabetes, and a fasting blood glucose level equal or greater than 7.0 mmol/L was an independent risk factor for predicting mortality in COVID-19 patients without a history of diabetes [93].

Dawn to sunset fasting improves insulin signaling, blood pressure, and lipid profile with a notable significant increase in high-density lipoprotein levels and leads to an anti-inflammatory effect via a decrease in adipose tissue and weight in the absence of strict regulation of caloric intake or food quality [94–101]. Several studies of dawn to sunset fasting conducted in subjects with obesity, type 2 diabetes mellitus, or metabolic syndrome showed that dawn to sunset fasting improves components of metabolic syndrome [17,47,57,98]. The improvement in metabolic components was associated with decreased pro-inflammatory cytokines and oxidative stress parameters and upregulation of the genes that play a pivotal role in immune defense [48,63,64,102]. A study conducted on 14 subjects with metabolic syndrome showed a significant reduction in body weight, body mass index, and waist circumference at the end of the 4th week during 4-week dawn to sunset fasting and one week after 4-week dawn to sunset fasting compared with the baseline levels [17]. This study also showed significant improvement in systolic, diastolic, and mean arterial blood pressures at the end of the 4th week during 4-week dawn to sunset fasting and a significant reduction in homeostatic model assessment for insulin resistance one week after 4-week dawn to sunset fasting compared with the baseline levels [17]. Another study showed that the levels of brain-derived neurotrophic factor (BDNF), a food intake regulator [103] decreased during 4-week dawn to sunset fasting compared with baseline BDNF levels, and there was a positive correlation between changes in the BDNF and TNF-α levels at the end of the 4th week during 4-week dawn to sunset fasting suggesting that BDNF may have a role in inflammation attenuated by dawn to sunset fasting [102]. As dawn to sunset fasting leads to improvement in metabolic parameters; this is one physiologic way of decreasing the risk of morbidity and mortality associated with COVID-19 [83–86].

3.6. Effect of dawn to sunset fasting on gut microbiome

A healthy immune system has been linked to a healthy gut microbiome [104]. However, patients with COVID-19 were shown to have a significantly altered gut microbiome compared with those without infection [105]. In COVID-19, the gut microbiota composition was associated with the disease severity and plasma levels of pro-inflammatory cytokines and chemokines and remained altered even after the viral clearance [105]. Other studies showed altered gut microbiome in patients with COVID-19 and a positive association between altered gut microbiota and severity of COVID-19 [106–108].

Studies of dawn to sunset fasting showed findings suggestive of beneficial alterations in the gut microbiome [109–111]. A study conducted on both healthy young and middle-aged cohorts showed a significantly increased gut microbiome diversity and remodeling of the gut microbiome in the young cohort at the end of dawn to sunset fasting month compared with baseline levels [109]. In the middle-aged cohort, there was a significant remodeling of the gut microbiome induced by dawn to sunset fasting, upregulation of Lachnospiraceae at the end of dawn to sunset fasting month and upregulation of Ruminococcacea one month after the completion of dawn to sunset fasting month compared with baseline levels [109]. The middle-aged cohort who did not fast had no significant change in microbiome composition and taxa during the study period [109]. Another study on 34 healthy subjects showed that dawn to sunset fasting affected beta diversity (assessment of variation in microbial composition between samples) rather than alpha diversity (assessment of microbiome diversity within a sample) [111]. While this study found a significant increase in Bacteroidetes and a decrease in Firmicutes in the Pakistani group, a similar effect was not observed in the Chinese group, likely related to the effect of diet on microbiome [111]. A smaller study showed a significant beta diversity and enrichment in the Bacteroidetes phylum after 29 days of dawn to sunset fasting [110]. The enrichment in Bacteroidetes phylum after dawn to sunset fasting is important because the reduction in Bacteroidetes/Firmicutes ratio was shown to play an important role in the development of obesity [112,113]. Both Lachnospiraceae and Ruminococcacea are bacteria that produce butyric acid that plays a role in reducing oxidative stress, inflammation, and risk of colon cancer [114–118]. Collectively, these studies suggest that dawn to sunset fasting induces favorable changes in the composition of the gut microbiome that can boost the innate and adaptive immune responses. Randomized controlled studies of dawn to sunset fasting with larger sample size are needed to further define the role of the gut microbiome on the immune system controlling for diet and circadian rhythm parameters.

4. Concerns regarding dawn to sunset fasting during COVID-19 pandemic

There is a concern that intermittent fasting leads to dehydration which can affect the mucociliary clearance of respiratory microbial organisms and cause broncho-pulmonary diseases [119]. However, no significant data support impaired mucociliary function in dawn to sunset fasting. A study compared the nasal mucociliary clearance time in 40 subjects who fasted for an average of 15 hours from “dawn to sunset” for 29 days (Ramadan fasting) and 26 subjects who fasted “non-stop” for 60 hours (Nineveh fasting) [120]. In subjects who practiced dawn to sunset Ramadan fasting, there was no significant impairment in mucociliary clearance time four weeks after the Ramadan fasting period compared with the mucociliary clearance time measured during the fasting period

[120]. In contrast to subjects who practiced dawn to sunset fasting, subjects who practiced Nineveh fasting had a significant prolongation of mucociliary clearance time four weeks after the fasting period compared with the mucociliary clearance time measured during the fasting period [120].

A second common concern with dawn to sunset fasting is dehydration that can potentially result in renal dysfunction. Several studies of dawn to sunset fasting found no significant dehydration or impairment in renal function [121–123]. It is important to recognize that during the COVID-19 pandemic, the use of masks and high-grade respirators for prolonged periods, especially in high-risk exposure settings, such as healthcare systems, may cause dehydration from fasting. Dehydration can result from the heat effects of prolonged personal protective equipment (PPE) use and the lack of opportunities to rest and have food and water breaks during the non-fasting period. As a result, dehydration can occur from the high demands of front-line work, which leads to a longer than the recommended period of fasting [125,126].

A third common concern with dawn to sunset fasting is potential sleep deprivation commonly due to early wake-up time for a pre-dawn breakfast. It is well-known that sleep deprivation can weaken immunity due to dysregulated functioning of immune cells and their responses [127–130]. Specifically, nighttime sleep deprivation can disrupt the circadian rhythm and increase oxidative stress [131]. Individuals practicing dawn to sunset fasting should have an early bedtime to ensure seven or more hours of daily sleep at night [23] to prevent sleep deprivation.

Individuals with chronic medical conditions (e.g., diabetes, chronic kidney disease, coronary artery disease, seizure disorder) should consult their physicians before practicing dawn to sunset fasting/Ramadan fasting and follow medical advice [22,124,132,133]. Patients with diabetes mellitus can be at risk for hypoglycemia if they fast long hours and the dose of their medications are not adjusted for mealtimes of dawn to sunset fasting [22,132,133]. International diabetes federation the Ramadan nutrition plan (RNP) for patients with diabetes provides a well-balanced nutrition strategy during dawn to sunset fasting/-Ramadan fasting that can be considered not only for patients with diabetes but also for individuals without diabetes who plan to practice dawn to sunset fasting [134].

Altogether, during the COVID-19 pandemic, it is crucial to follow safe practices for healthy dawn to sunset fasting/Ramadan fasting [135].

5. Conclusions

We have summarized the various physiologic effects of dawn to sunset fasting on the immune system. Overall, the health and immune benefits of dawn to sunset fasting not only have the potential to optimize the immune system function during the COVID-19 pandemic, but they can also lead to an improved metabolic profile, decreased risk of cancers, and other chronic inflammatory diseases. Studies are needed to assess and confirm the potential benefits of dawn to sunset fasting against SARS-CoV-2 directly.

CRediT authorship contribution statement

Sundus I. Bhatti: Writing – original draft, Writing – review & editing, contributed to the drafting and writing the manuscript and performed a critical review of the manuscript for important intellectual content. **Ayse L. Mindikoglu:** Writing – original draft, Writing – review & editing, contributed to the drafting and writing the manuscript and performed a critical review of the manuscript for important intellectual content.

Declaration of competing interest

None of the authors has a conflict of interest.

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