A Review of Vitamin A

Roger Bloxham and Antony Wakeford explore vitamin A’s role as a treatment for ageing and photodamaged skin

Introduction

Vitamins are organic compounds that the human body requires to effectively function, thus they have a direct affect on our health and wellbeing. They are derived from the diet in small amounts, and, as such, are often referred to as micronutrients. An organic compound is considered a vitamin if a lack of it results in clinical symptoms, known as vitamin deficiency.

Summary of vitamins

- **Vitamin A** is a term used for a group of fat-soluble compounds known as retinoids; these include retinol, retinal and retinoic acid. Their primary action is to affect gene expression and the production of Messenger RNA (mRNA), resulting in the production of proteins and the differentiation of epithelial cells and tissues, which develop from the ectoderm. Vitamin A therefore plays a key role in the development and integrity of the skin (the epidermis in particular), and the outer membranes of sensory organs such as the eye and neural membranes.1,2
- **Vitamin C**, or ascorbic acid, is an electron donor and is the primary and highly potent water-soluble non-enzyme antioxidant present in plasma and tissues throughout the body. It also acts as an electron donor for key enzymes involved in catecholamine synthesis (hormones involved in collagen hydroxylation) and subsequent collagen structure stabilisation as well as carnitine synthesis and subsequent mitochondrial activity.1,3
- **Vitamin E** describes a group of fat soluble compounds known as tocopherols. Vitamin E is a very effective antioxidant, which prevents or helps to slow down lipid oxidation and subsequent damage to cell membranes and membrane structures and lipoproteins that transport fats through the bloodstream.1,2
- **Vitamin D** is formed from cholesterol in the skin through a photolysis reaction stimulated by exposure to UV light. This fat-soluble compound plays a role in inducing protein synthesis and calcium absorption in the intestine and associated optimum calcium levels in the kidneys and bones.1,2
- **Vitamin K** is involved in the carboxylation of glutamic acid in a number of vitamin K dependent proteins; during the process it is converted to an epoxide form that can be regenerated to vitamin K within the body. Many of the blood clotting factor proteins are vitamin K dependent.1,2
- **The B-complex vitamins** are water soluble coenzymes:
  - **Thiamine (B1)** is involved in enzyme functions associated with carbohydrate metabolism.1,2
  - **Riboflavin (B2)** is a precursor of coenzymes that are involved in protein metabolism.1,2
  - **Niacin** is a coenzyme of dehydrogenases that plays a key role in the metabolism of proteins and carbohydrates.1,2
  - **Vitamin B6**, of which the most stable form is pyridoxal, is a coenzyme involved in protein metabolism.1,2
  - **Pantothenic Acid (B5)** is the main component of coenzyme-A and a key requirement for cell metabolism, the synthesis of essential fats, cholesterol and hormones, including melatonin.1,2
  - **Biotin** is the active site of five carboxylating enzymes required for the biosynthesis of fatty acids and gluconeogenesis.1,2
- **Folates**, including folic acid, are cofactors to enzymes that facilitate the transfer of carbon units in transfer reactions, particularly associated with the metabolism of DNA. Its effects are most prevalent in rapidly dividing cells such as red blood cells. It is also key to a process known as methylation and the associated gene expression responsible for the processing of proteins, phospholipids and cell differentiation.1,2,3
- **Vitamin B12** plays a key role in the metabolism of folate and coenzyme A; it is therefore closely linked to DNA metabolism and expression.1,2

Given the primary role of vitamin A in the production and differentiation of epithelial cells, which includes the skin and in particular the epidermis, as well as the fact that a lack of vitamin A causes observable changes in skin epithelial tissue, including epidermal thickening and hyperkeratosis,1 it is no surprise that retinoids became, and still are, a topic of dermatological research for skin conditions and treatments. This is the focus of the discussion below.

Vitamin A: How does our body get it and use it?

The retinoid compounds that the term vitamin A describes are all lipid soluble, and are related to the preformed vitamin A compound all-trans-retinol. This is the active bioavailable form of vitamin A. There are four main physiologic functions of retinoids in the body:4

1. To ensure normal embryonic development.
2. To facilitate normalised epithelial differentiation in varying tissue types, including the skin.
3. To maintain healthy vision through the production of rhodopsin, an 11-cis-retinaldehyde containing eye pigment that enables night vision.
4. To enable adequate immune function and lymphocyte survival.

Vitamin A and nutrition

Vitamin A levels within the body depend on levels of nutrition. Preformed vitamin A, predominantly in the form of retinyl esters (esterified retinol, mainly retinyl palmitate), is available from animal-based foods — liver, butter, cheese, egg yolks and oily fish are known to have a high content. It is also possible to derive vitamin A from vegetables and fruit via a relatively small sub-section of the many carotenoid compounds present in plants, particularly alpha and beta-carotenes. These are known as pro vitamin A.
compounds. In addition, some food items, such as margarine and low-fat spreads, are fortified with vitamin A. The different sources of vitamin A have different levels of potency available in food items. For example, retinyl esters are membrane-bound within storage cells within the animal tissue. The pro-vitamin A carotenoids are not only bound to lipids but are embedded in complex cellular structures within the plant material. Therefore the amount of the retinyl ester or carotenoid does not directly reflect the amount of vitamin A (retinol) available. Because of this, standardised units known as International Units (IU) or Retinol Equivalents (RE) are often used to express the levels available per compound, and to help provide a comparison across the different food sources.

There can be a wide variability in levels contained in the different food sources, for example 100g of pork liver has been shown to have 30,000 μg RE, whereas pork muscle has 6 μg RE and oily fish has 40 μg RE. There are risks associated with taking too much vitamin A. The UK National Health Service (NHS) has advised that having more than an average of 1.5mg a day vitamin A, over many years, may affect bones, making them more likely to fracture. They point out that this is particularly important for older people, especially women, who are already at risk of osteoporosis. This is when bone density reduces and there is a higher risk of fractures. Thus, women who have been through the menopause and older men, who have a higher risk of osteoporosis, are advised to avoid having more than 1.5mg of vitamin A per day from food and supplements. Eating liver or liver pâté more than once a week may result in too high a vitamin A intake, and it is advised that if liver is eaten every week, supplements containing vitamin A should not be taken. Additionally, if the dietary intake of vitamin D is too low, it is possible that there will be more risk of the harmful effects of too much vitamin A.

In addition to the osteoporosis risks associated with taking too much vitamin A detailed earlier, there are additional risks in pregnancy. Having large amounts of vitamin A can harm an unborn baby. It is advised that women who are pregnant, or who are thinking about becoming pregnant, should not eat liver or liver products, and should not take supplements that contain vitamin A. It is recommended that a GP or midwife be consulted for more information.

Vitamin A and bioavailability

Once the food has been consumed, digestion frees the retinol from the retinyl esters. The lipid soluble retinol is then inside a predominantly aqueous environment in the intestines and gut, with fatty acids and phospholipids and bile secretions. It then has to pass through the lipid-rich intestinal mucosal cells. Enzymes either cleave vegetable derived carotenoids as they pass through the intestinal mucosa to form retinol, or they remain as they are. Retinol is then re-esterified or is bound to a specific protein retinol binding protein (RBP), synthesised within the tissue, and passes into the blood stream. Any carotenoids or retinol that has become re-esterified in the intestinal cell wall is packaged in to lipoprotein particles and enters into the blood stream via lymph channels. The next step is storage, predominantly within the liver, in parenchymal cells. Retinol is detached from the RBP or the retinyl ester is removed from the circulating lipoprotein particle and then hydrolysed within the liver to produce retinol. The resulting retinol is then esterified for storage. The liver can also take up carotenoids from the lipoprotein particles for storage.

Stored retinyl esters in the liver are mobilised by hydrolytic release of retinol and binding to a RBP, produced in the liver, enabling it to be transported in the aqueous environment of the plasma in the blood stream to target tissues and cells. The levels of plasma vitamin A are maintained at approximately 2μmol/L. The circulating retinol RBP combination forms a further complex with a larger protein transthyretin, to ensure the retinol is not filtered out through the kidney. The bound retinol enters into the tissue through the cellular membrane, where the retinol binds to an intracellular binding protein (CRBP). Within the cell, retinol can be esterified, most likely to form a localised store, and more importantly it can be metabolised to form retinal (also known as retinaldehyde) and then retinoic acid. The conversions of retinol to ester forms or retinol are all reversible which, consequently, can regulate the levels of retinol and retinoic acid in the cells.

Vitamin A and biochemical activity

The cellular conversion of retinol to retinal and retinoic acid is fundamental to its biological role and ultimately its role in the treatment of ageing and photodamaged skin. In ocular tissue and specifically the retina, retinol is converted to retinal and then rhodopsin – the pigment required for low light vision. For the control of cell growth and differentiation in all other epithelial tissue retinol is converted to retinal and then to retinoic acid (of which there are two primary isomers). These bind to receptors in the nucleus (known as Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR) receptors), which in turn bind to specific elements of DNA and consequently regulate gene expression and transcription.

As such, vitamin A is essential for the biological functions previously mentioned. Vitamin A deficiency is rare in the western world but can be a major problem in the developing world with specific symptoms including night blindness and xerophthalmia, which can lead to permanent blindness. Other significant negative effects associated with deficiency include growth retardation in children, skin disorders and impaired immune function. Deficiency in pregnancy can lead to congenital malformation of the eyes, lung, cardiovascular and urinary systems.

In the environment of cosmetic dermatology and aesthetics, we do not usually have to deal with such issues of deficiency. Therefore, it is not necessary to provide additional information about vitamin A deficiency. However, it is important to remember that even in the absence of deficiency, a high intake of vitamin A can still have potential negative effects on the body.

Table 1: Table comparing pre-formed and pro vitamin A compounds:

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Quantity</th>
<th>Retinol Equivalents (RE)</th>
<th>International Units (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol</td>
<td>1μg</td>
<td>1.00</td>
<td>3.3</td>
</tr>
<tr>
<td>Retinyl Palmitate</td>
<td>1μg</td>
<td>0.55</td>
<td>1.8</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>1μg</td>
<td>0.17</td>
<td>0.6</td>
</tr>
</tbody>
</table>

(data adapted)
clinical focus with respect to vitamin A is for use in the treatment of physical and anatomical impairment of the epithelial tissues and cells that occurs i.e in the skin, as part of the ageing process and photodamage, and to treat other cosmetically impairing skin conditions such as pigmentation and acne.

Vitamin A and the clinical enhancement of aged and photodamaged skin

During skin ageing, the production and replacement of collagen, elastin and hyaluronic acid slows down as there are fewer dermal fibroblasts, and they operate less efficiently. Skin not damaged by photo radiation will age as a result of this, and become thinner, more lax and finely wrinkled.10,11 External factors, including UV radiation and smoking, accelerate the natural ageing process. In the 1990s, research showed that photodamaged skin had premature damage of the collagen bundles and amorphous amounts of elastotic material, which was likely due to increased synthesis of matrix metalloproteinases (MMPs) and subsequent collagen destruction.12,13 It was also demonstrated that photodamaged skin has reduced capacity to produce new collagen.14 This prematurely reduces the elasticity, firmness, and smoothness of the skin, resulting in coarser lines and wrinkles. Photodamaged skin is also differentiated from naturally aged skin by a thickened and rougher appearance.

With an understanding of the role of vitamin A within biological processes, and the mechanisms and effects of skin ageing and photodamage, it comes as no surprise that vitamin A is often considered an essential component of an evidence-based anti-ageing skin management programme.

The role of oral retinoids

The consumption of vitamin A via food substances or supplements could be considered to be a logical route to try and combat the effects of intrinsic skin ageing and photodamage. However, vitamin A deficiency is rare in the western world and it is known that average daily intakes of preformed retinol within the EU are well above the recommended reference intake.5 Despite this, aesthetic consultations for use in the rejuvenation of aged and photodamaged skin with an treatment of acne. There are currently no forms of tretinoin suitable in the UK. Both are combined with an antibiotic and indicated for the treatment of acne, with minimal dermal changes. Longer-term studies of approximately six months showed that these clinically significant improvements in fine and coarse wrinkles, sallowness, hyperpigmentation, roughness and epidermal structure continued, and that these improvements were maintained after the study periods. Interestingly, it was the studies of 12 months or more that showed clinical changes in the dermis, with new collagen production and normalisation of keratinocyte exfoliation and keratinization, and was used clinically in the treatment of ichthyses.19 In 1969, Kligman published the first clinical paper clearly demonstrating its clinical efficacy in the treatment of acne20 and in the early 1970s tretinoin was approved by the Food and Drugs Administration (FDA) in the USA as a prescription only medicine, the first retinoid approved as a medicine, for the treatment of mild to moderate acne.19

However, it took some time before the skin physiology-changing attributes of tretinoin were appreciated in the treatment of photodamaged and aged skin. In 1986 Kligman published a study showing that in photoaged skin, topical tretinoin 0.05% induced a normalisation of keratinocyte exfoliation and proliferation, along with improvement in keratinocyte morphology and function, extracellular matrix structure and formation, and angiogenesis.21 A review of clinical studies available for tretinoin summarised that the shorter-term studies of four to 16 weeks demonstrated physiological changes in the epidermis and significant enhancements in appearance but with minimal dermal changes. Longer-term studies of approximately six months showed that these clinically significant improvements in fine and coarse wrinkles, sallowness, hyperpigmentation, toughness and epidermal structure continued, and that these improvements were maintained after the study periods. Interestingly, it was the studies of 12 months or more that showed clinical changes in the dermis, with new collagen production and the regulation of damaged tissue.9,22 Topical tretinoin presented some potential adverse events, such as erythema and inflammation in the areas of application, as well as increased photosensitisation. It was for this reason that lower strength tretinoin was assessed and showed good results. 0.025% and 0.1% tretinoin produced statistically equivalent results after 48 weeks’ use, with significantly less adverse events in the lower strength group.22 In the USA, the FDA review of products containing tretinoin has, to date, designated them to be POMs.23 The same is true in the UK with respect to the Medicines and Healthcare products Regulatory Agency (MHRA)24, and the EU Cosmetics Regulation25 lists tretinoin as a substance prohibited in all cosmetic products. The electronic medicines compendium (eMC) website27 shows that there are two topical medicinal products containing tretinoin available in the UK. Both are combined with an antibiotic and indicated for the treatment of acne. There are currently no forms of tretinoin suitable for use in the rejuvenation of aged and photodamaged skin with an MHRA approved marketing application (MA).

Similarly, a study of men taking 50mg of beta-carotene on alternative days for 12 years, again more than 10 times the recommended daily intake, showed that it had no effect on the incidence of non-melanoma skin cancer when compared to the placebo group and there was no beneficial link associated with plasma levels of beta-carotene, vitamin A or vitamin E.18 Based on this, it is logical to conclude that oral intake of vitamin A is going to play a minimal role in treating ageing and photodamaged skin and, therefore, for an evidence-based approach, we need to focus on topical retinoids.

The role of topical pharmaceutical retinoids

As early as 1962, the effect of topical vitamin A in the form of tretinoin (all-trans-retinoic acid) was shown to affect epidermal differentiation and keratinization, and was used clinically in the treatment of ichthyses.19 In 1969, Kligman published the first clinical paper clearly demonstrating its clinical efficacy in the treatment of acne20 and in the early 1970s tretinoin was approved by the Food and Drugs Administration (FDA) in the USA as a prescription only medicine, the first retinoid approved as a medicine, for the treatment of mild to moderate acne.19

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requires that there is a bona fide unsolicited order, that the product is formulated in accordance with the requirement of a doctor or dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber registered in the UK, and the product is for use by one of their individual patients (on the basis of ‘special need’) on the practitioner’s direct personal responsibility. In addition, guidance from the prescriber’s governing body should be considered. For example, the Nursing and Midwifery Council (NMC) provide such guidance accessible via their website.29

The most recent generation of medicinal retinoids are synthetically produced. They were developed to have a more selective mechanism of action and better tolerability. Adapalene, the first synthetic retinoid, is readily taken up by the pilosebaceous unit (hair shaft, hair follicle, sebaceous gland) and was shown to directly bind to RAR receptors and regulate keratinisation and inflammation.9 There are cream and gel formulation POMs approved by the MHRA for the treatment of mild to moderate acne.14 Their short-term use over four weeks and longer-term use of up to nine months, have shown significant improvements in photoaged skin,30 although such use is not in accordance with the approved indications, and would be considered to be ‘off-label’ with respect to the currently available and approved medicines. Tazarotene is another synthetically produced retinoid approved in the UK in a gel form for the treatment of psoriasis.14

The role of topical cosmetic retinoids

Specific retinoids are also available for use as cosmetic ingredients in compliance with the Cosmetic Product Regulations and the EU Cosmetic Directive. With respect to their use in ageing and photodamaged skin, retinol has had established evidence-based cosmetic use since 1984, and is accorded ‘generally recognized as safe’ (GRAS) status by the FDA. Retinaldehyde (retinal) has generated clinical data supporting its use and the retinol derivatives such as retinyl palmitate are widely used due to their stability and ease of formulation, although less clinical evidence of their efficacy as a monotherapy is available.9 All of the retinoids referred to above require a biological conversion within the skin to form retinoic acid.9,31 The advantage of the cosmetic retinoids is that they are more widely available for use than medicinal products, and their skin tolerance has been shown to be significantly greater than tretinoin.32 The fact that they are also cosmetics allows greater flexibility with respect to formulation.

The evidence of the clinical efficacy of retinol is compelling. Kang et al showed that 1.6% retinol induced similar effects to 0.025% retinoic acid, without similar measurable skin irritation.33 The retinol caused epidermal thickening and enhanced expression of retinol binding protein mRNA, similar to that of retinoic acid. However, the erythema produced by retinol application was significantly less. Interestingly, they discovered that the retinoic acid levels found in the epidermis were approximately a thousand times less in the retinol treated skin compared to the retinoic acid treated skin, despite seeing similar clinical effects and markers. They postulated that the retinol was being converted to retinoic acid in a tightly controlled manner at physiologically relevant sites; the right amount at the right location within the skin. Further studies have shown that retinol is safe and effective in the treatment of photodamaged skin.31,34,35 It is acknowledged, however, that formulation is key as retinol-based products can be unstable, particularly on exposure to light and air.9 Because of the clinical value of retinol and the fact that its efficacy...
depends greatly on its stability and bioavailability, research and formulation developments continue. Gold et al demonstrated in 2013 the efficacy and tolerability of such a product, reporting a pilot study of a serum with retinol 1% in a novel oil-free aqueous protein rich suspension, showing improved visible signs of photodamage after eight and 12 weeks of daily use. Their subsequent study using 0.5% retinol in the same formulation showed that hyperpigmentation, telangiectasias, skin laxity, roughness and actinic keratosis showed significant improvement from baseline after four and eight weeks daily use of the formulation. Skin tolerability was reported to be good.33

**Conclusion**

When it comes to aged skin, and skin whose ageing process, structure and appearance has been worsened by photodamage, topical vitamin A plays a key role in its treatment and visible and physical enhancement. There are robust double blind placebo controlled clinical studies regarding the use of tretinoin (retinoic acid) in the treatment of aged and photodamaged skin.2,11,12,13,14,15,19

Whilst clinically visible effects can be seen after four weeks, the greatest physiological effects are seen after daily use of 12 months or more, and the studies show the treatment has a good safety profile over such periods. This indicates that on-going long-term treatment is desirable, although skin tolerability issues were often reported particularly in the early phases of treatment.

In the UK, the availability of tretinoin in topical formulations suitable for use in treating aged and photodamaged skin is currently limited to unlicensed medicinal products. These may only be supplied in accordance with the Human Medicines Regulations concerning unlicensed medicines for individual patient use and by prescribers able to prescribe such medicines, and in accordance with their governing body / council such as the General Medical Council. There is also compelling data for the efficacy of retinoids, available in cosmetics for the clinical improvement of aged and photodamaged skin.3,11,12,13,14,15,16

Cosmetics containing these ingredients are more widely available and generally display better skin tolerability than prescription-only tretinoin-based topical medicines. Within this category, retinoid-based formulations are supported by a high level of clinical data, although formulations need to address the inherent instability of retinol as an ingredient.3,10,11,12,13,14,15,16

On-going research and novel formulation enhancements means that retinoid-based cosmetics can and will continue to play a significant role in the clinical management of aged and photodamaged skin.

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**REFERENCES**


28. Toker-Samars et al. ‘A stabilized 0.1% retinol facial moisturizer improves the appearance of photodamaged skin in an eight-week, double-blind, vehicle-controlled study’, Journal of Drugs in Dermatology, 8(10) (2009), p. 932-936


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