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REVIEW ARTICLE

Fasting and calorie restriction modulate age-associated immunosenescence and inflammaging

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Abstract

Aging is a multifaceted process impacting cells, tissues, organs, and organ systems of the body. Like other systems, aging affects both the adaptive and the innate components of the immune system, a phenomenon known as immunosenescence. The deregulation of the immune system puts elderly individuals at higher risk of infection, lower response to vaccines, and increased incidence of cancer. In the Western world, overnutrition has increased the incidence of obesity (linked with chronic inflammation) which increases the risk of metabolic syndrome, cardiovascular disease, and cancer. Aging is also associated with inflammaging a sterile chronic inflammation that predisposes individuals to age-associated disease. Genetic manipulation of the nutrient-sensing pathway, fasting, and calorie restriction (CR) has been shown to increase the lifespan of model organisms. As well in humans, fasting and CR have also been shown to improve different health parameters. Yet the direct effect of fasting and CR on the aging immune system needs to be further explored. Identifying the effect of fasting and CR on the immune system and how it modulates different parameters of immunosenescence could be important in designing pharmacological or nutritional interventions that slow or revert immunosenescence and strengthen the immune system of elderly individuals. Furthermore, clinical intervention can also be planned, by incorporating fasting or CR with medication, chemotherapy, and vaccination regimes. This review discusses age-associated changes in the immune system and how these changes are modified by fasting and CR which add information on interventions that promote healthy aging and longevity in the growing aging population.

KEYWORDS
aging, calorie restriction, fasting, immunosenescence, inflammaging

1 | INTRODUCTION

Aging is a complex process, associated with the accumulation of damaged molecules, progressive loss in structure and function of cells, tissues, and organs, and increased vulnerability to death.[1] Even if the aging process is multifaceted and diverse, laboratory manipulation of genes in different laboratory model animals has increased the lifespan of these organisms. Most genes that are associated with increasing lifespan are part of the nutrient-sensing pathway and the mutation in these genes mimics the state of food shortage.[2]

The relationship between the effect of nutrition on longevity was first introduced to the scientific community by the experiment conducted by McCay CM et al, where they showed rats with retarded growth (due to starvation) showed a higher lifespan compared to mice under normal feeding cycles.[3]

Fasting is the voluntary prevention of ingestion of a minimum or no food and drinking calorie beverage for a period lasting from 12 h to 3 weeks depending on the intended purpose. Calorie restriction is decreasing the intake of calories by 20%–40%, without changing the pattern of meal frequency. Calorie restriction and fasting have been implemented for different purposes including delaying aging and prevention of disease.[4]

Undoubtedly nutrition is critical for proper immune response; previous works have shown that essential nutrients like vitamin A are crucial for effective adaptive immune response, for instance, it can impact the ILC3 (Innate lymphoid cells-3) immune response.[5] Similarly, fatty acids are crucial for the ILC2 immune response in clearing parasitic infection and its shortage leads to a decrease in ILC2-derived cytokines like IL-5 and IL-13.[6] In contrast, adaption of the Western world diet has been linked with immunopathological conditions like inflammatory bowel disease, multiple sclerosis, and asthma.[7]

Different mechanisms of fasting and CR have been linked with healthy aging trajectories in different organisms.[4] Yet the direct effect of fasting and CR on the aging immune system needs to be further explored. As fasting and CR are already being practiced by different religious groups and volunteers, understanding its effect on the immune cells can help in integrating it as a therapeutic strategy for treating cancer, infectious diseases, and noninfectious diseases and increasing vaccine response.

1.1 | Immunosenescence and its modulation with fasting and calorie restriction

Alongside other systems in the body, aging affects both the adaptive and the innate components of the immune system, a phenomenon known as immunosenescence. The deregulation of the immune system puts elderly individuals at higher risk of infection, lower response to vaccines, and increased incidence of cancer. Of the two systems, the adaptive part of the immune system is most impacted by aging.[8]

1.2 | The innate immune system and the impact of aging, fasting, and calorie restriction

Components of the innate immune system, like macrophages, neutrophils, natural killer cells, and dendritic cells are the first line of defense and initiate the adaptive immune response. Aging results in the phenotypic and functional changes of the innate immune cells, this results in the decrease in phagocytosis, defect in chemotaxis, and cellular signal transduction.[9]

1.3 | Neutrophils

Neutrophils are the first cells that arrive at the site of infection or inflammation. Once they arrive at the site, they are capable of phagocytosis, produce reactive oxygen species, produce proteolytic enzymes, and also able to form neutrophil extracellular traps (NETs) which trap pathogens and clear the pathogen after that they undergo apoptosis.[10]

Most studies have shown that the normal aging process does not affect the number of neutrophils,[11,12] others have shown an increase in number[13] and others showed a decrease in number with an increase in age.[14] Whereas the functionality of neutrophils like phagocytosis, use of free radicals to kill intracellular pathogens, and chemotaxis have been shown to decrease with age.[15] In humans, 72-h intensive fasting showed an increase in the number and frequency of neutrophils which is linked with a decrease in lymphocyte frequency. Transcriptomic and proteomic profiling revealed fasting increases the degranulation and activation profile of neutrophils. The expression of cytokines was also increased in neutrophils after fasting which indicates that fasting has a stimuli effect on neutrophils.[16]

1.4 | NK cells

Broadly the natural killer (NK) cells can be divided based on the expression of the CD56 molecule into $CD56^{bright}$ immunoregulatory role, and $CD56^{dim}$ cytotoxic population. Aging affects this population in a different manner where an expansion of $CD56^{dim}$ mature NK cells and a decline of $CD56^{bright}$ NK cells is observed with age.[17] In general, the number of NK cells increases with age but on a per-cell basis, the functionality decreases. This decrease in functionality is linked with intracellular molecules like granzyme A which decreases with age.[18]

In humans, calorie restriction has been shown to decrease the number of peripheral NK cells.[19] Acute 3-day fasting in mice showed that the number of NK cells remained the same, whereas the number of NK cells that express TNF-related apoptosis-inducing ligand $(TRAIL)^{+}$ and $CD69^{+}$ NK cells increased in fasting mice. Similarly, TRAIL-mediated antitumor activity of NK cells (partly regulated by HSP70) showed to increase in fasted mice compared to controls.[20]

1.5 | Monocytes and macrophages

Monocytes have cell surface receptors like Toll-like receptors (TLRs) and pattern recognition receptors (PRRs) that recognize pathogens and can respond by producing different inflammatory molecules. Using the cell surface markers, CD14 and CD16 monocytes can be divided into different subsets. The classical monocyte expresses high CD14 and no/low CD16 (CD14++CD16−/+), the intermediate monocytes express CD16 and high CD14 (CD14++CD16+), and the nonclassical monocytes have a higher level of CD16 with lower expression of CD14 (CD14+ CD16++).[21]

The proportion of CD16+ expressing intermediate and nonclassical monocytes increases with age. Compared to CD14++CD16− monocytes, CD14+CD16+ monocytes have shorter telomeres, increased expression of β-galactosidase, and produce more inflammatory molecules and are linked with pathologies like atherosclerosis in the elderly.[22] Similarly, the accumulation of nonclassical monocytes with age is associated with an increase in the production of TNF-α and IL-8 in the elderly, and also these monocytes express senescence-associated secretory phenotype (SASP), high levels of basal NF-κB and IL-1α level.[23]

During a period of fasting, monocytes express the ligand CXCR4 to migrate to the bone marrow and hibernate. These monocytes have distinct transcriptional features that alter their ability to respond to infection.[24] In humans, fasting decreases the number of circulation CD14+CD16− and CD14+CD16+ monocytes but does not affect the number of neutrophils. Similarly, fasting in mice decreased the number of pro-inflammatory monocytes expressing Ly-6C^{high} in the blood and different tissues including the lung, spleen, liver, and adipose tissue.[25]

Macrophages have intra and extracellular receptors that help them recognize infectious agents, involved in tissue damage signals and tissue homeostasis.[26] With aging, macrophages' ability to infiltrate the site of infection has been shown to decrease, which could compromise initiating the adaptive immune response.[27] On the other hand, intermittent fasting in overweight and obese women has been shown to increase infiltration of M1-macrophages (CD40^{+}) and M2-macrophages (CD163^{+}) into the adipose tissue and skeletal muscle, respectively.[28]

1.6 | Dendritic cells

Dendritic cells (DCs) are the most effective antigen-presenting cells (APCs) and have expressed cell surface molecules like MHC-II, CD80, and CD86 which make them effective in initiating an immune response. DCs are divided into two subclasses, which are plasmacytoid DCs (pDCs) and conventional DCs (cDCs) also known as myeloid DCs (mDCs). pDCs are lymphoid origin with a cell surface marker CD11c−CD123+ and use TLRs (TLR7 and TLR9) to identify viral components and secret types I and type II interferon, whereas mDCs (cDCs) are derived from myeloid progenitors surface marker CD11c+CD123− and are potent antigen-presenting cells bridging the innate and adaptive immune response.[29]

The impact of aging on the number of DCs is dissimilar; some studies have shown that both healthy elderly and frail elderly individuals showed a reduced number of pDCs compared to young adults, whereas no significant change in the number of mDCs was observed between the two groups.[30] Others showed the number of mDCs was maintained in individuals above the age of 20 years, whereas the number of pDCs decreased with age,[31] others also showed the number of both mDCs and pDCs were not affected by age.[32] Functionally, pDCs from elderly individuals secrete a lower level of interferon (IFN)-α linked with lower expression of TLR7 and TLR9.[30] Similarly aging impaired DCs phagocytosis and chemotaxis ability, and decreased PI3K signaling.[32]

Short-term fasting induces in higher number of CD103^{+}CD11b^{-} DCs in mesenteric lymph nodes and intestinal lamina propria.[33] A fasting mimicry diet has increased tissue infiltration of CD103+ dendritic cells in mice and helps in the activation of T cells.[34] Together, this could indicate that fasting or calorie restriction could help the immune response to fight cancer and infection by facilitating the tissue infiltration ability of dendritic cells.

1.7 | The adaptive immune response and the impact of aging, fasting, and calorie restriction

The adaptive immune system is crucial in controlling infection, vaccine response, and cancer immune surveillance and it is meaningfully affected by aging. Aging especially alters the structure of the thymus affecting the output of naïve T cells. Furthermore, age-dependent epigenetic modification like heterogeneity of DNA methylation and histone acetylation impacts the immune system of the elderly.[35]

1.8 | T cells

T cells express a unique cell surface receptor, the T cell receptor (TCR) which is used to recognize antigens bounded with MHC-I for CD8+ T cells and with MHC-II for CD4+ T cells. The CD8+ T cells have more of a cytotoxic function, whereas the CD4+ T cells function as helpers (activation of B cells and CD8 + T cells) and regulators of the immune response. The CD4 + T cells are heterogeneous and are further divided into T helper (Th) 1, Th2, Th17, Th22, Treg (regulatory T cells), and Tfh (T follicular cells). Phenotypically, the T cells can be distinguished as naïve T cells (CD45RA^{+}CCR7^{+}), central memory T cells (CD45RA^{-}CCR7^{+}), effector memory T cells (CD45RA^{-}CCR7^{-}CD45RO^{+}), and effector memory reexpressing CD45RA (TEMRA) T cells as (CD45RA^{+}CCR7^{-}).[36]

The proliferative capacity of hematopoietic stem cells (HSCs) and lymphoid output decrease with age and a shift toward myeloid progenitors leading to a decrease in naïve T cells with age.[37] By comparison, the loss of naïve CD4T cells can be compensated through peripheral cell division but the naïve CD8 T cells decrease dramatically in elderly individuals. With aging, expansion of phenotypically distinct CD8 effector T cells and a decrease in CD28 expression are observed.[38]

During dietary restriction, memory T cells develop a mechanism of long-term survival by adapting to a shortage of nutrients. Similarly, the number of memory T cells in the circulation and the secondary lymphoid organs decrease, and the population of memory T cells increases in the bone marrow.[39] Eight-week calorie restriction (CR) showed an increased number of naïve CD4 T cells and a decrease in memory CD4 T cells among participants under CR.[40] Similarly, 6 months of 10% and 30% calorie restriction increased T cell proliferation capacity and its response to delayed hypersensitivity.[41] On the contrary, long-term calorie restriction in healthy nonobese adults showed similar levels of cellular markers like CD8^{+}CD28^{-} T

cells and CD57 and PD-1 expressing T cells compared to control nonobese healthy adults.[42] Likewise, weight loss-associated calorie restriction decreases natural killer cells and weakens antiviral immunity.[19] Whereas in mice, DR suppresses cellular markers like PD-1, Tim3, KLRG1, and transcription factors NR4A1 and TOX which are linked with T cell exhaustion.[43] This indicates the complex interaction of fasting with cells of the immune system and further studies are needed to elucidate this interaction.

1.9 | B cells

B cells are the main players of humoral immunity and use membrane-bounded immunoglobulin (Ig) to identify the invading pathogen. Within the germinal center, antigen-engaged B cells undergo somatic mutation on the variable region of immunoglobulin resulting in B cells expressing high-affinity antibody-producing plasma cells and memory B cells against the pathogen.[44] Using cell surface markers including CD19, CD20, CD21, IgD, CD27, CD38, and CD24, B cells can be categorized into different groups. For instant resting, naïve B cells express IgD+CD27−CD38+CD24+CD21+, switched memory B cells express IgD−CD27+CD38−CD24−CD21− and plasma cells express IgD− CD27 ++ CD38+++ CD24−.[45]

Studies have shown that the telomerase activity of both naïve and memory B cells was maintained with age but the number of memory B cells increased with age.[46] The number of circulating naïve B cells decreases with age alongside the general decrease in lymphogenesis. The production of high-affinity antibodies and the decrease in response to vaccination have also been reported with an increase in age. The differentiation of memory cells into plasma cells is also affected by age.[47] The number of peripheral B-1 cells (expressing CD19+CD20+CD27+CD38$^{low/int}$ CD43+) and their ability to produce IgM decreases with age.[48]

Mice under 3 days of fasting and 2 weeks of 30% DR showed a decrease in the total number of CD19+B220+ B cells and an increase in the IgM+IgD+ B cells in the bone marrow compared to mice under ad libitum feeding. Likewise, immature transitional B cells expressing ($CD19^+B220^+IgM^+IgD^-$) and mature B cells expressing ($CD19^+B220^+IgM^+IgD^+$) depleted in the spleen of mice under dietary restricted and fasting compared to mice in ad libitum feeding.[49] Fasting also induces apoptosis of B cells, increases phagocytosis activity, decreases the number of naïve B cells in the Peyer's patches (PP), and facilitates the accumulation of naïve B cells in the bone marrow (Figure 1).[50]

1.10 | Effect of fasting and calorie restriction on inflammaging and autophagy

1.10.1 | Inflammaging

Inflammation is a crucial process that facilitates the maintenance and restoration of tissue and the clearance of pathogens. On the other hand, chronic inflammatory processes are linked with different pathologies, like rheumatoid arthritis. Aside from this pathological involvement of chronic inflammation, the aging process is linked with a low-grade, chronic, and sterile inflammation (an inflammation without infection) termed as "Inflammaging."[51]

The normal healthy aging process (aging without any clinical disease) is characterized by an increased level of pro-inflammatory biomarkers like increased levels of IL-6, CRP, IL-18, IL-8, IL-1, and TNF-α. Similarly, with aging, increased levels of chemokines like MCP-1 and RANTES and other molecules like sTNF-RI, sTNF-RII, and sCD30 have also been reported.[52,53] Beside the appearance of inflammaging in the normal aging process, it has been linked with many age-associated pathologies like cardiovascular disease, dementia, cancer, and diabetes.[54] Systemic high levels of TNF-α and IL-6 in older adults have been associated with the risk of CVD.[55] Whereas the use of anti-inflammatory molecules like TNF-α inhibitors in psoriasis and rheumatoid arthritis patients has decreased the risk of CVD.[56] Similarly, age-associated loss of muscle strength and muscle mass was associated with increased levels of TNF-α and IL-6.[57] Inflammaging has been linked with mild cognitive impairment, diabetes, cancer, chronic kidney impairment, and severe disease complications in infection like COVID-19 in elderly individuals.[58–61]

Consumption of excess food is linked with chronic inflammation,[62] and it contributes to different pathologies like type 2 diabetes, cardiovascular disease, atherosclerosis, metabolic syndrome, and nonalcoholic fatty liver diseases.[63] On the contrary lower levels of inflammatory mediators like C- reactive protein (CRP) and TNF-α were associated with healthy diets like fish, nuts, whole grains, fruits, and vegetables.[64] Individuals under a religious fasting regime showed a reduced level of circulatory pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β during the fasting period compared to before and after the fasting period.[65] Other studies also showed that in humans, 12 weeks of alternative day fasting has shown a decreased level of inflammatory molecules like CRP.[66] After 8 weeks of intermittent fasting, a significant decrease in the level of inflammatory molecules like IL-6, TNF-α, and IL-1β was observed.[67] To conclude inflammaging is one characteristic of aging and age-associated pathologies, overnutrition is also associated with a state of higher inflammation, whereas fasting and calorie restriction decreases the level of different inflammatory molecules and can contribute to healthy aging.

1.10.2 | Autophagy

Autophagy is an evolutionary conserved, self-degradation mechanism used for removing damaged molecules, aggregated proteins, and damaged organelles. The autophagy process encompasses different mechanisms employed by the cell to degrade cytoplasmic substrates which include microautophagy, macroautophagy, and chaperone-mediated autophagy. The autophagic proteolysis activity decreases with age and accumulation of mis-fold proteins, lipid droplets, and toxic insults inside the cytoplasm has been linked with

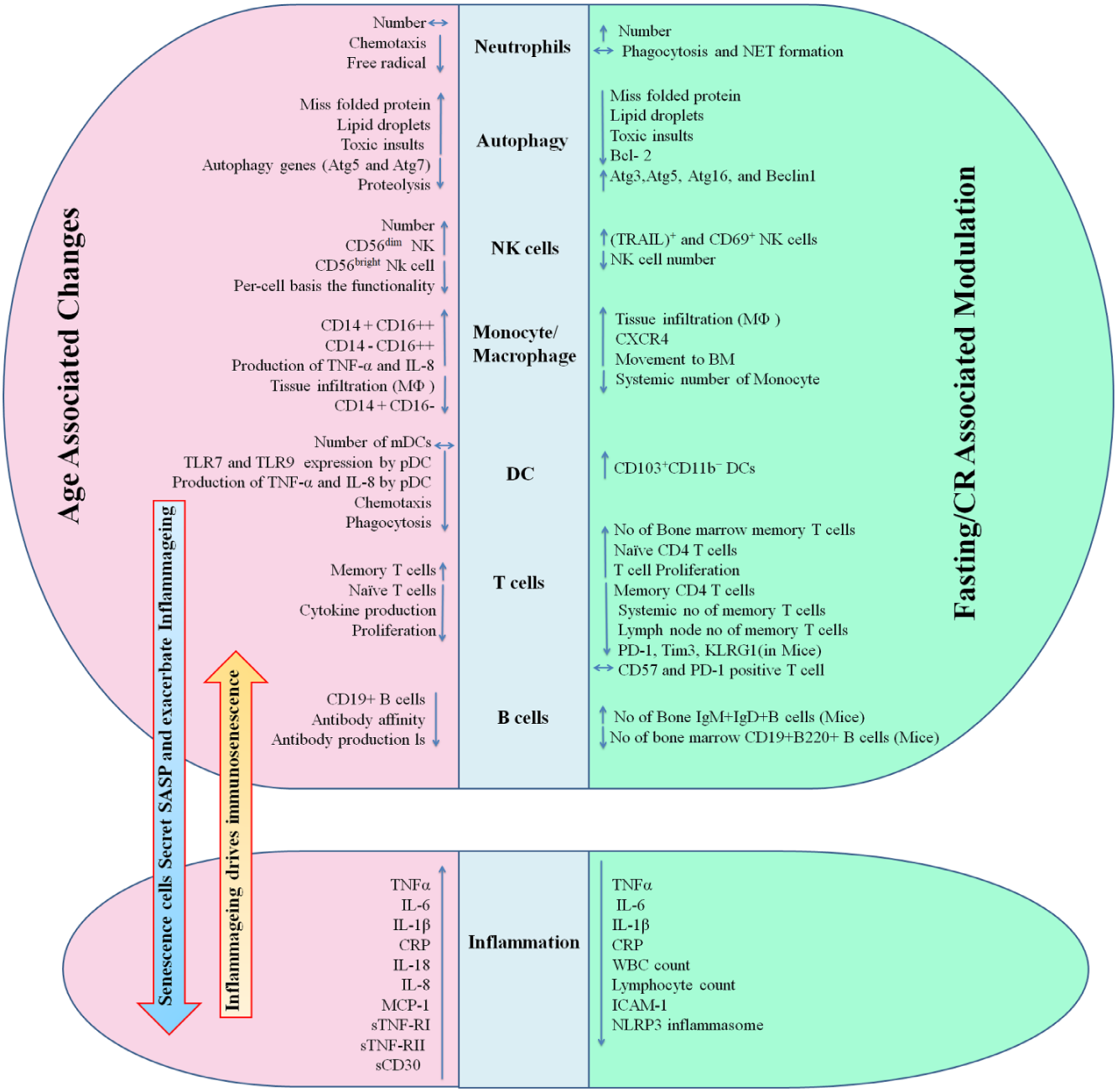

FIGURE 1 Effect of fasting or calorie restriction on phenotypic and functional changes associated with immunosenescence and inflammaging. The middle of the diagram (light blue) indicates the different immune cells and immune response (inflammation). The left side of the diagram (light red) indicates the phenotypic and functional changes in different cells associated with aging. Senescent cells accumulate with age and secrete senescence-associated secretory phenotype (SASP) which aggravates inflammaging at the same time inflammaging can drive immunosenescence (the two arrows on the left side). The right side of the diagram (light green) shows how fasting or calorie restriction modulates age-associated changes in the immune system.

age-associated pathologies like neurodegenerative disorders.[68] Genome-wide analysis revealed Atg5 and Atg7 which are genes involved in autophagy were downregulated in the human brain in normal aging.[69]

Inhibiting the autophagy process by pharmacological intervention or genetic modification cancels its positive effect on lifespan extension and its beneficial antiaging effect. This indicates the crucial role played by the autophagy process in extending lifespan.[70] In humans, proteomic profiling showed that intensive fasting for 72 h (water-only fasting) results in an increased level of proteins like Atg3, Atg5, Atg16, and Beclin1 play an important role in the process of autophagy process and a decrease in the level of proteins like Bcl-2 which inhibit autophagy. Similarly, it inhibits the apoptosis process in leucocytes together; this indicates that fasting is important or helps leucocytes in maintaining cellular homeostasis.[16]

TABLE 1 Summary of some human studies on the role of calorie restriction and fasting.

Mechanism employed	Changes in the immune system	Other observed effect	Participants	Reference
Five-day FMD (Fasting mimicking diet) followed by 16–23 days of refeeding (eight cycles) Each cycle is repeated every 21–28 days	At the end of 5-day FMD, a significant decrease of total monocytes (CD14+), decrease in immunosuppressive monocyte CD14 + HLA-DR−, and CD14 + PD-L1+ and low-density CD15+ granulocytes. The FMD also increase activated CD8+ T cells (CD8 + PD-1 + CD69+), and cytolytic CD3 − CD16 + CD56dim NK cells and decreased Tregs (CD4 + CD127 − CD25hiFOXP3+ cells)	Reduced median plasma glucose concentration, serum insulin, and serum IGF1 Increased average urinary ketones	One hundred and one patients with different cancers receiving different standard antitumor treatment (NCT03340935)	Vernieri et al., 2022[80]
Randomized 8 weeks of CR (Calorie restriction) diet	Reductions in effector memory CD4 T cells and Th1 subset and proportional increases in naïve CD4 T cells	Improvement of relevant lipid markers.	Thirty-six people with multiple sclerosis (MS) over 8 weeks (NCT02647502)	Fitzgerald KC et al[40]
Randomized 4 weeks of time-restricted eating (TRE) 8-h feeding window	TRE group showed an increase in leucocyte count and a decrease in neutrophils-to-lymphocytes ratio (NLR)	TRE reduced body weight and fat mass percentage with no change in fat-free mass, resulting in improvement in body composition	16 elite cyclists (<23 years) (NCT04320784)	Moro T et al[81]
Randomized 1-year study with CR and CR with exercise	CR and CR with exercise showed a decrease in CRP, SAA, IL-6, and neutrophil counts	CR and CR with exercise showed a decrease in BMI, waist circumference, and fasting glucose	439 women Overweight and obese postmenopausal women	Imayama I et al[82]
FMD or their regular diet (3 days before and during neoadjuvant chemotherapy)	DNA damage after chemotherapy was significantly less in CD45+ CD3+ T-lymphocytes from patients who had FMD as compared to patients using a regular diet	Pathological response 4/5 (90%–100% tumor cell loss) occurred more often in patients using FMD than in the control group. Stable/progressing disease in the FMD group compared to the control group. The more cycles of FMD were adhered to, the higher the percentage of tumor cell loss in the surgical specimen	Nondiabetic 131 patients with HER2-negative stage II/III breast cancer, with BMI over 18 kg/m^2 (NCT02126449)	de Groot et al., 2020[83]
A total of 60 h fasting. Fasting for 36 h before and ended 24 h after chemotherapy (4–6 chemotherapy cycles)	–	STF during chemotherapy is well tolerated and appears to improve QOL (quality of life) and fatigue during chemotherapy.	Thirty-four gynecological cancer, patients 4–6 planned chemotherapy cycles were included. (NCT01954836)	Bauersfeld et al., 2018[84]
Fasting for 24, 48, or 72 h (water-only fasting with a maximum total daily energy intake of 350 kcal/24 h period)	Reduced DNA damage in leucocytes from subjects who fasted for ≥48 h Fewer patients experienced grade 3 or 4 neutropenia in the 48 and 72-h fasting cohorts, as well as lower rates of grades 1 and 2 thrombocytopenia.	Fasting for up to 72 h, divided as 48 h before and 24 h after chemotherapy infusion, has shown to be safe and feasible in human cancer patients receiving platinum combination chemotherapy.	Twenty patients with different malignancies taking platinum-based chemotherapy (NCT00936364)	Dorff et al., 2016[85]

TABLE 1 (Continued)

Mechanism employed	Changes in the immune system	Other observed effect	Participants	Reference
Receive either a fasting-mimicking diet (FMD) or their regular diet for 3 days before and on the day of neoadjuvant chemotherapy.	–	Better emotional, physical, cognitive, and social functioning scores as well as lower fatigue, nausea, and insomnia symptom scores for patients adherent to the FMD in comparison with nonadherent patients and patients on their regular diet.	Nondiabetic 131 patients with HER2-negative stage II/III breast cancer, with BMI over 18 kg/ m^2 (NCT02126449)	Lugtenberg RT et al[86]
72-h fasting (Comparison of immune parameters before and after fasting)	Fasting enhanced autophagy levels through upregulation of key members involved in the upstream signals and within the autophagy machinery, whereas apoptosis was reduced by downturning of apoptotic gene expression, thereby increasing the leucocyte viability Fasting increases the peripheral number of neutrophils, and increased degranulation, and cytokine secretion by neutrophil		Eleven individuals (29–60 years) for the multi-omics study, 57 individuals (16–59 years) for routine blood test, and 40 participants (aged from 27 years to 67 years) for biochemical analysis (ChiCTR1900027451)	Qian J[16]
A multicenter, randomized clinical trial using 25% CR	CR reduced the level of circulating inflammatory markers, including total WBC and lymphocyte counts, ICAM-1, and leptin. The level of serum CRP and TNF-α concentrations were about 40% and 50% lower in the CR group, respectively. CR did not affect the delayed-type hypersensitivity skin response or antibody response to vaccines, nor did it cause the difference in clinically significant infections.	CR induced a 10.4% weight loss over the 2 years relative to the AL group.	Two hundred and eighteen healthy nonobese adults (20–50 years), were assigned 25% CR ($n = 143$) or an ad libitum (AL) diet ($n = 75$), and outcomes were tested at baseline, 12, and 24 months of CR. Phase 2 clinical trial (NCT00427193)	Phase 2 Meydani SN et al[87]
Randomized 6-month 30% or 10% CR comparison with baseline parameter	In both groups, calorie restriction increases T-cell proliferation, prostaglandin E2 production, and delayed-type hypersensitive reaction	Improvement of BMI	Forty-six overweight, nonobese (20–42 years) (NCT00099099)	Ahmed T et al[41]
24-h fast and then fed a fixed-calorie meal.	Fasting decreases the NLRP3 inflammasome activation		Nineteen healthy volunteers. Each subject underwent a 24-h fast and then was fed a fixed-calorie meal. (NCT02122575 and NCT00442195)	Traba J et al[88]
Compare 3–4 month CR with control group	The group under CR results in a decreased number of NK cells	The group under CR results in weight loss	Twenty-nine women with a body mass index (BMI) ≥ 30 kg/m^2 (20–45 years) (NCT03336086)	Mehrdad M et al[19]
Eight weeks of IF (Intermittent fasting)	IF increase CD40 + M1-macrophages in adipose tissue, and CD163 + M2-macrophages in muscle	IF resulted in greater weight, fat loss, and reductions in serum nonesterified fatty acids	Seventy-six overweight and obese women	Liu B et al[28]

(Continues)

TABLE 1 (Continued)

Mechanism employed	Changes in the immune system	Other observed effect	Participants	Reference
12 week of TRF (Time restricted feeding) comparison between young and old men	TRF decreases hematocrit levels, the total number of white blood cell count, and the percentage of lymphocytes, and neutrophils in young and older men.	No changes were identified in muscle power in all groups after TRF	Forty young and older men (20–50 years)	Gasmi M et al[89]
14 h fasting from dawn to sunset for 30 consecutive days.	A proteomic signature indicating remodeling of the immune system	Upregulate proteins that protect against obesity, diabetes, metabolic syndrome, Alzheimer's disease, and neuropsychiatric disorders. Anticancer proteomic signature	Fourteen healthy subjects	Mindikoglu AL et al[90]

1.11 | Fasting and calorie restriction in infection, chronic disease, and cancer

1.11.1 | Infection

Nutrients are crucial in maintaining the homeostasis of the body as well as providing key micronutrients like vitamins, iron, and zinc which are crucial for immune response.[71] Importantly, the effect of nutrients and calorie restriction in fighting a particular infection depends on the type of pathogens that infect the body. For instance, mice infected with the influenza virus were able to survive when fed glucose compared to mice that were fed with 2-deoxy-D-glucose (2DG) which blocks glycolysis, whereas in bacterial sepsis feeding glucose was detrimental.[72] On the other hand, mice under short-term fasting were protected from *Listeria monocytogenes* infection compared to mice under ad libitum fed by creating a Th1-biased environment.[33] Similarly, the bacterial load of *Mycobacterium tuberculosis* (MTB) was reduced in mice under CR. CR also enhances the intracellular killing and clearance of MTB and protects mice from MTB infection.[73] This indicates fasting can be planned with medication but the type of pathogens needs to be identified.

1.12 | Chronic disease

With aging, the incidence of chronic diseases like diabetes and cardiovascular disease increases. One of the root causes of these chronic diseases is obesity. Fasting and calorie restriction have been implemented as a strategy for weight reduction. Improvement in the level of blood glucose and insulin which are the main features of diabetes were also alleviated by CR and fasting. Similarly, CR and fasting showed a reduction of visceral fat which is one of the risk factors of diabetes. Fasting also modifies waist circumference, systolic blood pressure, body weight, and fasting plasma glucose.[74] Likewise, CR and fasting have been shown to decrease risk factors of cardiovascular disease like CRP, TNF-α, TNF-βand improve lipid profile.[75]

1.13 | Cancer

Immune cells can recognize altered peptides generated from malignant cells. This property of the immune cells is used for devising immunotherapy like activation of antitumor T cells, antagonistic and agonist immune checkpoint modulators, or adoptive transfer of engineered T cells to patients. Immunotherapy has improved the quality of life as well as the survival rate of cancer patients.[76]

Chronic calorie restriction has been shown to delay the incidence of cancer in rodents[77] and nonhuman primates.[78] Fasting alters the level of growth factors and metabolites that create an unfavorable survival environment for cancer cells as well as make them susceptible to cancer therapy.[79] Standard chemotherapy with a cycle of fasting-mimicking diet (FMD) showed a positive response to cancer. FMD reshaped the antitumor immunity of cancer patients,

like decreased immunosuppressive myeloid cells, regulatory T cells, and enhanced levels of intratumor cytotoxic CD8+ T cells and enrichment of IFNγ in these cells (Table 1).[80]

2 | CONCLUSION AND RECOMMENDATIONS

With an increasing number of elderly individuals across the globe, mechanisms that promote healthy aging are crucial. In general, evidence-based scientific experiments on fasting and calorie restriction have shown to promote healthy aging as well as to alleviate some markers of immunosenescence and inflammaging. Thus, similar to regular exercise, a vegetarian diet, etc., fasting/calorie restriction should also be considered part of a healthy lifestyle. Furthermore, fasting and calorie restriction increases the fitness of the immune system in fighting infection and cancer which are more common in the elderly.

As fasting and calorie restriction have long been part of human society and are being practiced by volunteers and religious groups, it can be easily integrated in planning medication for infectious disease, cancer, and in vaccine response. However, more data are needed especially on nutritional approaches including, the amount of nutrients, type of nutrients, and combination of nutrients that promote healthy aging and an effective immune response in humans. Furthermore, strategies on how to integrate fasting/calorie restriction in boosting immune response like the length of the intervention, and at what age is best to start fasting still need to be standardized so that its actual effect on the aging immune system can be clarified and used. Personalized parameters like age, BMI, comorbidity, and general health status of individuals should be considered when employing fasting/calorie restriction to avoid undesired side effects and to gain the maximum benefit.

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AMT conceptualized and wrote the manuscript.

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The author declares no conflict of interest.

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