5. Vitamin A

Physiology and metabolism

Vitamin A can be obtained in two ways: as preformed vitamin A (retinol) and as carotenoid pigments that can be cleaved in the body to give retinol. Preformed vitamin A (usually in the form of retinyl esters) occurs naturally only in animals. It is also synthesized for fortification of foodstuffs and inclusion in pharmaceutical preparations. Most of the vitamin A in European diets comes as preformed vitamin A, but a substantial contribution is made by carotenoids, mainly from plant foods, and overwhelmingly as β-carotene, although some other carotenoids can also act as provitamins A.

The two contributions have to be added to give the total vitamin A activity. The widely accepted convention is that as they usually come in the diet 6 μg β-carotene and 12 μg other provitamin A carotenoids can be considered to be nutritionally equivalent to 1 μg retinol. The weights of provitamin A carotenoids are converted to the equivalents of retinol and added to the weight of preformed retinol, to express the total vitamin A in terms of retinol equivalents, e.g. an intake of 1800 μg β-carotene plus 600 μg retinol would amount to 300 + 600 = 900 μg retinol equivalents [1]. Retinol equivalents are replacing the older international units (1 international unit = 0.3 μg retinol) as a measure of vitamin A activity, in part because of the problem of adding in the contribution of dietary carotenoids.

Provitamin A carotenoids raise a difficult problem of bioavailability. Carotenoids are absorbed better from some foodstuffs and diets than from others and the percentage converted to retinol depends to some extent on how much is ingested in a meal. The vitamin A potency will therefore vary quite substantially according to circumstances [1]. For practical purposes it is necessary to select some value that can be used routinely and the factors mentioned were chosen by an FAO/WHO Expert Group [1]. Taken over a period of time and a variety of foodstuffs, they are a crude but serviceable compromise. They have been used for many years and are internationally accepted; there seems no reason to propose any change.

The conversion of carotenoids to retinol takes place mainly in the intestinal mucosa. The newly formed retinol, along with any preformed retinol in the diet, is esterified in the intestinal mucosa and transported to the liver. The liver is the major organ for storage of reserves of esterified vitamin A. Retinyl esters in the liver are hydrolysed to free retinol, which is put into the plasma on a carrier protein, retinol-binding

protein. The rate of output of retinol from the liver is controlled so as to keep the plasma retinol concentration fairly constant. Dietary vitamin A surplus to immediate requirements is used to build up liver reserves, which can subsequently be drawn upon during any temporary dietary shortage.

Retinol is delivered by retinol-binding protein to the tissues that utilize it. In the eye it serves in its aldehyde form as the light-gathering part of the visual pigments. In other organs it has different functions, being necessary for growth and development and for the normal differentiation of cells; in this role, perhaps in the form of retinoic acid, it appears to react with nuclear receptors to modify gene expression [2].

Levels of deficiency and excess

The reserves of retinyl esters in the liver can be used to maintain the plasma retinol concentration reasonably constant, so normal delivery to target organs can continue. Only when the liver reserves are exhausted does the plasma retinol concentration fall below 20 µg/dl (0.7 µmol/L) and deficiency signs begin to appear. An early indication is impaired adaptation to low-intensity light (night blindness). Other signs show, and in the later stages dryness of the conjunctiva and cornea (xerophthalmia) develops, which can lead to permanent eye damage.

Intakes of vitamin A in excess of needs are used to build up liver reserves of retinyl esters. If however very large amounts of retinol and retinyl esters are ingested, they can overwhelm this liver mechanism and cause liver and bone damage, hair loss, double vision, vomiting, headaches and other abnormalities.

Large single doses (e.g. 300 mg in adults) can cause acute toxicity, but hypervitaminosis A usually arises from chronic ingestion of retinol or retinyl esters, not necessarily in very large amounts (e.g. 15 mg per day) but sufficient over a period of time to build up stocks that exceed the liver's ability to store or destroy them [3]. It has been suggested that even lower daily doses can cause liver damage if taken for long enough [4].

Worst of all, retinol and retinyl esters are highly teratogenic [3], probably as a consequence of the excessive formation of retinoic acid, which modulates gene expression [2] and is a natural morphogen [5]. The lowest intake of retinol (free or esterified) that has teratogenic potential cannot be estimated reliably from the available data. Regular consumption of more than 6,000 µg per day has been associated with birth defects, but the risk seems not to be high unless much larger amounts are taken; chronic intakes of 30,000 µg per day will almost certainly be teratogenic [3].

It is recommended that single doses of retinol and retinyl esters should not exceed 120 mg retinol equivalents, and regular intakes should not exceed 9,000 µg/d for adult men, and 7,500 µg/d for women that are not pregnant or likely to become pregnant [6]. Pregnant women should not take supplementary vitamin A except under medical supervision. Proportionately lower amounts are suggested for children [6].

β-Carotene does not cause hypervitaminosis A because it cannot be converted to retinol sufficiently quickly.

Methods of establishing physiological requirements

As mentioned, vitamin A absorbed in excess of immediate needs is stored in the liver in esterified form. The size of the liver reserve is therefore the best objective measure of vitamin A status, and is commonly used for post-mortem studies.

A biochemical measure that can be easily made in living subjects is the plasma retinol concentration, but this is an insensitive indicator of vitamin A status, for a homoeostatic mechanism maintains the plasma level reasonably constant over quite a wide range of liver reserves. The plasma retinol concentration falls to a potentially hazardous level only in the later stages of deficiency, when other signs are beginning to show.

Most recommendations for the vitamin A requirements of adults have been based on repletion studies with vitamin A-depleted human volunteers. The best known are the so-called Sheffield experiment in UK [7] and a later, and more thorough, American investigation [8,9]. In these studies increasing doses of vitamin A were given to depleted volunteers to cure deficiency signs such as impaired dark adaptation, abnormal electroretinograms, follicular hyperkeratosis and lowered blood haemoglobin and also to restore normal plasma retinol concentrations.

Another approach suggested by Olson [10] defines vitamin A status in terms of an adequate body pool size, conveniently expressed in terms of the liver vitamin A content. Olson proposed as a criterion for vitamin A sufficiency a liver concentration of 20 µg retinol (or the equivalent in the esterified form) per g wet weight liver. This level for vitamin A reserves meets a number of criteria [7].

1. No clinical signs of deficiency have been noted in subjects with this liver concentration.

2. This liver concentration will maintain a steady-state concentration of retinol in the plasma above 20 µg/dl (0.7 µmol/L).

3. This concentration should maintain an adult on a diet containing no vitamin A free from deficiency signs for a period of months.

Translation of physiological requirements into dietary intake

Olson [10] suggested a method of calculating the mean dietary intake needed to maintain a liver retinol concentration of 20 µg/g assuming that the liver reserves represent 90% of the total body vitamin A and the efficiency of storage in the liver of an ingested dose of vitamin A is 50% (reported values 40-90%).

Studies with radioactive vitamin A in eight adult male volunteers [5] gave a mean fractional catabolic rate, i.e. the percentage of total body stores lost per day, of 0.5%. Calculations based on this and the assumptions mentioned gave a mean dietary intake of 6.7 µg retinol per kilogram body weight per day. For a 75 kg man this would be 503 µg/d; for a 62 kg woman, 415 µg/d.

The coefficient of variation for the rates of depletion in these experimental subjects was about 20%, so the mean ± 2SD daily dietary requirement would be 503 µg ± 201 for men and 415 µg ± 166 for women.

Although these calculations rest on a number of assumptions that have to be arbitrary and will not hold in all circumstances, the derived requirements appear consistent with the effects on deficiency signs observed in depletion-repletion studies in human volunteers [7,8,9]. They also provide some indication of what the range of individual requirements might be, even though only eight subjects were investigated. Such calculations have been used as the basis of the latest FAO/WHO [11] and UK [12] recommendations.

Other reviewing bodies have preferred to base their recommendations on repletion studies. Some indeed specifically reject the body pool approach [13,14], in part because of some doubts about the assumptions underlying the calculations, but mainly because it was thought safer to have reserves in the liver higher than 20 µg/g, and to aim for a plasma retinol concentration above 30 µg/dl (1 µmol/L) rather than 20 µg/dl (0.7 µmol/L). Mild deficiency signs have been reported in some American volunteers depleted of vitamin A when plasma concentrations were between 20 and 30 µg/dl (0.7-1.0 µmol/L) [13]. To maintain plasma retinol concentrations over 30 µg/dl a mean daily intake of 900 µg appeared to be needed in adult men; the current US RDA for adult men is set at 1000 µg. For adult women it is 800 µg/d [13].

Repletion studies however tend to overestimate requirements because deficiency signs often take some time to improve when a small curative dose of vitamin A is

given, and there is understandable reluctance to keep subjects on low intakes for prolonged periods.

Both the body pool calculations and the interpretations of the results of repletion experiments are open to criticism not least because both have to be based on a small number of subjects. There are also differences of opinion on what criterion of vitamin A sufficiency should be adopted, notably in terms of the plasma retinol concentration.

Although a homoeostatic mechanism maintains the plasma retinol concentration reasonably constant in an individual, the levels differ between communities. In industrialised countries the values are usually high, e.g. in a recent survey in UK, the mean plasma retinol concentrations for adult men and women were 63 µg/dl (2.2 µmol/L) and 54 µg/dl (1.9 µmol/L) respectively [15]. In other parts of the world much lower concentrations seem compatible with normal function and health. For example, many Thais maintain concentrations below 30 µg/dl (1 µmol/L) even when liver stores are quite high [16].

It is unclear why in prosperous communities high plasma retinol concentrations are normal and why some such subjects when given an A-low diet start to develop deficiency signs at plasma concentrations well above those maintaining health and normal function in other countries. The possibility should be considered that some populations have adapted to a high dietary intake of retinol and their high plasma concentrations are a consequence of that adaptation.

Europeans and North Americans are unlikely to need plasma retinol concentrations higher than are adequate for many other nations. The National Research Council [13] recommended for USA an allowance of 1000 µg/d in order to maintain a plasma retinol concentration of 30 µg/dl (1 µmol/L) in most adult men. Making reasonable assumptions about the coefficient of variation and the consequent range of needs, one would predict, if this recommendation is realistic, that large numbers of men in the world would receive less than the minimum necessary and vitamin A deficiency would be far more widespread than it is. It seems doubtful if it is necessary to maintain a plasma retinol concentration above 30 µg/dl (1 µmol/L) for the whole population.

There seems no need to encourage high consumption of vitamin A in Europe. Intakes appear to be adequate; there is no deficiency. In North America there is some concern about excessive intakes of vitamin A [3]. This Committee [17] has advised women who are or might become pregnant to avoid eating liver because of its high vitamin A content, and has recommended pregnant women not to take supplementary vitamin A in amounts greater than the RDA (here PRI).

In these circumstances it seems better to discourage rather than encourage higher vitamin A intakes. It is proposed that recommendations be based on the body pool procedure as described, i.e. that used by FAO/WHO [8] but with body weights appropriate for Europeans. The rounded off values for adult men and women, expressed in retinol equivalents/d are:

Population Reference Intakes	700 µg (men), 600 µg (women);
Average Requirements	500 µg (men), 400 µg (women);
Lowest Threshold Intakes	300 µg (men), 250 µg (women).

Children

Whereas adult needs for vitamin A seem to be determined largely by the destruction of body stores, children have a requirement for growth, but no good evidence is available for estimating population reference intakes for children.

Most recommendations for formula-fed infants are based on the amounts in breast milk, e.g. the most recent FAO/WHO value of 350 µg retinol equivalents/d [11]. This is likely to be an overestimate as no breast-fed infants ever show signs of A-deficiency, even on intakes of 100-200 µg/d [18,19]. The value of 350 µg retinol equivalents/d is however proposed as the PRI for infants 6-11m.

PRIs for older children are put forward to make a smooth transition from the infant to adult values as shown in the summary. There is little direct evidence to support these values, but they appear unlikely to be underestimates; Reddy [20] has reported that a daily intake of about 300 µg will meet the requirements of pre-school children.

Pregnancy

In pregnancy extra vitamin A is required for the growth of the fetus, for its maintenance, for providing some small reserves for the fetus, and for maternal tissue growth. Much of the requirement for newborn infants seems to be for growth. The fetus grows rapidly during the third trimester, and presumably has needs rising towards those of the newborn.

Recommendations for adult females are intended to maintain a liver concentration of 20 µg retinol equivalents per gram wet weight. Women with such a liver retinol concentration would need an extra supply of retinol to cover the demands of pregnancy. An increment of 100 µg daily throughout pregnancy would enhance

maternal storage to provide adequate vitamin A for the growing fetus in late pregnancy. A PRI of 700 µg retinol equivalents per day is proposed.

Many European women will have intakes of vitamin A higher than that when not pregnant, so their habitual diet will be ample for pregnancy. As mentioned, vitamin A is highly teratogenic, and consumption by pregnant women of more than 6,000 µg per day has been associated with birth defects [3]. Pregnant women on a good diet should not take supplementary vitamin A except under medical advice.

Lactation

If it is assumed that 350 µg retinol is supplied in the milk, the mother needs to have this replaced. The increment proposed throughout lactation is 350 µg retinol equivalents/d.

Summary

(all as µg retinol equivalents/d)

Adults	*Males*	*Females*
Average Requirements	500	400
Population Reference Intake	700	600
Lowest Threshold Intake	300	250

Population Reference Intakes for other groups

Children: **Age Group**		**PRI** *(µg retinol equivalents/d)*
	6 - 11 m	350
	1 - 3 y	400
	4 - 6 y	400
	7 - 10 y	500
Males	11 - 14 y	600
	15 - 17 y	700
Females	11 - 14 y	600
	15 - 17 y	600
Lactation		950
Pregnancy		700 (total intake) (Supplements to be taken only under medical advice)

Potentially harmful intakes of retinol (free and esterified)

Single doses should not exceed 120 mg.

Regular intakes should not be greater than the following [15]:

Adults	
Men	9000 µg/d
Women that are not pregnant or likely to become pregnant*	7500 µg/d

Infants	6 -11 m	900 µg/d
Children	1 - 3 y	1800 µg/d
	4 - 6 y	3000 µg/d
	7 -10 y	4500 µg/d
	11-17 y	6000 µg/d

Therapeutic doses may exceed these limits, but only under medical supervision.

* Pregnant women should not take supplementary vitamin A except under medical supervision.

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