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

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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

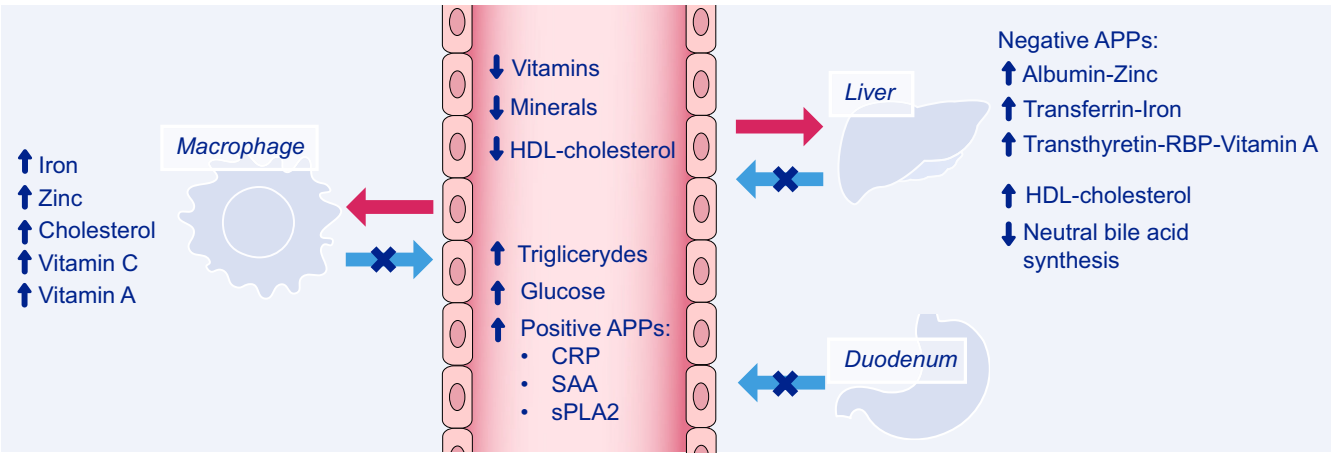

FIGURE 1 Nutrients are concealed during the acute phase response. Upon immune activation most micronutrients such as iron, zinc, vitamin A, C, D, and E are removed from the circulation with their carrier, which usually are negative acute phase proteins such as transferrin, albumin and transthyretin and 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

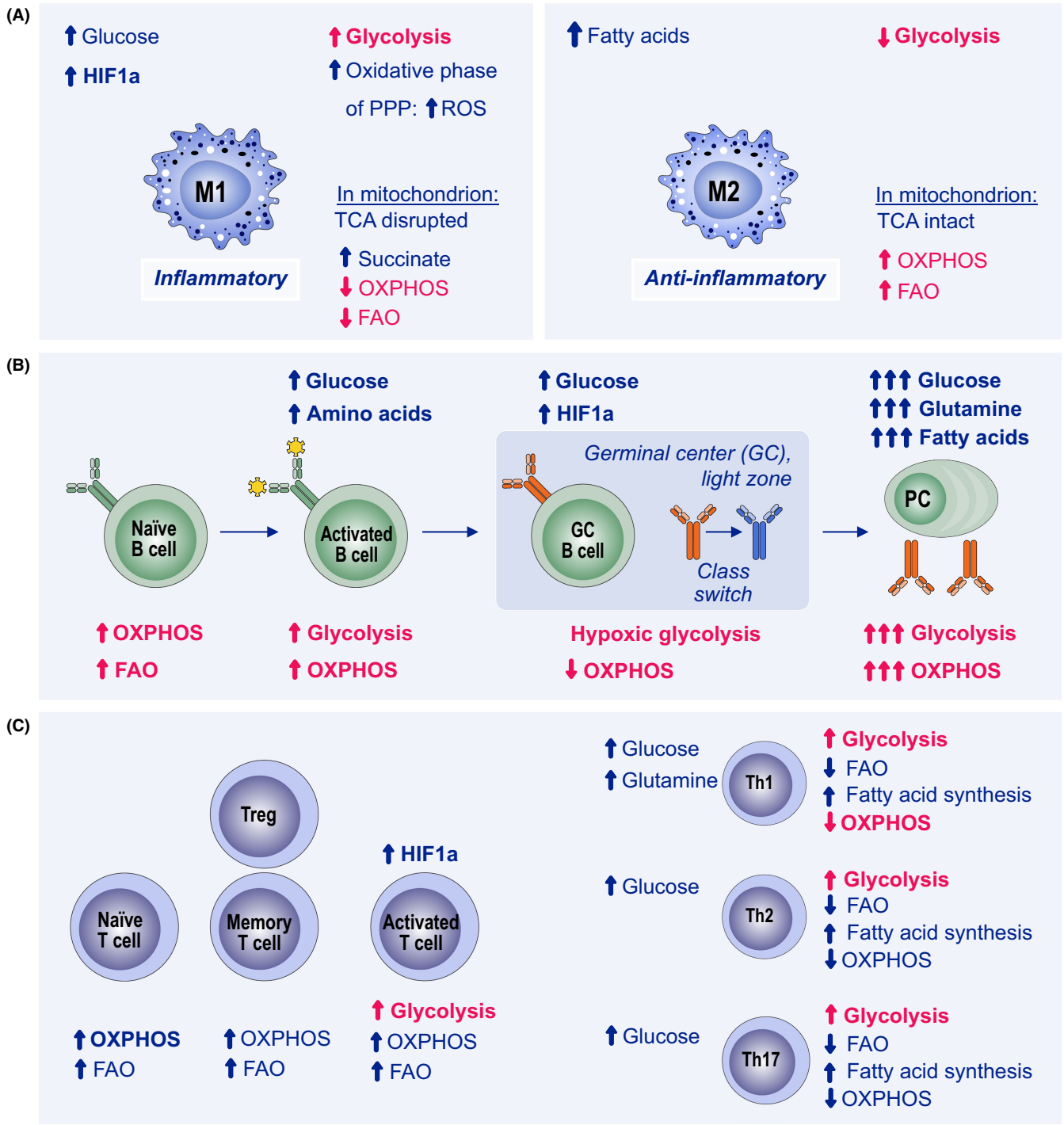

FIGURE 2 Differential metabolic demands of immune cells upon inflammation. In general, hypoxia initiates immune activation and shifts, (A). regulatory macrophages, (B) naïve B and (C) T cells from aerobic fatty acid oxidation FAO and mitochondrial oxidative phosphorylation OXPHOS toward anaerobic glycolysis (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

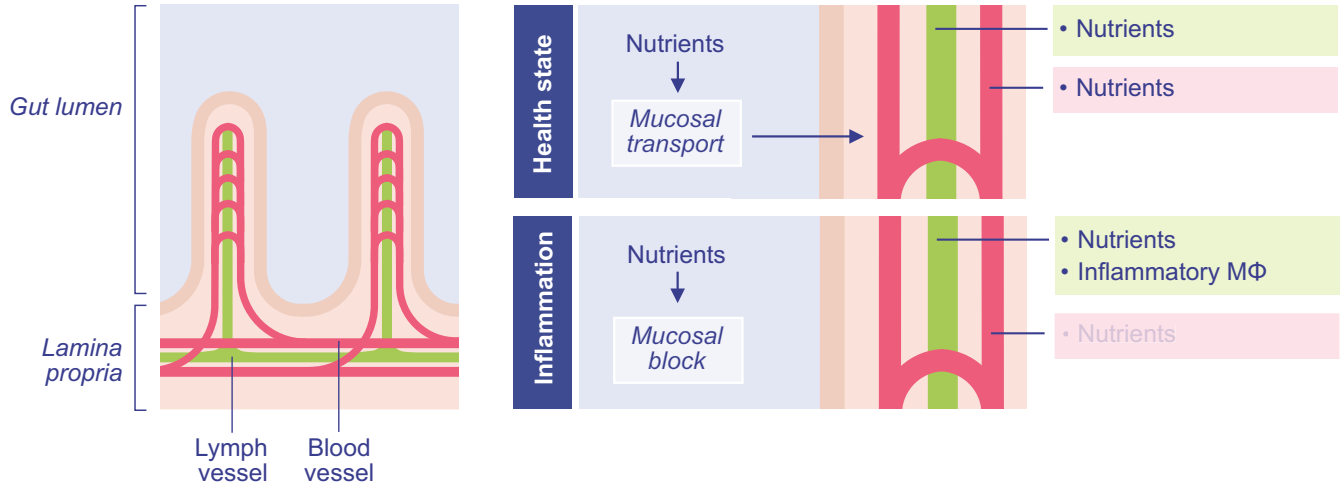

FIGURE 3 Inflammation does not compromise dietary micronutrient uptake via the lymph. Most nutrients are absorbed into the blood stream and enter via the portal vein of the liver. However, some nutrients, such as fats and digestion-resistant proteins, are absorbed into the lymph system first. Upon inflammation, 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

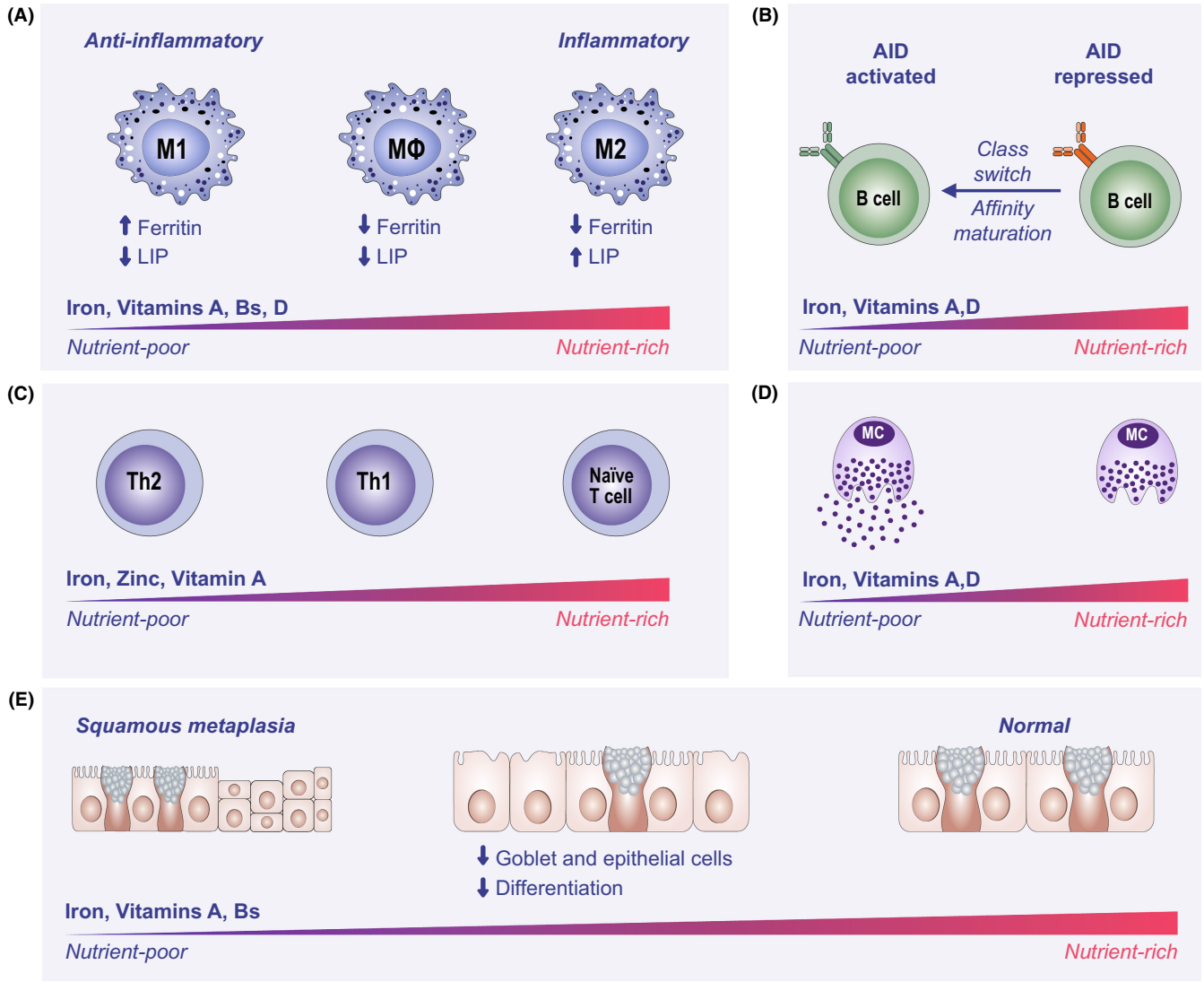

FIGURE 4 Impact of micronutritional deficiencies on immune cells. (A) Regulatory M2 macrophages are crucial for distributing nutrients such as iron in the human body and are characterized by a large labile iron pool (LIP) and a low ferritin content, while inflammatory macrophages have an iron-retention 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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REFERENCES

1. Crook J, Horgas A, Yoon SJ, Grundmann O, Johnson-Mallard V. Insufficient vitamin C levels among adults in the United States: results from the NHANES surveys, 2003-2006. *Nutrients*. 2021;13(11):3910.
2. Agarwal S, Reider C, Brooks JR, Fulgoni VL 3rd. Comparison of prevalence of inadequate nutrient intake based on body weight status of adults in the United States: an analysis of NHANES 2001-2008. *J Am Coll Nutr*. 2015;34(2):126-134.
3. Higgins KA, Bi X, Davis BJ, Barraj LM, Scrafford CG, Murphy MM. Adequacy of total usual micronutrient intakes among pregnant women in the United States by level of dairy consumption, NHANES 2003-2016. *Nutr Health*. 2022;28(4):621-631.
4. Preiser JC, Arabi YM, Berger MM, et al. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. *Crit Care*. 2021;25(1):424.
5. Beal T, White JM, Arsenault JE, et al. Micronutrient gaps during the complementary feeding period in South Asia: a comprehensive nutrient gap assessment. *Nutr Rev*. 2021;79(Suppl 1):26-34.
6. Tam E, Keats EC, Rind F, Das JK, Bhutta AZA. Micronutrient supplementation and fortification interventions on health and development outcomes among children under-five in low- and middle-income countries: a systematic review and meta-analysis. *Nutrients*. 2020;12(2):289.
7. Centers for Disease C, Prevention. Vitamin a deficiency among children–Federated States of Micronesia, 2000. *MMWR Morb Mortal Wkly Rep*. 2001;50(24):509-512.
8. Cho ME, Hansen JL, Sauer BC, Cheung AK, Agarwal A, Greene T. Heart failure hospitalization risk associated with iron status in veterans with CKD. *Clin J Am Soc Nephrol*. 2021;16(4):522-531.
   Important study linking iron-deficiency with heart failure in patients with chronic kidney disease.
9. Guedes M, Muenz D, Zee J, et al. Serum biomarkers of iron stores are associated with worse physical health-related quality of life

in nondialysis-dependent chronic kidney disease patients with or without anemia. *Nephrol Dial Transplant*. 2021;36(9):1694-1703.
10. Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199-2209.
11. Singh AK, Cizman B, Carroll K, et al. Efficacy and safety of daprodustat for treatment of anemia of chronic kidney disease in incident dialysis patients: a randomized clinical trial. *JAMA Intern Med*. 2022;182(6):592-602.
12. Ambrosy AP, von Haehling S, Kalra PR, et al. Safety and efficacy of intravenous ferric derisomaltose compared to iron sucrose for iron deficiency anemia in patients with chronic kidney disease with and without heart failure. *Am J Cardiol*. 2021;152:138-145.
13. Pisani A, Riccio E, Sabbatini M, Andreucci M, Del Rio A, Visciano B. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. *Nephrol Dial Transplant*. 2015;30(4):645-652.
14. Chen WS, Liu CY, Lee HT, et al. Effects of intravenous iron saccharate on improving severe anemia in rheumatoid arthritis patients. *Clin Rheumatol*. 2012;31(3):469-477.
15. Luo J, Wang X, Yuan L, Guo L. Iron deficiency, a risk factor of thyroid disorders in reproductive-age and pregnant women: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2021;12:629831.
16. Kisaoglu H, Baba O, Kalyoncu M. Hematologic manifestations of juvenile systemic lupus erythematosus: an emphasis on anemia. *Lupus*. 2022;31(6):730-736.
17. Mittal S, Agarwal P, Wakhlu A, Kumar A, Mehrotra R, Mittal S. Anaemia in systemic lupus erythematosus based on iron studies and soluble transferrin receptor levels. *J Clin Diagn Res*. 2016;10(6):EC08-EC11.
18. Chang R, Chu KA, Lin MC, Chu YH, Hung YM, Wei JC. Newly diagnosed iron deficiency anemia and subsequent autoimmune disease: a matched cohort study in Taiwan. *Curr Med Res Opin*. 2020;36(6):985-992.
Important study that assiocate iron deficiency anemia with a greater risk for the development of autoimmune diseases within 2 years.
19. Maas LA, Krishna M, Parian AM. Ironing it all out: a comprehensive review of iron deficiency anemia in inflammatory bowel disease patients. *Dig Dis Sci*. 2022;68:357-369.
20. Gordon M, Sinopoulou V, Iheozor-Ejiofor Z, et al. Interventions for treating iron deficiency anaemia in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2021;1:CD013529.
21. Wyart E, Hsu MY, Sartori R, et al. Iron supplementation is sufficient to rescue skeletal muscle mass and function in cancer cachexia. *EMBO Rep*. 2022;23(4):e53746.
22. Ludwig H, Evstatiev R, Kornek G, et al. Iron metabolism and iron supplementation in cancer patients. *Wien Klin Wochenschr*. 2015;127(23–24):907-919.
23. Escobar Alvarez Y, de Las Penas Bataller R, Perez Altozano J, et al. SEOM clinical guidelines for anaemia treatment in cancer patients (2020). *Clin Transl Oncol*. 2021;23(5):931-939.
24. Bartosik T, Jensen SA, Afify SM, et al. Ameliorating atopy by compensating micronutritional deficiencies in immune cells: a double-blind placebo-controlled pilot study. *J Allergy Clin Immunol Pract*. 2022;10(7):1889.e9-1902.e9.
25. Petje LM, Jensen SA, Szikora S, et al. Functional iron-deficiency in women with allergic rhinitis is associated with symptoms after nasal provocation and lack of iron-sequestering microbes. *Allergy*. 2021;76(9):2882-2886.
26. Teng IC, Tseng SH, Aulia B, Shih CK, Bai CH, Chang JS. Can diet-induced weight loss improve iron homoeostasis in patients with obesity: a systematic review and meta-analysis. *Obes Rev*. 2020;21(12):e13080.
27. Zhao L, Zhang X, Shen Y, Fang X, Wang Y, Wang F. Obesity and iron deficiency: a quantitative meta-analysis. *Obes Rev*. 2015;16(12):1081-1093.
28. Yanoff LB, Menzie CM, Denkinger B, et al. Inflammation and iron deficiency in the hypoferremia of obesity. *Int J Obes (Lond)*. 2007;31(9):1412-1419.
29. Hegarty C, Breen C, Fearon NM, Heneghan HM, Docherty NG, Gletsu MN. Assessment of baseline rates of functional and absolute iron deficiency in bariatric surgery candidates: a retrospective study. *Surg Obes Relat Dis*. 2021;17(12):2009-2014.
30. Shidfar F, Amani S, Vafa M, et al. Effects of iron supplementation with and without docosahexaenoic acid on the cardiovascular disease risk based on Paraoxonase-1, hs-CRP, and ApoB/ApoA-I ratio in women with iron deficiency anemia. *Biol Trace Elem Res*. 2016;169(1):34-40.
31. Abrams B, Duncan D, Hertz-Picciotto I. A prospective study of dietary intake and acquired immune deficiency syndrome in HIV-seropositive homosexual men. *J Acquir Immune Defic Syndr (1988)*. 1993;6(8):949-958.
32. Imdad A, Mayo-Wilson E, Haykal MR, et al. Vitamin a supplementation for preventing morbidity and mortality in children from six months to five years of age. *Cochrane Database Syst Rev*. 2022;3(3):CD008524.
Important study re-confirming that vitamin A supplementation is linked with a reduced all-cause morbidity and mortality.
33. Ghashut RA, McMillan DC, Kinsella J, Talwar D. Erythrocyte concentrations of B1, B2, B6 but not plasma C and E are reliable indicators of nutrition status in the presence of systemic inflammation. *Clin Nutr ESPEN*. 2017;17:54-62.
34. Supriyadi R, Koswara MIA, Soelaeman MA, Huang I. The effect of antioxidants supplementation on oxidative stress and proinflammatory biomarkers in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2023;27(4):1413-1426.
35. Buchmann K. Evolution of innate immunity: clues from invertebrates via fish to mammals. *Front Immunol*. 2014;5:459.
36. Valente de Souza L, Hoffmann A, Weiss G. Impact of bacterial infections on erythropoiesis. *Expert Rev Anti Infect Ther*. 2021;19(5):619-633.
37. Branch AH, Stoudenmire JL, Seib KL, Cornelissen CN. Acclimation to nutritional immunity and metal intoxication requires zinc, manganese, and copper homeostasis in the pathogenic *Neisseriae*. *Front Cell Infect Microbiol*. 2022;12:909888.
38. Healy C, Munoz-Wolf N, Strydom J, et al. Nutritional immunity: the impact of metals on lung immune cells and the airway microbiome during chronic respiratory disease. *Respir Res*. 2021;22(1):133.
39. Stover PJ, Caudill MA. Genetic and epigenetic contributions to human nutrition and health: managing genome-diet interactions. *J Am Diet Assoc*. 2008;108(9):1480-1487.
40. Fakhimahmadi A, Hasanaj I, Hofstetter G, et al. Nutritional provision of iron complexes by the major allergen alt a 1 to human immune cells decreases its presentation. *Int J Mol Sci*. 2023;24(15):11934.
41. Vijay K, Shibasini M, Sivasakthivelan P, Kavitha T. Microbial siderophores as molecular shuttles for metal cations: sources, sinks and application perspectives. *Arch Microbiol*. 2023;205(9):322.
42. Murdoch CC, Skaar EP. Nutritional immunity: the battle for nutrient metals at the host-pathogen interface. *Nat Rev Microbiol*. 2022;20(11):657-670.
Nice review on nutritional immunity in bacteria and humans.
43. Siso-Terraza P, Luis-Villarroya A, Fourcroy P, et al. Accumulation and secretion of coumarinolignans and other coumarins in

Arabidopsis thaliana roots in response to iron deficiency at high pH. *Front Plant Sci*. 2016;7:1711.
44. Connorton JM, Balk J, Rodriguez-Celma J. Iron homeostasis in plants - a brief overview. *Metallomics*. 2017;9(7):813-823.
45. Belmonte JA, Ibanez L, Ras MR, et al. Iron metabolism in burned children. *Eur J Pediatr*. 1999;158(7):556-559.
46. Baumgartner J, Smuts CM, Aeberli I, Malan L, Tjalsma H, Zimmermann MB. Overweight impairs efficacy of iron supplementation in iron-deficient south African children: a randomized controlled intervention. *Int J Obes (Lond)*. 2013;37(1):24-30.
47. Jorgensen JM, Yang Z, Lonnerdal B, Chantry CJ, Dewey KG. Effect of iron supplementation during lactation on maternal iron status and oxidative stress: a randomized controlled trial. *Matern Child Nutr*. 2017;13(4):e12394.
48. Cercamondi CI, Stoffel NU, Moretti D, et al. Iron homeostasis during anemia of inflammation: a prospective study of patients with tuberculosis. *Blood*. 2021;138(15):1293-1303.
49. Roth-Walter F. Iron-deficiency in atopic diseases: innate immune priming by allergens and Siderophores. *Front Allergy*. 2022;3:859922.
50. Peroni DG, Hufnagl K, Comberiati P, Roth-Walter F. Lack of iron, zinc, and vitamins as a contributor to the etiology of atopic diseases. *Front Nutr*. 2022;9:1032481.
51. Roth-Walter F, Pacios LF, Bianchini R, Jensen-Jarolim E. Linking iron-deficiency with allergy: role of molecular allergens and the microbiome. *Metallomics*. 2017;9(12):1676-1692.
52. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*. 2017;9:1211.
53. Gwamaka M, Kurtis JD, Sorensen BE, et al. Iron deficiency protects against severe plasmodium falciparum malaria and death in young children. *Clin Infect Dis*. 2012;54(8):1137-1144.
54. Muriuki JM, Mentzer AJ, Kimita W, et al. Iron status and associated malaria risk among African children. *Clin Infect Dis*. 2019;68(11):1807-1814.
Important study confirming decreased risk for parasetemia in children with iron-deficiency.
55. Nyakeriga AM, Troye-Blomberg M, Dorfman JR, et al. Iron deficiency and malaria among children living on the coast of Kenya. *J Infect Dis*. 2004;190(3):439-447.
56. Cegielski JP, Arab L, Cornoni-Huntley J. Nutritional risk factors for tuberculosis among adults in the United States, 1971-1992. *Am J Epidemiol*. 2012;176(5):409-422.
57. Boelaert JR, Vandecasteele SJ, Appelberg R, Gordeuk VR. The effect of the host's iron status on tuberculosis. *J Infect Dis*. 2007;195(12):1745-1753.
58. McDermid JM, Hennig BJ, van der Sande M, et al. Host iron redistribution as a risk factor for incident tuberculosis in HIV infection: an 11-year retrospective cohort study. *BMC Infect Dis*. 2013;13:48.
59. Isanaka S, Mugusi F, Urassa W, et al. Iron deficiency and anemia predict mortality in patients with tuberculosis. *J Nutr*. 2012;142(2):350-357.
60. Kerkhoff AD, Meintjes G, Opie J, et al. Anaemia in patients with HIV-associated TB: relative contributions of anaemia of chronic disease and iron deficiency. *Int J Tuberc Lung Dis*. 2016;20(2):193-201.
61. Lv Y, Chen L, Liang X, et al. Association between iron status and the risk of adverse outcomes in COVID-19. *Clin Nutr*. 2021;40(5):3462-3469.
62. Siegel EM, Patel N, Lu B, et al. Circulating biomarkers of iron storage and clearance of incident human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):859-865.
63. Hejazi N, Mazloom Z, Zand F, Rezaianzadeh A, Nikandish R. The beneficial effects of alpha-Lipoic acid in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. *Asian J Anesthesiol*. 2018;56(2):45-55.
64. Antebi H, Mansoor O, Ferrier C, et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr*. 2004;28(3):142-148.
65. Dehghani F, Sezavar Seyedi Jandaghi SH, Janani L, Sarebanhassanabadi M, Emamat H, Vafa M. Effects of quercetin supplementation on inflammatory factors and quality of life in post-myocardial infarction patients: a double blind, placebo-controlled, randomized clinical trial. *Phytother Res*. 2021;35(4):2085-2098.
66. Dhankar N, Gupta R, Jain SL, Mandal S, Sarkar B. Perturbation of monocyte subsets in iron-deficient children - a shift to a pro-inflammatory state? *Allergol Immunopathol (Madr)*. 2021;49(6):42-47.
67. Munoz C, Olivares M, Schlesinger L, Lopez M, Letelier A. Increased in vitro tumour necrosis factor-alpha production in iron deficiency anemia. *Eur Cytokine Netw*. 1994;5(4):401-404.
68. Baum P, Toyka KV, Bluher M, Kosacka J, Nowicki M. Inflammatory mechanisms in the pathophysiology of diabetic peripheral neuropathy (DN)-new aspects. *Int J Mol Sci*. 2021;22(19):10835.
69. Friso S, Jacques PF, Wilson PW, Rosenberg IH, Selhub J. Low circulating vitamin B(6) is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. *Circulation*. 2001;103(23):2788-2791.
70. Chiang E-P, Smith DE, Selhub J, Dallal G, Wang Y-C, Roubenoff R. Inflammation causes tissue-specific depletion of vitamin B6. *Arthritis Res Ther*. 2005;7(6):R1254-R1262.
71. Pusceddu I, Herrmann W, Kleber ME, et al. Subclinical inflammation, telomere shortening, homocysteine, vitamin B6, and mortality: the Ludwigshafen risk and cardiovascular health study. *Eur J Nutr*. 2020;59(4):1399-1411.
72. Sande JS, Ulvik A, Midttun O, et al. Vitamin B-6 status correlates with disease activity in rheumatoid arthritis patients during treatment with TNFalpha inhibitors. *J Nutr*. 2019;149(5):770-775.
73. Rabbani E, Golgiri F, Janani L, et al. Randomized study of the effects of zinc, vitamin a, and magnesium Co-supplementation on thyroid function, oxidative stress, and hs-CRP in patients with hypothyroidism. *Biol Trace Elem Res*. 2021;199(11):4074-4083.
74. Asbaghi O, Sadeghian M, Nazarian B, et al. The effect of vitamin E supplementation on selected inflammatory biomarkers in adults: a systematic review and meta-analysis of randomized clinical trials. *Sci Rep*. 2020;10(1):17234.
75. Sohouli MH, Farahmand F, Alimadadi H, et al. Vitamin D therapy in pediatric patients with inflammatory bowel disease: a systematic review and meta-analysis. *World J Pediatr*. 2023;19(1):48-57.
76. Guo X, Liu C, Huang Y. Efficacy and safety of vitamin D adjuvant therapy for ulcerative colitis: a meta-analysis. *Comput Math Methods Med*. 2022;2022:6836942.
77. Gwenzi T, Zhu A, Schrotz-King P, Schottker B, Hoffmeister M, Brenner H. Effects of vitamin D supplementation on inflammatory response in patients with cancer and precancerous lesions: systematic review and meta-analysis of randomized trials. *Clin Nutr*. 2023;42(7):1142-1150.
78. Asbaghi O, Sadeghian M, Mozaffari-Khosravi H, et al. The effect of vitamin d-calcium co-supplementation on inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Cytokine*. 2020;129:155050.
79. Pita-Rodriguez GM, Chavez-Chong C, Lambert-Lamazares B, et al. Influence of inflammation on assessing iron-deficiency anemia in Cuban preschool children. *MEDICC Rev*. 2021;23(3–4):37-45.
80. de Dios O, Navarro P, Ortega-Senovilla H, et al. Plasma retinol levels and high-sensitivity C-reactive protein in prepubertal children. *Nutrients*. 2018;10(9):1257.
81. Chimhashu T, Verhoef H, Symington EA, et al. Comparison of test performance of two commonly used multiplex assays to measure micronutrient and inflammatory markers in serum: results

from a survey among pregnant women in South Africa. *Br J Nutr*. 2023;1-22:1-8.
82. Wang H, Zhang R, Shen J, et al. Circulating level of blood iron and copper associated with inflammation and disease activity of rheumatoid arthritis. *Biol Trace Elem Res*. 2023;201(1):90-97.
83. Williams AM, Ladva CN, Leon JS, et al. Changes in micronutrient and inflammation serum biomarker concentrations after a norovirus human challenge. *Am J Clin Nutr*. 2019;110(6):1456-1464.
84. Finamore A, Roselli M, Merendino N, Nobili F, Vignolini F, Mengheri E. Zinc deficiency suppresses the development of oral tolerance in rats. *J Nutr*. 2003;133(1):191-198.
85. Carman JA, Hayes CE. Abnormal regulation of IFN-gamma secretion in vitamin a deficiency. *J Immunol*. 1991;147(4):1247-1252.
86. Cantorna MT, Nashold FE, Hayes CE. Vitamin A deficiency results in a priming environment conducive for Th1 cell development. *Eur J Immunol*. 1995;25(6):1673-1679.
87. World Health Organization, ed. *Vitamin and Mineral Requirements in Human Nutrition*. 2nd ed. World Health Organization; 2005.
88. Louw JA, Werbeck A, Louw ME, Kotze TJ, Cooper R, Labadarios D. Blood vitamin concentrations during the acute-phase response. *Crit Care Med*. 1992;20(7):934-941.
89. Feingold KR, Grunfeld C. Effect of inflammation on HDL structure and function. *Curr Opin Lipidol*. 2016;27(5):521-530.
Excellent review on HDL and inflammation.
90. Khovidhunkit W, Kim MS, Memon RA, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res*. 2004;45(7):1169-1196.
Seminal review detailing the role of lipids in the acute phase response.
91. Erlinger TP, Miller ER 3rd, Charleston J, Appel LJ. Inflammation modifies the effects of a reduced-fat low-cholesterol diet on lipids: results from the DASH-sodium trial. *Circulation*. 2003;108(2):150-154.
92. Collier B, Dossett LA, May AK, Diaz JJ. Glucose control and the inflammatory response. *Nutr Clin Pract*. 2008;23(1):3-15.
93. Zenewicz LA. Oxygen levels and immunological studies. *Front Immunol*. 2017;8:324.
94. Corcoran SE, O'Neill LA. HIF1alpha and metabolic reprogramming in inflammation. *J Clin Invest*. 2016;126(10):3699-3707.
95. Martins G, Franca A, Viola P, et al. Intake of ultra-processed foods is associated with inflammatory markers in Brazilian adolescents. *Public Health Nutr*. 2022;25(3):591-599.
96. Silva Dos Santos F, Costa Mintem G, de Oliveira IO, et al. Consumption of ultra-processed foods and interleukin-6 in two cohorts from high- and middle-income countries. *Br J Nutr*. 2022;1-11. doi:10.1017/S0007114522000551. Online ahead of print.
97. Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. *Clin Exp Allergy*. 2015;45(1):177-183.
98. Yoo HC, Yu YC, Sung Y, Han JM. Glutamine reliance in cell metabolism. *Exp Mol Med*. 2020;52(9):1496-1516.
99. Rodriguez-Coira J, Villasenor A, Izquierdo E, et al. The importance of metabolism for immune homeostasis in allergic diseases. *Front Immunol*. 2021;12:692004.
100. Freemerman AJ, Johnson AR, Sacks GN, et al. Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype. *J Biol Chem*. 2014;289(11):7884-7896.
101. Covarrubias AJ, Aksoylar HI, Yu J, et al. Akt-mTORC1 signaling regulates Acly to integrate metabolic input to control of macrophage activation. *Elife*. 2016;5:e11612.
102. van den Bossche J, O'Neill LA, Menon D. Macrophage immunometabolism: where are we (going)? *Trends Immunol*. 2017;38(6):395-406.
103. Tan Z, Xie N, Cui H, et al. Pyruvate dehydrogenase kinase 1 participates in macrophage polarization via regulating glucose metabolism. *J Immunol*. 2015;194(12):6082-6089.
104. Huang SC, Smith AM, Everts B, et al. Metabolic reprogramming mediated by the mTORC2-IRF4 signaling Axis is essential for macrophage alternative activation. *Immunity*. 2016;45(4):817-830.
105. Vats D, Mukundan L, Odegaard JI, et al. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. *Cell Metab*. 2006;4(1):13-24.
106. Kumari R, Jat P. Mechanisms of cellular senescence: cell cycle arrest and senescence associated secretory phenotype. *Front Cell Dev Biol*. 2021;9:645593.
107. Frasca D, Diaz A, Romero M, Garcia D, Blomberg BB. B cell immunosenescence. *Annu Rev Cell Dev Biol*. 2020;36:551-574.
108. Zhou X, Zhu X, Zeng H. Fatty acid metabolism in adaptive immunity. *FEBS J*. 2023;290(3):584-599.
109. Kouidhi S, Elgaaied AB, Chouaib S. Impact of metabolism on T-cell differentiation and function and cross talk with tumor microenvironment. *Front Immunol*. 2017;8:270.
110. de Rosa V, Galgani M, Porcellini A, et al. Glycolysis controls the induction of human regulatory T cells by modulating the expression of FOXP3 exon 2 splicing variants. *Nat Immunol*. 2015;16(11):1174-1184.
111. Chang WK, Yang KD, Shaio MF. Effect of glutamine on Th1 and Th2 cytokine responses of human peripheral blood mononuclear cells. *Clin Immunol*. 1999;93(3):294-301.
112. Caris AV, Lira FS, de Mello MT, Oyama LM, dos Santos RV. Carbohydrate and glutamine supplementation modulates the Th1/Th2 balance after exercise performed at a simulated altitude of 4500 m. *Nutrition*. 2014;30(11–12):1331-1336.
Beautiful mechanistic study conducted in humans assessing the impact of hypoxia, carbohydrate and glutamine on glucose and inflammation markers.
113. Herb M, Schramm M. Functions of ROS in macrophages and antimicrobial immunity. *Antioxidants (Basel)*. 2021;10(2):313.
114. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. *Antioxid Redox Signal*. 2014;20(7):1126-1167.
115. Frein D, Schildknecht S, Bachschmid M, Ullrich V. Redox regulation: a new challenge for pharmacology. *Biochem Pharmacol*. 2005;70(6):811-823.
116. Brune B, Dehne N, Grossmann N, et al. Redox control of inflammation in macrophages. *Antioxid Redox Signal*. 2013;19(6):595-637.
117. Ben Anes A, Ben Nasr H, Fetoui H, et al. Alteration in systemic markers of oxidative and antioxidative status in Tunisian patients with asthma: relationships with clinical severity and airflow limitation. *J Asthma*. 2016;53(3):227-237.
118. Samsamikor M, Daryani NE, Asl PR, Hekmatdoost A. Resveratrol supplementation and oxidative/anti-oxidative status in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. *Arch Med Res*. 2016;47(4):304-309.
119. Canestrari F, Buoncristiani U, Galli F, et al. Redox state, antioxidative activity and lipid peroxidation in erythrocytes and plasma of chronic ambulatory peritoneal dialysis patients. *Clin Chim Acta*. 1995;234(1–2):127-136.
120. Ristow M, Zarse K, Oberbach A, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci U S A*. 2009;106(21):8665-8670.
121. Garcia-Larsen V, Del Giacco SR, Moreira A, et al. Asthma and dietary intake: an overview of systematic reviews. *Allergy*. 2016;71(4):433-442.
122. Yanez JA, Wang SW, Knemeyer IW, Wirth MA, Alton KB. Intestinal lymphatic transport for drug delivery. *Adv Drug Deliv Rev*. 2011;63(10–11):923-942.
123. Kim KW, Song JH. Emerging roles of lymphatic vasculature in immunity. *Immune Netw*. 2017;17(1):68-76.

124. Null M, Arbor TC, Agarwal M. *Anatomy, Lymphatic System*. StatPearls; 2023.
125. Santambrogio L. The lymphatic fluid. *Int Rev Cell Mol Biol*. 2018;337:111-133.
126. Crosby WH. Mucosal block. An evaluation of concepts relating to control of iron absorption. *Semin Hematol*. 1966;3(4):299-313.
127. Hahn PF, Bale WF, Ross JF, Balfour WM, Whipple GH. Radioactive iron absorption by gastro-intestinal tract: influence of anemia, anoxia, and antecedent feeding distribution in growing dogs. *J Exp Med*. 1943;78(3):169-188.
First description of the mucosal block decreasing the bioavailability of iron at the enterocyte-level.
128. Nicolas G, Bennoun M, Devaux I, et al. Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. *Proc Natl Acad Sci USA*. 2001;98(15):8780-8785.
129. Rubin LP, Ross AC, Stephensen CB, Bohn T, Tanumihardjo SA. Metabolic effects of inflammation on vitamin a and carotenoids in humans and animal models. *Adv Nutr*. 2017;8(2):197-212.
130. Peroni DG, Trambusti I, Di Cicco ME, Nuzzi G. Vitamin D in pediatric health and disease. *Pediatr Allergy Immunol*. 2020;31(Suppl 24):54-57.
131. Halsted CH, Reisenauer AM, Shane B, Tamura T. Availability of monoglutamyl and polyglutamyl folates in normal subjects and in patients with coeliac sprue. *Gut*. 1978;19(10):886-891.
132. Symonds EL, O'Mahony C, Lapthorne S, et al. Bifidobacterium infantis 35624 protects against salmonella-induced reductions in digestive enzyme activity in mice by attenuation of the host inflammatory response. *Clin Transl Gastroenterol*. 2012;3(5):e15.
Important study emphasizing the decreased bioavailability of nutrients in obese subjects despite similar intake.
133. Aeberli I, Hurrell RF, Zimmermann MB. Overweight children have higher circulating hepcidin concentrations and lower iron status but have dietary iron intakes and bioavailability comparable with normal weight children. *Int J Obes (Lond)*. 2009;33(10):1111-1117.
134. Hurrell RF. Influence of inflammatory disorders and infection on iron absorption and efficacy of iron-fortified foods. *Nestle Nutr Inst Workshop Ser*. 2012;70:107-116.
135. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. *JAMA*. 2017;317(19):1958-1966.
136. Ambrosy AP, Lewis GD, Malhotra R, et al. Identifying responders to oral iron supplementation in heart failure with a reduced ejection fraction: a post-hoc analysis of the IRONOUT-HF trial. *J Cardiovasc Med (Hagerstown)*. 2019;20(4):223-225.
137. Russo G, Guardabasso V, Romano F, et al. Monitoring oral iron therapy in children with iron deficiency anemia: an observational, prospective, multicenter study of AIEOP patients (Associazione Italiana Emato-Oncologia Pediatrica). *Ann Hematol*. 2020;99(3):413-420.
138. Gomez-Ramirez S, Brilli E, Tarantino G, Munoz M. Sucrosomial® Iron: a new generation iron for improving Oral supplementation. *Pharmaceuticals (Basel)*. 2018;11(4):97.
139. Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron deficiency in chronic kidney disease: updates on pathophysiology, diagnosis, and treatment. *J Am Soc Nephrol*. 2020;31(3):456-468.
140. Giliberti A, Curcio A, Marchitto N, et al. Comparison of ferric sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate, and Selenomethionine as therapeutic option for chronic kidney disease patients with improvement in inflammatory status. *Nutrients*. 2022;14(10):2116.
141. Jain A. Seed storage protein, functional diversity and association with allergy. *Allergies*. 2023;3(1):25-38.
142. Rybicka I. The handbook of minerals on a gluten-free diet. *Nutrients*. 2018;10(11):1683.
143. Li Z, Xiao Z, Jiang M, Zhang Y. A comparison on the binding mechanisms of zein and gliadin with curcumin to guide the self-assembly of nanoparticles for delivery purpose. *J Agric Food Res*. 2023;13:100660.
144. Shewry P. What is gluten-why is it special? *Front Nutr*. 2019;6:101.
145. Natalia Carolina Moraes E-B, Cileide Maria Medeiros C, Clovis AS. Storage protein composition during germination and its association with physiological seed quality in common bean. *Acta Sci Agron*. 2021;44(1):e53434.
146. Regner A, Szepannek N, Wiederstein M, et al. Binding to iron quercetin complexes increases the antioxidant capacity of the major birch pollen allergen bet v 1 and reduces its allergenicity. *Antioxidants (Basel)*. 2022;12(1):42.
Mechanistic study giving evidence that pathogenesis-related protein Bet v 1 acts immunoregulatory while providing nutrients (iron complexes) to human immune cells.
147. Afify SM, Pali-Scholl I, Hufnagl K, et al. Bovine Holo-Beta-Lactoglobulin cross-protects against pollen allergies in an innate manner in BALB/c mice: potential model for the farm effect. *Front Immunol*. 2021;12:176.
148. Afify SM, Regner A, Pacios LF, et al. Micronutritional supplementation with a holoBLG-based FSMP (food for special medical purposes)-lozenge alleviates allergic symptoms in BALB/c mice: imitating the protective farm effect. *Clin Exp Allergy*. 2021;52:426-441.
149. Hufnagl K, Afify SM, Braun N, et al. Retinoic acid-loading of the major birch pollen allergen bet v 1 may improve specific allergen immunotherapy: in silico, in vitro and in vivo data in BALB/c mice. *Allergy*. 2020;75(8):2073-2077.
150. Hufnagl K, Ghosh D, Wagner S, et al. Retinoic acid prevents immunogenicity of milk lipocalin Bos d 5 through binding to its immunodominant T-cell epitope. *Sci Rep*. 2018;8(1):1598.
151. Hufnagl K, Jensen-Jarolim E. Vitamin A and D in allergy: from experimental animal models and cellular studies to human disease. *Allergo J Int*. 2018;27(3):72-78.
152. Hufnagl K, Jensen-Jarolim E. Does a carrot a day keep the allergy away? *Immunol Lett*. 2019;206:54-58.
153. Hufnagl K, Kromp L, Bianchini R, et al. Bet v 1 from birch pollen is a hypoallergen with vitamin D3 in the pocket. *Allergy*. 2021;76(12):3801-3804.
154. Roth-Walter F, Afify SM, Pacios LF, et al. Cow's milk protein beta-lactoglobulin confers resilience against allergy by targeting complexed iron into immune cells. *J Allergy Clin Immunol*. 2021;147(1):321.e4-334.e4.
155. Roth-Walter F, Gomez-Casado C, Pacios LF, et al. Bet v 1 from birch pollen is a Lipocalin-like protein acting as allergen only when devoid of iron by promoting Th2 lymphocytes. *J Biol Chem*. 2014;289:23329.
156. Roth-Walter F, Pacios LF, Gomez-Casado C, et al. The major cow milk allergen Bos d 5 manipulates T-helper cells depending on its load with siderophore-bound iron. *PloS One*. 2014;9(8):e104803.
157. Ghatak SK, Majumdar D, Singha A, et al. Peanut protein sensitivity towards trace iron: a novel mode to ebb allergic response. *Food Chem*. 2015;176:308-313.
158. Chruszcz M, Chew FT, Hoffmann-Sommergruber K, et al. Allergens and their associated small molecule ligands-their dual role in sensitization. *Allergy*. 2021;76(8):2367-2382.
159. Pali-Scholl I, Bianchini R, Afify SM, et al. Secretory protein beta-lactoglobulin in cattle stable dust may contribute to the allergy-protective farm effect. *Clin Transl Allergy*. 2022;12(2):e12125.
160. Missaoui K, Gonzalez-Klein Z, Pazos-Castro D, et al. Plant non-specific lipid transfer proteins: an overview. *Plant Physiol Biochem*. 2022;171:115-127.
161. Shewry PR, Beaudoin F, Jenkins J, Griffiths-Jones S, Mills EN. Plant protein families and their relationships to food allergy. *Biochem Soc Trans*. 2002;30(Pt 6):906-910.

162. Radauer C, Breiteneder H. Evolutionary biology of plant food allergens. *J Allergy Clin Immunol*. 2007;120(3):518-525.
163. Wei X, Kim W-S, Song B, Oehrle NW, Liu S, Krishnan HB. Soybean mutants lacking abundant seed storage proteins are impaired in mobilization of storage reserves and germination. *ACS Omega*. 2020;5(14):8065-8075.
164. Lehmann K, Schweimer K, Reese G, et al. Structure and stability of 2S albumin-type peanut allergens: implications for the severity of peanut allergic reactions. *Biochem J*. 2006;395(3):463-472.
165. Li T, Han K, Feng G, et al. Bile acid profile influences digestion resistance and antigenicity of soybean 7S protein. *J Agric Food Chem*. 2023;71(6):2999-3009.
166. Martos G, Contreras P, Molina E, Lopez-Fandino R. Egg white ovalbumin digestion mimicking physiological conditions. *J Agric Food Chem*. 2010;58(9):5640-5648.
167. Halabi A, Croguennec T, Bouhallab S, Dupont D, Deglaire A. Modification of protein structures by altering the whey protein profile and heat treatment affects in vitro static digestion of model infant milk formulas. *Food Funct*. 2020;11(8):6933-6945.
168. Lönnerdal B, Iyer S. Lactoferrin: molecular structure and biological function. *Annu Rev Nutr*. 1995;15(1):93-110.
169. Zhang P, Iqbal S, Deng R, et al. Impact of elderly gastrointestinal alterations on gastric emptying and enzymatic hydrolysis of skim milk: an in vitro study using a dynamic stomach system. *Food Chem*. 2023;402:134365.
170. Vissers YM, Blanc F, Skov PS, et al. Effect of heating and glycation on the allergenicity of 2S albumins (Ara h 2/6) from peanut. *PloS One*. 2011;6(8):e23998.
171. Roth-Walter F, Berin MC, Arnaboldi P, et al. Pasteurization of milk proteins promotes allergic sensitization by enhancing uptake through Peyer's patches. *Allergy*. 2008;63(7):882-890.
172. Liu HC, Chen WL, Mao SJ. Antioxidant nature of bovine milk beta-lactoglobulin. *J Dairy Sci*. 2007;90(2):547-555.
173. Chambers SJ, Wickham MSJ, Regoli M, Bertelli E, Gunning PA, Nicoletti C. Rapid in vivo transport of proteins from digested allergen across pre-sensitized gut. *Biochem Biophys Res Commun*. 2004;325(4):1258-1263.
174. Li J, Wang Y, Tang L, et al. Dietary medium-chain triglycerides promote oral allergic sensitization and orally induced anaphylaxis to peanut protein in mice. *J Allergy Clin Immunol*. 2013;131(2):442-450.
175. Cohn JS, Kamili A, Wat E, Chung RW, Tandy S. Reduction in intestinal cholesterol absorption by various food components: mechanisms and implications. *Atheroscler Suppl*. 2010;11(1):45-48.
176. Wang Y, Ghoshal S, Ward M, de Villiers W, Woodward J, Eckhardt E. Chylomicrons promote intestinal absorption and systemic dissemination of dietary antigen (ovalbumin) in mice. *PloS One*. 2009;4(12):e8442.
Beautiful mechanistic study showing ovalbumin uptake occurs via the lymph and is facilated by fat molecules.
177. Kilshaw PJ, Cant AJ. The passage of maternal dietary proteins into human breast milk. *Int Arch Allergy Appl Immunol*. 1984;75(1):8-15.
178. Dzieciatkowska M, D'Alessandro A, Moore EE, et al. Lymph is not a plasma ultrafiltrate: a proteomic analysis of injured patients. *Shock*. 2014;42(6):485-498.
Important study describing the lymph proteom of human trauma patients.
179. Li X, Wei L, Jia L, et al. Identification and characterization of cow's milk proteins from the rat intestinal lymph using a proteomic strategy. *Proteomics*. 2013;13(17):2649-2656.
180. Fukushima Y, Kawata Y, Onda T, Kitagawa M. Long-term consumption of whey hydrolysate formula by lactating women reduces the transfer of beta-lactoglobulin into human milk. *J Nutr Sci Vitaminol (Tokyo)*. 1997;43(6):673-678.
181. Mansouri A, Gueant JL, Capiaumont J, Pelosi P, Nabet P, Haertle T. Plasma membrane receptor for beta-lactoglobulin and retinol-binding protein in murine hybridomas. *Biofactors*. 1998;7(4):287-298.
182. Li JY, Paragas N, Ned RM, et al. Scara5 is a ferritin receptor mediating non-transferrin iron delivery. *Dev Cell*. 2009;16(1):35-46.
183. Sohrabi SM, Niazi A, Chahardoli M, Hortamani A, Setoodeh P. In silico investigation of lactoferrin protein characterizations for the prediction of anti-microbial properties. *Mol Biol Res Commun*. 2014;3(2):85-100.
184. Bryniarski MA, Yee BM, Chaves LD, Stahura CM, Yacoub R, Morris ME. Megalin-mediated albumin endocytosis in cultured murine mesangial cells. *Biochem Biophys Res Commun*. 2020;529(3):740-746.
185. Moreno FJ, Rubio LA, Olano A, Clemente A. Uptake of 2S albumin allergens, Ber e 1 and Ses i 1, across human intestinal epithelial Caco-2 cell monolayers. *J Agric Food Chem*. 2006;54(22):8631-8639.
186. Mika M, Wikiera A, Antonczyk A, Grabacka M. Food stabilizing antioxidants increase nutrient bioavailability in the in vitro model. *J Am Coll Nutr*. 2017;36(7):579-585.
187. White WS, Zhou Y, Crane A, Dixon P, Quadt F, Flendrig LM. Modeling the dose effects of soybean oil in salad dressing on carotenoid and fat-soluble vitamin bioavailability in salad vegetables. *Am J Clin Nutr*. 2017;106(4):1041-1051.
188. Guillen B, Atherton NS. Short bowel syndrome. In: *StatPearls*. Stat Pearls Publishing LLC; 2023. Copyright 2023.
189. Nohesara S, Abdolmaleky HM, Thiagalingam S. Epigenetic aberrations in major psychiatric diseases related to diet and gut microbiome alterations. *Genes (Basel)*. 2023;14(7):1506.
190. Temba GS, Vadaq N, Kullaya V, et al. Differences in the inflammatory proteome of east African and Western European adults and associations with environmental and dietary factors. *Elife*. 2023;12:e82297.
191. Kang H. Regulation of acetylation states by nutrients in the inhibition of vascular inflammation and atherosclerosis. *Int J Mol Sci*. 2023;24(11):9338.
192. Lewinsky RH, Jensen TG, Moller J, Stensballe A, Olsen J, Troelsen JT. T-13910 DNA variant associated with lactase persistence interacts with Oct-1 and stimulates lactase promoter activity in vitro. *Hum Mol Genet*. 2005;14(24):3945-3953.
193. Lunjani N, Ahearn-Ford S, Dube FS, Hlela C, O'Mahony L. Mechanisms of microbe-immune system dialogue within the skin. *Genes Immun*. 2021;22(5–6):276-288.
194. Lunjani N, Walsh LJ, Venter C, et al. Environmental influences on childhood asthma-the effect of diet and microbiome on asthma. *Pediatr Allergy Immunol*. 2022;33(12):e13892.
195. Hosseinkhani F, Heinken A, Thiele I, Lindenburg PW, Harms AC, Hankemeier T. The contribution of gut bacterial metabolites in the human immune signaling pathway of non-communicable diseases. *Gut Microbes*. 2021;13(1):1-22.
196. Barcik W, Wawrzyniak M, Akdis CA, O'Mahony L. Immune regulation by histamine and histamine-secreting bacteria. *Curr Opin Immunol*. 2017;48:108-113.
197. Forde B, Yao L, Shaha R, Murphy S, Lunjani N, O'Mahony L. Immunomodulation by foods and microbes: unravelling the molecular tango. *Allergy*. 2022;77(12):3513-3526.
198. Gagliardi A, Totino V, Cacciotti F, et al. Rebuilding the gut microbiota ecosystem. *Int J Environ Res Public Health*. 2018;15(8):1679.
199. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*. 2009;9(5):313-323.
200. Cosovanu C, Resch P, Jordan S, et al. Intestinal epithelial c-Maf expression determines enterocyte differentiation and nutrient uptake in mice. *J Exp Med*. 2022;219(12):e20220233.
201. De Vadder F, Grasset E, Manneras Holm L, et al. Gut microbiota regulates maturation of the adult enteric nervous

system via enteric serotonin networks. *Proc Natl Acad Sci U S A*. 2018;115(25):6458-6463.
202. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. 2014;6(263):263ra158.
203. Precup G, Vodnar D-C. Gut Prevotella as a possible biomarker of diet and its eubiotic versus dysbiotic roles: a comprehensive literature review. *Br J Nutr*. 2019;122(2):131-140.
204. Culp EJ, Goodman AL. Cross-feeding in the gut microbiome: ecology and mechanisms. *Cell Host Microbe*. 2023;31(4):485-499.
205. Roduit C, Frei R, Ferstl R, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy*. 2019;74(4):799-809.
206. Venter C, Palumbo MP, Glueck DH, et al. The maternal diet index in pregnancy is associated with offspring allergic diseases: the healthy start study. *Allergy*. 2022;77(1):162-172.
207. Kim H, Rebholz CM, Hegde S, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. *BMJ Nutr Prev Health*. 2021;4(1):257-266.
208. Li J, Ghosh TS, McCann R, et al. Robust cross-cohort gut microbiome associations with COVID-19 severity. *Gut Microbes*. 2023;15(1):2242615.
209. Albrich WC, Ghosh TS, Ahearn-Ford S, et al. A high-risk gut microbiota configuration associates with fatal hyperinflammatory immune and metabolic responses to SARS-CoV-2. *Gut Microbes*. 2022;14(1):2073131.
210. Parmanand BA, Kellingray L, Le Gall G, Basit AW, Fairweather-Tait S, Narbad A. A decrease in iron availability to human gut microbiome reduces the growth of potentially pathogenic gut bacteria; an in vitro colonic fermentation study. *J Nutr Biochem*. 2019;67:20-27.
211. Muleviciene A, D'Amico F, Turroni S, Candela M, Jankauskiene A. Iron deficiency anemia-related gut microbiota dysbiosis in infants and young children: a pilot study. *Acta Microbiol Immunol Hung*. 2018;65(4):551-564.
212. Zakrzewski M, Wilkins SJ, Helman SL, et al. Supplementation with Sucrosomial(R) iron leads to favourable changes in the intestinal microbiome when compared to ferrous sulfate in mice. *Biometals*. 2022;35(1):27-38.
213. Chen H, Wu W, Tang S, et al. Altered fecal microbial and metabolic profile reveals potential mechanisms underlying iron deficiency anemia in pregnant women in China. *Bosn J Basic Med Sci*. 2022;22(6):923-933.
214. Seo H, Yoon SY, Ul-Haq A, et al. The effects of iron deficiency on the gut microbiota in women of childbearing age. *Nutrients*. 2023;15(3):691.
215. Soriano-Lerma A, Garcia-Burgos M, Alferez MJM, et al. Gut microbiome-short-chain fatty acids interplay in the context of iron deficiency anaemia. *Eur J Nutr*. 2022;61(1):399-412.
216. Wu Y, Wan J, Choe U, et al. Interactions between food and gut microbiota: impact on human health. *Annu Rev Food Sci Technol*. 2019;10(1):389-408.
217. Diaz-Rodriguez K, Pacheco-Aranibar J, Manrique-Sam C, et al. Intestinal microbiota in children with anemia in southern Peru through next-generation sequencing technology. *Children (Basel)*. 2022;9(11):1615.
218. Delgadinho M, Ginete C, Santos B, et al. Microbial gut evaluation in an angolan paediatric population with sickle cell disease. *J Cell Mol Med*. 2022;26(21):5360-5368.
219. Lv Z, Wang Y, Yang T, et al. Vitamin a deficiency impacts the structural segregation of gut microbiota in children with persistent diarrhea. *J Clin Biochem Nutr*. 2016;59(2):113-121.
220. Feng D, Chen B, Zeng B, et al. Fecal microbiota from children with vitamin a deficiency impair colonic barrier function in germ-free mice: the possible role of alterative bile acid metabolites. *Nutrition*. 2021;90:111274.
221. Michalovich D, Rodriguez-Perez N, Smolinska S, et al. Obesity and disease severity magnify disturbed microbiome-immune interactions in asthma patients. *Nat Commun*. 2019;10(1):5711.
222. Walter J, O'Mahony L. The importance of social networks-an ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma. *Allergy*. 2019;74(11):2248-2251.
223. Venter C, Meyer RW, Greenhawt M, et al. Role of dietary fiber in promoting immune health-an EAACI position paper. *Allergy*. 2022;77(11):3185-3198.
224. Barcik W, Boutin RCT, Sokolowska M, Finlay BB. The role of lung and gut microbiota in the pathology of asthma. *Immunity*. 2020;52(2):241-255.
225. Losol P, Sokolowska M, Chang YS. Interactions between microbiome and underlying mechanisms in asthma. *Respir Med*. 2023;208:107118.
226. WHO, Allen L, de Benoist B, Dary O, Hurrell R. *Guidelines on food fortification with micronutrients*. In: Organization WH, Nations FaAOotU, eds. WHO; 2006:341.
227. Mousa TY, Mousa OY. Nicotinic acid deficiency. In: *StatPearls*. StatPearls Publishing. Copyright 2023.
228. Nino-Narvion J, Rojo-Lopez MI, Martinez-Santos P, et al. NAD+ precursors and intestinal inflammation: therapeutic insights involving gut microbiota. *Nutrients*. 2023;15(13):2992.
229. Zhong W, Li Q, Zhang W, Sun Q, Sun X, Zhou Z. Modulation of intestinal barrier and bacterial endotoxin production contributes to the beneficial effect of nicotinic acid on alcohol-induced Endotoxemia and hepatic inflammation in rats. *Biomolecules*. 2015;5(4):2643-2658.
230. Cichocki F, Zhang B, Wu CY, et al. Nicotinamide enhances natural killer cell function and yields remissions in patients with non-Hodgkin lymphoma. *Sci Transl Med*. 2023;15(705):eade3341.
231. Kang H, Park YK, Lee JY. Nicotinamide riboside, an NAD(+) precursor, attenuates inflammation and oxidative stress by activating sirtuin 1 in alcohol-stimulated macrophages. *Lab Invest*. 2021;101(9):1225-1237.
232. Sidor K, Jeznach A, Hoser G, Skirecki T. 1-Methylnicotinamide (1-MNA) inhibits the activation of the NLRP3 inflammasome in human macrophages. *Int Immunopharmacol*. 2023;121:110445.
233. Ullegaddi R, Powers HJ, Gariballa SE. B-group vitamin supplementation mitigates oxidative damage after acute ischaemic stroke. *Clin Sci (Lond)*. 2004;107(5):477-484.
234. Ulvik A, Midttun O, Pedersen ER, Nygard O, Ueland PM. Association of plasma B-6 vitamers with systemic markers of inflammation before and after pyridoxine treatment in patients with stable angina pectoris. *Am J Clin Nutr*. 2012;95(5):1072-1078.
235. Kiblawi R, Holowatyj AN, Gigic B, et al. One-carbon metabolites, B vitamins and associations with systemic inflammation and angiogenesis biomarkers among colorectal cancer patients: results from the ColoCare study. *Br J Nutr*. 2020;123(10):1187-1200.
236. Kelly PJ, Kistler JP, Shih VE, et al. Inflammation, homocysteine, and vitamin B6 status after ischemic stroke. *Stroke*. 2004;35(1):12-15.
237. Ullegaddi R, Powers HJ, Gariballa SE. Antioxidant supplementation with or without B-group vitamins after acute ischemic stroke: a randomized controlled trial. *JPEN J Parenter Enteral Nutr*. 2006;30(2):108-114.
238. Tabassi Z, Bagheri S, Samimi M, et al. Clinical and metabolic response to vitamin D supplementation in endometrial hyperplasia: a randomized, double-blind, placebo-controlled trial. *Horm Cancer*. 2017;8(3):185-195.
239. Foroozanfard F, Jamilian M, Bahmani F, et al. Calcium plus vitamin D supplementation influences biomarkers of inflammation and oxidative stress in overweight and vitamin D-deficient women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. *Clin Endocrinol (Oxf)*. 2015;83(6):888-894.

240. Jamilian M, Amirani E, Asemi Z. The effects of vitamin D and probiotic co-supplementation on glucose homeostasis, inflammation, oxidative stress and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 2019;38(5):2098-2105.
241. Talari HR, Zakizade M, Soleimani A, et al. Effects of magnesium supplementation on carotid intima-media thickness and metabolic profiles in diabetic haemodialysis patients: a randomised, double-blind, placebo-controlled trial. *Br J Nutr*. 2019;121(7):809-817.
Nice conducted randomized trial highlighting the remarkable impact of magnesium in reducing inflammation and improving the health outcome in diabetic haemodialysis patients.
242. Razzaghi R, Pidar F, Momen-Heravi M, Bahmani F, Akbari H, Asemi Z. Magnesium supplementation and the effects on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *Biol Trace Elem Res*. 2018;181(2):207-215.
243. Hennigar SR, McClung JP. Hepcidin attenuates zinc efflux in Caco-2 cells. *J Nutr*. 2016;146(11):2167-2173.
244. Moser PB, Borel J, Majerus T, Anderson RA. Serum zinc and urinary zinc excretion of trauma patients. *Nutr Res*. 1985;5(3):253-261.
245. Uddin MG, Hossain MS, Rahman MA, Uddin A, Bhuiyan MS. Elemental zinc is inversely associated with C-reactive protein and oxidative stress in chronic liver disease. *Biol Trace Elem Res*. 2017;178(2):189-193.
246. Imdad A, Rogner J, Sherwani RN, et al. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years. *Cochrane Database Syst Rev*. 2023;3(3):CD009384.
247. Freiberg MS, Cheng DM, Gnatienko N, et al. Effect of zinc supplementation vs placebo on mortality risk and HIV disease progression among HIV-positive adults with heavy alcohol use: a randomized clinical trial. *JAMA Netw Open*. 2020;3(5):e204330.
248. Banupriya N, Vishnu Bhat B, Benet BD, Sridhar MG, Parija SC. Efficacy of zinc supplementation on serum calprotectin, inflammatory cytokines and outcome in neonatal sepsis - a randomized controlled trial. *J Matern Fetal Neonatal Med*. 2017;30(13):1627-1631.
249. Elfarargy MS, Al-Ashmawy G, Abu-Risha S, Khattab H. Zinc supplementation in preterm neonates with late-onset sepsis: is it beneficial? *Am J Perinatol*. 2022;39(10):1097-1103.
250. Terrin G, Berni Canani R, Passariello A, et al. Zinc supplementation reduces morbidity and mortality in very-low-birth-weight preterm neonates: a hospital-based randomized, placebo-controlled trial in an industrialized country. *Am J Clin Nutr*. 2013;98(6):1468-1474.
251. Jamilian M, Mirhosseini N, Eslahi M, et al. The effects of magnesium-zinc-calcium-vitamin D co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in gestational diabetes. *BMC Pregnancy Childbirth*. 2019;19(1):107.
252. Kim HN, Kim SH, Eun YM, Song SW. Effects of zinc, magnesium, and chromium supplementation on cardiometabolic risk in adults with metabolic syndrome: a double-blind, placebo-controlled randomised trial. *J Trace Elem Med Biol*. 2018;48:166-171.
253. Kim J, Ahn J. Effect of zinc supplementation on inflammatory markers and adipokines in young obese women. *Biol Trace Elem Res*. 2014;157(2):101-106.
254. Bao B, Prasad AS, Beck FW, et al. Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent. *Am J Clin Nutr*. 2010;91(6):1634-1641.
255. Mesdaghinia E, Naderi F, Bahmani F, Chamani M, Ghaderi A, Asemi Z. The effects of zinc supplementation on clinical response and metabolic profiles in pregnant women at risk for intrauterine growth restriction: a randomized, double-blind, placebo-controlled trial. *J Matern Fetal Neonatal Med*. 2021;34(9):1382-1388.
256. Afshar Ebrahimi F, Foroozanfard F, Aghadavod E, Bahmani F, Asemi Z. The effects of magnesium and zinc Co-supplementation on biomarkers of inflammation and oxidative stress, and gene expression related to inflammation in polycystic ovary syndrome: a randomized controlled clinical trial. *Biol Trace Elem Res*. 2018;184(2):300-307.
257. Venter C, Meyer RW, Nwaru BI, et al. EAACI position paper: influence of dietary fatty acids on asthma, food allergy, and atopic dermatitis. *Allergy*. 2019;74(8):1429-1444.
258. Radzikowska U, Rinaldi AO, Celebi Sozener Z, et al. The Influence of dietary fatty acids on immune responses. *Nutrients*. 2019;11(12):2990.
259. Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z. Clinical and metabolic response to flaxseed oil omega-3 fatty acids supplementation in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *J Diabetes Complications*. 2017;31(9):1394-1400.
260. Camaschella C, Girelli D. The changing landscape of iron deficiency. *Mol Aspects Med*. 2020;75:100861.
261. Gedfie S, Getawa S, Melku M. Prevalence and associated factors of iron deficiency and iron deficiency anemia among Under-5 children: a systematic review and meta-analysis. *Glob Pediatr Health*. 2022;9:2333794X221110860.
262. Cappellini MD, Comin-Colet J, de Francisco A, et al. Iron deficiency across chronic inflammatory conditions: international expert opinion on definition, diagnosis, and management. *Am J Hematol*. 2017;92(10):1068-1078.
263. Papadopoulou C, Reinhold J, Gruner-Hegge N, et al. Prognostic value of three iron deficiency definitions in patients with advanced heart failure. *Eur J Heart Fail*. 2023. doi:10.1002/ejhf.2949. Online ahead of print.
Important study assessing the prognostic values of three iron deficiency definition to assess health outcomes in heart failure patients.
264. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. *Ann N Y Acad Sci*. 2019;1450(1):15-31.
265. World Health Organization. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity*. World Health Organization; 2011.
266. Safiri S, Kolahi A-A, Noori M, et al. Burden of anemia and its underlying causes in 204 countries and territories, 1990–2019: results from the global burden of disease study 2019. *J Hematol Oncol*. 2021;14(1):185.
267. United Nations Children's Fund UNU. *Iron Deficiency Anaemia Assessment, Prevention, and Control. A guide for programme managers*. World Health Organization; 2001.
268. Organization WWH. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011. Vitamin and Mineral Nutrition Information System. Accessed April 19, 2021. http://www.who.int/vmnis/indicators/haemoglobin.pdf
269. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*. 2016;164(3):337-340.
270. Otero GA, Pliego-Rivero FB, Porcayo-Mercado R, Mendieta-Alcantara G. Working memory impairment and recovery in iron deficient children. *Clin Neurophysiol*. 2008;119(8):1739-1746.
271. West KP Jr, Shamim AA, Mehra S, et al. Effect of maternal multiple micronutrient vs iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: the JiVitA-3 randomized trial. *JAMA*. 2014;312(24):2649-2658.
272. Docherty KF, Welsh P, Verma S, et al. Iron deficiency in heart failure and effect of Dapagliflozin: findings from DAPA-HF. *Circulation*. 2022;146(13):980-994.
273. O'Brien ME, Kupka R, Msamanga GI, Saathoff E, Hunter DJ, Fawzi WW. Anemia is an independent predictor of mortality and

immunologic progression of disease among women with HIV in Tanzania. *J Acquir Immune Defic Syndr*. 2005;40(2):219-225.
274. Pries-Heje MM, Hasselbalch RB, Wiingaard C, et al. Severity of anaemia and association with all-cause mortality in patients with medically managed left-sided endocarditis. *Heart*. 2022;108(11):882-888.
275. Dahlquist DT, Stellingwerff T, Dieter BP, McKenzie DC, Koehle MS. Effects of macro- and micronutrients on exercise-induced hepcidin response in highly trained endurance athletes. *Appl Physiol Nutr Metab*. 2017;42(10):1036-1043.
276. Richards T, Miles LF, Clevenger B, et al. The association between iron deficiency and outcomes: a secondary analysis of the intravenous iron therapy to treat iron deficiency anaemia in patients undergoing major abdominal surgery (PREVENTT) trial. *Anaesthesia*. 2023;78(3):320-329.
277. Ntenda PAM, Chirambo AC, Nkoka O, El-Meidany WM, Goupeyou-Youmsi J. Implication of asymptomatic and clinical *Plasmodium falciparum* infections on biomarkers of iron status among school-aged children in Malawi. *Malar J*. 2022;21(1):278.
278. Ikeda-Taniguchi M, Takahashi K, Shishido K, Honda H. Total iron binding capacity is a predictor for muscle loss in maintenance hemodialysis patients. *Clin Exp Nephrol*. 2022;26(6):583-592.
279. Birgegard G, Samuelsson J, Ahlstrand E, et al. Inflammatory functional iron deficiency common in myelofibrosis, contributes to anaemia and impairs quality of life. From the Nordic MPN study group. *Eur J Haematol*. 2019;102(3):235-240.
280. Winn NC, Volk KM, Hasty AH. Regulation of tissue iron homeostasis: the macrophage "ferrostat". *JCI Insight*. 2020;5(2):e132964.
281. Corna G, Campana L, Pignatti E, et al. Polarization dictates iron handling by inflammatory and alternatively activated macrophages. *Haematologica*. 2010;95(11):1814-1822.
282. Nyakeriga AM, Williams TN, Marsh K, et al. Cytokine mRNA expression and iron status in children living in a malaria endemic area. *Scand J Immunol*. 2005;61(4):370-375.
283. Helmby H, Kullberg M, Troye-Blomberg M. Expansion of IL-3-responsive IL-4-producing non-B non-T cells correlates with anemia and IL-3 production in mice infected with blood-stage plasmodium chabaudi malaria. *Eur J Immunol*. 1998;28(8):2559-2570.
284. Jason J, Archibald LK, Nwanyanwu OC, et al. The effects of iron deficiency on lymphocyte cytokine production and activation: preservation of hepatic iron but not at all cost. *Clin Exp Immunol*. 2001;126(3):466-473.
285. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. *J Nutr*. 2001;131(2S-2):568S-579S; discussion 580S.
286. Hallquist NA, McNeil LK, Lockwood JF, Sherman AR. Maternal-iron-deficiency effects on peritoneal macrophage and peritoneal natural-killer-cell cytotoxicity in rat pups. *Am J Clin Nutr*. 1992;55(3):741-746.
287. Littwitz-Salomon E, Moreira D, Frost JN, et al. Metabolic requirements of NK cells during the acute response against retroviral infection. *Nat Commun*. 2021;12(1):5376.
288. Dickson KB, Zhou J. Role of reactive oxygen species and iron in host defense against infection. *FBL*. 2020;25(8):1600-1616.
289. Khan A, Singh P, Srivastava A. Synthesis, nature and utility of universal iron chelator - Siderophore: a review. *Microbiol Res*. 2018;212-213:103-111.
290. Ni S, Yuan Y, Kuang Y, Li X. Iron metabolism and immune regulation. *Front Immunol*. 2022;13:816282.
291. Thorson JA, Smith KM, Gomez F, Naumann PW, Kemp JD. Role of iron in T cell activation: TH1 clones differ from TH2 clones in their sensitivity to inhibition of DNA synthesis caused by IgG Mabs against the transferrin receptor and the iron chelator deferoxamine. *Cell Immunol*. 1991;134(1):126-137.
292. Regis G, Bosticardo M, Conti L, et al. Iron regulates T-lymphocyte sensitivity to the IFN-gamma/STAT1 signaling pathway in vitro and in vivo. *Blood*. 2005;105(8):3214-3221.
293. Naderi N, Etaati Z, Rezvani Joibari M, Sobhani SA, Hosseni TS. Immune deviation in recurrent vulvovaginal candidiasis: correlation with iron deficiency anemia. *Iran J Immunol*. 2013;10(2):118-126.
294. Li G, Pone EJ, Tran DC, et al. Iron inhibits activation-induced cytidine deaminase enzymatic activity and modulates immunoglobulin class switch DNA recombination. *J Biol Chem*. 2012;287(25):21520-21529.
295. Jang KJ, Mano H, Aoki K, et al. Mitochondrial function provides instructive signals for activation-induced B-cell fates. *Nat Commun*. 2015;6:6750.
296. Noha MA, Enas AE, Aly E, Mohamed AE. Multidisciplinary biomarkers aggrieve morbidity in schistosomiasis. *Trop Biomed*. 2019;36(4):833-844.
297. Oluwole O, Arinola OG, Adu MD, et al. Relationships between plasma micronutrients, serum IgE, and skin test reactivity and asthma among school children in rural Southwest Nigeria. *J Biomark*. 2014;2014:106150.
298. Mibei EK, Otieno WO, Orago AS, Stoute JA. Distinct pattern of class and subclass antibodies in immune complexes of children with cerebral malaria and severe malarial anaemia. *Parasite Immunol*. 2008;30(6–7):334-341.
299. Le HT, Brouwer ID, Verhoef H, Nguyen KC, Kok FJ. Anemia and intestinal parasite infection in school children in rural Vietnam. *Asia Pac J Clin Nutr*. 2007;16(4):716-723.
300. Kojima K, Omoto E, Katayama Y, et al. Autoimmune hemolytic anemia in allergic granulomatous angitis (Churg-Strauss syndrome). *Int J Hematol*. 1996;63(2):149-154.
301. Shaheen SO, Macdonald-Wallis C, Lawlor DA, Henderson AJ. Haemoglobin concentrations in pregnancy and respiratory and allergic outcomes in childhood: birth cohort study. *Clin Exp Allergy*. 2017;47(12):1615-1624.
302. Le Huong T, Brouwer ID, Nguyen KC, Burema J, Kok FJ. The effect of iron fortification and de-worming on anaemia and iron status of Vietnamese schoolchildren. *Br J Nutr*. 2007;97(5):955-962.
303. Magro AM, Brai M. Evidence for lipoxygenase activity in induction of histamine release from rat peritoneal mast cells by chelated iron. *Immunology*. 1983;49(1):1-8.
304. Lombardo T, Ferro G, Frontini V, Percolla S. High-dose intravenous desferrioxamine (DFO) delivery in four thalassemic patients allergic to subcutaneous DFO administration. *Am J Hematol*. 1996;51(1):90-92.
305. Jeong HJ, Chung HS, Lee BR, et al. Expression of proinflammatory cytokines via HIF-1alpha and NF-kappaB activation on desferrioxamine-stimulated HMC-1 cells. *Biochem Biophys Res Commun*. 2003;306(4):805-811.
306. Shalit M, Tedeschi A, Miadonna A, Levi-Schaffer F. Desferal (desferrioxamine)–a novel activator of connective tissue-type mast cells. *J Allergy Clin Immunol*. 1991;88(6):854-860.
307. Mecheri S, Peltre G, Lapeyre J, David B. Biological effect of transferrin on mast cell mediator release during the passive cutaneous anaphylaxis reaction: a possible inhibition mechanism involving iron. *Ann Inst Pasteur Immunol*. 1987;138(2):213-221.
308. Theobald K, Gross-Weege W, Keymling J, Konig W. Purification of serum proteins with inhibitory activity on the histamine release in vitro and/or in vivo. *Int Arch Allergy Appl Immunol*. 1987;82(3–4):295-297.
309. Nakashima K, Takeuchi T, Shirakawa T. Differentiation, distribution, and chemical state of intracellular trace elements in LAD2 mast cell line. *Biol Trace Elem Res*. 2005;108(1–3):105-114.
310. Tetens I, Larsen TM, Kristensen MB, et al. The importance of dietary composition for efficacy of iron absorption measured in a whole

diet that includes rye bread fortified with ferrous fumerate: a radioisotope study in young women. *Br J Nutr*. 2005;94(5):720-726.
311. Zecchinati F, Barranco MM, Arana MR, et al. Reversion of down-regulation of intestinal multidrug resistance-associated protein 2 in fructose-fed rats by geraniol and vitamin C: potential role of inflammatory response and oxidative stress. *J Nutr Biochem*. 2019;68:7-15.
312. Turnlund JR, Smith RG, Kretsch MJ, Keyes WR, Shah AG. Milk's effect on the bioavailability of iron from cereal-based diets in young women by use of in vitro and in vivo methods. *Am J Clin Nutr*. 1990;52(2):373-378.
313. Kies CV. Mineral utilization of vegetarians: impact of variation in fat intake. *Am J Clin Nutr*. 1988;48(3 Suppl):884-887.
314. Kapsokefalou M, Miller DD. Lean beef and beef fat interact to enhance nonheme iron absorption in rats. *J Nutr*. 1993;123(8):1429-1434.
315. Martinez-Torres C, Leets I, Taylor P, Ramirez J, del Valle CM, Layrisse M. Heme, ferritin and vegetable iron absorption in humans from meals denatured of heme iron during the cooking of beef. *J Nutr*. 1986;116(9):1720-1725.
316. Cediel G, Olivares M, Gaitan D, Flores S, Brito A, Pizarro F. Effect of trypsin and mucin on heme iron bioavailability in humans. *Biol Trace Elem Res*. 2012;150(1–3):37-41.
317. Bach Kristensen M, Hels O, Morberg C, Marving J, Bugel S, Tetens I. Pork meat increases iron absorption from a 5-day fully controlled diet when compared to a vegetarian diet with similar vitamin C and phytic acid content. *Br J Nutr*. 2005;94(1):78-83.
318. Baech SB, Hansen M, Bukhave K, et al. Nonheme-iron absorption from a phytate-rich meal is increased by the addition of small amounts of pork meat. *Am J Clin Nutr*. 2003;77(1):173-179.
319. Hunt JR. High-, but not low-bioavailability diets enable substantial control of women's iron absorption in relation to body iron stores, with minimal adaptation within several weeks. *Am J Clin Nutr*. 2003;78(6):1168-1177.
320. Hallberg L, Hoppe M, Andersson M, Hulthen L. The role of meat to improve the critical iron balance during weaning. *Pediatrics*. 2003;111(4 Pt 1):864-870.
321. Heath AL, Skeaff CM, O'Brien SM, Williams SM, Gibson RS. Can dietary treatment of non-anemic iron deficiency improve iron status? *J Am Coll Nutr*. 2001;20(5):477-484.
322. Hunt JR, Roughead ZK. Adaptation of iron absorption in men consuming diets with high or low iron bioavailability. *Am J Clin Nutr*. 2000;71(1):94-102.
323. Imessaoudene A, Merzouk H, Berroukeche F, et al. Beneficial effects of quercetin-iron complexes on serum and tissue lipids and redox status in obese rats. *J Nutr Biochem*. 2016;29:107-115.
324. Mazhar M, Kabir N, Simjee SU. Quercetin modulates iron homeostasis and iNOS expression of splenic macrophages in a rat model of iron deficiency anemia. *Chin J Nat Med*. 2018;16(8):580-589.
325. Bicer N, Yildiz E, Yegani AA, Aksu F. Synthesis of curcumin complexes with iron(iii) and manganese(ii), and effects of curcumin–iron(iii) on Alzheimer's disease. *New J Chem*. 2018;42(10):8098-8104.
326. Tiekou Lorinczova H, Begum G, Temouri L, Renshaw D, Zariwala MG. Co-Administration of Iron and Bioavailable Curcumin Reduces Levels of systemic markers of inflammation and oxidative stress in a placebo-controlled randomised study. *Nutrients*. 2022;14(3):712.
327. Bokhari F, Derbyshire E, Li W, Brennan CS, Stojceska V. A study to establish whether food-based approaches can improve serum iron levels in child-bearing aged women. *J Hum Nutr Diet*. 2012;25(1):95-100.
328. Davidsson L, Dimitriou T, Walczyk T, Hurrell RF. Iron absorption from experimental infant formulas based on pea (*Pisum sativum*)-protein isolate: the effect of phytic acid and ascorbic acid. *Br J Nutr*. 2001;85(1):59-63.
329. DellaValle DM, Glahn RP, Shaff JE, O'Brien KO. Iron absorption from an intrinsically labeled lentil meal is low but upregulated in women with poor iron status. *J Nutr*. 2015;145(10):2253-2257.
330. Gaitan D, Flores S, Saavedra P, et al. Calcium does not inhibit the absorption of 5 milligrams of nonheme or heme iron at doses less than 800 milligrams in nonpregnant women. *J Nutr*. 2011;141(9):1652-1656.
331. Gaitan D, Olivares M, Lonnerdal B, Brito A, Pizarro F. Non-heme iron as ferrous sulfate does not interact with heme iron absorption in humans. *Biol Trace Elem Res*. 2012;150(1–3):68-73.
332. Grinder-Pedersen L, Bukhave K, Jensen M, Hojgaard L, Hansen M. Calcium from milk or calcium-fortified foods does not inhibit nonheme-iron absorption from a whole diet consumed over a 4-d period. *Am J Clin Nutr*. 2004;80(2):404-409.
333. Abrams SA, Griffin IJ, Davila P, Liang L. Calcium fortification of breakfast cereal enhances calcium absorption in children without affecting iron absorption. *J Pediatr*. 2001;139(4):522-526.
334. Reddy MB, Cook JD. Effect of calcium intake on nonheme-iron absorption from a complete diet. *Am J Clin Nutr*. 1997;65(6):1820-1825.
335. Erichsen K, Ulvik RJ, Nysaeter G, et al. Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. *Scand J Gastroenterol*. 2005;40(9):1058-1065.
336. Rampton DS, Goodhand JR, Joshi NM, et al. Oral iron treatment response and predictors in Anaemic adolescents and adults with IBD: a prospective controlled open-label trial. *J Crohns Colitis*. 2017;11(6):706-715.
337. Stoffel NU, Zimmermann MB, Cepeda-Lopez AC, et al. Maternal iron kinetics and maternal-fetal iron transfer in normal-weight and overweight pregnancy. *Am J Clin Nutr*. 2022;115(4):1166-1179.
338. Htet MK, Fahmida U, Dillon D, Akib A, Utomo B, Thurnham DI. Is iron supplementation influenced by sub-clinical inflammation? A randomized controlled trial among adolescent schoolgirls in Myanmar. *Nutrients*. 2019;11(4):918.
339. Hoa PT, Khan NC, van Beusekom C, Gross R, Conde WL, Khoi HD. Milk fortified with iron or iron supplementation to improve nutritional status of pregnant women: an intervention trial from rural Vietnam. *Food Nutr Bull*. 2005;26(1):32-38.
340. Virtanen MA, Svahn CJ, Viinikka LU, Raiha NC, Siimes MA, Axelsson IE. Iron-fortified and unfortified cow's milk: effects on iron intakes and iron status in young children. *Acta Paediatr*. 2001;90(7):724-731.
341. Walczyk T, Muthayya S, Wegmuller R, et al. Inhibition of iron absorption by calcium is modest in an iron-fortified, casein- and whey-based drink in Indian children and is easily compensated for by addition of ascorbic acid. *J Nutr*. 2014;144(11):1703-1709.
342. Hertrampf E, Olivares M, Walter T, et al. Iron-deficiency anemia in the nursing infant: its elimination with iron-fortified milk. *Rev Med Chil*. 1990;118(12):1330-1337.
343. Roy Choudhury D, Nair Krishnapillai M, Nagalla B, et al. Guava with an institutional supplementary meal improves iron status of preschoolers: a cluster-randomized controlled trial. *Ann N Y Acad Sci*. 2021;1492(1):82-95.
344. Berseth CL, van Aerde JE, Gross S, Stolz SI, Harris CL, Hansen JW. Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier. *Pediatrics*. 2004;114(6):e699-e706.
345. Chinnappan A, Sharma A, Agarwal R, Thukral A, Deorari A, Sankar MJ. Fortification of breast Milk with preterm formula powder vs human Milk fortifier in preterm neonates: a randomized noninferiority trial. *JAMA Pediatr*. 2021;175(8):790-796.
346. Begin F, Santizo MC, Peerson JM, Torun B, Brown KH. Effects of bovine serum concentrate, with or without supplemental micronutrients, on the growth, morbidity, and micronutrient status of young children in a low-income, peri-urban Guatemalan community. *Eur J Clin Nutr*. 2008;62(1):39-50.
347. Lepanto MS, Rosa L, Cutone A, Conte MP, Paesano R, Valenti P. Efficacy of lactoferrin oral administration in the Treatment

of anemia and anemia of inflammation in pregnant and non-pregnant women: an interventional study. *Front Immunol*. 2018;9:2123.
348. Rosa L, Lepanto MS, Cutone A, et al. Influence of oral administration mode on the efficacy of commercial bovine Lactoferrin against iron and inflammatory homeostasis disorders. *Biometals*. 2020;33(2–3):159-168.
349. Cichon B, Fabiansen C, Iuel-Brockdorf AS, et al. Impact of food supplements on hemoglobin, iron status, and inflammation in children with moderate acute malnutrition: a 2 x 2 x 3 factorial randomized trial in Burkina Faso. *Am J Clin Nutr*. 2018;107(2):278-286.
350. Kim EY, Pai TK, Han O. Effect of bioactive dietary polyphenols on zinc transport across the intestinal Caco-2 cell monolayers. *J Agric Food Chem*. 2011;59(8):3606-3612.
351. Jin CW, You GY, He YF, Tang C, Wu P, Zheng SJ. Iron deficiency-induced secretion of phenolics facilitates the reutilization of root apoplastic iron in red clover. *Plant Physiol*. 2007;144(1):278-285.
352. Luscher A, Gasser V, Bumann D, Mislin GLA, Schalk IJ, Kohler T. Plant-derived Catechols are substrates of TonB-dependent transporters and sensitize *Pseudomonas aeruginosa* to Siderophore-drug conjugates. *MBio*. 2022;13(4):e0149822.
Study highlighting the role of phenolics as iron chelator and a dietary source for iron in microbes.
353. Wang X, Li Y, Han L, Li J, Liu C, Sun C. Role of flavonoids in the treatment of iron overload. *Front Cell Dev Biol*. 2021;9:685364.
354. Yin M, Liu Y, Chen Y. Iron metabolism: an emerging therapeutic target underlying the anti-cancer effect of quercetin. *Free Radic Res*. 2021;55(3):296-303.
355. Sajadi Hezaveh Z, Azarkeivan A, Janani L, Hosseini S, Shidfar F. The effect of quercetin on iron overload and inflammation in beta-thalassemia major patients: a double-blind randomized clinical trial. *Complement Ther Med*. 2019;46:24-28.
356. Zhang H, Xu Z, Zhao H, et al. Anthocyanin supplementation improves anti-oxidative and anti-inflammatory capacity in a dose-response manner in subjects with dyslipidemia. *Redox Biol*. 2020;32:101474.
357. Wood LG, Garg ML, Smart JM, Scott HA, Barker D, Gibson PG. Manipulating antioxidant intake in asthma: a randomized controlled trial. *Am J Clin Nutr*. 2012;96(3):534-543.
358. Asthma. GGIf. Global strategy for asthma management and prevention. *Asthma*. GGIf:ed2023. https://ginasthma.org/2023-gina-main-report/
359. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2011;127(3):724-733. e721-e730.
360. Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, Panagiotakos DB, Priftis KN, Nagel G. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2013;24(4):330-338.
361. Kolacek M, Muchova J, Dvorakova M, et al. Effect of natural polyphenols (Pycnogenol) on oxidative stress markers in children suffering from Crohn's disease–a pilot study. *Free Radic Res*. 2013;47(8):624-634.
362. Shafabakhsh R, Asemi Z, Reiner Z, Soleimani A, Aghadavod E, Bahmani F. The effects of Nano-curcumin on metabolic status in patients with diabetes on hemodialysis, a randomized, double blind, Placebo-Controlled Trial. *Iran J Kidney Dis*. 2020;14(4):290-299.
363. Saraf-Bank S, Ahmadi A, Paknahad Z, Maracy M, Nourian M. Effects of curcumin supplementation on markers of inflammation and oxidative stress among healthy overweight and obese girl adolescents: a randomized placebo-controlled clinical trial. *Phytother Res*. 2019;33(8):2015-2022.
364. Helli B, Gerami H, Kavianpour M, Heybar H, Hosseini SK, Haghighian HK. Curcumin nanomicelle improves lipid profile, stress oxidative factors and inflammatory markers in patients undergoing coronary elective angioplasty; a randomized clinical trial. *Endocr Metab Immune Disord Drug Targets*. 2021;21(11):2090-2098.
365. Jacob K, Periago MJ, Bohm V, Berruezo GR. Influence of lycopene and vitamin C from tomato juice on biomarkers of oxidative stress and inflammation. *Br J Nutr*. 2008;99(1):137-146.
366. Wang Q, Han P, Zhang M, et al. Supplementation of black rice pigment fraction improves antioxidant and anti-inflammatory status in patients with coronary heart disease. *Asia Pac J Clin Nutr*. 2007;16(Suppl 1):295-301.
367. Sudini K, Diette GB, Breysse PN, et al. A randomized controlled trial of the effect of broccoli sprouts on antioxidant gene expression and airway inflammation in asthmatics. *J Allergy Clin Immunol Pract*. 2016;4(5):932-940.
368. Esmaeilinezhad Z, Barati-Boldaji R, Brett NR, et al. The effect of synbiotics pomegranate juice on cardiovascular risk factors in PCOS patients: a randomized, triple-blinded, controlled trial. *J Endocrinol Invest*. 2020;43(4):539-548.
369. Pour FK, Aryaeian N, Mokhtare M, et al. The effect of saffron supplementation on some inflammatory and oxidative markers, leptin, adiponectin, and body composition in patients with nonalcoholic fatty liver disease: a double-blind randomized clinical trial. *Phytother Res*. 2020;34(12):3367-3378.
370. Wang MX, Jiao JH, Li ZY, Liu RR, Shi Q, Ma L. Lutein supplementation reduces plasma lipid peroxidation and C-reactive protein in healthy nonsmokers. *Atherosclerosis*. 2013;227(2):380-385.
371. Daneshvar Kakhaki R, Ostadmohammadi V, Kouchaki E, et al. Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clin Neurol Neurosurg*. 2020;195:105878.
372. Nachvak SM, Shabanpur M, Mostafai R, Heidari Moghaddam R, Moludi J. L-carnitine supplementation reduces biomarkers of inflammatory and oxidative stress in patients with coronary artery disease: a randomised controlled trial. *Arch Physiol Biochem*. 2023;129(1):61-68.
373. Hashemi G, Mirjalili M, Basiri Z, et al. A pilot study to evaluate the effects of Oral N-acetyl cysteine on inflammatory and oxidative stress biomarkers in rheumatoid arthritis. *Curr Rheumatol Rev*. 2019;15(3):246-253.
374. Dalgard C, Nielsen F, Morrow JD, et al. Supplementation with orange and blackcurrant juice, but not vitamin E, improves inflammatory markers in patients with peripheral arterial disease. *Br J Nutr*. 2009;101(2):263-269.
375. Gandhi M, Elfeky O, Ertugrul H, Chela HK, Daglilar E. Scurvy: rediscovering a forgotten disease. *Diseases*. 2023;11(2):78.
376. Radke DI, Homayr AL, Stoppe C, Elke G. Vitamin C in critical illness: end of the story or still a place? *Curr Opin Crit Care*. 2023;29(4):339-345.
377. Safety WTNaF. *Guidelines on food fortification with micronutrients*. World Health Organization; 2006. Accessed October 18, 2022.
378. Wang Z, Liu L, Liu L. Vitamin C as a treatment for organ failure in sepsis. *Eur J Med Res*. 2023;28(1):222.
379. Nabzdyk CS, Bittner EA. Vitamin C in the critically ill - indications and controversies. *World J Crit Care Med*. 2018;7(5):52-61.
380. Allen S, Britton JR, Leonardi-Bee JA. Association between antioxidant vitamins and asthma outcome measures: systematic review and meta-analysis. *Thorax*. 2009;64(7):610-619.
381. Crook JM, Yoon SL, Grundmann O, Horgas A, Johnson-Mallard V. Subclinical vitamin C plasma levels associated with increased risk of CAD diagnosis via inflammation: results from the NHANES 2003-2006 surveys. *Nutrients*. 2023;15(3):584.
382. Ellulu MS, Rahmat A, Patimah I, Khaza'ai H, Abed Y. Effect of vitamin C on inflammation and metabolic markers in hypertensive and/or diabetic obese adults: a randomized controlled trial. *Drug des Devel Ther*. 2015;9:3405-3412.

383. Ullegaddi R, Powers HJ, Gariballa SE. Antioxidant supplementation enhances antioxidant capacity and mitigates oxidative damage following acute ischaemic stroke. *Eur J Clin Nutr*. 2005;59(12):1367-1373.
384. Aisa-Alvarez A, Perez-Torres I, Guarner-Lans V, et al. Randomized clinical trial of antioxidant therapy patients with septic shock and organ dysfunction in the ICU: SOFA score reduction by improvement of the enzymatic and non-enzymatic antioxidant system. *Cell*. 2023;12(9):1330.
385. Baye K, Laillou A, Seyoum Y, Zvandaziva C, Chimanya K, Nyawo M. Estimates of child mortality reductions attributed to vitamin a supplementation in sub-Saharan Africa: scale up, scale back, or refocus? *Am J Clin Nutr*. 2022;116(2):426-434.
386. Basu S, Khanna P, Srivastava R, Kumar A. Oral vitamin a supplementation in very low birth weight neonates: a randomized controlled trial. *Eur J Pediatr*. 2019;178(8):1255-1265.
387. Glasziou PP, Mackerras DE. Vitamin a supplementation in infectious diseases: a meta-analysis. *BMJ*. 1993;306(6874):366-370.
388. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins a and D take Centre stage. *Nat Rev Immunol*. 2008;8(9):685-698.
389. Reifen R, Nur T, Ghebermeskel K, Zaiger G, Urizky R, Pines M. Vitamin a deficiency exacerbates inflammation in a rat model of colitis through activation of nuclear factor-kappaB and collagen formation. *J Nutr*. 2002;132(9):2743-2747.
390. Amimo JO, Michael H, Chepngeno J, Raev SA, Saif LJ, Vlasova AN. Immune impairment associated with vitamin a deficiency: insights from clinical studies and animal model research. *Nutrients*. 2022;14(23):5038.
391. Bos A, van Egmond M, Mebius R. The role of retinoic acid in the production of immunoglobulin a. *Mucosal Immunol*. 2022;15(4):562-572.
392. O'Connor C, Varshosaz P, Moise AR. Mechanisms of feedback regulation of vitamin a metabolism. *Nutrients*. 2022;14(6):1312.
393. Rhodes J, Oliver S. Retinoids as regulators of macrophage function. *Immunology*. 1980;40(3):467-472.
394. Kim SY, Koo JE, Song MR, Lee JY. Retinol suppresses the activation of toll-like receptors in MyD88- and STAT1-independent manners. *Inflammation*. 2013;36(2):426-433.
395. Zhu YN, Gu XL, Wang LY, Guan N, Li CG. All-trans retinoic acid promotes M2 macrophage polarization in vitro by activating the p38MAPK/STAT6 signaling pathway. *Immunol Invest*. 2023;52(3):298-318.
396. Liu N, Kawahira N, Nakashima Y, et al. Notch and retinoic acid signals regulate macrophage formation from endocardium downstream of Nkx2-5. *Nat Commun*. 2023;14(1):5398.
397. Hiraga H, Chinda D, Maeda T, et al. Vitamin a promotes the fusion of Autophagolysosomes and prevents excessive Inflammasome activation in dextran sulfate sodium-induced colitis. *Int J Mol Sci*. 2023;24(10):8684.
398. Nurrahmah QI, Madhyastha R, Madhyastha H, Purbasari B, Maruyama M, Nakajima Y. Retinoic acid abrogates LPS-induced inflammatory response via negative regulation of NF-kappa B/miR-21 signaling. *Immunopharmacol Immunotoxicol*. 2021;43(3):299-308.
399. Penkert RR, Jones BG, Hacker H, Partridge JF, Hurwitz JL. Vitamin a differentially regulates cytokine expression in respiratory epithelial and macrophage cell lines. *Cytokine*. 2017;91:1-5.
400. Pinos I, Yu J, Pilli N, Kane MA, Amengual J. Functional characterization of interleukin 4 and retinoic acid signaling crosstalk during alternative macrophage activation. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2023;1868(4):159291.
401. Minet-Quinard R, Farges MC, Thivat E, et al. Neutrophils are immune cells preferentially targeted by retinoic acid in elderly subjects. *Immun Ageing*. 2010;7(1):10.
402. Seo GY, Lee JM, Jang YS, et al. Mechanism underlying the suppressor activity of retinoic acid on IL4-induced IgE synthesis and its physiological implication. *Cell Immunol*. 2017;322:49-55.
403. Ruhl R, Garcia A, Schweigert FJ, Worm M. Modulation of cytokine production by low and high retinoid diets in ovalbumin-sensitized mice. *Int J Vitam Nutr Res*. 2004;74(4):279-284.
404. Pantazi E, Marks E, Stolarczyk E, Lycke N, Noelle RJ, Elgueta R. Cutting edge: retinoic acid signaling in B cells is essential for Oral immunization and microflora composition. *J Immunol*. 2015;195(4):1368-1371.
405. Sun CM, Hall JA, Blank RB, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J Exp Med*. 2007;204(8):1775-1785.
406. Turfkruyer M, Rekima A, Macchiaverni P, et al. Oral tolerance is inefficient in neonatal mice due to a physiological vitamin a deficiency. *Mucosal Immunol*. 2016;9(2):479-491.
407. Sato Y, Akiyama H, Matsuoka H, et al. Dietary carotenoids inhibit oral sensitization and the development of food allergy. *J Agric Food Chem*. 2010;58(12):7180-7186.
408. Bando N, Yamanishi R, Terao J. Inhibition of immunoglobulin E production in allergic model mice by supplementation with vitamin E and beta-carotene. *Biosci Biotechnol Biochem*. 2003;67(10):2176-2182.
409. De Luca LM, Roop D, Huang FL. Vitamin a: a key nutrient for the maintenance of epithelial differentiation. *Acta Vitaminol Enzymol*. 1985;7:13-20.
410. Lotan R. Squamous cell differentiation markers in normal, premalignant, and malignant epithelium: effects of retinoids. *J Cell Biochem Suppl*. 1993;17F:167-174.
411. Sundelin J, Busch C, Das K, et al. Structure and tissue distribution of some retinoid-binding proteins. *J Invest Dermatol*. 1983;81(1 Suppl):59s-63s.
412. Chopra DP, Cooney RA, Taylor GW. Effects of vitamin a deficiency on cell proliferation and morphology of trachea of the hamster. *Cell Tissue Kinet*. 1990;23(6):575-586.
413. Mellody KT, Bradley EJ, Mambwe B, et al. Multifaceted amelioration of cutaneous photoageing by (0.3%) retinol. *Int J Cosmet Sci*. 2022;44(6):625-635.
414. Ng-Blichfeldt JP, Schrik A, Kortekaas RK, et al. Retinoic acid signaling balances adult distal lung epithelial progenitor cell growth and differentiation. *EBioMedicine*. 2018;36:461-474.
415. Li Y, Gao Y, Cui T, et al. Retinoic acid facilitates toll-like receptor 4 expression to improve intestinal barrier function through retinoic acid receptor Beta. *Cell Physiol Biochem*. 2017;42(4):1390-1406.
416. Yang H, Chen JS, Zou WJ, et al. Vitamin a deficiency exacerbates extrinsic atopic dermatitis development by potentiating type 2 helper T cell-type inflammation and mast cell activation. *Clin Exp Allergy*. 2020;50(8):942-953.
417. Qi C, Tu H, Zhao Y, et al. Breast milk-derived *Limosilactobacillus reuteri* prevents atopic dermatitis in mice via activating retinol absorption and metabolism in Peyer's patches. *Mol Nutr Food Res*. 2023;67(2):e2200444.
418. Kurashima Y, Amiya T, Fujisawa K, et al. The enzyme Cyp26b1 mediates inhibition of mast cell activation by fibroblasts to maintain skin-barrier homeostasis. *Immunity*. 2014;40(4):530-541.
419. Babina M, Artuc M, Guhl S, Zuberbier T. Retinoic acid negatively impacts proliferation and MC(TC) specific attributes of human skin derived mast cells, but reinforces allergic Stimulability. *Int J Mol Sci*. 2017;18(3):525.
420. Cantwell ME, Foreman JC. The actions of retinal and retinoic acid on histamine release from rat peritoneal mast cells. *Eur J Pharmacol*. 1989;160(1):43-51.
421. Larange A, Cheroutre H. Retinoic acid and retinoic acid receptors as pleiotropic modulators of the immune system. *Annu Rev Immunol*. 2016;34:369-394.

422. Shi Z, Ohno H, Satoh-Takayama N. Dietary derived micronutrients modulate immune responses through innate lymphoid cells. *Front Immunol*. 2021;12:670632.
423. Maiani G, Caston MJ, Catasta G, et al. Carotenoids: actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. *Mol Nutr Food Res*. 2009;53(Suppl 2):S194-S218.
424. Reboul E. Absorption of vitamin a and carotenoids by the enterocyte: focus on transport proteins. *Nutrients*. 2013;5(9):3563-3581.
425. Perusek L, Maeda T. Vitamin a derivatives as treatment options for retinal degenerative diseases. *Nutrients*. 2013;5(7):2646-2666.
426. Micronutrients IoMUPo. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academies Press; 2001.
427. Castenmiller JJ, West CE. Bioavailability and bioconversion of carotenoids. *Annu Rev Nutr*. 1998;18:19-38.
428. Tanumihardjo SA. Factors influencing the conversion of carotenoids to retinol: bioavailability to bioconversion to bioefficacy. *Int J Vitam Nutr Res*. 2002;72(1):40-45.
429. Monaco HL. Three-dimensional structure of the transthyretin-retinol-binding protein complex. *Clin Chem Lab Med*. 2002;40(12):1229-1236.
430. Rosales FJ, Jang JT, Pinero DJ, Erikson KM, Beard JL, Ross AC. Iron deficiency in young rats alters the distribution of vitamin a between plasma and liver and between hepatic retinol and retinyl esters. *J Nutr*. 1999;129(6):1223-1228.
431. Green MH, Ford JL, Green JB. Development of a compartmental model to investigate the Influence of inflammation on predictions of vitamin a Total body stores by retinol isotope dilution in theoretical humans. *J Nutr*. 2021;151(3):731-741.
432. Mayland C, Allen KR, Degg TJ, Bennet M. Micronutrient concentrations in patients with malignant disease: effect of the inflammatory response. *Ann Clin Biochem*. 2004;41(Pt 2):138-141.
433. Campbell RK, Shaikh S, Schulze K, et al. Micronutrient and inflammation status following one year of complementary food supplementation in 18-month-old rural Bangladeshi children: a randomized controlled trial. *Nutrients*. 2020;12(5):1452.
434. Morita H, Kubo T, Ruckert B, et al. Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid. *J Allergy Clin Immunol*. 2019;143(6):2190.e9-2201.e9.
435. Konieczna P, Akdis CA, Quigley EM, Shanahan F, O'Mahony L. Portrait of an immunoregulatory Bifidobacterium. *Gut Microbes*. 2012;3(3):261-266.
436. Cusick SE, Tielsch JM, Ramsan M, et al. Short-term effects of vitamin a and antimalarial treatment on erythropoiesis in severely anemic Zanzibari preschool children. *Am J Clin Nutr*. 2005;82(2):406-412.
Clinical and mechanistical study assessing vitamin a supplementation in anemic children.
437. Dong S, Xia H, Wang F, Sun G. The effect of red palm oil on vitamin a deficiency: a meta-analysis of randomized controlled trials. *Nutrients*. 2017;9(12):1281.
438. Canfield LM, Kaminsky RG, Taren DL, Shaw E, Sander JK. Red palm oil in the maternal diet increases provitamin a carotenoids in breastmilk and serum of the mother-infant dyad. *Eur J Nutr*. 2001;40(1):30-38.
439. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. *Aliment Pharmacol Ther*. 2007;26(6):795-806.
440. Grover Z, Lewindon P. Two-year outcomes after exclusive enteral nutrition induction are superior to corticosteroids in pediatric Crohn's disease treated early with Thiopurines. *Dig Dis Sci*. 2015;60(10):3069-3074.
Important study, showing that nutrients have a similar efficacy than corticosteroids in pediatric crohn's disease patients.
441. Nourmohammadi M, Moradi Moghdam O, Niakan Lahiji M, Vahdat SZ. High-fat low-carbohydrate enteral feeding enriched with olive oil and acute respiratory failure: a double-blind, randomized, controlled trial. *Clin Nutr ESPEN*. 2022;52:144-150.
442. Gram-Kampmann EM, Olesen TB, Hansen CD, et al. A six-month low-carbohydrate diet high in fat does not adversely affect endothelial function or markers of low-grade inflammation in patients with type 2 diabetes: an open-label randomized controlled trial. *Cardiovasc Diabetol*. 2023;22(1):212.
443. Jonasson L, Guldbrand H, Lundberg AK, Nystrom FH. Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. *Ann Med*. 2014;46(3):182-187.
444. Alzahrani AH, Skytte MJ, Samkani A, et al. Effects of a self-prepared carbohydrate-reduced high-protein diet on cardiovascular disease risk markers in patients with type 2 diabetes. *Nutrients*. 2021;13(5):1694.
445. Esposito K, Marfella R, Ciotola M, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004;292(12):1440-1446.
446. Yurtdas G, Akbulut G, Baran M, Yilmaz C. The effects of Mediterranean diet on hepatic steatosis, oxidative stress, and inflammation in adolescents with non-alcoholic fatty liver disease: a randomized controlled trial. *Pediatr Obes*. 2022;17(4):e12872.
447. Dynka D, Kowalcze K, Charuta A, Paziewska A. The ketogenic diet and cardiovascular diseases. *Nutrients*. 2023;15(15):3368.
448. Li H, Zeng F, Huang C, et al. The potential role of glucose metabolism, lipid metabolism, and amino acid metabolism in the treatment of Parkinson's disease. *CNS Neurosci Ther*. 2023. doi:10.1111/cns.14411. Online ahead of print.
449. Sadu Singh BK, Narayanan SS, Khor BH, et al. Composition and functionality of lipid emulsions in parenteral nutrition: examining evidence in clinical applications. *Front Pharmacol*. 2020;11:506.
450. Karagiannis F, Peukert K, Surace L, et al. Impaired ketogenesis ties metabolism to T cell dysfunction in COVID-19. *Nature*. 2022;609(7928):801-807.
451. Roager HM, Vogt JK, Kristensen M, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. *Gut*. 2019;68(1):83-93.
452. Batifoulier F, Verny MA, Chanliaud E, Rémésy C, Demigné C. Variability of B vitamin concentrations in wheat grain, milling fractions and bread products. *Eur J Agron*. 2006;25(2):163-169.
453. Markova M, Pivovarova O, Hornemann S, et al. Isocaloric diets high in animal or plant protein reduce liver fat and inflammation in individuals with type 2 diabetes. *Gastroenterology*. 2017;152(3):571.e8-585.e8.
Important study highlighting the impact of proteins in reducing inflammation in diabetic individuals.
454. Maduro IP, Nonino CB, Sakamoto LM, Meirelles MG, Cardeal Da Costa JA, Marchini JS. Red meat snacks for chronic hemodialysis patients: effect on inflammatory activity (a pilot study). *Ren Fail*. 2013;35(6):830-834.
455. Nora CL, Zhang L, Castro RJ, et al. Effects of mixed nut consumption on LDL cholesterol, lipoprotein(a), and other cardiometabolic risk factors in overweight and obese adults. *Nutr Metab Cardiovasc Dis*. 2023;33(8):1529-1538.
456. Rajaram S, Connell KM, Sabate J. Effect of almond-enriched high-monounsaturated fat diet on selected markers of inflammation: a randomised, controlled, crossover study. *Br J Nutr*. 2010;103(6):907-912.

457. Prokopidis K, Mazidi M, Sankaranarayanan R, Tajik B, McArdle A, Isanejad M. Effects of whey and soy protein supplementation on inflammatory cytokines in older adults: a systematic review and meta-analysis. *Br J Nutr*. 2023;129(5):759-770.
458. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. *Clin Immunol*. 2005;117(2):104-111.

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