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REVIEW ARTICLE

Nutrition in chronic inflammatory conditions: Bypassing the mucosal block for micronutrients

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Abstract

Nutritional Immunity is one of the most ancient innate immune responses, during which the body can restrict nutrients availability to pathogens and restricts their uptake by the gut mucosa (mucosal block). Though this can be a beneficial strategy during infection, it also is associated with non-communicable diseases—where the pathogen is missing; leading to increased morbidity and mortality as micronutritional uptake and distribution in the body is hindered. Here, we discuss the acute immune response in respect to nutrients, the opposing nutritional demands of regulatory and inflammatory cells and particularly focus on some nutrients linked with inflammation such as iron, vitamins A, Bs, C, and other antioxidants. We propose that while the absorption of certain micronutrients is hindered during inflammation, the dietary lymph path remains available. As such, several clinical trials investigated the role of the lymphatic system during protein absorption, following a ketogenic diet and an increased intake of antioxidants, vitamins, and minerals, in reducing inflammation and ameliorating disease.

KEYWORDS
antioxidants, chronic inflammation, iron, lipids, lymph, micronutrients, mucosal block, polyphenols, vitamin A, vitamin B, vitamin C, zinc

1 | INTRODUCTION

Even though individuals, particularly those in industrialized societies, have access to a diverse array of foods, the bioavailability of certain micronutrients can be compromised due to dietary habits and underlying metabolic and immunological conditions potentially leading to unmet micronutrient requirements. The NHANES study revealed inadequate intake of vitamin A, vitamin C,[1] vitamin D, vitamin E, calcium, and magnesium in 40% of the Americans, with particularly obese people having diminished micronutrient intake,[2] but also in pregnant women.[3]

The intricate connection between nutrition and immunity is evident, especially in intensive care units,[4] and is crucial in infectious diseases and chronic illnesses. Micronutritional deficiencies are known to drive inflammation and are associated with increased morbidity and mortality[5–7] in various diseases including congestive heart failure,[8–10] chronic kidney diseases[11–13] autoimmune thyroid diseases,[14–18] inflammatory bowel disease,[19,20] cancer,[21–23] atopic diseases[24,25] and even in obesity.[26–29]

Understanding the role of specific nutrients during inflammation and the body's response to dietary nutrient absorption in healthy, nutrient-deprived, or inflamed conditions is essential for developing strategies to increase bioavailability of dietary nutrients in non-communicable diseases through dietary means. In this paper, we explore the nutrient-dependent acute immune response, with a focus on nutrients linked to inflammation and supported by double-blind placebo-controlled trials, such as iron,[30,31] vitamins A,[32] C,[33] and other antioxidants such as polyphenols.[34]

2 | NUTRITIONAL IMMUNITY

Nutrients including minerals and vitamins play essential roles in various body functions (Table 1). Consequently, organisms ranging from bacteria to mammals will fiercely compete for these nutrients. In respect to immune cells, macrophage, and macrophage-like cells in multicellular animals[35] are at the forefront of this competition. This phenomenon, termed "nutritional immunity,"[36,37] represents one of the most conserved activities of the innate immune system. It involves immune cells limiting the availability of nutrients to restrict these vital substances from invading pathogens, while tightly regulating host immune cell responses and functions.[38] As such, all organisms have the capacity to sense and adapt to their nutrient environment by altering the expression of proteins that function in metabolic and signaling pathways.[39] Prominent examples in mammals include the regulation of gene transcription by vitamin A or vitamin D through interaction with their respective nuclear receptors.

Bacteria and fungi[40,41] employ strategies such as secreting low molecular compounds and proteins to capture essential minerals.[42] The infected host, whether it be plants[43,44] or humans, counterrespond in this tug of war.

The human body adapts by altering the transport and distribution of micronutrients by blocking their mobilization[45] and inhibiting absorption[46–48] by organs like the liver, spleen, and macrophages,[49–52] all as part of the acute phase response.

2.1 | Low-grade inflammation result in functional deficiencies

Low-grade inflammation resulting from mild nutritional deficiencies can modulate the immune system and provide protection. For example, mild iron deficiency, leading to subclinical inflammation, has been shown to protect against parasite infestations such as the malaria pathogen *Plasmodium falciparum*,[53–55] bacterial infections such as Mycobacterium tuberculosis[54,56,57,58,59] and viral infections.[57,58] However, when pathogens overcome these nutritional defenses and infest the host, the host's conditions deteriorates and lead to anemia of chronic inflammation.[60–62]

It has to be emphasized that nutrient-poor conditions alone can prime the immune system. Nutritional factors directly modulate the immune system, with both excess and deficit being detrimental. These factors include total calorie intake (both excess and deficit), fat intake, fat type, for example, alpha-lipoic acid,[63] omega 6 versus 3 fatty acids,[64] sugar, vitamin A/carotenoids, vitamin B6, C, D, and E, iron, zinc, selenium, and antioxidants.[65]

In apparently healthy individuals, deficiencies in iron,[66–68] vitamin B6,[69–72] vitamin A,[73] vitamin E,[33,74] vitamin D[75–78] are associated with elevated CRP levels,[79–81] an increase in granulocytes and monocytes[66] resembling features of a normal acute phase response.

2.2 | The acute phase response

Upon immune activation due to, for example, tissue injury, infection or nutritional deficiencies, pro-inflammatory cytokines, nitric oxide (NO), and glucocorticoids modulate the systemic acute phase reaction and the hepatic acute phase proteins response. One of the earliest physiological responses is to conceal micronutrients and block their dietary absorption.

Consequently, the levels of minerals such as iron[68,82,83] and zinc,[84] and vitamins (A, B6, C, D)[83,85,86] in the circulation decrease along with their binding partners, typically negative acute phase proteins such as transferrin (binding iron),[87] albumin (binding 70% of all circulating zinc) and transthyretin (binding indirectly Vitamin A). Inflammation also alters the lipid composition[88] leading to a decline in anti-inflammatory HDL cholesterol,[89] an increase in rather inflammatory LDL-cholesterol and elevated triglyceride levels in the circulation.[89] Hypertriglyceridemia is a sensitive part of the host response, with enhanced adipose tissue lipolysis, increased hepatic fatty acid synthesis and suppressed fatty acid oxidation (FAO) and ketogenesis.[90,91] Additionally, inflammation affects glucose levels, and persistent hyperglycemia is known to promote inflammation.[92]

TABLE 1 Micronutrients and their major function in humans.

	Main function
Minerals	
Calcium	Most abundant mineral in body, most calcium stored in bones and teeth for structure and hardness, helps with blood clotting, important for muscle movements, sending and receiving nerve signals, helps in hormonal and mediator release, important for normal heart beat
Copper	Involved in energy production, iron metabolism including ceruloplasmin, neuropeptive activation, helps in collagen production, important for bones and connective tissue as well as neurotransmitter synthesis, keeps immune system healthy
Iron	Oxygenate the blood; convert blood sugar to energy, Immune booster, aids cognitive function and supports healthy skin, hair, and nails.
Magnesium	Helps maintain normal nerve, muscle function and a steady heartbeat, support the immune system and bones, regulate blood glucose levels, aids in energy and protein production, regulated by intake and VitD, estrogen and parathyorid hormone (PTH), 90–95% reabsorbed in the ascending loop of Henle in the kidney and urine excretion
Phosphor	For growth, maintenance and repair, help in regulating other vitamins and minerals (vitamin D, iodine, magnesium, and zinc) and ATP, cell membranes, DNA
Potassium	Maintaining normal blood pressure, transmitting nerve signals and controlling muscle contracts, moves nutrients into cell and waste product out of cells (pH and electrolyte regulator).
Sodium	Linked with potassium, helps in nerve impulse, muscle movements and electrolyte household
Zinc	Involved in cell division and growth, wound healing, carbohydrate breakdown, enhance insulin action, necessary for the sense of smell and taste, beneficial against age-related macular degeneration
Vitamins	
Vitamin A/retinol	Important for vision, growth, cell division, reproduction, and immunity, helps maintaining healthy teeth, skeletal and soft tissue, mucus membranes and skin
Vitamin B1/thyamine	Essential for mitochondrial membrane development and synaptic membrane function, essential in carbohydrate and amino acid metabolism/breakdown, helps for nerve system, fat, and protein metabolism
Vitamin B2/riboflavin	Converts tryptophan into niacin, maintaining the mucus membranes in the gut, maintaining a healthy liver, eyes, nerves, muscle, skin; improves iron as well as folic acid and vitamin B1, B3, and B6 absorption and iron mobilization
Vitamin B3/Niacin: nicotinic acid, nicotinamide	B vitamin, converts nutrients into energy; create cholesterol and fats, create and repair DNA, increases HDL cholesterol and lowers triglyceride levels in the blood, and exert antioxidant effects
Vitamin B5/pantothenate	B vitamin, essential for production of coenzyme A involved in nutrient breakdown and production of red blood cells and the neurotransmitter acetylcholine involved in muscle contraction and nerve signaling
Vitamin B6/pyridoxine	Pyridoxal 5′-phosphate (PLP), the metabolically active form of vitamin B-6: essential for heme synthesis, in antibody production, for protein break down and regulating normal blood sugar levels, important for normal brain development and a healthy nerve and immune system;
Vitamin B9/folic acid	Essential in production of red blood cells and fetal development; helps in metabolizing homocysteine, which can damage blood vessels
Vitamin C/ascorbic acid	Enhances non-heme iron absorption and iron mobilization from stores, needed for blood vessels, cartilage, muscle, and collagen formation in bones as well as in the wound healing, and a healthy immune system. important for the maintenance of cartilage, bones, and teeth. supplementation increases hemoglobin and ferritin in children and non-pregnant women
Vitamin D	Low vitamin D level lead to decreased local calcitriol production in the bone marrow, which limit erythropoiesis; calcitriol helps in dietary calcium and phosphor absorption, keeps bones strong, regulates immune system, nerve and muscle function
Vitamin E/ alpha-tocopherols	Protective effect on polyunsaturated fatty acids in the membrane of red blood cells
Nutrients	
Glucose	Energy source, as glycogen for storage of carbohydrates or conversion to fat; important energy source for the brain and nervous system

(Continues)

TABLE 1 (Continued)

	Main function
Cholesterin	HDL cholesterin and LDL cholesterin bind toxins, with cholesterin essential for bile acid generation (bile is anti-inflammatory itself and has direct impact on microbes and nutrient absorption) and oxysterol synthesis and controlling bacterial colonization; precursor of steroid hormones such as glucocorticoids, sexual hormones, and Vitamin D
Triglycerides	Type of fat, long-term storage form of energy that are stored as lipid droplets in, for example, skeletal muscle, the liver or in fat cells to supply energy when needed; can be hydrolyzed to produce fatty acids for energy production through beta oxidation/oxidative phosphorylation; simple sugars from refined carbohydrates and sugar-sweetened beverages are a major contributor to triglyceride synthesis in the western diet
Carbohydrate	Energy source, controls blood sugar, participate in cholesterol and triglyceride metabolism and helps in fermentation, decreases sodium excretion

Inflammation, also impact the oxygen levels and vice versa. Inflammation is accompanied by hypoxia, while hypoxia itself can trigger inflammation[93,94] (Table 2).

Hence, immune activation and inflammation result in decreased availability of minerals, vitamins, and oxygen, along with elevated triglyceride and glucose levels (Figure 1).

The association between the consumption of commercial ultra-processed food (lacking micronutrients, but rich in added sugars and hydrogenated fat) and inflammation[95–97] may partly be explained by the nutrient profiles of ultra-processed foods that simulate inflammation of the acute phase response.

Key changes in the blood upon inflammation

- Decrease in minerals such as iron and zinc
- Decrease in vitamins
- Decrease in HDL cholesterol
- Decrease in nutrient-associated proteins: transferrin, albumin, transthyretin
- Decrease in oxygen
- Increase in triglycerides and glucose
- Increase in positive acute phase proteins: serum amyloid A SAA, Lipopolysaccharide binding protein LBP, C-reactive protein CRP

2.3 | Different nutritional demands of pro-inflammatory and regulatory cells

The underlying cause for the rise in glucose and triglycerides is that the enhanced and usually acute nutritional demands of inflammatory immune cells have to be promoted.

The energy requirements of immune cells usually can be met via (1) glycolysis requiring sugar, (2) fatty acid oxidation FAO requiring lipids, (3) glutaminolysis requiring the amino acid glutamine to support mitochondrial oxidative metabolism, and (4) via beta oxidation/oxidative phosphorylation (OXPHOS) that generates energy in form of adenosine triphosphate (ATP) during mitochondrial respiration in the electron transfer chain (ETC) and requires oxygen. Thus, in case of aerobic glycolysis, both glycolysis and OXPHOS are increased, while under hypoxia glycolysis is anaerobic, meaning glycolysis is increased while OXPHOS is decreased. Hypoxia is also known to increase uptake of glutamin into the cells[98] and thus glutamin is an additional nutrient source for immune proliferation when oxygen levels are low.

2.3.1 | Inflammation promotes a glycolytic, anaerobic metabolism

Inflammatory immune cells exhibit a distinct metabolic profile with high glycolysis, glutaminolysis, low OXPHOS, and FAO under low oxygen conditions. In contrast, regulatory, immature, and memory cells predominantly rely on aerobic conditions, with energy primarily provided by FAO and OXPHOS. However, there are several exceptions of this rule and the metabolic status of different cell subsets in humans is only started to be defined in health and in various diseases.[99] For example, inflammatory macrophages display high glucose uptake and glycolysis, retaining lipids, and trace elements such as iron due to hypoxia-induced low OXPHOS.[100] M2 macrophages, on the other hand, promote OXPHOS and FAO, with lower glucose uptake and glycolysis and actively contributing to nutrient recycling and distribution.[101–106]

B cells are activated under hypoxic conditions shifting from aerobic FAO to anaerobic glycolysis.[107] These metabolic changes drive class-switch and affinity maturation. Particularly plasma cells have very high energy demands for their antibody production, which they fuel via glycolysis, FAO, and glutaminolysis.

Similarly, while naïve, Tregs and memory T cells rely mainly on aerobic FAO, effector T cells (Th1, Th2, Th17) rely on glycolysis and de novo fatty acid biosynthesis to produces intrinsic long-chain fatty acids and lipids such as diacylglyceride (DAG) and phospholipids.[108] The food types also seem to affect the effector T-cell subtypes[109,110] with glutamine and carbohydrate supplementation being shown in clinical trials to favor more Th1 than Th2 cell responses under hypoxic conditions.[111,112]

Indeed, already the nutritional requirements for regulatory/inflammatory cells suggest that a ketogenic diet may meet the nutritional demands of regulatory cells better than a diet that is rich in simple sugars and providing fuel for inflammation (Figure 2).

TABLE 2 Nutrients and the acute phase response.

Negative acute phase reactants			
Carrier	**Nutrient**	**Acute phase**	**Ref**
Albumin, Histidine-rich glycoprotein (HRG)	Zinc, Vitamin B6	↓	85
Transferrin, lactoferrin	Iron	↓	85
	Calcium	↓	85
HDL	Cholesterol ester	↓	85,86,319
Transthyretin	Thyroxin and RBP	↓	320
Retinol-binding protein, RBP	Vitamin A	↓	320
Free active form	Vitamin D	↓	32,386
	Vitamin E	↓	322,323
	Folate	↓	324
Free, leukocytes	Vitamin C	↓	88
Histidine rich glycoprotein, HRG	Heme, heparin-zinc, heparan sulfate, divalent metal ions	↓	325
Serpins (protease inhibitors)		↓	325
Alpha-2 macroglobulin (Protease inhibitor)	Zinc, copper	↓	326
	Omega-3 fatty acids	↓	322
Positive acute phase reactants			
Carrier	**Ligand**	**Acute phase**	**Ref**
	Glucose	↑	85
c-reactive protein (CRP)	LPS, phosphocholine, nuclear antigens, FcγRI, FcγRIIa, and FcγRIIb	Up to 1000-fold ↑	85,458
apo serum amyloid A (SAA) without lipids		Up to 1000-fold ↑	85
α1-acid glycoprotein (AGP) (lipocalin), apoform is degraded in liver	Serotonin, platelet activating factor, histamine, melatonin, environmental ligands	↑	75,327,328
NGAL/LCN2 apoform without ligands			75
Ceruloplasmin	Cu	up to 1.5-fold↑	85,329,330
Complement factor c3		Up to 1.5-fold↑	85
Haptoglobulin	Hemoglobin	Up to 3-fold↑	85
Fibrinogen		Up to 3-fold↑	85
LDL	Triglyceride-rich	≈↑	86
α-globulins	LPS	Up to 3-fold↑	
Vitamin D binding protein (Keeps Vitamin D inactivated)	Vitamin D	↑	331,332
Secretory phospholipase A2		↑	86

2.3.2 | Hypoxia—generation of reactive oxygen species and oxidative stress

A very important aspect of hypoxia is that it drives the formation of reactive oxygen species (ROS). Though ROS at physiological concentration regulate differentiation, senescence, and apoptosis and is used to fight infections,[113] prolonged and chronic ROS production are considered central in the progression of inflammatory diseases.[114]

Oxidative stress emerges when an imbalance exists toward more pro-oxidative radicals such as superoxide radical anion, hydrogen peroxide, alkoxy and peroxyradicals, and peroxynitrite (often combined under the term ROS) and too low levels of reducing components such as ascorbate, glutathione, vitamin E, lipoic acid, NADPH, or NADH. The inability of cells to clear these radicals for an extended period may result in pathophysiological events such as protein oxidation, DNA damage and lipid oxidation and irreversible cell/tissue damage.[115,116] In this respect, studies assessing the antioxidative status in patients suffering from chronic inflammatory diseases such as asthma,[117] ulcerative colitis[118] or patient on peritoneal dialysis[119] consistently report lower endogenous antioxidant levels compared with their healthy counterpart. Antioxidants such as polyphenols[120] and vitamins[121] (as also discussed in the later sections) are able to counteract the

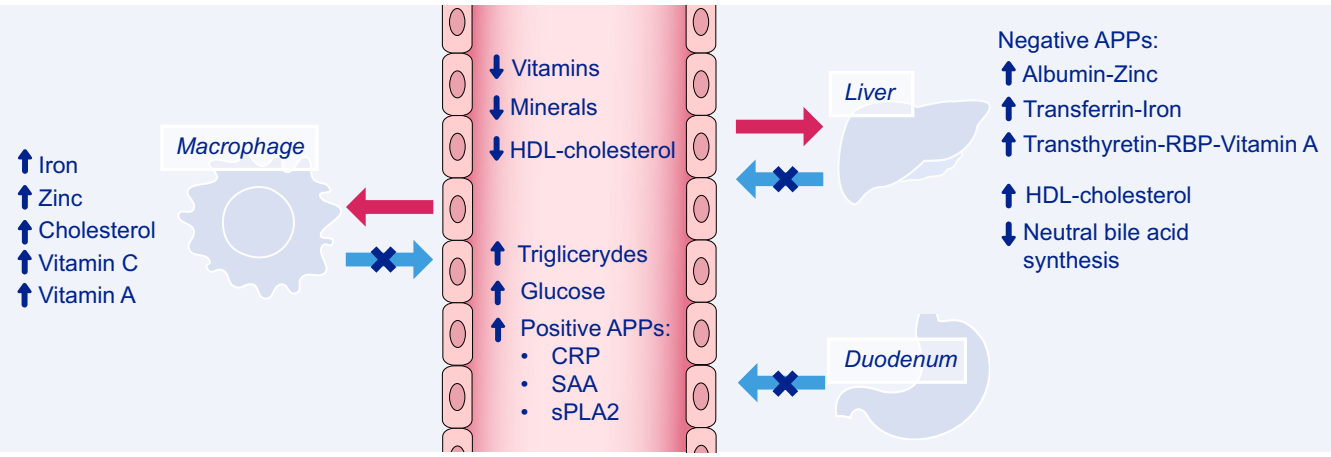

FIGURE 1 Nutrients are concealed during the acute phase response. Upon immune activation most micronutrients such as iron, zinc, vitamin A, C, D, and E are removed from the circulation with their carrier, which usually are negative acute phase proteins such as transferrin, albumin and transthyretin and are stored in the liver and macrophages. In contrast, energy is provided by increased lipolysis and increased hepatic glucose output due to cortisone decreasing insulin sensitivity.

destructive potential of these radicals shown in healthy and patients suffering from chronic inflammation.

Key cellular metabolic changes in inflammation

- Hypoxia ➔ Increased ROS formation➔ increased oxidative stress
- Increased glycolysis ➔ Increased glucose uptake
- Decrease fatty acid oxidation
- Decrease oxidative phosphorylation ➔ Increased glucose/glutamine uptake

3 | DIETARY ABSORPTION OF NUTRIENTS: THE BIOAVAILABILITY DIFFERS IN HEALTHY AND INFLAMED CONDITIONS

Nutrient absorption from food can primarily occur through two routes[122]: The first route involves direct absorption into the venous blood stream via enterocytes for nutrients like glucose and amino acids before reaching the liver through the portal vein. Equally significant is the second route, which involves absorption through the lymphatic system. The lymphatic system, comprised of lymphatic vessels, is a vital transport system specialized in carrying nutrients and waste products alongside the blood system.[123–125]

For most nutrients transport can occur via both paths. However, during inflammation, micronutrients are only absorbed to a reduced extent ("mucosal block"[126,127]) since the body wants to "starve out" a supposed infection. This is due to hepcidin for iron,[49] which is considered the master regulator for blocking dietary iron absorption and iron mobilization from the tissues.[128] However, inflammation also restrict uptake—by not fully deciphered mechanisms of several other micronutrients such as vitamin A,[129] and zinc.[130] Folate uptake is reduced in subjects with coeliac disease[131] upon inflammation and this occurs despite that the epithelial barrier integrity is compromised. Brush border enzymatic activity can be reduced in the ileum following infection, or LPS injection, which may indicate a more global dysregulation of nutrient absorption by enterocytes during an acute inflammatory response.[132]

In fact, several studies have shown that though nutrient intake of healthy and subjects with subclinical inflammation may be similar, the bioavailability of iron, zinc, and vitamin A was significantly reduced.[25,133–136]

As iron deficiency is an independent risk factor for mortality,[136] attempts to circumvent the mucosal route in heart failure patients have already been successfully exploited, in which iron in liposomes or starch-like particles for lymphoid uptake[137–140] were used.

Thus, it is crucial to understand, that while the mucosal block exist for micronutrients during inflammatory conditions, nutrients still can be absorbed via the lymph, as it allows downstream monitoring by the immune cells and in the lymph nodes (Figure 3).

3.1 | Proteins uptake via the lymph as facilitators for nutrient absorption

Proteins are essential for human health, particularly in muscle repair and recovery. However, not all proteins are equal, and their benefits during inflammation depend on various factors. Some proteins, often involved in nutrient accumulation during processes like seed germination, also play a role in host defense against diseases. Similarly, animal-derived proteins, such as albumins, lipocalins, transferrins, and globulins, serve as carriers for nutrients, binding to carbohydrates, minerals, lipids, phenolics, and vitamins.

Particularly, the proteins able to bind to nutrients and important for nutrient accumulation during seed germination, for example, are usually also involved in host defense and provide resistance to disease. These include seed storage proteins[141] which include the large prolamin superfamily[142–144] comprised of lipid transfer proteins, 2S

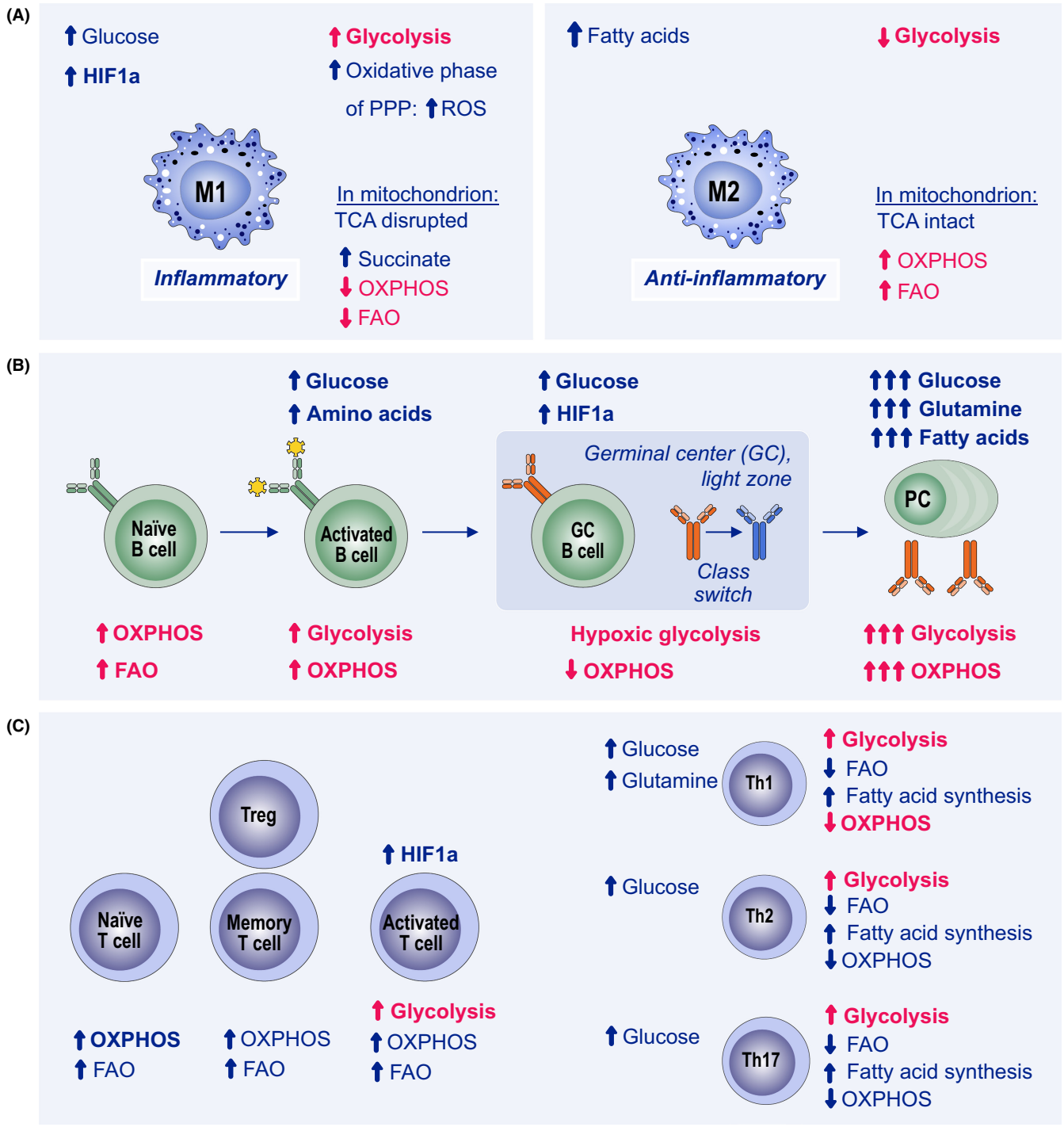

FIGURE 2 Differential metabolic demands of immune cells upon inflammation. In general, hypoxia initiates immune activation and shifts, (A). regulatory macrophages, (B) naïve B and (C) T cells from aerobic fatty acid oxidation FAO and mitochondrial oxidative phosphorylation OXPHOS toward anaerobic glycolysis (in which OXPHOS declines). Increased glycolysis, with reduced OXPHOS are the metabolic characteristics of inflammatory M1 macrophages, activated B cells, and effector T cells.

albumins, cereal prolamins, and the cupins consisting of globulins (legumin-like proteins) and conglutins (vicilin-like proteins) as well as pathogenesis-related proteins.[141] From animal sources animal proteins such as albumins, lipocalins, transferrins, and globulins are similarly serving as carrier for nutrients binding to carbohydrates,[145] minerals,[146–159] lipids,[160–163] phenolics,[146,154–156] and vitamins[149–153] and often play a regulatory role in host defense.

Many of the aforementioned food proteins are quite resistant to proteolysis as known for 2S albumins[164] and cupins[165] and for the animal-derived ovalbumin[166] and lactalbumin,[167] lactoferrins,[168] lipocalin beta-lactoglobulin,[169] while some of these are sensitive to heat and specific food processing techniques leading to their aggregation.[170,171] They, thus, can maintain their nutrient-carrying abilities, if not destroyed by proteases or heat-treatment[172] and their

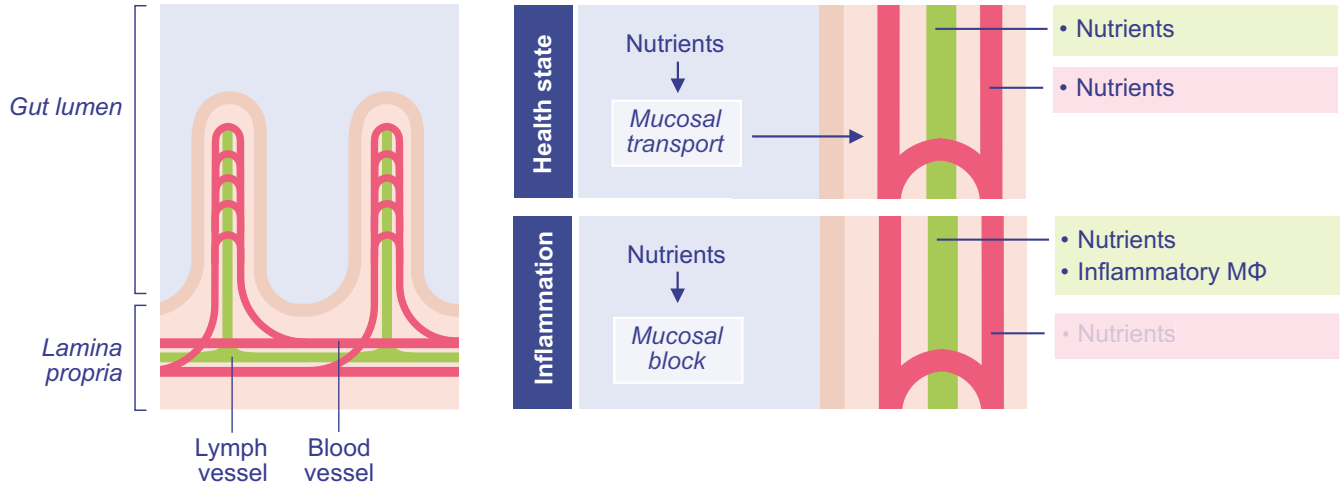

FIGURE 3 Inflammation does not compromise dietary micronutrient uptake via the lymph. Most nutrients are absorbed into the blood stream and enter via the portal vein of the liver. However, some nutrients, such as fats and digestion-resistant proteins, are absorbed into the lymph system first. Upon inflammation, uptake of several minerals and vitamins via the blood path is impeded, whereas nutritional supply via the "lymph path" remains accessible.

uptake is either directly via the lymph[171,173] or can, particularly in combination with lipids, occur via chylomicrons into the lymph system as shown for peanut[174] soy protein,[175] egg proteins,[176,177] and very well-studied for whey proteins.[171,177–180] Interestingly, despite that these are food proteins and exogenous, receptor-mediated uptake has been described for a large number of these proteins.[181–185] For many food proteins, fat binding to these proteins (in nut proteins for example) facilitates their lymphatic uptake. As processing often reduce binding of these proteins to fat or remove the fat, this may also reduce the bioavailability of the nutrient-carrying-capacity of these proteins.

Phenolic antioxidants such as catechines and vitamin E have been implied to support chylomicron-uptake,[186] and there is a linear relationship in the chylomicron transport, thus bioavailability of fat-soluble nutrients such as α-carotene, lycopene, phylloquinone, and retinyl palmitate, with the addition of oil[187] in human studies.

As such, circumvention of the "mucosal block" under inflammatory conditions can occur also with proteins functioning as carrier for micronutrients and phenolic compounds promoting chylomicron formation, but that is highly dependent on the presence and binding to fat molecules.

3.2 | Dietary bioavailability differs in individuals

3.2.1 | Genes and epigenetic

Nutrient absorption is likewise influenced by both the genetic predisposition and the epigenetic signature of the individual. The genetical determination of normal small intestinal length ranges significantly from 3 to 8.5 m,[188] impacting an individual's ability to utilize nutrients effectively. The first 100 cm of the jejunum primarily host the absorption of most nutrients, while the last 100 cm of the ileum are crucial for B12 and bile salts absorption, and magnesium finds its absorption site in the terminal ileum and proximal colon.[188]

Consequently, individuals with an inherently shorter small intestinal length may face challenges in nutrient bioavailability, attributed to a diminished absorptive surface and increased difficulty processing fiber-rich foods.

Metabolic imprinting begins in the embryonic stage, a vulnerable period susceptible to nutrient-induced adaptations. Genetic variations play a pivotal role in determining the bioavailability of specific nutrients, contributing to diverse nutrient requirements among individuals and influencing the risk of chronic inflammatory diseases.[39,189,190]

Notably, compounds such as carotenoids, polyphenols, and vitamins play a regulatory role in gene acetylation states, mediated by histone deacetylases (HDACs), ultimately leading to sirtuin activation.[191] Many single nucleotide polymorphisms (SNPs) are positive gene regulators for nutrient utilization, with for example the SNP T-13910 variant near the lactase gene enabling carriers to produce this enzyme throughout adulthood and to tolerate milk.[192] In short, nutrients deeply affect epigenetic regulation, with the genetic disposition also altering the bioavailability of nutrients.

3.2.2 | Microbiota

Human mucosal surfaces and body cavities harbor diverse communities of commensal microbes that play essential roles in regulation of host metabolic responses, epithelial barrier function, immune education, and immune regulation.[193,194] Microbial-derived factors are integral components of immune and metabolic functions required for host health and survival. These host effects are

partially induced by activation of host pattern recognition receptors to microbial-derived danger signals, but increasingly the role of bacterial metabolites in shaping host immune function is being recognized.[195,196] Immunoregulatory bacterial metabolites can trigger host G protein-coupled receptors (GPCRs), aryl hydrocarbon receptors (AhRs), nuclear hormone receptors such as the farnesoid X receptor, or can directly modulate gene expression through epigenetic mechanisms.[197] Importantly, many immunoregulatory bacterial metabolites are derived from dietary ingredients (e.g., fiber, tryptophan), linking diet and lifestyle to immune health via microbial mechanisms.[198] The microbiome has a larger repertoire of digestive enzymes than do its hosts, which enables break down of indigestible macromolecules (polysaccharides, etc.) or the synthesis of vitamins. Moreover, germ-free mice are immune deficient[199] and the maturation and nutrient-sensing abilities of the epithelial barrier,[200] of the enteric nerve system[201] and the blood–brain barrier[202] also being compromised. For example, Bacteroides, Roseburia, Ruminococcus, and Bifidobacterium species are known to utilize undigested carbohydrates to provide the host with energy and carbon sources in form of short-chain fatty acids (SCFAs), a major group of metabolites derived from colonic fermentation of dietary fibers, and important for maintaining epithelial barrier function. The microbial species usually specialize to metabolize certain food types—with for example Prevotella species correlating with the consumption of a plant-rich diet, high in complex carbohydrates, fiber, and fruits and vegetables.[203] The generated metabolites not only benefit the host, but are also used within the microbial communities, in which cross-feeding is the norm.[204] Consumption of a higher diversity of fruits, vegetables, and fermented foods were associated with a reduced risk of atopic disorders and asthma in children, potentially mediated in part by microbial-derived butyrate and propionate.[205,206] Similarly, adults who more regularly consumed plant-based or pescatarian diets had lower odds of developing severe COVID-19,[207–209] which correlates with the gut microbiota changes observed in patients with severe COVID-19 disease.

A reduced nutritional intake is known to shift the gut microbiome. For example, iron deficiency results in a reduction of *Bifidobacterium*,[210–212] *Bacteroides*,[213] and *Faecalibacterium*[214] and causes a shift in SCFA[215] as well as siderophore-production,[213] while an increase of the Actinobacteria phylum[216–218] is reported. Vitamin A deficiency rather promotes *Enterococcus* in children with diarrhea,[219] while *Bacteroides* and *Bifidobacterium* are decreased.[220]

Relatively recent changes in dietary habits and microbiota composition have resulted in reduced levels of immune regulatory metabolites that are expected and evolutionarily hardwired into immune cell development and decision-making processes. The lack of immune regulatory molecules, potentially coupled with excess pro-inflammatory mediators, results in a hypersensitive immune system that reacts inappropriately to non-pathogenic stimuli and does not respond effectively to infection but is associated with a poorly regulated immune system that contributes to increased risk of inflammatory disease throughout the lifespan.[221–225]

4 | IDENTIFYING NUTRITIONAL TRIGGERS FOR INFLAMMATION

The most prevalent deficiencies worldwide are for iron, Vitamin A and iodine.[87] While less prevalent also lack of Vitamin Bs, C, D, E, and minerals such as zinc, magnesium are known to promote inflammation.

4.1 | Vitamin Bs

Vitamin Bs are water soluble, and readily destroyed by cooking in water and by heat (exception is niacin, which is resistant to heat), with milling nearly removing all Vitamin B1-B3s. As a consequence, particularly wheat and corn flour are usually re-fortified with these vitamins.[226] Vitamin B3 also named niacin, is mainly found in protein-rich food, and as such Vitamin B deficiencies are more likely to occur when the diet is low in animal products, fruits and vegetables, and where cereals are milled prior to consumption. Particularly, pregnant and lactating women, infants, and children are at the highest risk of vitamin B deficiencies.

Vitamin B3 is given in supplements such as nicotinic acid or nicotinamide. It is unique as it can be synthesized by tryptophan though with quite low efficiency as 60 mg tryptophan is needed to produce 1 mg niacin. High doses of niacin, but not nicotinamide may cause flushing. The functional cofactors derived from niacin is nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP), which are essential for oxidative processes and thus in the metabolism of carbohydrates, proteins, and fats.[227] Deficiencies here results in pellagra characterized by dementia, dermatitis, and diarrhea.[227] NAD+ precursors play a crucial role in maintaining the integrity of the gut barrier and deficiencies are associated with enhanced gut inflammation and leakage, and dysbiosis,[228] whereas niacin supplementation effects intestinal cell proliferation and health in piglets and improved intestinal epithelial integrity and inflammation markers of chronic alcohol fed rats.[229] As essential co-factor, nicotinic acid also boosts macrophage activity and NK function[230] and acts as an antioxidants able to scavenge radicals and suppress inflammatory mediators.[231,232]

Vitamin B supplementation is able to improve markers of inflammation[233] in acute ischemic stroke as well as in patients with stable angina pectoris.[234] Inflammation is also linked to Vitamin B6 (pyridoxine, Pyridoxal 5′-phosphate) deficiencies,[235,236] with multivitamins in general known to reduce inflammation markers in the intensive care units.[237]

4.2 | Vitamin D

Individuals suffering from chronic inflammatory conditions usually also have a lower antioxidative status[34] and vitamin D[75–78] status. Here, supplementation alone has been able to reduce complication and health status in women with endometrial hyperplasia[238]

and in combination with calcium in women polycystic ovary syndrome.[239] Similarly, in combination with probiotics several trials have shown improvement in the metabolic and inflammatory status.[240]

4.3 | Magnesium

Magnesium supplementation alone was sufficient to reduce inflammation in diabetic hemodialysis patients[241] and likewise improved wound healing in patients with diabetic foot ulcer.[242]

4.4 | Zinc

During inflammation, zinc levels in the blood (serum) decrease due to increased storage in the liver and reduced dietary uptake[243] but not due to excess urinary excretion[244] and lower zinc level are often observed in patients with chronic inflammation.[245]

Zinc supplementation did not change all-cause mortality and morbidity in children, but reduced the risk of all-cause diarrhea, and improved slightly growth in children between 0.5 and 12 years.[246] Similarly, zinc supplementation did not improve the outcome in HIV adults with heavy alcohol use.[247] However, in several RCT-trials in neonates with sepsis zinc in addition to antibiotics significantly reduced inflammatory markers and sometimes mortality.[248–250] Zinc co-supplementation with other micronutrients were shown in several trial to reduce inflammation markers and improve the health outcome in gestational diabetes[251] and subjects with metabolic syndrome[252,253] as well as in elderly subjects.[254]

Zinc intake in pregnant women have been shown in a number of studies to reduced inflammation markers,[255] and in combination with magnesium, zinc lowered CRP levels in a double-blind placebo-controlled trial.[256]

4.5 | Omega 3

Fatty acids (FAs), obtained from our diet, are crucial not only as energy sources but also as vital elements in cell structure. They significantly impact the immune system, both in maintaining health and in disease states.[257] Both saturated and unsaturated FAs affect how innate and adaptive immune cells function. They do this by altering the cells' membrane composition and fluidity and interacting with specific receptors. A disruption in the balance of saturated versus unsaturated FAs, as well as an imbalance between omega-6 and omega-3 polyunsaturated FAs, can disrupt immune system balance. This imbalance is a contributing factor in the development of various allergic, autoimmune, and metabolic disorders.[258]

Individuals with inflammation also lack beneficial lipids, with omega-3-supplementation improving wound healing in subjects with diabetic foot ulcer.[259]

Indeed, in-depth knowledge of the bioavailability about these micronutrients in inflamed conditions and specific diseases is essential to prevent and ameliorate chronic disease courses.

5 | IRON

The most common nutrient deficiency in the world is iron deficiency, with worldwide estimated 1.4 billion people affected. Particularly, children under 5 years, adolescents, and women of childbearing age have the highest risk, but also lifestyle factors such as a vegan diet, blood donations, and elite endurance athletes are at higher risk.[260] The global pooled prevalence for 2022 is 16% for iron-deficient anemia and 18% for iron deficiency.[261]

5.1 | Iron deficiency—absolute and functional

Iron homeostasis is highly complex and thus there is still no international consensus that unambiguously defines iron deficiency.[262] Common definitions of iron deficiency is to have serum iron concentration ≤13 μmol/L and transferrin saturation below 20%.[263] According to the clinical definition, iron deficiency is an insufficient number of red blood cells,[264,265] while the WHO, UNICEF and UNU determine absolute iron deficiency (=anemia), on the basis of certain threshold values for hemoglobin that depend on age, sex, and altitude.[266,267]

Anemia represents an extreme form[268] as about 84% of all cells in the human body are erythrocytes[269] and a small change here is significant. In these severe cases, iron deficiency leads to anemia, low immune function, cognitive impairment in children,[270] premature birth and low birth weight in babies[271] and is also associated with an increased mortality.[272–274] However, iron deficiency can also be "functional" and also mixed forms exists. Functional iron deficiency occurs in conditions, where not enough iron is "mobilized" and result in impaired cellular and tissue functions. Functional iron deficiency is directly linked with inflammation and is present during any infectious, inflammatory, or malignant disease. Likewise, also high-performance athletes due to exercise-induced inflammation and obese people due to the presence of low-grade inflammation are suffering from functional iron deficiency.[275]

When suffering from functional iron deficiency, ferritin-levels are normal or elevated ranging from 30–500 μg/L,[276–279] while transferrin saturation (TSAT) values are below 20% and—dependent on inflammation severity—inflammation markers such as C-reactive protein (CRP; for low-grade inflammation high sensitivity-CRP) or α1-acid glycoprotein (AGP) are elevated.[79] Body iron stores may be adequate in "functional iron deficiency"; however, there are reduced levels of "metabolic active iron" as iron is not accessible. Here, iron is concealed intracellularly in ferritin "cages" predominantly in reticuloendothelial cells—primarily consisting of macrophages and monocytes[49] and thus within immune cells.

5.2 | Iron and immunity

5.2.1 | Macrophages

The crucial role of macrophages as a center for nutrient distribution and recycling can be appreciated by the fact that while about 1–2 mg of iron is absorbed daily through the intestine, 20–30 mg of iron is recycled primarily by splenic macrophages from senescent red blood cells.[51]

Though well recognized by their surveillance role during infection and their phagocytic clearing of apoptotic/senescent cells, macrophages are also central for sensing the nutritional demands of the surrounding tissue and supplying this essential micronutrient to the tissues.[280] The prototypical pro-inflammatory M1 macrophage can be distinguished from their regulatory M2 counterpart by their iron handling. Pro-inflammatory M1 macrophages do not distribute iron but hide intracellularly iron within ferritin to make the nutrient inaccessible for pathogens. M1 macrophages thus display increased ferritin levels, while their labile iron pool (LIP), representing the metabolic active iron levels for distribution, is low. In contrast, regulatory M2 have low ferritin levels, a large labile iron pool and express high levels of iron uptake and export markers, such as the hemoglobin/haptoglobin receptor CD163 essential for heme iron import and marker for M2 cells.[281] By default the regulatory phenotype of macrophages changes under iron-deficient conditions. In the absence of iron, iron-turnover decrease, resulting in a decline of the labile iron acquiring classical characteristics of inflammatory macrophages.[49]

Iron deficiency is therefore linked to C-reactive protein, CRP, and low-grade inflammation,[68,282–284] with pro-inflammatory signatures reported in the monocytic cells in children[66] and infants[67] with iron deficiency, while increasing the labile iron pool is associated with an immature, regulatory macrophage phenotype[146,154] (Figure 4).

5.2.2 | Neutrophils

Iron is not only an essential nutrient but is also required for ROS-generation, in which neutrophils, monocytes, or NK cells use iron as a catalyst to combat pathogens.[285–287] Indeed, during infections ROS is generated either (1) by complex I and III of the mitochondrial electron transfer chain, which harbor metal centers primarily in the form of iron-sulfurs clusters,[288] (2) other intracellular sources such as peroxisomes and the endoplasmic reticulum, (3) iron-loaded lactoferrin releasing ferrous iron. They generate ROS "on demand," with iron deficiency hampering the appropriate function of these enzymes.[288,289] Consequently, under iron-deficient conditions microbicidal killing is impaired as the finely tuned machinery for ROS formation "on demand" is hampered[288] and this despite that an increased activity is observed in these cells.

5.2.3 | T cells

T cells are also affected by iron deficiency. Iron-sufficient conditions can inhibit Th1, Th2, and Th17 differentiation.[290] In contrast, iron deficiency is initially associated with Th1-signatures (e.g., IL6, TNFα, and IFN-γ).[284] A continued shortage as seen in severe cases of iron-deficient anemia is associated with Th2 skewing and increase in the cytokine IL4[282–284] in humans. This shift from Th1 toward Th2 milieu is understood to be due to the particularly sensitive nature of Th1 cells to iron deprivation.[291] The Th1 IFN-gamma/STAT1 signaling pathway[292] is regulated by iron, resulting that under iron-deficient conditions the survival of Th2 cells is favored[51,291,293] (Figure 4).

5.2.4 | B cells

B cells are resistant to iron-deficient conditions. Iron represses in B cells the activation-induced cytidine deaminase (AID), an enzyme responsible for class-switching and affinity maturation, with iron deficiency facilitating its activation.[294] Iron deficiency hampers also the transfer of ferrous iron to the protoporphyrin IX in the mitochondria, thereby hampering heme synthesis and maintaining Bach2 activation in B cells.[295]

In addition, iron deficiency is associated with elevated IgE levels[296,297]—irrespective of the cause.[298–301] Iron fortification strategies, but not deworming is able to reduce IgE levels and improve iron status in Vietnamese children[302] (Figure 4).

5.2.5 | Mast cells

Mast cells are very sensitive to nutrient-restricted conditions. The iron chelator deferoxamine (a bacterial siderophore isolated from Streptomyces) is used to treat iron overload in the clinics. It can locally deplete iron from tissues, resulting that mast cells degranulate concentration-dependently[303,304] releasing histamine and inflammatory mediators[305] in vitro,[306] and in the human skin.[303,304] It is so effective, that there were even endeavors to use it instead of histamine as positive control for skin tests.[306] Vice versa, import of iron-sated transferrin, lactoferrin, and beta-lactoglobulin stabilizes mast cells and reduce their readiness for degranulation.[148,307–309]

To summarize, the most important aspect of iron deficiency is the general priming of immune cells, which react particularly sensitive to nutritional threats (Figure 4).

5.3 | Bioavailability

5.3.1 | Factors to increase bioavailability

In general, iron uptake occurs in the duodenum and upper jejunum with Vitamin C,[310,311] dairy products,[312] but also fat[313,314] enhancing

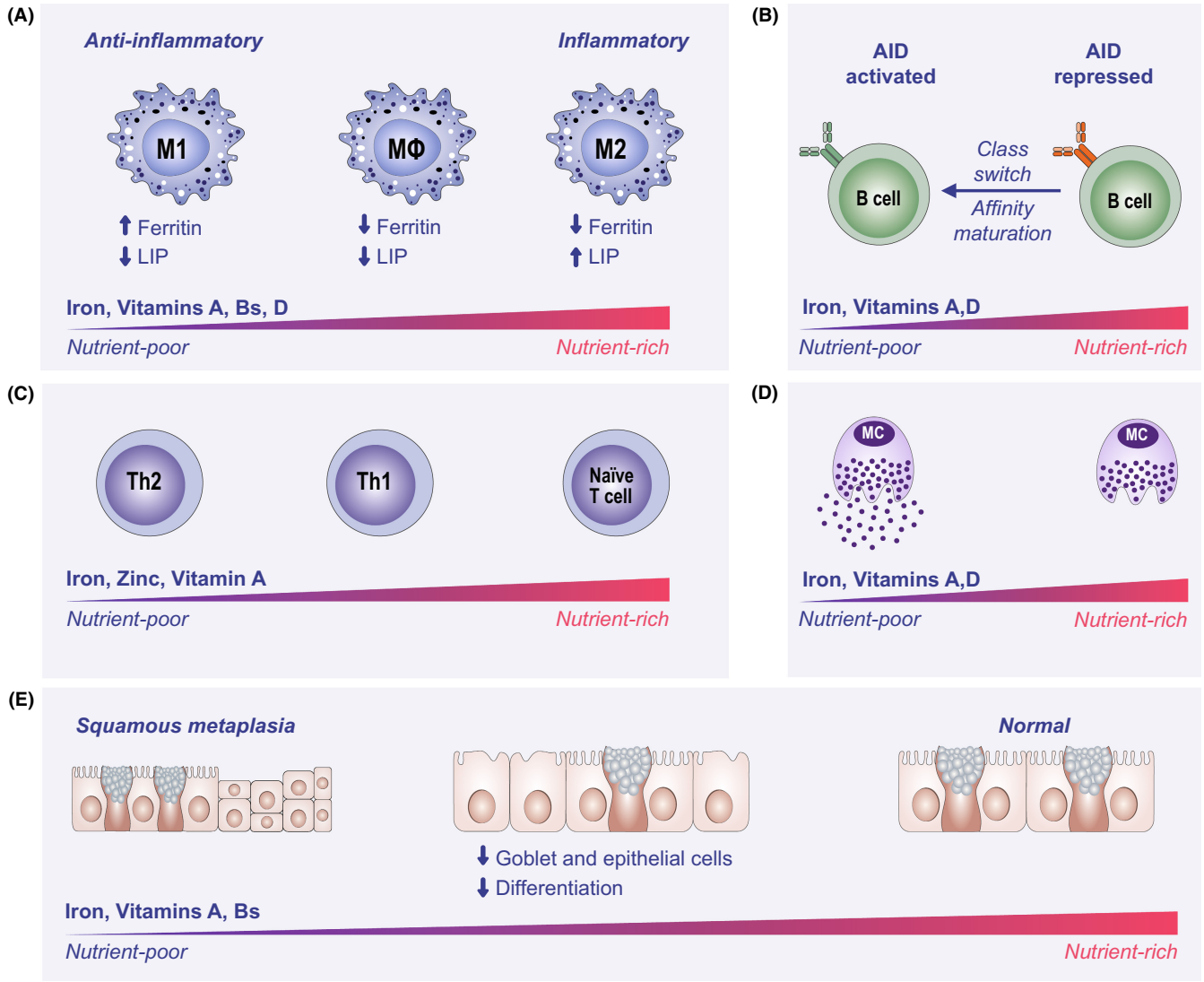

FIGURE 4 Impact of micronutritional deficiencies on immune cells. (A) Regulatory M2 macrophages are crucial for distributing nutrients such as iron in the human body and are characterized by a large labile iron pool (LIP) and a low ferritin content, while inflammatory macrophages have an iron-retention phenotype with a low LIP and high ferritin levels. A reduced iron, vitamin A and fatty acids supply decreases the labile iron content and nutrient supply of M2-macrophages and shifts the macrophage toward a more pro-inflammatory signature. (B) Fat-soluble vitamins are needed for iron mobilization, while iron represses the activation-induced deaminidase (AID) in B cells, resulting that a deficit of micronutrients promotes its activation result in antibody class-switching and affinity maturation. (C) Th1 cells are particularly sensitive to nutritional deficits, resulting that prolonged deficiencies in micronutrients of minerals and vitamins promote a Th2 dominated immune response. (D) Also the readiness of mast cells to degranulate is increased under nutrient-restricted conditions. (E) Nutritional deficits of vitamins and minerals also have a negative impact on epithelial cell number and differentiation, resulting in decreased mucus production, increased susceptibility for infections, and altered cell morphology leading to cellular changes such as squamous metaplasia.

iron absorption.[140,310] Though heme-iron is considered superior in its uptake, the presence of non-heme iron is required for best bioavailability.[315,316] Non-heme iron is also absorbed better, in the presence of heme iron.[317–322] Improved uptake has been shown when flavonoids such as quercetin are in complex with iron, leading to improved antioxidative as well as iron status in vivo.[323,324] Similarly, improved uptake was shown for healthy volunteers supplemented with curcumin iron III complexes.[325,326]

5.3.2 | Factors that decrease bioavailability

Phytates and large polyphenols such as tannins that bind iron[327,328] hinder uptake.[329] Though calcium can impede iron absorption, this only seemed to be true to a modest degree of about 20%, when excessive high amount of calcium was consumed.[330–334] Iron absorption is impeded upon immune activation due to hepcidin, and thus oral iron may even enhance disease activity in inflammatory bowel

diseases due to decreased uptake[335,336] and does not improve the iron status in obese patients.[46,337]

In the presence of low-grade inflammation, clinical trials have shown that the addition of vitamin A,[338] vitamin C,[140,310] antioxidants improve dietary iron uptake. Low-hemoglobin levels in pregnant women were also negatively correlated with the breast milk iron content.[339]

5.4 | Clinical trials with dietary iron to improve iron status

Oral iron treatment improves the iron status in healthy individuals. Also iron fortified milk can significantly improve the iron status in children,[340] which is little affected by calcium and greatly enhanced by vitamin C.[341,342] The addition of guava which is rich in Vitamin C, but not banana or cucumber in a supplementary nutrition program was able to increase iron and Vitamin C levels in 2–4 year old children in India.[343] Importantly, iron in milk was associated with a decreased risk for infection and sepsis in preterm infants.[344] In preterm neonates, a preterm formula powder containing calcium, phosphorus, iron, vitamin D, and multivitamins resulted in lower feed intolerance and was otherwise comparable than human milk fortifier.[345]

Similarly, whey protein fortified with multivitamin resulted in the lowest rate of anemia in a low income Guatemalan community.[346] In pregnant women iron-fortified milk compared to iron-tablets alone improved similarly the iron status, but was associated also with an additional nutritional health benefit.[339] Another clinical intervention trial reported that iron-saturated lactoferrin was superior to standard iron sulfate therapy in improving inflammation along iron markers in women affected by anemia of chronic inflammation.[347,348] While iron supplementation of iron in combination with vitamin A improved the iron status in anemic adolescent with subclinical inflammation.[339]

Liposomal iron and/or a combination of ferric sodium EDTA with vitamin C, folic acid, copper gluconate, zinc gluconate, and selenomethionine was also able to improve iron and inflammatory markers in subjects with chronic kidney disease.[140] Similarly, also, lipid-based nutrients were superior in improving iron levels than corn-soy blend in Burkina Faso.[349]

These results suggest that while the mucosal block is present, the addition of milk, iron-carrying proteins or whey products with vitamin A, C, and/or liposomal iron is able to improve by oral means the iron status in the presence of inflammation.

6 | ANTIOXIDANTS

Many low molecular weight molecules have described antioxidant activities such as glutathione, N-acetylcysteine, polyphenols including anthocyanins, flavonoids such as quercetin and catechins, and carotenoids (divided into carotenes such as alpha—and beta-carotenes and xanthophylls including ß-cryptoxanthin, lutein, and zeaxanthin) and vitamins in general. A common feature is that these nutrients or nutritional factors can scavenge free radicals thereby protecting cells and tissues.

While their mechanism of action differs dependent on their chemical structure, many either directly or indirectly have an impact on iron homeostasis. Polyphenols with a catechin core-structure such as epigallocatechin-3-gallate present in green tea extract for example, complex iron with high affinity, while procyanidins as present in grape seed extract[350] impair zinc,[350] but not iron uptake. Plant phenolic compounds sequester iron for plant nutrition[351] and also microbes use phenolics for iron acquisition.[352] Therapeutical application of quercetin for example[353–355] exploits the affinity of phenolics for iron.

6.1 | Clinical trials with antioxidants to improve overall health outcomes

Many polyphenols such as anthocyanins have been shown to improve health outcome in subjects with dyslipidemia and lower inflammatory markers in a concentration-dependent manner.[356] Several systematic reviews support the intake of antioxidants. The GINA guidelines 2023 recommend the consumption of fruits to prevent asthma, improve asthma control and reduce the risk of asthma exacerbation (Evidence A).[357–359] A Mediterranean diet may also be associated with a decreased risk for asthma in children.[360]

Beneficial effects were shown with polyphenol supplementation in children with Crohn's disease.[361] Similarly, curcumin supplementation improved health and inflammation marker in diabetic hemodialysis patients,[362] obese subjects[363] and patients undergoing coronary elective angioplasty.[364] Also lycopene supplementation with or without vitamin C reduced CRP levels in healthy volunteers[365] and 6-month supplementation with black rice pigment, rich in polyphenols and micronutrients, improved their oxidative and inflammatory status in coronary heart disease patients.[366] However, 3-day consumption of broccoli sprouts was neither sufficient to change inflammation marker nor reduce fractional exhaled nitric oxide levels in asthmatics.[367] Pomegranate juice, rich in polyphenols, and vitamin C has been able to reduce CRP levels in patients with Polycystic ovarian syndrome,[368] while saffron (rich in minerals such as magnesium, safranal, carotenes) decreased hs-CRP in nonalcoholic fatty liver disease.[369]

Also, a dose-dependent decrease in the CRP levels has been demonstrated in healthy non-smokers after lutein supplementation.[370] Melatonin supplementation was also able to improve health outcome and inflammation in Parkinson's disease.[371] Carnitine supplementation required for transport of long-chain fatty acids for FAO, improved inflammatory and oxidative stress in patients with coronary artery disease.[372] N-acetyl cysteine supplementation improved similar inflammation and oxidative status in rheumatoid arthritis patients.[373] Antioxidants in orange and blackcurrant juice, but not Vitamin E, were effective in improving systemic inflammation markers in subjects with arterial disease.[374]

Thus, antioxidants are pivotal to reduce inflammation and intake should be increased or supplements should be considered in patients suffering from chronic inflammatory diseases.

7 | VITAMIN C

Vitamin C is synthesized by many animals in their liver, but humans lack this capability. Vitamin C deficiency results in the potential lethal manifestation of scurfy, characterized by hyperkeratosis, bleeding, rashes, swollen joints, and anemia,[375] which can be corrected by Vitamin C supplementation.

Vitamin C is an important antioxidant protecting cells from damage, enhancing the immune cell function and is essential during wound healing. Its main metabolic function is the maintenance of collagen formation, catecholamine synthesis and carnitine biosynthesis as well as improving dietary iron absorption.[376]

7.1 | Bioavailability

Dietary bioavailability of the water-soluble vitamin C is not affected in inflammatory conditions with circulating plasma vitamin C level reflecting recent vitamin C intake and white blood cell ascorbic acid concentration closely relating to tissue stores.[377]

During inflammation vitamin C decline in the circulation, may be the consequence of new immune cells emerging from the bone marrow, that are low in Vitamin C.

Vitamin C is widely available in foods of plant and animal origin, but the best sources are fresh fruits, vegetables, and offal. Germination increases the vitamin C content in grains and pulses. However, vitamin C is sensitive to oxygen, light, heat, and alkaline conditions which results in significant losses during storage and cooking.

Deficiencies often result due to a low consumption of fresh fruits and vegetables, perhaps due to seasonal availabilities or high cost, but may also be deficient in individuals living on a restricted diet, in institutionalized elderly or in chronic alcoholics. As vitamin C increases iron absorption from food, a low vitamin C intake will exacerbate any iron deficiency issues.

7.2 | Vitamin C and inflammation

Vitamin C decline is associated with elevated CRP levels with leukocyte vitamin C concentration decreasing after surgery or a common cold. Vitamin C supplementation is regaining interest in the treatment of critically ill patients undergoing cardiac procedures, with acute burn injuries, during sepsis[378] and in reducing pain.[379]

Low vitamin C levels are often reported in patients suffering from chronic inflammatory diseases such as asthma,[380] elderly people with a high risk of subclinical inflammation and with cardiovascular diseases.[88,381]

Vitamin C supplementation improved health outcomes and inflammation markers in several cohorts, such as obese subjects[382] and acute ischemic shock patients[383] and septic shock patients.[384] Hence, vitamin C strongly impacts immune cells. Its bioavailability is not affected during inflammation with vitamin C supplementation generally considered beneficial.

8 | VITAMIN A

About a quarter of a billion children worldwide are estimated to have subclinical or clinically relevant low serum vitamin A levels,[6,7] with Vitamin A supplementation associated with reduce "all-cause mortality" and "all-cause morbidity".[385–387]

Vitamin A is vital for normal vision, reproduction, and growth, for epithelial tissue integrity and immunity.[151,388] More severe forms of Vitamin A deficiency may manifest in clinical ocular signs such as night blindness and xerophthalmia. However, subclinical vitamin A deficiency is associated with worsening outcomes and disease progression in a number of conditions as well as is associated with iron deficiency and inflammation.[226,389]

During inflammation, vitamin A levels decline in the circulation, similar to zinc. It is possible to overestimate vitamin A deficiency based on serum retinol levels alone. The dietary needs for vitamin A are normally provided for as preformed retinol (mainly as retinyl ester) and provitamin A carotenoids.

8.1 | Vitamin A and immunity

Vitamin A is of central importance for mucosal immunity, which is reviewed in detailed elsewhere[390–392] with only some basic immune mechanistic aspects given here.

8.1.1 | Macrophages and neutrophils

Vitamin A has a regulatory role in macrophages, by suppressing expression of Fc receptors[393] and toll like receptors,[394] while promoting an M2 regulatory phenotype via p38MAPK/STAT6.[395] Indeed, suppressing retinol-signaling (as present in vitamin A deficiency) is essential for macrophage differentiation.[396] Inflammation is increased by vitamin A deficiency as retinol suppresses the inflammasome cascade in macrophages.[397–399]

IL4 induces retinol production and excretion in macrophages in a STAT6-dependent manner.[400] In contrast, retinoic acid is essential to convert immature myeloid cells to mature neutrophilic cells with vitamin A supplementation affecting predominantly migration and maturation of neutrophils[401] (Figure 4).

8.1.2 | Lymphoid cells

Similarly to iron deficiency, vitamin A deficiency leads initially to a Th1 response, giving rise to the production of IFNγ[85,86] and negatively affecting the antibody response, with persistent deficiency resulting in a Th2-biased[402,403] and elevated IgE levels in vivo.[402] Vitamin A and vitamin D seems to be required for IgA antibody production[391] with a lack in retinoic acid signaling abrogating antigen-specific IgA responses in B cells and affecting the microbiota composition.[404] Retinoic acid promotes the expansion of innate lymphoid cell ILC3s and enables dendritic cells to produce retinoic acid for T-regulatory cells differentiation.[405] In support of this, retinoic deficient mice have impaired oral tolerance[406] that can be restored by oral supplementation with carotenoids[407,408] (Figure 4).

8.1.3 | Epithelial cells and mast cells

Vitamin A and some retinoids are central to maintain normal epithelial cell differentiation as vitamin A deficiency leads to squamous epithelial cell differentiation[409,410] and hyperkeratosis.[411] Supplementation reverses squamous metaplasia in vivo[412] and topical retinol application improves epithelial cell integrity and fillagrin expression[413] of UV-damaged skin. In addition, lung epithelial cell proliferation is suppressed by vitamin A intake[414] and retinoic acid intake was able to improve intestinal epithelial cell differentiation and barrier function.[415] Vitamin A deficiency exacerbates atopic dermatitis development by potentiating Th2-type inflammation and mast cell activation,[416] with retinol absorption improving atopic dermatitis symptoms.[417]

There seems to exist a complex relationship between mast cells and vitamin A.[418] Retinol-pathways are enriched in cutaneous mast cells and here vitamin A seems to enhance the antigen-specific degranulation of mast cells.[419] Others reported a concentration-dependent stabilizing effect on mast cells and histamine release in vitro[420] and in vivo[151,421,422] (Figure 4).

8.2 | Vitamin A bioavailability

Vitamin A bioavailability varies dependent on its form and the presence of fat, with all forms being sensitive to light and oxygen. Various food preparation techniques, such as cooking, grinding, and the addition of oil, can improve the absorption of food carotenoids.[423] Indeed, individuals at risk for vitamin A deficiency are those consuming most of their vitamin A needs from provitamin carotenoid sources and where minimal fat is available.[87]

Preformed vitamin A (retinol) is an unstable and in commercial preparation it is esterified generally with palmitic or acetic acid, to more stable esters. Together with provitamin A (ß-carotenes), retinyl acetate, and retinyl palmitates are used to fortify foods.[226]

Retinol and retinyl ester are predominantly found in animal food sources, with retinyl ester following the lymph route, whereas retinol itself is thought to be transported predominantly through the bloodstream to target tissues, such as the retina.[424,425] Importantly, retinol uptake is reported to be impaired[129] during inflammation.

They are emulsified by bile acids and pancreatic lipase, before entering the enterocytes, where they are converted to retinyl esters to be packed into chylomicrons. Chylomicrons enter the lymphatic system, before they enter via the subclavian vein the blood stream. If not immediately needed from the tissues, retinol is re-esterified and retained in the fat-storing cells of the liver. As the conversion rate of beta-carotene to retinyl ester is with 12:1 and for other provitamin A carotenoids is with 24:1 very low,[87,426,427] the addition of oil is of utmost importance to increase the bioavailability of food carotenoids[428] via the lymph system.

Upon hydrolysis of stored retinyl esters, retinol binds to unoccupied retinol-binding protein (apo-RBP) in the liver or peripheral tissues, before the RBP-retinol complex (holoRBP) is secreted into the blood. There it associates with another hepatically synthesized protein, transthyretin. The large size of transthyretin–RBP–retinol complex prevents its loss via the kidney,[429] but allows circulation in the blood and delivers the lipophilic retinol to tissues. Here, holoRBP transiently associates with the tissue membrane and specific intracellular proteins extract retinol.

Dietary restriction in energy, proteins, and some micronutrients, such as zinc and iron,[430] can limit the synthesis of proteins important for vitamin A mobilization, with altered kidney dysfunction increasing urinary vitamin A loss.

8.3 | Vitamin A and inflammation

Retinol is also closely linked to the immune system. Serum retinol declines[431,432] as CRP levels increases[80,433] in infections and inflammatory diseases. Retinoic acid directly impacts many immune cell subsets, such as innate lymphoid cells, dendritic cells, and lymphocytes, while the immunomodulatory mechanisms of specific microbial species include the induction of retinoic acid metabolism in host cells.[434,435] Vitamin A can significantly decrease erythropoietin concentration and lead to a rapid reduction in inflammation markers, while iron from stores is mobilized for new erythrocyte production.[436] Indeed, vitamin A supplementation alone can reduce the risk of anemia by improving hemoglobin levels. As vitamin A and carotene uptake occurs via the lymph the addition of oil has been demonstrated to improve serum retinol concentrations.[437,438] Reduced vitamin A levels has been reported repeatedly in epidemiological studies in asthmatic patients.[357,380]

9 | CLINICAL TRIALS WITH WHOLE FOOD THAT INFLUENCE INFLAMMATORY RESPONSES

Foods possess remarkable immunomodulatory potential. In fact, a well-balanced nutritional diet, including enteral and regular

food-based approaches, has shown particular efficacy in children with active Crohn's disease. It exhibits a comparable effectiveness in inducing remission, mirroring the outcomes achieved with corticosteroids.[439,440]

9.1 | High-fat/ketogenic diet

In double-blind placebo-controlled trials focused on acute respiratory failure, a high-fat, low-carbohydrate diet exhibited notable effects by reducing CRP levels, while significantly enhancing the body's antioxidant capacity.[441]

Studies involving type 2 diabetic patients underscore the positive impact of a low-carbohydrate, high-fat diet in reducing inflammatory markers.[442–444]

Another randomized controlled trial (RCT) revealed that obese individuals benefited from a high-fat, low-carbohydrate diet in terms of inflammation markers when compared to a low-fat, high-carb diet. Similarly, subjects with metabolic syndrome experienced reductions in systemic inflammation markers by adhering to a Mediterranean diet rich in mono- and polyunsaturated fats, as opposed to a control group following a prudent diet.[445]

Ketogenic diets have also been associated with reduced inflammation in various studies,[446–448] with the specific lipid composition playing a crucial role in achieving desired clinical outcomes.[449] Mechanistically, ketogenesis induced by fasting and hetogenic diet induces production of ketone bodies, included β-hydroxybutyrate (BHB). It has been demonstrated in preclinical models that in acute infections, such as COVID-19 ketogenic diet restores the impaired metabolism and functions of CD4+T cells and reduces mortality due to COVID-19 infection[450].

9.2 | Whole grain

Double-blind placebo-controlled trials have highlighted the benefits of a whole grain diet over a refined grain diet, resulting in significant reductions in body weight and lower inflammation parameters such as IL-6 and CRP in individuals at risk of developing metabolic syndrome.[451] This suggests that several nutrients and fibers lacking in refined grains, such as iron and zinc, B vitamins, and folate[452] are beneficial.

9.3 | High protein

A protein-rich diet has demonstrated benefits in type 2 diabetes patients, with both plant-based and animal-based protein-rich diet associated with a significant reduction in liver fat and hepatic inflammation, independent of body weight.[453] Additionally, chronic hemodialysis patients benefitted from an iron and protein-rich diet resulting in lower CRP-values.[454] However, while mixed nut consumption for 4 months lowered body fat, only a trend toward improved inflammatory marker were observed in obese adults.[455]

Two weeks of a fat-rich almond diet was also able to improve CRP levels.[456] Furthermore, meta-analyses have confirmed that dietary supplementation with whey or soy proteins effectively reduces inflammatory mediators such as IL-6 and TNF-alpha, exerting an anti-inflammatory effect, particularly in individuals affected by sarcopenia.[457]

In summary, clinical trials involving subjects with chronic inflammation have indicated that a low-carbohydrate ketogenic diet rich in proteins, minerals, and antioxidants can lead to improvements in inflammatory parameters.

10 | CONCLUSION

Nutritional deficiencies can trigger inflammation, representing one of the most evolutionary conserved innate defense mechanisms. It is therefore of utmost importance to identify the lacking nutrients that foster inflammation in a particular disease setting. Given that nutrient uptake is often compromised in an inflammatory setting, the use of digestion-resistant carrier proteins for micronutrients and antioxidants, combined with a ketogenic diet or higher fat intakes becomes important for improving bioavailability through the lymphatic system. As inflammation generates reactive oxygen species, it is advisable to increase the intake of or consider supplementation with antioxidants in the form of vitamins and polyphenols. Simultaneously, it is recommended to avoid foods with high sugar and triglyceride content. Consequently, in numerous chronic inflammatory diseases, nutritional deficiencies can be mitigated by incorporating foods that align with lymphatic pathways absorption.

Diet during chronic inflammation

Ketogenic, low-carbohydrate diet

- Include sources of unsaturated fats such as seed, nuts, avocados, plant oils and oily fish.
- Avoid sugary drinks, starchy foods.
- Avoid ultra-processed food (with low micronutrient content)

Proteins

- Consumption of digestion-resistant proteins (soy, milk, nuts, egg, fish) shuttling micronutrients and antioxidants

Iron

- Decreased under inflammatory conditions. Affected by vitamin C, vitamin A, and vitamin D deficiency.
- Improved bioavailability with vitamin C, vitamin A, and lipids.
- Improved bioavailability by addition of milk/whey and vitamin A and C under inflammatory conditions.

Vitamin A

- Decreased under inflammatory conditions. Affected by zinc and iron deficiency.
- Addition of oil is essential to improve bioavailability.

Vitamin C

- Decreased under inflammatory conditions.
- Greater demand of vitamin C under inflammatory conditions.

Antioxidants

- Decreased under inflammatory conditions.
- Greater demand of antioxidants under inflammatory conditions.

GLOSSARY

Abbreviations	Glossary
AID	Activation-induced cytidine deaminase: involved in somatic hypermutation (SHM), gene conversion, and class-switch recombination (CSR) in B-lymphocytes by deaminating C to U during transcription of Ig-variable (V) and Ig-switch (S) region DNA; essential for B-cell terminal differentiation and efficient antibody responses.
Anemia of chronic inflammation	Anemia of inflammation, also called anemia of chronic disease: common typically normocytic normochromic anemia caused by an underlying inflammatory disease.
ATP	Adenosine triphosphate, a compound consisting of adenosine bonded to three phosphate groups. The breakage of one phosphate linkage (to form adenosine diphosphate, ADP) provides energy for physiological processes such as muscular contraction, nerve impulse propagation, condensate dissolution, and chemical synthesis.
BACH2	BTB domain and CNC homolog 2; Is a key transcriptional regulator of adaptive immunity, crucial for the maintenance of regulatory T-cell function and B-cell maturation; Induces apoptosis in response to oxidative stress through repression of the anti-apoptotic factor HMOX1. Positively regulates the nuclear import of actin.
Carnitin	Essential co-factor that helps transport long-chain fatty acids into the mitochondria so that they can be oxidized to produce energy in the form of ATP.
CRP	An acute phase protein produced by the liver; either present as a pentamer in circulation or as a non-soluble monomer in tissue; promotes agglutination, bacterial capsular swelling, phagocytosis, and complement fixation through its calcium-dependent binding to phosphorylcholine. Can interact with DNA and histones.
CSR	Class-switch recombination: DNA recombination process that replaces the immunoglobulin (Ig) constant region for the isotype for better protection against the pathogen.
ETC	Electron transfer chain: series of protein complexes and organic molecules bound to the inner mitochondrial membrane, in which electrons pass through in a series of redox reactions, to release energy in form of ATP. Oxygen acts as the terminal electron acceptor in the electron transport chain.
FAO	Fatty acid oxidation = beta oxidation in the mitochondria, catabolic process by which fatty acid molecules are broken down to generate acetyl-CoA, which enters the citric acid cycle, and NADH and FADH2, which are co-enzymes used in the electron transport chain.
Glutaminolysis	Metabolic pathway that breaks down the amino acid glutamine into glutamate, ammonia, and carbon dioxide; occurs in the mitochondria of cells.
glycolysis	Metabolic pathway that converts glucose into pyruvate. Occurs in the cytosol and is oxygen-independent.
HDACs	Class of enzymes that remove acetyl groups (O=C-CH3) from an ε-N-acetyl lysine amino acid on both histone and non-histone proteins, HDACs allow histones to wrap the DNA more tightly H2B, H3, and H4), thereby acting as epigenetic repressor.
HIF-1a	Hypoxia-inducible factor 1 alpha: master transcriptional regulator of the cellular and systemic homeostatic response to hypoxia by activating the transcription of genes, including erythropoietin, glucose transporters, glycolytic enzymes, vascular endothelial growth factor to increase oxygen delivery or facilitate metabolic adaptation to hypoxia enhanced activity by interaction with NCOA1 and/or NCOA2.
mucosal block	First described for iron, that described the regulatory element of enterocytes in restricting the bioavailability of nutrients.
OXPHOS	Oxidative phosphorylation: nutrients are oxidized to gain energy in form of ATP.
PUFA	Poly unsaturated fatty acids: have more than one double-bound.
RAG	Recombination-activating genes: catalyze the rearrangement of immunoglobulin genes in B cells and T-cell receptor genes.
ROS	Reactive oxygen species: highly reactive chemicals formed from oxygen, for example, peroxides, superoxide, hydroxyl radical, are produced during respiration in mitochondria to gain ATP or by environmental stressors (e.g., drugs, UV, metals).
SCFS	Short-chain fatty acids are fatty acids of two to six carbon atoms, which usually are produced by the gut microbiota during the fermentation of polysaccharides.
SIRT1	Sirtuin 1: NAD+-dependent deacetylase: regulator in cell cycle, response to DNA damage, metabolism, apoptosis and autophagy, involved in DNA damage response, Involved in lipid metabolism.
SIRT3	Sirtuin 3: NAD+-dependent deacetylase, found exclusively in mitochondria, where it can eliminate reactive oxygen species, inhibit apoptosis,
Sirtuin	NAD-dependent deacetylase sirtuin, family of signaling proteins involved in metabolic regulation; possess either mono-ADP-ribosyltransferase or deacylase activity.
SNPs	Most common type of genetic variation among people.

Abbreviations	Glossary
Squamous metaplasia	Mature, non-squamous epithelium is replaced by stratified squamous epithelium.
STAT6	Signal transducer and activator of transcription 6, involved in signal transduction and as transcription factor. Involved in IL4/interleukin-4- and IL3/interleukin-3-mediated signaling; induce the expression of BCL2L1/BCL-X(L) responsible for the anti-apoptotic activity of IL4.
TCA	Tricarboxylic acid cycle, alias Krebs, or citric acid cycle is the main source of energy for cells and an important part of aerobic respiration.

AUTHOR CONTRIBUTIONS

FRW coordinated, structured, wrote the manuscript, and prepared the first draft figures, which were re-designed by Anna Głobińska, the Allergy Graphics Editor. RBC MS, DP, LOM, EV, CV contributed to writing and critically revised the manuscript for the intellectual content. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

FRW is lead inventor of EP2894478 (applicant Biomedical International R+D, Austria), has served as an investigator and received personal fees for Biomedical Int R&D, Allergy Therapeutics, Bencard Allergy and Lofarma. FRW is the founder of ViaLym. LOM reports consultancy with Precision Biotics, research grants from GlaxoSmithKline and Chiesi, and participation in speaker bureau for Nestle, Yakult, Reckitt, and Abbott. CV reports grants from Reckitt Benckiser, grants from FA Research and Education, and grants from National Peanut Board, personal fees from Reckitt Benckiser, Nestle Nutrition Institute, Danone, Abbott Nutrition, and Else Nutrition. MS reports research grants from SNSF, GSK, Novartis, and participation in speaker bureau for AstraZeneca. RBC had the following relevant financial relationships with the following manufacturers: Ch. Hansen (research grant, speaker), Humana (research grant), iHealth (research grant), Kraft-Heinz (research grant, speaker), Mead Johnson Nutrition (research grant, speaker), Nestlè (research grant), Novalac (research grant), Nutricia (research grant, speaker), Sanofi (research grant, speaker) as part of publicly funded research projects with the support of the NIH, EU, the Italian Ministry of Health and the Italian Ministry of the University and Research. DP, EV have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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