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Immunity and Infection Risk: COVID-19 Ramadan Rapid Review

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Background

As Ramadan approaches, it is clear that there will be little evidence to accurately assess how fasting will affect the immune response to, and the susceptibility of contracting COVID-19. However, there is a growing corpus of literature looking at the biochemical and clinical effects of fasting on the immune system which informs the following discussion. It must be noted here that the literature explores various definitions of fasting; this review focuses on studies looking at Ramadan fasting and generally excludes others unless directly relevant.

Current Evidence

Fasting and the Immune System

Wang et al (2016) demonstrated that oral administration of glucose increased mortality in mice systemically infected with Listeria, whereas the administration of 2-deoxy-D-glucose, which competes with glucose utilisation, promoted survival of the mice. By contrast, the authors found that glucose availability and utilisation are critical for surviving influenza infection. They explained this by demonstrating that in bacterial infection, glucose utilisation inhibited ketogenesis, leading to impaired tolerance of reactive oxygen species mediated brain damage and death. On the other hand, glucose availability and utilisation in viral inflammation promoted cellular adaptation to stress caused by the unfolded protein response.

Latifynia et al (2007) investigated the influence of Ramadan fasting on the innate immune system (part of the body's defence against pathogens) - specifically examining neutrophil respiratory burst and circulating immune complexes. They did not identify any statistically significant changes on neutrophil activity in patients undertaking Ramadan fasting. The same authors (2008) studied the effect of Ramadan fasting on C3 and C4 levels (another part of the body's defence against pathogens) and likewise found no significant alterations in their levels as a result of Ramadan fasting. These findings were echoed by Lahdimawan et al (2014), who also demonstrated Ramadan fasting decreases oxidative stress on macrophages. This is in conflict with Bahammam et al (2016), Delpazir et al (2015) and Asgary et al (2000) who demonstrate a lack of significant change in oxidative stress after Ramadan fasting.

Faris et al (2012) demonstrated that the pro-inflammatory cytokines Il-1B, IL-6 and TNF-alpha showed a significant decrease during Ramadan fasting. Mohammed et al (2010) and Chennaoui et al (2009) (25) demonstrated similar results, although not reaching significance. On the other hand, Lahdimawan et al (2013) found significantly increased levels of TNF-alpha levels during fasting and Feizollahzadeh et al (2014) demonstrated that TNF-alpha levels remained unchanged.

Develioglu et al (2013) demonstrated that serum IgG and serum IgA concentrations decreased significantly during Ramadan fasting, but still remained within normal limits. Serum IgM levels remained stable however. These findings were echoed by Bahijri et al (2015).

Collins et al (2019) discovered enhanced T cell protection against infections and tumors when an animal's caloric intake was reduced by 50 percent.

Nagai et al (2019) demonstrated that while short-term fasting (less than 24 hours) did not compromise an animal's ability to heal a wound or fight off infection, longer fasts did indeed begin to cause problems. When starved for 48 hours before skin injury or infection, significant immune response impairments were noticed.

In a systematic review on the immunomodulatory effects of Ramadan fasting, Adawi et al (2017) state that Ramadan

fasting has been shown to "only mildly influence the immune system and the alterations induced are transient, returning to basal pre-Ramadan status shortly afterward." The evidence upon which this is based consists of observational studies with small sample sizes however based on the available evidence, this conclusion appears appropriate. There is some evidence to suggest the fasting may be detrimental in viral infections and beneficial in bacterial infections, but the evidence upon which this is based largely consists of animal studies.

Fasting and Infection Risk

Brazzagi et al (2015) performed a narrative review on 51 articles that covered a variety of infections, in particular HIV, where they conclude from 3 studies that fasting "might not be detrimental for those suffering from stable HIV". They also quote the following works:

Leung et al (2014), whose retrospective analysis of 3,485 Bangladeshi patients with diarrheal illness in a single centre from 1996-2012, found no statistical difference in illness and diarrheal pathogens between Ramadan and the control period of 30 days prior to Ramadan. There was a higher incidence of severe thirst and longer duration of hospitalization for those who presented in Ramadan than the control period, but rates of other variables including duration of diarrhea, drowsiness, severe dehydration, and use of intravenous rehydration were not significantly different.

Davoudabadi, Akbari and Rasoulnezhad (2005) performed a retrospective study of histologically diagnosed acute appendicitis in a single centre in Iran between 2000-2002 in the months before, during and after Ramadan. They identified 1,773 patients and found the incidence of acute appendicitis to be significantly lower in Ramadan. They postulated this could be due to bowel-rest that occurs in Ramadan. Sulu et al (2010) carried out a retrospective study in 2 centres in Turkey on acute appendicitis, again diagnosed by histology. They found no significant difference in outcomes or patient characteristics as a result of Ramadan.

Salahuddin (2015) writes in an opinion piece that dehydration during Ramadan fasting may impair the flushing effect that normally clears the bladder of debris, preventing stagnation and bacterial colonization.

In an observational study Sari, Varasteh and Sajedi (2010) compared the tear protein content of 60 healthy volunteers before and during Ramadan. They found the activity of lysozyme, lactoferrin and alpha amylase enzymes decreased in fasting samples.

Sacko et al (1999) performed a randomized, single-blind, placebo-controlled trial to investigate Ramadan fasting and the efficacy of single-dose anti-helminth medication. They reported no significant difference with the efficacy of pyrantel, mebendazole and albendazole in treating Necator americanus hookworm infections 10 days post treatment during Ramadan.

Halasa (2014) writes in another opinion piece on the effect of Ramadan fasting on emergency clinic attendances in Jordan, comparing data of 7,770 attendances in Ramadan (September) 2010 with a sample of 10,000 attendances in May 2010. She found that the reasons for attendance were similar - young patients with upper respiratory tract infection and acute simple gastroenteritis - but patients modified the timing of their presentation towards the later half of the day.

These are similar to the findings of Pekdemir et al (2008), who looked at 2079 patients in Turkey and found no significant difference in the clinical or demographic features of patients admitted to the emergency department in Ramadan, compared with the 30-days immediately after as a control. Elbarsha et al (2018) looked at 186 diabetic patients who were admitted at a single center during Ramadan in Libya, and were compared with 216 diabetic admissions 2 months later as a control group. This analysis showed no difference in infectious disease being the reason for admission.

Summary of evidence

Most studies on the effect of fasting and immunity are on animal models and are inconclusive. The mainstay of studies looking at infection in Ramadan are retrospective analyses which are difficult to generalise, though one RCT showed no difference in anti-helminth drug activity during Ramadan. Overall, existing evidence is poor and of limited use in basing recommendations.

Recommendations

Data regarding COVID-19 is emerging and the role of dehydration and caloric restriction in disease progression are uncertain. From clinical experience, immunocompetent individuals without comorbidities who are adequately hydrated, nourished and rested, are capable of fasting the month of Ramdan without increased risks of infection. Patients with comorbidities and/or immune suppression are strongly advised to seek timely medical advice before fasting. Unwell patients must give strong consideration to breaking their fast, especially if they display COVID-19 symptoms. Patients who are prone to urinary tract infections are advised to intensely hydrate during non-fasting hours.

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