Metabolic Effects of Inflammation on Vitamin A and Carotenoids in Humans and Animal Models[1–3]

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ABSTRACT

The association between inflammation and vitamin A (VA) metabolism and status assessment has been documented in multiple studies with animals and humans. The relation between inflammation and carotenoid status is less clear. Nonetheless, it is well known that carotenoids are associated with certain health benefits. Understanding these relations is key to improving health outcomes and mortality risk in infants and young children. Hyporetinolemia, i.e., low serum retinol concentrations, occurs during inflammation, and this can lead to the misdiagnosis of VA deficiency. On the other hand, inflammation causes impaired VA absorption and urinary losses that can precipitate VA deficiency in at-risk groups of children. Many epidemiologic studies have suggested that high dietary carotenoid intake and elevated plasma concentrations are correlated with a decreased risk of several chronic diseases; however, large-scale carotenoid supplementation trials have been unable to confirm the health benefits and in some cases resulted in controversial results. However, it has been documented that dietary carotenoids and retinoids play important roles in innate and acquired immunity and in the body's response to inflammation. Although animal models have been useful in investigating retinoid effects on developmental immunity, it is more challenging to tease out the effects of carotenoids because of differences in the absorption, kinetics, and metabolism between humans and animal models. The current understanding of the relations between inflammation and retinoid and carotenoid metabolism and status are the topics of this review. *Adv Nutr* 2017;8:197–212.

Keywords: biomarkers, cytokines, infection, retinol, retinol-binding protein, sequestration, urinary loss

Introduction

Many factors influence the plasma transport, tissue uptake, and metabolism of vitamin A (VA)[9] and carotenoids, including nonmodifiable factors such as age, sex, and genetic predisposition (1–3) and modifiable factors such as smoking, diet, and exercise. Inflammation is a "hard-wired" systemic response to infection or injury but may also be modified by anti-inflammatory hormones, cytokines, and drugs.

Inflammation is a component of injury response that is necessary for tissue repair and represents a program of metabolic changes necessary for survival (4), but if the process is prolonged or excessive, it becomes potentially life-threatening. Acute inflammation may be triggered by an infection or a sterile stimulus such as LPS that can be used to induce inflammation experimentally.

Inflammation (acute or chronic) relies on several mediators that transmit signals in the bloodstream or other fluids. These mediators include a variety of cytokines (e.g., ILs, interferons, chemokines), NO, intercellular adhesion molecules, or other messenger molecules, such as prostaglandins. Many mediators are regulated further upstream by transcription factors. Among those involved in inflammation are NF-κB, which is related to the release of several cytokines (e.g., IL-6, IL-8, TNF-α, IL-1β) and MAPKs (Figure 1). In addition, because of the interactions between oxidative stress and inflammation, nuclear factor (erythroid-derived 2)–like 2 (Nrf2) appears to play a fundamental role, strengthening the body's antioxidant enzymatic defenses (5), which include superoxide dismutase, glutathione peroxidase, catalase, and heme oxygenase 1.
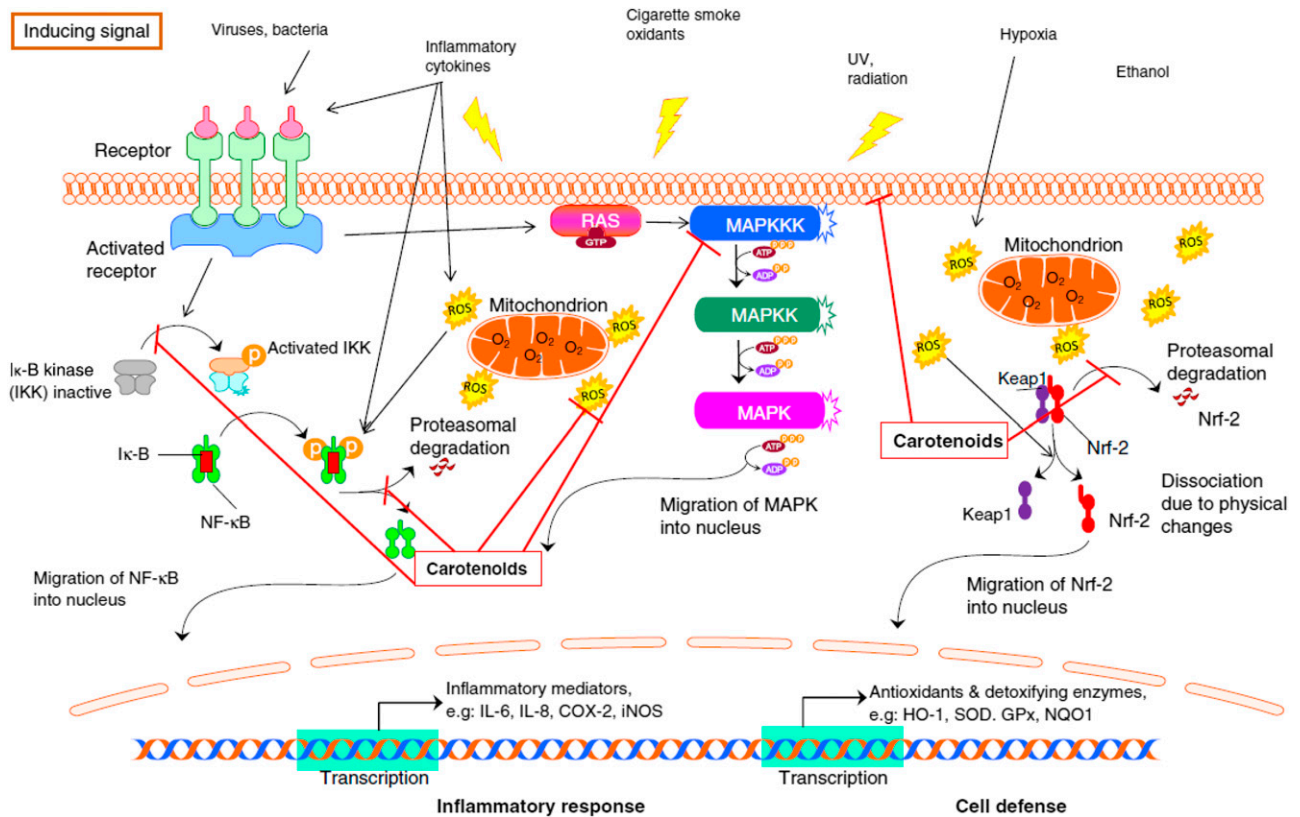
FIGURE 1 The current understanding of the role of carotenoids in the mitigation of negative effects of ROS in response to insults. COX-2, cyclooxygenase 2; GPx, glutathione peroxidase; HO-1, heme oxygenase 1; IKK, IκB kinase; iNOS, inducible NO synthase; NQO1, NADPH quinone dehydrogenase 1; Nrf-2, nuclear factor (erythroid-derived 2)–like 2; RAS, proteins with intrinsic GTPase activity involved in cellular signal transduction; ROS, reactive oxygen species; SOD, superoxide dismutase. Reproduced from reference 5 with permission.

VA intake and metabolism are seriously altered during the acute-phase response (APR) to inflammation (**Figure 2**) (6). The APR is a systemic metabolic response to infection, trauma, or tissue injury that induces fever, increases the synthesis of inflammatory cytokines, and enhances white blood cell production. The APR is well conserved among vertebrate species (7). This review discusses VA and carotenoid metabolism and biomarkers during inflammation, with a particular emphasis on infants and children in relation to animal models.

Current Status of Knowledge

Inflammation as a modifier of vitamin A transport and metabolism

Retinol-binding protein (RBP) and transthyretin form the plasma transport complex for retinol; both proteins are chiefly synthesized in the liver (8), the major organ involved in the APR (9). The APR results in dramatic alterations in protein synthesis and energy metabolism (10). A principal characteristic of the APR is the hepatic synthesis and secretion of acute-phase proteins (APPs) that play anti-infective roles and, consequently, function in response to tissue injury after trauma or infection (9). The leading regulators of the APR in hepatocytes are IL-1 and IL-6 (11). The kinetics of APP responses vary; C-reactive protein (CRP) changes

most rapidly and increases dramatically in plasma within 8 h of APR induction. Other APPs, such as α1-acid glycoprotein (AGP), increase more slowly and remain elevated during convalescence.

Both RBP and transthyretin R are negative APPs because their concentrations decline during the APR. Retinol binds nearly stoichiometrically to RBP; thus, they are equally affected. The reduction in plasma holo-RBP (RBP bound to retinol) occurs quickly, even before CRP and AGP have reached peak concentrations. The rapidity of the response may be caused by the inherently short half-life of RBP (~12 h in adults) (12, 13), which must be continuously synthesized to maintain normal holo-RBP concentrations (14). The APR may reduce plasma amino acid concentrations (15), which further inhibits RBP synthesis, a process that is sensitive to protein and calorie malnutrition (16).

Low serum retinol (SR), i.e., hyporetinolemia, has been reported in children and adults in association with acute infections (e.g., measles, malaria, diarrhea, HIV), multiple morbidities (17), and trauma (18). Several studies have provided evidence that retinol and RBP concentrations are inversely correlated with serum concentrations of IL-6, the major regulator of the APR because it induces the gene expression of many APPs (9).
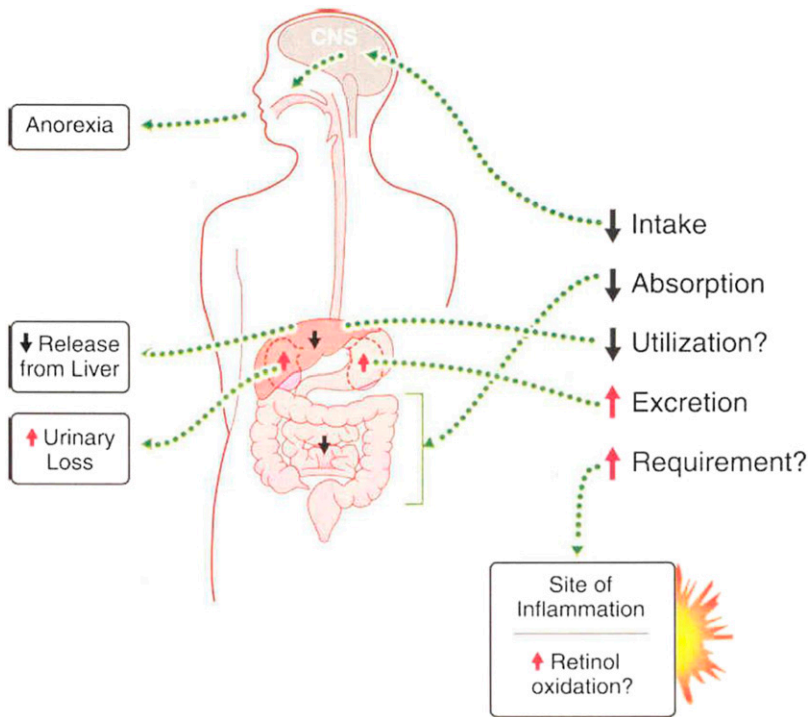
FIGURE 2 Inflammation can negatively affect vitamin A balance through decreased dietary intake, reduced intestinal absorption, and increased urinary excretion. Inflammation may also cause the sequestration of vitamin A in the liver, which leads to hyporetinolemia. Reproduced from reference 6 with permission.

Animal studies of hyporetinolemia during inflammation. The most common experimental models of inflammation induce the APR with LPS, which is a natural component of the outer wall of gram-negative bacteria that causes sterile inflammation (19). The response to LPS is dose-dependent, wherein lower doses induce an APR and higher doses result in vascular collapse and death. LPS signals through toll-like receptor 4, which triggers signal transduction cascades that result in the activation and nuclear translocation of NF-κB, which induces the release of proinflammatory cytokines TNF-α, IL-1, IL-6, and type 1 interferons (20). LPS acts rapidly, triggering the APR within hours (21). In the liver, IL-6 alone is sufficient to initiate similar changes by signaling through glycoprotein 130 and signal transducer and activator of transcription 3 pathways (11, 21). In rats treated with low-dose LPS sufficient to elevate body temperature but not cause serious lethargy or sickness, SR concentrations reached a nadir between 12 and 24 h, with a reduction ≥50% (22, 23). Serum RBP declined with similar kinetics (22), and although liver RBP synthesis was substantially reduced by 24-h post-LPS treatment, liver retinol concentration was maintained. RBP 4 (*Rbp4*) mRNA concentrations in the liver were reduced to 50% of the control value by 12 h after LPS treatment. This work provided evidence that inflammation-induced hyporetinolemia is caused by a reduction in liver RBP synthesis that was initiated by the reduced transcription of *Rbp4*. Similar results were obtained in a rat model of inflammation induced by recombinant human IL-6 that caused a more dramatic and prolonged decline in SR, possibly caused by persistent inflammation (24).

Although RBP was substantially reduced in the liver and kidney, these organs responded differently regarding *Rbp4* mRNA. *Rbp4* mRNA was reduced in the liver but did not change in the kidney, which is normally between ∼5% and 10% of the liver concentration (8). Because the decrease in *Rbp4* mRNA in the liver was coincident with or preceded the decrease in serum RBP, a reduced rate of transcription may account for the hyporetinolemia (22). The reduction in RBP but not its mRNA in the kidney may signify that the reduction in RBP is caused by reduced uptake, low RBP in serum, or the reduced reuptake of RBP after filtration, which occurs normally (25).

The "look-alike" problem. A practical concern is that if SR and RBP concentrations are reduced by inflammation, the results lend a false impression regarding VA status. An experimental illustration is shown in **Figure 3** for an animal study in which low SR resulting from dietary restriction was quantitatively similar to hyporetinolemia induced by LPS in animals fed adequate VA. Whereas in experimental settings causality is known, in human settings, in which dietary intake often is uncertain or seasonal, low SR concentrations could easily be attributed to nutritional inadequacy when, in fact, they are caused by inflammation. Although this look-alike problem is now well recognized, the ap-propriate interventions remain uncertain. One opinion is that low SR, regardless of etiology, signifies that the uptake of retinol by tissues might be restricted, and the low values should receive intervention. Another opinion is that low SR values might be adjustable by measuring markers of inflammation, such as CRP or AGP, with the use of these factors as covariates to assess what the adjusted
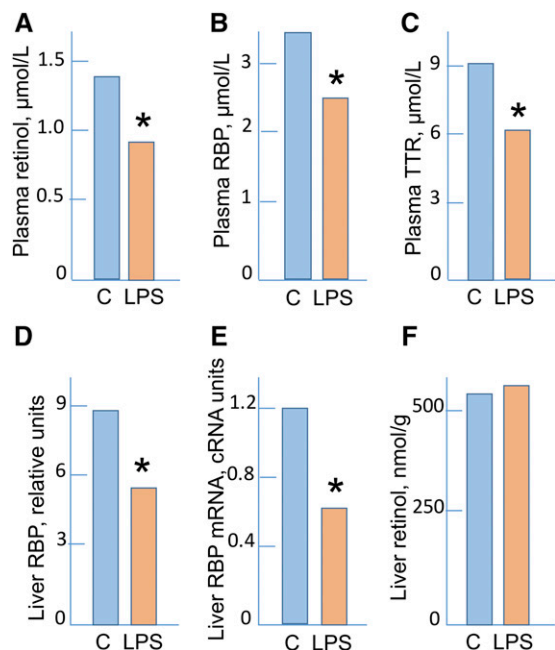
FIGURE 3 Plasma retinol (A), RBP (B), and TTR (C) and liver RBP (D), RBP mRNA (E), and retinol (F) in control rats and in rats after the induction of inflammation by the administration of LPS. Data are means, $n = 5$. Results are for 24 h after the administration of LPS except for panel E, which represents results at 12 h. Data are from reference 22. *Different from C, $P < 0.02$. C, control group; RBP, retinol-binding protein; TTR, transthyretin.

SR concentrations would be in the absence of inflammation (26). In this approach, inflammation is viewed as an interference to the assessment of whether VA liver stores may or may not be adequate. How one assesses these approaches depends on the question being addressed. In either case, understanding the etiology of low SR is critical for properly addressing the underlying problem.

An NIH-sponsored working group, Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence, reviewed the literature on inflammation and biomarkers of micronutrient status for several micronutrients (27). The review provides useful guidance to clinicians, researchers, and programmatic planners with regard to the impact of inflammation on micronutrient biology and biomarkers. The findings are intended to be integrated into the Biomarkers of Nutrition for Development project (28). Researchers in European countries have conducted a similar review on the impact of inflammation on biomarkers (29).

Redistribution of retinol during the APR. In well-nourished humans, SR concentrations return to normal values during the convalescent/resolution stage of infection. This suggests that the APR involves a redistribution of retinol from plasma to other body compartments, from which it is later able to return to plasma. A redistribution rather than a net loss may also be inferred from the results of animal studies in which the urinary loss of retinol during

infection was quantitatively small compared with normal VA turnover (23). In the VA-adequate state, the plasma retinol pool is small compared with the body reserves with which it equilibrates (30). Consequently, determining the "missing plasma retinol" in tissues can be challenging. Nevertheless, the use of [³H]retinol tracer kinetics together with mathematical modeling of the data have shed light on the trafficking of retinol during inflammation (31). In rats in which [³H]retinol was orally administered and time elapsed for equilibration, the induction of inflammation resulted within 1 d in a downward deviation of the plasma [³H]retinol decay curve that was of greater magnitude in recombinant human IL-6–treated rats than in LPS-treated rats. However, during the resolution of the APR (∼10 d), the plasma [³H]retinol curve increased and followed the trajectory established before inflammation induction (**Figure 4**). Mathematical modeling indicated a 79% reduction in the hepatic mobilization of retinol within 15 h after LPS administration and a 75% reduction by 5.6 h after the IL-6 injection. The results imply that retinol exits plasma transiently during inflammation and accumulates in the liver, but based on its reappearance there is not an appreciable irreversible retinol loss (24). It was hypothesized that inflammation-induced hyporetinolemia reflects a sequestration of plasma retinol that is associated with impaired mobilization of retinol caused by reduced RBP synthesis.

Inflammation during VA deficiency and repletion. VA deficiency and inflammation may interact to result in a quantitatively greater reduction in plasma retinol than from either condition alone (23). When marginally VA-deficient rats were supplemented with an oral dose of VA to simulate a relative dose response (RDR) test (32), the increase in plasma retinol after the oral dose in rats with inflammation was less than that of VA-marginal rats without inflammation (23, 33). Thus, LPS-induced inflammation limited but did not completely prevent the ability of VA supplementation to improve plasma retinol concentrations. In addition, the physiologic response of plasma retinol to a VA supplement provided for repletion may be altered qualitatively in an induced state of inflammation, whereas retinyl esters accumulate in the plasma (23). This finding suggests that the hydrolysis of newly absorbed VA, transported as retinyl ester in chylomicra or their remnants, was delayed. Lipoprotein lipase activity is known to be reduced by LPS (34, 35). Consistent with the hypothesized delay in chylomicron clearance, liver retinyl esters were lower in the LPS- and VA-supplemented group (23). Reduced hepatic metabolism has also been suggested by the reduction in the liver of mRNA concentrations for several genes involved in VA uptake, β-carotene and retinol metabolism (e.g., β-carotene oxygenase 1, lecithin retinol acyltransferase and dehydrogenase/reductase 3), and retinoic acid (RA) oxidation (e.g., cytochrome P450 family 26) (36). In addition, studies in other models have shown
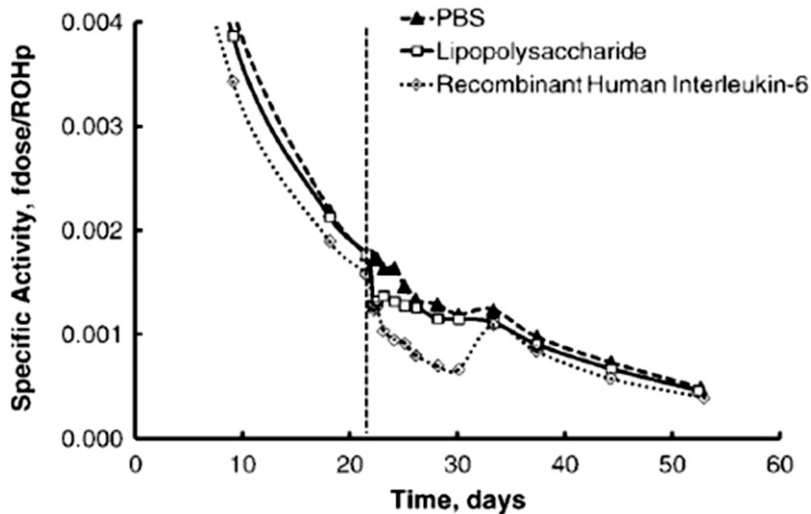
FIGURE 4 The specific activity, calculated as the fraction of the dose divided by the plasma retinol concentration, in rat plasma during an insult with PBS (*n* = 2 for 3 and 7 d), LPS (*n* = 5 for 3 d), or recombinant human IL-6 (*n* = 5 for 7 d). The dashed line is the time that the insult was initially administered. The model-based compartmental analysis indicates a reduced mobilization of hepatic vitamin A during inflammation in rats. fdose; fraction of dose; ROHp; plasma retinol. This research was originally published in the *Journal of Lipid Research* (31). Gieng SH, Green MH, Green JB, Rosales FJ. Model-based compartmental analysis indicates a reduced mobilization of hepatic vitamin A during inflammation in rats. J Lipid Res 2007;48:904–13. ©2007 the American Society for Biochemistry and Molecular Biology. Reproduced from reference 31 with permission.

that liver injury results in the gradual mobilization or loss of retinyl esters from stellate cells, which can eventually lead to liver fibrosis (37). Inflammation also alters the distribution and metabolism of RA, the major active metabolite of VA. When inflammation was induced by low-dose LPS in rats with marginal VA status, [³H]RA uptake and metabolism to polar metabolites were considerably reduced (38, 39).

Infections increase the risk of VA deficiency

Nutritionists have recognized for several decades that infectious diseases can increase the risk of malnutrition in children (40). Diarrhea and lower respiratory tract infections have a particularly pronounced effect on infant growth (41), presumably because of a combination of illness severity, such as pneumonia, and increased stool frequency (e.g., diarrhea is a common childhood illness in regions with inadequate sanitation). Relatively few studies have demonstrated the effects of infection on the risk of specific nutritional deficiencies. With regard to VA, an observational study in Indonesia demonstrated an association between respiratory infections and diarrhea on the increased risk for xerophthalmia, the principal clinical manifestation of VA deficiency (42). Common infections (e.g., chickenpox, respiratory infections) have been implicated in the depletion of liver stores or failure of VA intake to maintain liver stores (43, 44). The observation that common childhood infections increases the risk of VA deficiency is an important public health concern in many areas of the world because deficiency can lead to blindness (45) and death (46).

Infections increase the risk of malnutrition by a variety of mechanisms that were originally described for vitamin B-12 (47) and reviewed for VA (6). Although the specific categories vary among authors, they generally include decreased food intake, impaired nutrient absorption, direct nutrient loss, altered transport to target tissues, and increased metabolic requirements or catabolic losses. Indeed, acute infections during childhood cause decreased food intake, which is often lower with higher illness severity. In community-based studies of generally healthy children, the occurrence of acute respiratory infections decreased caloric intake by 8% relative to periods when children were asymptomatic; the decrease was 11% for children with malaria (48) and 18% with diarrheal illness (49). Measles generally cause a more severe infection, and a study showed a caloric deficit of 75% compared with intake during recovery (50), although the intake during recovery might be slightly higher than normal. Interestingly, a community-based study of infants that quantified breastmilk and food intake showed that although the total energy intake from nonbreastmilk sources was decreased by diarrhea and fever, the intake of breastmilk was not affected (51), offering further benefits for breastfeeding.

Enteric infections can decrease the absorption of many nutrients. Enteric infections damage the intestinal epithelium and decrease the expression of brush-border enzymes such as lactase, as shown in a piglet model of neonatal diarrhea (52). Intestinal barrier damage during mild *Ascaris* infections of children also decreases lactose absorption, which recovers upon antiworm treatment (53). For VA provided as β-carotene, absorption may be improved by roundworm treatment (54). The absorption of physiologic doses of preformed VA is generally quite high (~99%) but is lower (70–80%) in children with diarrhea, an *Ascaris* infection, and nonenteric infections such as pneumonia (55, 56). Although the mechanisms of this absorptive defect are unclear, impaired absorption contributes to an increased risk of VA deficiency in children with low dietary intakes.

After absorption, several infections can cause direct nutrient loss, perhaps from intestinal "leakiness" resulting in protein-losing enteropathy, which occurs with postmeasles diarrhea (57), or by the direct loss of blood, which occurs during hookworm infection and leads to iron-deficiency anemia (58). Considerable amounts of VA can be lost in the urine as a result of proximal tubular dysfunction in the kidney (6). Low-molecular-weight plasma proteins,

including RBP, filtered through the glomerulus are normally reabsorbed in the proximal tubule (6). One hospital-based study (59) found that adults with severe infections, such as pneumonia or sepsis, excreted a mean of 223 μg retinol/d (presumably bound to RBP), which is 25% of the RDA for men and 32% for women. In that study, 24% excreted >1 RDA/d, indicating that severe infections could result in substantial urinary losses. (It should be noted that the use of aminoglycoside antibiotics, potentially toxic to kidney tubular epithelium, can be a contributing factor to urinary VA loss). Children with sepsis also excrete substantial VA in the urine, whereas children with pneumonia and diarrhea excrete lower amounts (60). Losses may continue for several days (61) and are associated with a high fever and evidence of kidney tubular dysfunction (e.g., increased urinary concentrations of β2 microglobulin).

During the APR, the decrease in SR concentration caused in part by the decreased mobilization from the liver (31) suggests that retinol availability in peripheral tissues may be diminished. In the eye, the retina is sensitive to low SR concentrations because it expresses stimulated by retinoic acid 6, the cell-surface binding receptor for RBP (62). Clinical and genetic data (6) have suggested that low SR during the APR may decrease retina sensitivity to light, perhaps as a result of decreased availability of retinal for rhodopsin formation. It is not known whether other tissues have specific effects from retinol limitation during the APR (e.g., for producing the RA needed for regulating gene expression). It is possible that limited VA availability in the immune system might be beneficial, perhaps by altering the type of immune response to particular pathogens, because RA is produced by immune cells and directly regulates the differentiation and survival of particular subsets of immune cells, particularly T lymphocytes (63). Carotenoid concentrations may also be lower during the APR (64), but the implications of this lowered concentration are unclear. It is not known whether the decline in carotenoid concentrations is transient, as for retinol, or if it represents "lost" carotenoids from increased catabolism or diminished intakes during illness.

During infection, requirements for some nutrients may increase because of increased utilization or catabolism. The resting metabolic rate is increased during HIV infection (65), which demands increased caloric intake to prevent weight loss at equivalent levels of activity. In addition, classical studies of model infections of human volunteers have shown increased nitrogen loss as a result of protein catabolism (66). With regard to VA during the APR, consistent evidence of increased metabolism or catabolism has not been demonstrated. However, tissue carotenoid pools decrease during the induction of an APR in chickens (67), suggesting catabolic losses. Interestingly, tissue carotenoid pools are more resistant to change at low dietary carotenoid concentrations. Similar data are not available from humans, but oxidative metabolism induced during inflammation might result in decreased tissue carotenoids. Consequently, altered metabolism of provitamin A carotenoids during infection could adversely affect VA status.
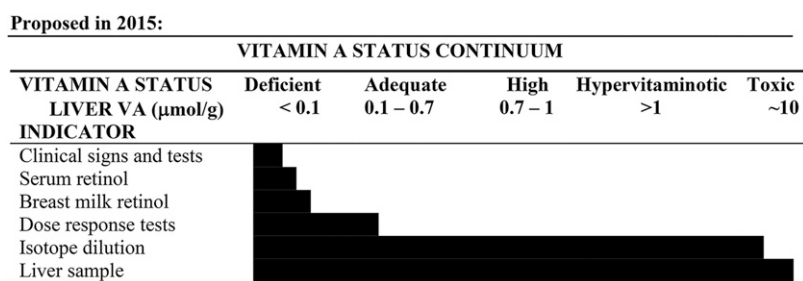
Assessment of VA status during inflammation

Methods used to assess VA status are often affected by the APR. The most common methods used to assess VA status include the clinical evaluation of eye symptoms, serum and breastmilk retinol concentrations, dose-response tests, and isotope dilution assays (**Figure 5**) (68). This section describes how each method may be affected during an APR.

Biological and functional clinical tests. A close association exists between xerophthalmia (e.g., Bitot's spots, nightblindness) and the APR assessed with the use of AGP and CRP (69, 70). Supplementation with VA increased plasma retinol concentrations during deficiency but did not affect AGP and CRP concentrations in children with and without xerophthalmia (70). Furthermore, corneal involvement in children who have an acute infection, such as measles, is commonly observed (71). Measles is a known precipitating factor for the development of xerophthalmia in children with VA deficiency (72). In fact, the WHO still recommends giving 2 high-dose VA supplements 24 h apart for children in developing countries who have measles. VA supplements reduce the number of measles-related deaths, replenish body stores, and prevent xerophthalmia (73).

SR concentrations. Both RBP and transthyretin are depressed during infection and inflammation. In the kidney,

FIGURE 5 The current understanding of the relation of total liver reserves (expressed as μmol retinol/g liver) and the dynamic working range of the listed biomarker. Clinical signs of deficiency and depressed serum retinol concentrations occur during severe vitamin A depletion. Breastmilk retinol is a unique indicator for lactating women and can be extrapolated to infants. The dose-response tests offer more information on liver reserves than serum retinol concentrations alone. Isotope dilution is the only indirect biomarker that has utility along the entire continuum of reserves compared with a liver biopsy, which has limited feasibility but is considered the gold standard. Reproduced from reference 68 with permission.

Proposed in 2015:

VITAMIN A STATUS CONTINUUM					
VITAMIN A STATUS LIVER VA (μmol/g) INDICATOR	**Deficient** < 0.1	**Adequate** 0.1 – 0.7	**High** 0.7 – 1	**Hypervitaminotic** >1	**Toxic** ~10
Clinical signs and tests					
Serum retinol					
Breast milk retinol					
Dose response tests					
Isotope dilution					
Liver sample					

RBP becomes uncoupled from transthyretin, and during a high fever holo-RBP is not reabsorbed but excreted in the urine (6). SR concentrations are a static measure usually performed on previously collected samples. The release of plasma retinol bound to RBP from the liver is homeostatically controlled, and therefore it does not change over a wide range of liver reserves (74). As a biomarker of VA status, it may not respond to interventions (68, 75). In rats, SR was actually higher after VA withdrawal in the group that received marginal daily VA (76) than in the groups that received more than the daily requirement (76, 77). In children, SR concentrations did not differ after treatment with high-dose supplements (78) or after feeding with high β-carotene–biofortified maize (79, 80).

Measuring CRP and AGP is recommended in surveys to evaluate the impact of inflammation on SR concentrations (79, 81). In Zambian children, negative shifts in SR concentrations became apparent based on the degree of inflammation (68, 81) (**Figure 6**A). By correcting for inflammation to lower the threshold of acceptable SR concentrations (82), the percentage of individuals with SR concentrations <0.7 μmol/L decreased from 17% to 3% (81).

Breastmilk retinol concentrations. The degree to which inflammation affects breastmilk retinol concentrations is not currently known to our knowledge. One report from rural Zambian mothers did not find an association in a preliminary analysis (83). Considering that breastmilk retinol is derived from RBP and chylomicron delivery, this topic needs further evaluation. In rats, chylomicra contribute ~40% of milk retinol (84), and in lactating sows 13–26% of tracer doses were either detected in milk or measured in nursing offspring (85, 86). It is likely that RBP-delivered retinol accounts for 60–85% of breastmilk retinol in humans. If SR is depressed during inflammation, breastmilk concentrations may become depressed, especially in women who have low dietary intakes.

Dose-response tests. Two dose-response tests are available for assessing status in surveys and intervention studies. The RDR and modified RDR (MRDR) tests are based on the principle of accumulated RBP during VA depletion released after a challenge dose (87). The major difference is that the RDR uses retinyl ester, whereas the MRDR uses 3,4-didehydroretinyl acetate (68). Attributes of dose-response tests are that they only require HPLC for analysis and provide more information than SR regarding liver VA reserves (Figure 5). The RDR uses 2 blood samples—at baseline and 5 h after dosage—and may be affected by inflammation, as observed in Peruvian children (88). The MRDR measures newly ingested didehydroretinol in a single blood sample and is therefore distinguishable from circulating retinol. Three separate trials in infants and
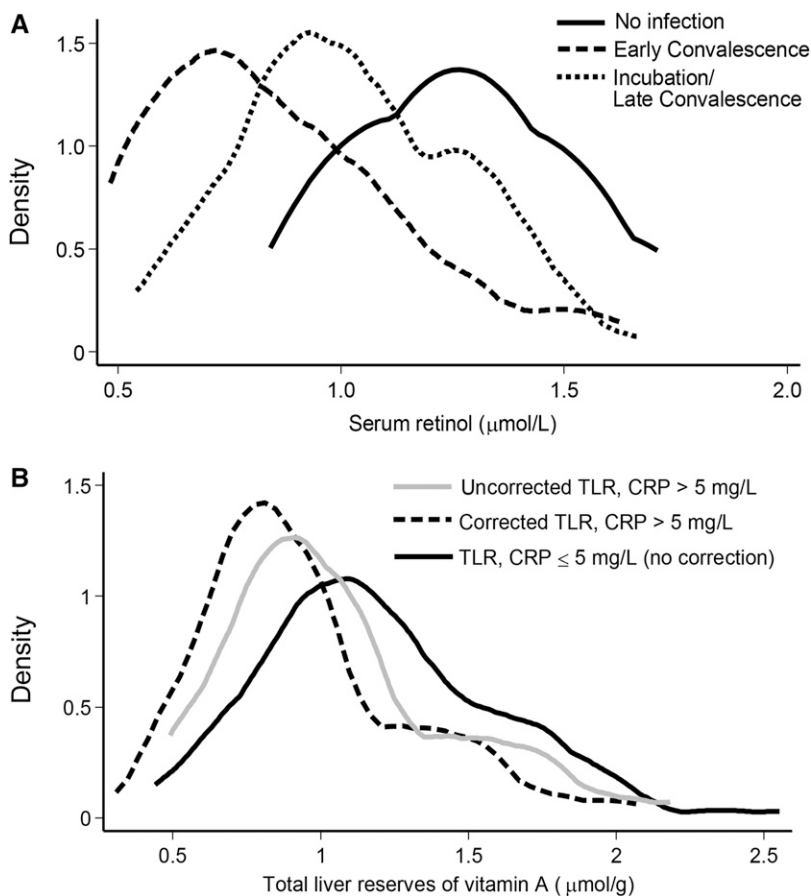

FIGURE 6 The impact of elevated acute-phase proteins on serum retinol concentrations in children (A). The curve on the far right reflects the distribution in children without inflammation. The middle curve reflects children who are in late convalescence (only AGP elevated), and the curve on the far left demonstrates serum retinol concentrations during early convalescence when both CRP and AGP are elevated. (B) The influence of adding an extra correction factor in the calculations for total liver retinol reserves in Zambian children with elevated CRP. If nonsymptomatic inflammation affects absorption, the relation would be the opposite; i.e., TLRs would be overestimated. Kernel density estimations produce a smoothed curve of data. AGP, α₁-acid glycoprotein; CRP, C-reactive protein; TLR, total liver reserve. Panel A is reproduced from reference 68 with permission.

children did not detect an influence of the APR on MRDR values (79, 89, 90).

The dose-response tests are qualitative measures of liver VA reserves (68). Although infection and inflammation may reduce dose absorption (55, 56), the response depends more on the accumulation of RBP in the liver than on the absolute dose absorbed. This is in contrast to retinol isotope dilution (RID) tests that rely on the amount of dose absorbed for accurate calculations.

RID tests. RID tests are the most sensitive methods for assessing VA status because they provide information on liver reserves from deficiency through hypervitaminosis A (68). A baseline blood sample is typically taken before dosage with either deuterated or [^{13}C]retinyl acetate, followed by another blood sample 3–21 d after dosage depending on the application (91, 92). The impact of inflammation on RID test accuracy is currently a subject of field-based research. The factors that may be affected by inflammation include the amount of tracer absorbed (55, 56) and specific activity of retinol in the serum compared with the liver (31).

In India, radioactive tracer dose absorption was reduced from 99.2% in healthy children to 74.3% in children with infections (55). In Zambia, the absorption of a 5-mg dose was 81.2% in 3 children without illness and 62.4% in a child who was ill (93). Therefore, it may be appropriate to decrease the amount of tracer absorbed in the equation used to calculate total body stores (80, 92). However, when this assumption was applied to Zambian children, the distribution curve of calculated VA reserves (micromoles per gram of liver) in children with a CRP >5 mg/L was slightly lower than in those without elevated CRP (Figure 6B). If these children had reduced dose absorption, liver reserve calculations should have been artificially elevated. By correcting the equation for decreased tracer absorption in children with asymptomatic inflammation, the distribution curve shifted them to even lower calculated reserves (Figure 6B). None of the children enrolled had a fever or serious illness because these were exclusion criteria (80).

A common infection in some African countries is malaria. VA-deficient mice were made resistant to malaria by administering VA (94). In vitro, 9-*cis*-RA increased the phagocytosis of *Plasmodium falciparum*–parasitized erythrocytes, increased parasite clearance, and reduced proinflammatory cytokine responses (95). The association between malaria in humans and VA status is, to our knowledge, not known. In Zambian children from 4 villages, total body VA reserves were highest in the village that did not have asymptomatic malaria (96). This observation might imply that asymptomatic malaria does not affect RID test accuracy. If the other villages have a greater prevalence of malaria, which might result in a lower absorption of the tracer dose, then total body stores would be calculated to be lower in the village that did not have malaria, but this was not observed.

The specific activity of radioactive retinol to plasma retinol was affected by administering LPS or recombinant human IL-6 to rats (31) (Figure 4). Not only were SR concentrations reduced by ∼47 and ∼65% (31), respectively, but the change in serum specific activity suggested the heavier isotope was sequestered in the liver. The specific activity resolved quickly after the cessation of the inflammatory agents. Therefore, RID tests may be influenced during times of active infection. Best practice is not to enroll children who have an active fever in VA surveys or studies because the illness may affect dose absorption, retention, and the specific activity difference between serum and the liver.

Epidemiologic studies related to carotenoid metabolism and inflammation

Interrelation of carotenoids, inflammation, and oxidative stress. Carotenoid metabolism is altered during inflammation, and carotenoid status can in return influence inflammation and oxidative stress. Several epidemiologic studies, including meta-analyses, have suggested that a high dietary intake of carotenoids and elevated plasma concentrations are correlated with a decreased risk of cardiovascular diseases (97), type 2 diabetes mellitus (98), and certain types of cancer (99, 100), often by ≤30%, including all-cause mortality (101). These findings were originally attributed to antioxidant effects because isolated carotenoids are effective free-radical scavengers in vitro (102). Some of these associations may have been misinterpreted; i.e., low carotenoid concentrations may have resulted from the diseases rather than contributory factors.

However, several large-scale supplementation trials that incorporated carotenoids were unable to confirm health benefits, including the α-Tocopherol β-Carotene Cancer Prevention trial (103) and β-Carotene and Retinol Efficacy Trial (104). In fact, increased mortality occurred from lung cancer in smokers at daily doses of 20 mg (with 50 mg α-tocopherol) and 30 mg β-carotene (with 25,000 IU VA). Likewise, meta-analyses suggested increased all-cause mortality for subjects taking β-carotene supplements (105, 106). The comparative or combined treatment of 25,000 IU VA, however, has not been evaluated to our knowledge. It has been hypothesized that higher carotenoid doses may act as prooxidants in smokers' lungs, especially when administered in isolated form. Two long-term β-carotene supplementation trials in China did not report adverse effects; however, this may be explained by coexisting poor VA status caused by low intakes (107).

Because of limited carotenoid bioavailability [∼10–40% (108)] and low achievable plasma concentrations (∼2 μmol/L), the direct antioxidant effects may not fully account for the attributed carotenoid-related health effects. Instead, other mechanisms, such as the alteration of intracellular-signaling cascades and/or gene expression, may be more important. Carotenoids interact with several transduction cascades, reducing NF-κB and stimulating Nrf2 translocation (5). Carotenoids can block signal transduction at various stages by binding to cysteine residues (Michael adduct reaction) of nucleophilic proteins, depending on their cellular concentration and the general inflammatory state. For example,

carotenoids have been reported to bind to the kinase responsible for the phosphorylation of the inhibitory protein of NF-κB, consequently blocking the ubiquitylation and dissociation of the inhibitor from the NF-κB complex and preventing the translocation of the free NF-κB subunits to the nucleus (109). Similarly, for Nrf2, carotenoids can bind to Nrf2 and/or its Kelch-like ECH-associated protein 1 inhibitor, promoting the dissociation from Nrf2, which then translocates and activates gene expression (110). However, as outlined in the next section, the effects are generally found to depend on the concentration, cell type investigated, cell inflammatory state, and type of carotenoid or carotenoid metabolite.

In vitro studies and mechanistic insights. Multiple in vitro studies with carotenoids, their oxidation products, or their metabolites have exposed cells or tissues to high concentrations, such as Caco-2 intestinal cells, immune cells, the liver, adipose, and the retina. Despite limitations, such as studying isolated cells, using high concentrations, solubilization in organic solvents, lack of stability of carotenoids, and short-term exposures, these studies interrogated mechanistic effects without ethical restrictions (111). Several studies that used a wide range of cell models have suggested both anti-inflammatory and antioxidant effects (5). For example, lycopene at physiologic concentrations resulted in reduced TNF-α activity in inflammation-stimulated human mammary cancer and osteoblast cell lines. Interestingly, this effect was stronger for lycopene hydrophilic degradation products (after UV radiation) and its derivatives (109). In another trial, aldehyde derivatives with a carbon chain length of 12 and those having a methyl group with 3 carbon atoms from the terminal aldehyde had the strongest effects on Nrf2 translocation in the human breast and prostate cancer cells (112). In fact, studies have proposed that β-carotene oxygenase 1 and 2 cleavage products are better candidates for binding to cysteine residues of both NF-κB and Nrf2 because of their higher solubility in the cytosol and electrophilicity (109, 112).

To overcome the limitations of excluding digestive processes and studying isolated carotenoids, Caco-2 cells and a Caco-2:HT-29THP-1 triple culture (90:10 ratio coculture plus THP-1 cells in the basolateral compartment) were exposed to the digesta of plum and cabbage varieties rich in carotenoids and polyphenols. IL-6 and IL-8 release was partly reduced and was related to decreased NF-κB and Nrf2 expression and translocation (113). However, the digesta of foods low in carotenoids and polyphenols showed similar results, suggesting other bioactive compounds as causal agents.

Many carotenoids escape absorption in the small intestine, and processes regarding carotenoid metabolism and degradation in the colon have been overlooked (114, 115). In vitro studies have suggested that carotenoids are only partly recovered in the colonic fraction (10–50%) (116, 117). From other phytochemical studies with polyphenols, it is evident that microbiota can promote molecular ring fission, deglycosylation, hydrolysis, deglucuronidation, and demethylation reactions (115). No data to our knowledge are available for carotenoids. It may be speculated that potential polar degradation products could be produced, which may be bioactive.

Short-term animal and human intervention trials. Several animal studies have confirmed the positive effects of carotenoids on inflammation markers (5). Interestingly, the bioactivity of polar degradation products has recently been studied. In a rat study with lutein-derived products created by UV irradiation, degradation products more strongly ameliorated NO, malondialdeyhde, prostaglandin E2, TNF-α, and IL-6 than lutein itself (118). Contrarily, supraphysiologic RA doses (1–10 μmol/L) were associated with prooxidative effects (119) compared with lower doses (<1 μmol/L) (5), emphasizing the importance of exposure concentration. Other carotenoid metabolites, such as apo10-lycopenoic acid, were stronger activators of RA receptor (RAR) and retinoid X receptor in animal trials than lycopene (120, 121), suggesting VA-like behavior (122). In addition, apo10-lycopenoid acid upregulated sirtuin 1 enzymatic activity in *ob/ob* mice, preventing fatty liver formation (123). In liver cells, several β-carotene cleavage products (β-apo14′-carotenal, β-apo14′-carotenoic acid, and β-apo13-carotenone) competed with RA binding to RAR, highlighting their involvement in cell growth and differentiation (124). Whether the metabolism of these apocarotenoids is in turn influenced by inflammation is to our knowledge currently unknown.

Contrary to long-term supplementation trials, several short- and midterm intervention trials with whole foods, especially tomato products rich in lycopene, have suggested health benefits for generally healthy and overweight people, as measured by favorable changes in markers of inflammation (IL-6, IL-8, TNF-α, IL-1β, CRP, NF-κB) and oxidative stress (e.g., improved superoxide dismutase, glutathione peroxidase, catalase, heme oxygenase 1, Nrf2) (Figure 1) (5). For example, in a randomized controlled trial, consuming a tomato beverage (16 mg carotenoids/d) for 26 d reduced plasma TNF-α concentrations in healthy subjects by 34% (125). Most studies that used carotenoid-rich foods, however, have shown limited effects in healthy subjects (125–127). Supplementation trials on subjects with chronic inflammation have been more promising. For instance, lycopene (70 mg/wk for 12 wk) improved the inflammation marker serum amyloid A in middle-aged overweight subjects by ~30% (128), but the study was not placebo-controlled. In a placebo-controlled study, lutein (20 mg/d dissolved in oil as a gelatin capsule) taken for 3 mo by early arthritis patients improved plasma IL-6 (defined as carotid intima media thickness as >750 μm for individuals aged <59 y or >850 μm for those aged >60 y) (129) and monocyte-chemoattractant protein 1 compared with a placebo by −150 and −100 pg/mL, respectively. Several studies have highlighted rather high interindividual differences regarding carotenoid absorption, degradation, metabolism, and excretion partly because of

genetic differences in several single-nucleotide polymorphisms on lutein (130), lycopene (131), and β-carotene absorption (3, 132), which may partly explain variable intervention responses.

Vitamin A, carotenoids, and inflammation in pregnancy and infancy

Dietary carotenoids and retinoids play important roles in innate and acquired immunity during pregnancy and development. In particular, VA deficiency, which affects ∼190 million children worldwide, increases the likelihood of early-childhood mortality because of common infections (133, 134). In VA-deficient or -insufficient states, the increased susceptibility to immune-mediated and inflammatory disorders is related to impaired responses to infection, impaired epithelial barrier function (6, 135), and immunologic defects. Responses to mucosal pathogens are impaired when VA stores are low partly because VA metabolites promote the functional maturation of innate immune cells (6, 63, 136, 137).

VA and cellular immunity during development. VA-deficient animals exhibit abnormalities in the blood and splenic lymphocyte numbers. T- and occasionally B-cell populations are reduced, and myeloid lineage cells, especially granulocytes, tend to increase (138, 139). Granulocyte stimulation likely results from the insufficient RA-mediated inhibition of granulocyte-macrophage colony-stimulating factor (140), which is reversible with RA administration (139). RA signaling plays a critical role in the development of B cells, the major cell mediators of humoral immunity. VA and RA regulate B-cell maturation and differentiation at multiple combinatorial levels that control and often potentiate antibody production. VA deficiency reduces the number of fetal B-cell progenitors, whereas a pan-RAR antagonist, LE540, inhibits both fetal and adult B-cell lymphopoiesis in vitro (141). Although physiologic concentrations of RA inhibit the proliferation of normal B-cell progenitors (142), they apparently influence multiple stages of B-cell lymphopoiesis and accelerate the generation of CD19+/IgM+ B cells (143). These results suggest that RA helps to sustain the microenvironment for B-cell development and maintain a functional B-cell pool essential for the response to antigens (137).

CD4+/CD8+ T cells differentiate in the thymus. In humans, thymic development starts before birth and ceases during puberty with thymic involution (144). As previously mentioned, VA deficiency is accompanied by immune deficiency and susceptibility to a wide range of infectious diseases (145, 146). In addition, marked atrophy of the thymus and spleen is observed in VA-deficient animals (147). A pertinent observation in developmental immunity is that RA-synthesizing enzyme activity peaks at the same time as RAR responsiveness, a time during which thymic cellularity is highest and T-cell selection is most pronounced (148). Direct data on the effects of carotenoids on thymic selection remain unavailable to our knowledge.

Lymphocyte proliferative responses to mitogens are also retinoid-dependent (149, 150). In pregnant mice, VA and β-carotene supplementation affected immune cell functions during ontogenesis (151). Beginning at conception, dams were provided with a control diet or different retinoid- and carotenoid-enriched (4500 retinol equivalents/kg) diets. The percentage and total numbers of splenic mononuclear cells were determined serially throughout gestation. VA and β-carotene supplementation variously increased lymphocyte numbers in early and midpregnancy and increased T:B-cell ratios (151). In addition, in mice, maternal VA supplementation via intraperitoneal injections increased serum IgM and T-helper cell (Th) 2–specific IgG1 concentrations in the progeny (152). Nevertheless, during the first month of lactation in a human β-carotene supplementation study neither lactation nor β-carotene supplementation affected T-cell proliferation (153).

T-effector cells differentiate into several subtypes and include Th1 (defense against intracellular bacteria and protozoa), Th2 (humoral immune stimulators against extracellular parasites), Th17 (proinflammatory autoimmunity regulators), and immunosuppressive T-regulatory cells. In postnatal development, VA regulates the Th1:Th2 switch and thereby modifies immune and inflammatory responses (152, 154).

Investigating carotenoid effects on developmental immunity in animal models has been more challenging because of pronounced differences in carotenoid absorption, kinetics, and metabolism between humans and rodents (155). Nevertheless, some investigations have suggested important roles in T-cell polarization for several presumably nonprovitamin A carotenoids. One example is fucoxanthin-mediated T-regulatory induction and Th17 inhibition, which leads to suppressed inflammation and autoimmunity (156).

Carotenoids and inflammation in pregnancy and fetal development. The inflammatory response is tightly regulated during reproduction, embryonic and fetal development, and postnatal transition into infancy. During implantation in humans, the expression of proinflammatory cytokines such as IL-6, IL-15, and TNF-α promotes placental trophoblast invasion into the maternal endometrium, myometrium, and uterine vasculature; this tissue invasion results in the recruitment and activation of maternal immune cells. However, after the uteroplacental bed is established during the first trimester, the normal pregnancy state is characterized by immune quiescence, namely a Th2 cytokine profile, and the suppression of the maternal immunologic rejection of the "foreign" fetoplacental unit (157). A proinflammatory Th1 cytokine state is reactivated during parturition (158). In contrast, preeclampsia (a hypertensive disorder that causes substantial maternal and offspring morbidities and mortality) increases uteroplacental inflammation and the persistence of proinflammatory Th1 cytokine concentrations compared with normal pregnancy.

Preeclampsia is a state of both oxidative and inflammatory stress. Consequently, antioxidant and anti-inflammatory supplementation has been proposed to prevent or lessen its

severity (159). Analyses of maternal carotenoid concentrations have suggested inverse relations between plasma lutein, α- and β-carotene, and lycopene and the risk/severity of preeclampsia and diabetes mellitus (160–164), 2 pregnancy-related pro-oxidant and proinflammatory conditions. Of course, these findings might have resulted from the disease, dietary intake, or both. In support of a salutary role in pregnancy, Lorenzoni et al. (165) observed that lutein supplementation in pregnant women with gestational diabetes reduced newborn oxidative stress, as measured by blood total hydroxyperoxide concentrations.

VA, carotenoids, and inflammation in newborns. Intermittent or sustained systemic inflammation contributes to the pathogenesis of most disorders associated with prematurity, including brain damage and neurodevelopmental disorders (166, 167). In preterm and term infants, both the prevention of and therapy for hypoxic-ischemic brain injury increasingly emphasizes the interference with neurotoxic and neuroinflammatory cascades, with emphasis on endogenous neuroprotective mechanisms (168, 169). Both RA (170) and lutein (171) suppress neuroinflammation mediated by astrocytes and microglia, 2 cell types important in acute brain injury that accompanies preterm and term birth (172). The mechanisms of carotenoid (lutein, astaxanthin)-mediated neuroprotection include blocking the actions of NF-κB signaling on microglial and astrocyte activation, neuronal inflammation, inflammatory cytokine and chemokine release, and neuronal cell death (173).

Human milk contains various carotenoids, of which lutein is often predominant (174, 175). In term newborns, lutein supplementation suppresses measures of systemic oxidant stress (176, 177). In the retinopathy of prematurity, the principal cause of blindness in children in industrialized countries, systemic and localized neuroretinal inflammation plays a major pathogenic role (178, 179). Carotenoids, particularly lutein, suppress both systemic inflammation (measured by CRP) and retinopathy severity in preterm infants (179). It is important to note that lutein supplementation (or repletion) has similar antioxidant and anti-inflammatory effects in preterm infant and adult diabetic neovascular retinopathies (180). In experimental animal models, lutein and astaxanthin (181) suppress inflammation and improve retinal function in diabetic retinopathy. Wolfberry (goji; *Lycium barbarum*), an Asian fruit traditionally consumed to prevent eye diseases, is a particularly zeaxanthin-rich dietary source. In diabetic mice, wolfberry ameliorated retinopathy, suppressed inflammation, and provided retinal protection, effects that were mimicked by zeaxanthin or lutein in vitro (182).

Xanthophyll carotenoids exert anti-inflammatory and immunomodulatory activities in several mammalian systems. Mechanisms may include the inhibition of oxidative stress, inflammatory mediators, and lipid peroxidation; inhibition of proinflammatory NF-κB and MAPK signaling (Figure 1); blockage of advanced glycation end-product formation; suppression of scavenger receptor expression; suppression of lymphocyte and macrophage activation (183);

and modulation of T-cell polarization, such as increasing T-regulatory and decreasing Th17 cell expansion (137). Recent data have suggested that xanthophylls are regulators of macrophage-dependent immune responses. The human dietary xanthophyll astaxanthin, which is found in pink-orange fish and crustaceans, drives IL-10 production in anti-inflammatory M2 macrophages; similarly, lutein and astaxanthin support monocyte polarization away from the "killer" M1 macrophage phenotype to M2 macrophages (LP Rubin, unpublished data, 2014). In the liver inflammatory-disorder nonalcoholic fatty liver disease, an increasingly common comorbidity of obesity, dietary xanthophylls (including β-cryptoxanthin and astaxanthin) offer important preventive and treatment strategies. Experimentally, these carotenoids decrease hepatic inflammatory damage by restraining M1 macrophage activation or by driving M2 activation (184).

Conclusions

Inflammation affects retinoid and carotenoid metabolism. The roles of VA and carotenoids as potential modulators of developmental immunity, the APR, and inflammation, especially in light of global endemic VA insufficiency and low carotenoid intakes, warrant further investigation. Infections decrease VA intake as a result of infection-induced anorexia and decreased VA absorption from the intestine. VA may also be lost in substantial amounts in the urine during infection. In addition, plasma retinol may be sequestered in tissues, leading to a reduction in SR concentrations, which implies that assessing VA status with the use of SR or RBP during inflammation is problematic. These factors account for the increased risk of VA deficiency associated with infection. However, VA requirements are currently not known to be substantially increased by infections, a phenomenon that needs further evaluation considering the losses that occur in urine during acute infections. In addition, retinol mobilization from the liver decreases during the APR, perhaps having adverse effects on VA availability to target tissues, especially the retina. Furthermore, some biomarkers of VA status are affected by the APR, and this needs to be considered in population-based assessments.

Regarding carotenoid health benefits, a discrepancy exists between epidemiologic studies that have suggested benefits related to carotenoid intake and tissue concentrations and controversial results from interventions involving β-carotene. Nevertheless, in clinical trials and animal models, carotenoid supplementation (particularly lutein) to young infants reduced systemic inflammation, the inflammatory response in retinopathy of prematurity, and the neuroinflammation that accompanies hypoxic-ischemic brain injury. In general, information on carotenoid bioactivity is incomplete, and questions related to dose response, metabolism, and synergism may explain some findings. Several studies have suggested that carotenoid metabolites are bioactive, including enzymatic cleavage products (apocarotenals), and act as better targets for transcription factors such as NF-κB and Nrf2. Lower-to-intermediate concentrations may exert positive

effects on gene expression and antioxidant effects, whereas higher concentrations act pro-oxidatively. Further nuclear targets, such as the implication of RAR/retinoid X receptor and potential VA-like effects, also deserve more attention. Finally, our knowledge on carotenoid processes in the colon and interaction with the microbiota is nil. As long as these aspects remain marginally understood, our comprehension of the role of carotenoids in chronic diseases and inflammation will be far from complete.

Acknowledgments

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