The Role of Vitamin A in Wound Healing

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Abstract
Vitamin A is an essential micronutrient that comes in multiple forms, including retinols, retinals, and retinoic acids. Dietary vitamin A is absorbed as retinol from preformed retinoids or as pro–vitamin A carotenoids that are converted into retinol in the enterocyte. These are then delivered to the liver for storage via chylomicrons and later released into the circulation and to its biologically active tissues bound to retinol-binding protein. Vitamin A is a crucial component of many important and diverse biological functions, including reproduction, embryological development, cellular differentiation, growth, immunity, and vision. Vitamin A functions mostly through nuclear retinoic acid receptors, retinoid X receptors, and peroxisome proliferator-activated receptors. Retinoids regulate the growth and differentiation of many cell types within skin, and its deficiency leads to abnormal epithelial keratinization. In wounded tissue, vitamin A stimulates epidermal turnover, increases the rate of re-epithelialization, and restores epithelial structure. Retinoids have the unique ability to reverse the inhibitory effects of anti-inflammatory steroids on wound healing. In addition to its role in the inflammatory phase of wound healing, retinoic acid has been demonstrated to enhance production of extracellular matrix components such as collagen type I and fibronectin, increase proliferation of keratinocytes and fibroblasts, and decrease levels of degrading matrix metalloproteinases. (Nutr Clin Pract. 2019;00:1–6)

Keywords
inflammation; retinoids; skin; vitamin A; wound healing

Introduction

Biochemistry
Vitamin A refers to a group of small fat-soluble molecules composed of a cyclic ring, polyene side chain, and a polar end group. The major biologically active forms of vitamin A are retinol, retinal, and retinoic acid, which contain an alcohol, an aldehyde, or a carboxylic acid end group, respectively (Figure 1). “Retinoids” denote all natural and synthetic compounds that structurally resemble vitamin A, including those derivatives that are not biologically active.1 Vitamin A is an essential micronutrient that is unable to be synthesized in the human body and needs to be acquired by exogenous, mainly dietary, means.

Carotenoids are a large family of light-absorbing pigments biosynthesized by many plants and fruits; the subsets that can be metabolically converted into vitamin A are known as provitamin A carotenoids.2 The most notable of these is β-carotene, commonly found in carrots, which can be enzymatically cleaved to yield 2 vitamin A molecules (Figure 1).3 Other dietary provitamin A carotenoids include α-carotene and β-cryptoxanthin.4 Ingestion of dairy, fish, and meats (most notably, liver) comprise the main dietary source of preformed retinoids, namely retinol and retinyl esters.4

Absorption and Storage
Prior to enterocyte absorption, retinyl esters are converted to retinol by luminal and small-intestinal brush border ester hydrolases (Figure 2).5,6 Absorbed retinol is then re-esterified to retinyl ester in the enterocyte and packaged into chylomicrons. Dietary β-carotene uptake is mediated by the SR-B1 membrane transporter and is either packaged directly into chylomicrons or cleaved into retinaldehyde in the enterocyte by β-carotene oxygenase 1.7–9 Retinaldehyde may then be reduced into retinol by intestinal retinaldehyde reductase, esterified, and packaged into chylomicrons as retinyl esters.4 These chylomicrons are subsequently transported through the lymphatic system into the general circulation.
circulation. Most dietary retinoid is then delivered and stored in the liver, with the remainder distributed to other tissues throughout the body. In the hepatocyte, retinyl ester can be hydrolyzed to retinol for storage, but the majority is transported as retinyl ester (primarily retinyl palmitate) to hepatic stellate cells for storage in intracellular lipid droplets. When stored retinol is released from hepatocytes into the circulation, it is bound to plasma retinol-binding protein (RBP4), which is synthesized by hepatocytes; this complex is the predominant circulating form of vitamin A in the fasting state. This complex is stabilized by transthyretin (TTR), which reduces renal excretion. The delivery of retinol to extrahepatic tissues appears to involve cellular receptors for RBP4.

**Physiology**

Vitamin A is a crucial component of many important and diverse biological functions, including reproduction, embryological development, cellular differentiation, growth, immunity, and vision. In the eye, the active metabolite 11-cis-retinaldehyde is present in photoreceptor cells and serves as a cofactor for rhodopsin production, which is essential for vision. Vitamin A also regulates the expression of a number of genes through its interactions with various cytosolic and nuclear receptors. These actions are primarily mediated by all-trans-retinoic acid, 9-cis retinoic acid, and 13-cis retinoic acid. All-trans retinoic acid is a ligand for the family of nuclear retinoic acid receptors (RARα, β, and γ) and retinoid X receptors (RXRα, β, and γ), the latter being also activated by 9-cis retinoic acid and 13-cis retinoic acid. Over 500 genes have been identified as responding directly or indirectly to retinoic acid. Binding of retinoic acid to nuclear RARs results in regulation of genes related to growth arrest and cell differentiation. This mechanism is particularly noteworthy for maintenance of normal immune function, in which retinoic acid produced by antigen-presenting cells is essential in T-lymphocyte differentiation and cytokine production via its interaction with RARα. On the other hand, binding of retinoic acid to peroxisome proliferator-activated receptors (PPARs)—preferentially expressed in adipose tissue, brain, skin, and muscle—results in regulation of genes involved in energy homeostasis, insulin response, and cell proliferation.
Nutrition Requirement and Derangements

The recommended dietary allowance (RDA) for adult men and women is 900 and 700 μg retinol activity equivalents (RAEs) per day, which increases to 770 and 1300 μg RAE in pregnant and lactating women, respectively. The tolerable upper limit for adults is 3000 μg/d. Vitamin A toxicity occurs with long-term ingestion of 3–4 times the recommended daily allowance; meanwhile, β-carotene does not appear to have any toxic effects, secondary to the recommended daily allowance; meanwhile, β-carotene is a relatively safe way to increase vitamin A status without risking toxicity. For reference, the general conversion ratio of dietary β-carotene to vitamin A is 12 μg of β-carotene required to form 1 μg of retinol.

Excess dietary intake of preformed vitamin A has teratogenic effects, specifically associated with cranial–neural-crest defects. Among a study of 22,748 women, the ratio of such defects was 3.5 for those mothers who consumed >15,000 IU of preformed vitamin A per day compared with those who consumed 5000 IU or less. When considering an intake of at least 10,000 IU/d from vitamin A supplementation alone, this ratio was 4.8. Hypervitaminosis A is also associated with increased bone loss and turnover, altered skeletal development in children, and increased occurrence of spontaneous bone fractures. Other severe manifestations of chronic hypervitaminosis A include hepatosteatosis and fibrosis, potentially leading to cirrhosis, and pseudotumor cerebri. Acute hypervitaminosis A, described initially in arctic explorers after feeding on animal livers, results in gastrointestinal symptoms including pain, vomiting, anorexia, and diarrhea followed by hair loss and skin desquamation.

On the other hand, vitamin A deficiency, although rare in high-income countries, is the leading cause of preventable blindness in developing countries and increases the risk for infectious diseases and diarrheal illness. Vitamin A supplementation for children up to 5 years of age in these regions is recommended, as multiple meta-analyses have demonstrated a mortality benefit. Other patient groups at risk include those with malabsorptive disorders such as pancreatic insufficiency, short-bowel syndrome, Crohn’s disease, celiac disease, or post–bariatric surgery, which all may potentially affect absorption of the fat-soluble vitamins in the terminal ileum. Vitamin A deficiency has also been implicated in impaired wound healing. Significantly lower levels of vitamin A and carotene have been noted in elderly patients with chronic leg ulcers compared with age- and sex-matched controls, which may be related to low intake or to increased utilization due to the prolonged inflammatory phase. Vitamin A deficiency can be diagnosed clinically or through measurement of fasting serum retinol levels (deficiency <0.7 μM/L.). Of note, serum vitamin A concentrations (bioavailability) may be low despite adequate total vitamin A stores in the setting of systemic inflammation or severe malnutrition, due in large part to decreased levels of RBP secondary to loss from capillary leak or decreased production, respectively.

Vitamin A and the Skin

Vitamin A plays an essential role in skin health; it has been recognized since the 1920s that deficiency leads to abnormal epithelial keratinization. Today, despite continued incomplete understanding of the mechanistic effects of vitamin A in the skin, natural and synthetic retinoids are used pharmacologically for treatment of a number of skin disorders including psoriasis, acne vulgaris, and photodamage.

Once retinol is taken up into the skin from plasma, it is bound to cellular RBP type 1. Levels of cellular retinoic acid protein-I are lowest in the basal cells of the epidermis, with increasing expression toward the superficial layers. Retinol may also be metabolized to retinoic acid, which is then bound to cellular retinoic acid-binding protein. Acylation of retinol into retinyl esters accounts for the largest proportion of total vitamin A in the human skin, comprising approximately 54% in the basal epidermal layer and 71% in the superficial layers.

Intracellular levels of vitamin A–binding proteins are altered in hyperproliferative conditions such as psoriasis, basal cell carcinomas, and squamous cell carcinomas, implicating an abnormal metabolism of retinoids in these disorders. Moreover, retinoids have beneficial effects in other conditions characterized by abnormal fibrotic proliferation, such as hypertrophic scars, keloids, and scleroderma.

Retinoids regulate the growth and differentiation of many cell types within skin. The actions of retinoids are mediated through 2 families of nuclear receptors belonging to the steroid hormone receptor superfamily. The RARs and RXRs bind and activate distinct response elements of genes required to maintain differentiation and proliferation in epithelial tissues. The ligand for these receptors is retinoic acid.

Expression of RAR and RXR occurs in keratinocytes, hair follicles, dermal fibroblasts, and melanocytes. Vitamin A modulates immune responses via these nuclear receptors which induce T-lymphocyte and monocyte activation as well as B-cell differentiation. In the skin, contact hypersensitivity, mediated by T lymphocytes, is enhanced by vitamin A.

Additionally, retinol also decreases levels of degrading matrix metalloproteinases in aged skin and reduces metalloproteinase induction by ultraviolet-B (UV-B) irradiation via transrepression of activating protein 1 (AP-1). Topical retinyl palmitate prevents UV-B–induced DNA damage and
erythema in humans, likely related to its spectral properties rather than to activation of nuclear receptors.53

Vitamin A and Wound Healing

It has been known for a long time that vitamin A deficiency leads to delayed epithelialization and wound healing, manifested by impaired wound closure and decreased rates of collagen synthesis and cross-linking of newly formed collagen. Topical application or oral ingestion of vitamin A–containing foods reverses this deficit, confirming the century-old folk use of cod liver oil as a remedy for poor healing. Subsequently, it was shown, mainly in animals, that supplemental vitamin A increases the inflammatory response, angiogenesis, and reparative collagen synthesis in incisional wounds.54 Similar fibrogenic responses were noted with colon anastomoses and in models of adhesion formation.55 Vitamin A stimulates epidermal turnover, increases the rate of re-epithelialization in wounded skin, and restores epithelial structure. The topical application or oral ingestion of retinoids appears similar in effectiveness. As mentioned above, retinoids act by binding to specific receptors in both the cytoplasm and the nucleus, thus affecting cell division, differentiation, RNA and protein synthesis, and lysosome-membrane stabilization.

Although frank vitamin A deficiency is infrequent in the Western world, subclinical deficiency is common. Diets deficient in fresh vegetables and meats account for low levels of vitamin A intake, which can result in frank deficiency in the setting of burns, fractures, and surgical interventions. All of these injuries lead to decreases in plasma vitamin A levels, RBP, and increased urinary excretion of vitamin A.56,57 In addition, hyperactive adrenal cortisol activity, as seen during heightened stress, or administration of high doses of cortisone results in decreased liver, plasma, and adrenal levels of vitamin A.58 For this reason, systemic inflammatory states in general are associated with low levels of vitamin A.59

Anti-inflammatory glucocorticoids markedly affect most aspects of wound healing. When administered early after injury, high corticosteroid levels delay the appearance of inflammatory cells, fibroblasts, the deposition of ground substance, collagen, regenerating capillaries, contraction, and epithelial migration. The best-known vulnerary effect of retinoids is their unique ability to reverse the inhibitory effects of anti-inflammatory steroids on wound healing, except for wound contraction. Impairment of the inflammatory response, tensile strength, and collagen accumulation in cutaneous wounds after steroid treatment are partially, but significantly, reversed by retinoid administration.59,60 Similar observations have been made when studying flexor tendon repair, healing of rat femoral fractures, vessel repair, and healing of intestinal anastomoses.31,62-65 Although steroid use and subsequent delay of healing is a well-recognized clinical problem, the mechanisms of steroid retardation or reversal by retinoids are still incompletely understood. Glucocorticoid treatment results in decreased levels of transforming growth factor beta (TGF-β) and insulin like growth factor 1 (IGF-I) as well as reduced hydroxyproline content in granulation tissue, which are all at least partially reversed with oral all-trans-retinoic acid and 9-cis-retinoic acid.56 Both glucocorticoids and retinoids regulate alpha-2 type I procollagen promoter activity.67 Unsurprisingly, in addition to its role in the inflammatory phase of wound healing, retinoic acid has been demonstrated to enhance production of extracellular matrix components such as collagen type I and fibronectin and increase proliferation of keratinocytes and fibroblasts in organ and monolayer culture.58

Additionally, vitamin A may also combat postoperative immune depression that is not related to steroids, improving survival in surgically induced abdominal sepsis.69,70 The underlying mechanism is believed to involve enhancement of the early inflammatory phase and stimulation of the local immune response through increased number of monocytes and macrophages at the wound site, modulation of collagen breakdown via collagenase activity, and promotion of epithelial cell differentiation.14

Conclusions and Implications for Clinical Practice

Nutrition supplementation with vitamin A in the perioperative setting has been supported mostly by evidence demonstrating that vitamin A may reverse the deleterious effects on skin and fascial healing of corticosteroids.31,60,71 Based on these data, in select populations, daily vitamin A supplementation of 25,000 IU before and after elective surgery has been proposed, a dose that appears safe when administered in the short term to nonpregnant adults. Populations that may benefit from such supplementation include patients who are immunodeficient or have been treated with corticosteroids, as well as surgical patients with sepsis, fractures, tendon damage, or vitamin A deficiency. In the immunosuppressed post–organ-transplant population, there is the theoretical concern that the use of vitamin A may result in enhanced rejection; such fears have not been borne out with some transplant surgeons at our institution providing a 2-week perioperative supplement of vitamin A (25,000 units) to alleviate the anti–wound-healing effects of steroids and other immunosuppressive agents.

In conclusion, retinoids appear to serve a number of roles toward skin health and healing through activation of nuclear receptors and modulation of gene transcription. These include the regulation of growth and differentiation of numerous cell types within the skin, including keratinocytes and fibroblasts; modulation of the extracellular matrix through increased collagen and fibronectin
production paired with decreased collagenase activity; and recruitment of local inflammatory mechanisms to promote wound healing.

However, despite the multiple mechanisms by which retinoids appear to affect the integrity of skin and healing wounds, much of the relevant literature is outdated or confined to animal models. There is a notable lack of large, well-controlled, or recent human in vivo studies, which contributes to the lack of clear clinical guidelines for its use, despite the potential promise.

**Statement of Authorship**

M. E. Polcz and A. Barbul equally contributed to the conception and design of the manuscript, and M. E. Polcz and A. Barbul drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

**References**