

Non-Pro-Vitamin A and Pro-Vitamin A Carotenoids in Atopy Development

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Key Words

Atopy · Carotenoids · Vitamin A

Abstract

Carotenoids are important derivatives of the human diet and occur in high concentrations in the human organism. Various carotenoids are also present in human breast milk and are transferred to breast-fed children. The alternative to breast-feeding is supplementation with an infant milk formula, but these formulas contain only a limited variety of carotenoids. Our question is: 'What is the function of various carotenoids in human nutrition with a special emphasis on child development and the development of atopy?' In this review, the mechanisms of action of the most important non-pro-vitamin A and pro-vitamin A carotenoids: α -carotene, β -carotene, β -cryptoxanthin, lutein, zeaxanthin, lycopene and retinoids are discussed. In summary, the combination of carotenoids, especially lycopene, seems to be of great importance, and exclusive usage of β -carotene in infant formula may yield in an increased atopy prevalence mediated in various target organs like the skin, lungs and immune competent cells. We conclude that the determination of novel bioactive metabolites of various carotenoids, at various stages in different organs during atopy development, might be the key to understanding the potential importance of carotenoids on atopy development.

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Introduction

Vitamin A/Retinoids

The term 'vitamin A' designates all compounds that possess qualitatively the biological activity of the VA-alcohol (retinol), such as retinal, retinyl esters and various pro-vitamin A carotenoids. The term retinoid comprises all natural and synthetic compounds exhibiting a similar structure and/or effectiveness to retinol and therefore also includes retinoic acids [1].

Serum levels of retinol are under homeostatic regulation [2], while pro-vitamin A carotenoids and retinoic acid concentrations vary depending on various physiological and nutritional situations [3–7]. Serum retinol varies only under conditions like inflammation and pregnancy due to the involvement of vitamin A in these processes [8–10]. Lower serum retinol concentrations are present during inflammation and pregnancy, which may indicate that less retinoids are needed to decrease inflammation in target organs during pregnancy and/or inflammation. This topic is still under discussion.

Lactation is another physiological process where retinoids and carotenoids are not homeostatically regulated in breast milk [6, 11–14]. Low or high dietary intake of retinoids and carotenoids results in low or increased concentrations of retinoids and carotenoids in breast milk [15, 16].

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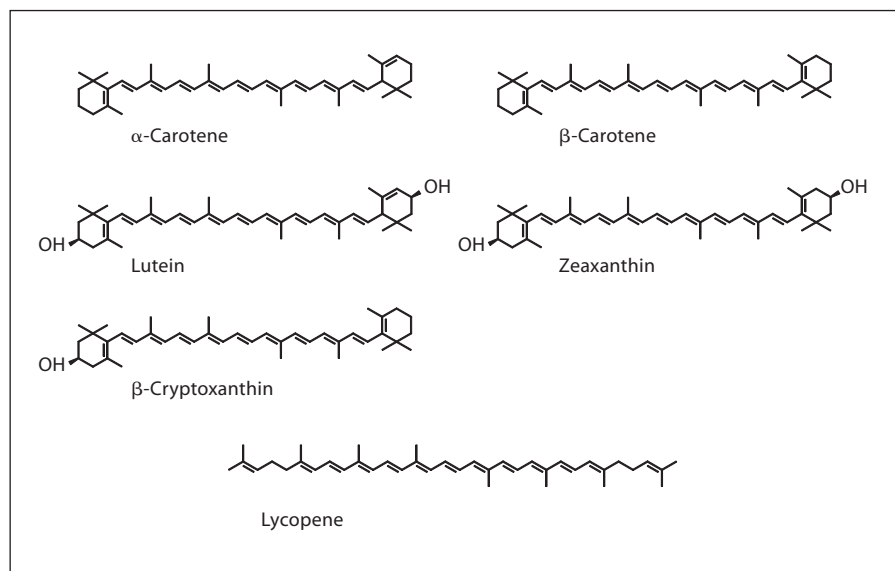


Fig. 1. Chemical structures of the most common carotenoids in human nutrition.

Non-Pro-Vitamin A and Pro-Vitamin A Carotenoids

Carotenoids are a large family of compounds of about 600 naturally occurring molecules ranging from hydrophobic to lipophilic, and from colorless to red, orange, yellow and blue pigments present in fungi, algae, bacteria, flora and fauna. Only about 60 carotenoids are important for human nutrition and also occur in the human organism [17, 18].

Carotenoids could mainly be considered as precursors for further downstream bioactive metabolites like the retinoic acids, and further still, nonidentified and not deeply investigated carotenoid metabolites [15, 19]. Novel studies have described carotenoids as nutritional markers which reflect the current dietary intake [6, 7, 20]. The fact that carotenoids are biomarkers is important, because when we evaluate serum carotenoid concentrations, we have a hint as to what these individuals (in our case, the children and mothers) eat. With carotenoids as biomarkers, we can draw conclusions about which diets may promote and which may prevent atopy development.

In figure 1, we summarize the most abundant carotenoids. (1) The carotenoids α -carotene, β -carotene and β -cryptoxanthin are direct precursors for retinal after beta-carotene oxygenase 1 (BCO-1)-mediated central cleavage to retinal and further to retinol and/or retinoic acid (fig. 2) [21, 22]. In ‘Western civilisation’ β -carotene is, in addition to lycopene (mainly in the USA), the carotenoid with the highest concentration in the human serum [23, 24] and a intake of β -carotene results in higher all-trans retinoic acid (ATRA) concentrations [5, 25, 26].

(2) Lycopene is the red pigment of tomatoes and is present in the human nutrition in tomato-based products [17, 18]. It is present in the human organism in the trans-form but also in the form of various geometric isomers [27, 28]. Up till now, there has been no direct indication that lycopene might be a pro-vitamin A carotenoid, but various studies point out that it may be a full or partial pro-vitamin A carotenoid [29]. Lycopene metabolism has only been marginally identified, but it seems to be mediated mainly via BCO-2 pathways [30–32]. Potent bioactive lycopene metabolites have been partly identified, but these seem to not be the main physiological/nutritional relevant lycopene-metabolites [30, 32, 33]. (3) Lutein and zeaxanthin are hydroxyl-conjugated carotenoid derivatives and these hydroxyl-/oxo-conjugated carotenoids are called: xanthophylls. Xanthophyll metabolites seem to obtain only minor vitamin A activity [34, 35] and their metabolism and biological function are not fully understood. Lutein and zeaxanthin seem to be important to serve as anti-retina degradation factors [36]. The yellow spot in the retina has high concentrations of lutein/zeaxanthin [37]; in fact, it is yellow because of these two yellow pigments. Lutein/zeaxanthin function in the retina is not completely understood, but it is suggested that it is localized in the membranes in order to filter high-energy blue light and to protect the organism from photon-induced negative effects.

In various studies, it is described that lutein can interfere with the uptake of β -carotene and its metabolism to bioactive retinoids. The exact molecular mechanism of

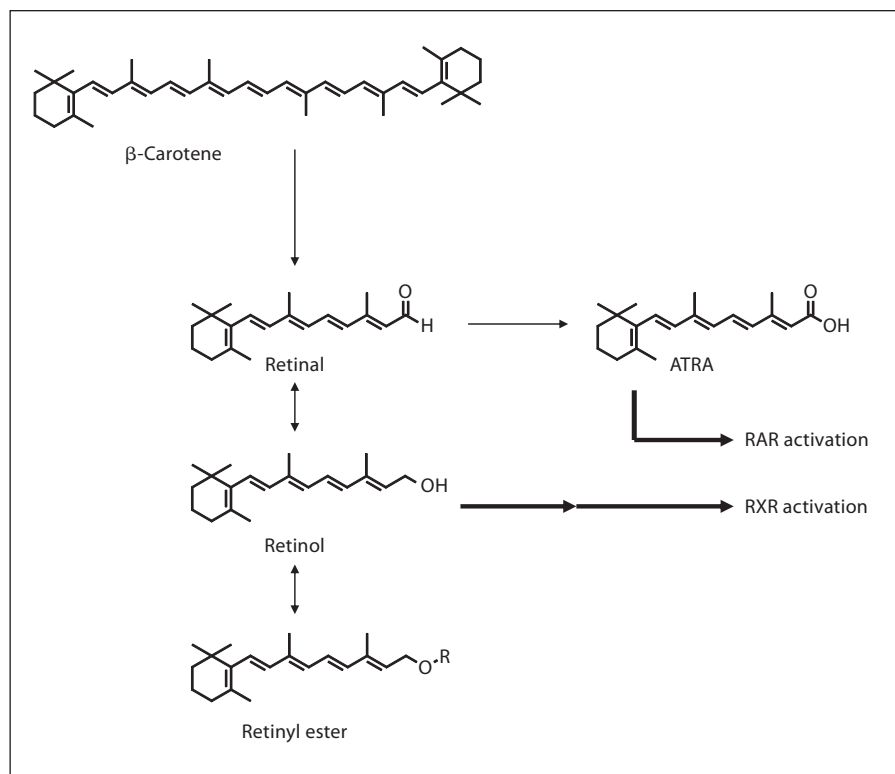


Fig. 2. Carotenoid and retinoid metabolism to bioactive nuclear receptor-activating ligand ATRA.

this phenomenon is not known and interference with intracellular uptake and interference with BCO-mediated metabolism are under discussion [38, 39].

Vitamin: 'The Problem'

The term 'vitamin' promises health and wellness. The general population knows that vitamins are essential for human nutrition and that we need to consume them to stay healthy because they can have various beneficial effects. Mainly based on knowledge distributed by the media, people also know that fruits and vegetables contain high amounts of vitamins, and can therefore be associated with beneficial effects on health. It is, however, not well known that grains, dairy products and meat are also major sources of various vitamins [40].

Hence, vitamins are also highly bioactive derivatives or their precursors, and high ingestions of specific derivatives can also induce various negative effects in organisms [41–43]. In particular, the lipid-soluble vitamins A, E and D can induce severe toxic effects after high dietary ingestions.

The distributed half-knowledge via the media claims that an 'unbalanced' Western-based diet is associated with vitamin intake that is too low. A daily dietary intake

of nearly unrealistic amounts of fruits and vegetables (e.g. the 850 g per day in the '5-a-day' campaign) is needed to reach the recommended daily allowances (RDA). Based on such RDA, just a very low percentage of the population seems by definition to have a 'healthy and balanced' diet. Due to these RDA being very high, many confused customers switch to easily accessible vitamin-supplemented convenience foods and vitamin supplements to complement their 'unbalanced' Western nutrition [44]. In contrast, scientific studies display a different perspective, namely that various vitamins are ingested in sufficient or even too-high amounts in the Western diet; this applies particularly to vitamin A [45]. Pro-vitamin A carotenoids are added to various convenience foods for coloration and as 'healthy' antioxidants [46]. Indeed, food products (including infant nutrition) are highly supplemented with vitamins in strongly increased concentrations to ensure a sufficient amount is retained inside the product until the date of expiry [47–50].

The fact that vitamin A must be a healthy derivative, because it is a 'vitamin' and that pro-vitamin A carotenoids are 'healthy', nontoxic pro-vitamin A derivatives avoid a current discussion that high vitamin A/pro-vitamin A carotenoid intake may indeed be partly responsi-

Table 1. Summary of RAR- and RXR-mediated effects relevant for allergic diseases

RAR activation:

Th1 → Th2 shift
Increased epidermal hyperproliferation
Increased epidermal differentiation
Reduced sebum secretion
Increased chemokine secretion
Eosinophilia
Increased bacterial colonization
Increased lymphocyte proliferation
Increased TSLP production

RXR activation:

Increased chemokine expression
Increased epidermal homeostasis
Increased epidermal inflammation
Increased systemic inflammation
Increased retinoid signaling in the skin
Increased TSLP regulation
Th1 → Th2 shift

ble for an increased risk of atopy in Western society. So far, no direct negative association between altered carotenoid/vitamin A/retinoid ingestion and increased atopy risk has been found, but a direct connection has already been suggested [51].

Nuclear Hormone Receptors, Carotenoids/Retinoids and Atopy

Recent studies have displayed that pro-vitamin A carotenoids, but also non-pro-vitamin A carotenoids can be metabolized to various bioactive derivatives (fig. 2) [15, 22]. Due to the complexity of carotenoid metabolism and the high number of nutritionally relevant carotenoids, this topic has been only very marginally studied, with β -carotene and lycopene (the most abundant nutritionally relevant carotenoids) being the main focus of scientific observations. Activation of the nuclear receptors, retinoic acid receptor (RAR), retinoid-X receptor (RXR) and peroxisome proliferator-activated receptor (PPAR) has been reported by carotenoid metabolites. The nutritional significance for the human situation is still elusive, but we expect that carotenoids other than α -/ β -carotene can be metabolized to potent bioactive nuclear receptor-activating derivatives and thereby modify various important physiological effects [29, 32, 34, 35].

The RAR and RXR response pathways, in particular, are of great importance for skin/epidermal homeostasis and inflammatory processes including various processes involved in atopy development.

RAR- and RXR-dependent pathways are involved in atopy development in the immune system, skin and lungs [15, 52–54]. While for RAR, the endogenous ligand ATRA is well documented and can be easily detected via HPLC techniques [55–57], the endogenous RXR ligand is still a mystery. It is known that an isomer of the retinoic acid the 9-*cis* retinoic acid can activate the RAR and the RXR, but unfortunately, this 9-*cis* retinoic acid has never been detected in sufficient endogenous concentrations by analytical expert groups [56–58]. Various publications report that this RXR ligand is derived from fatty acids [59] or retinol [52] as an additional bioactive retinoid (fig. 2).

Numerous features like epidermal permeability [60], epidermal hyperproliferation [61], epidermal differentiation [54, 62–64], sebum secretion [65], Th1/Th2 balance [52, 66–68], apoptosis [69], lymphocyte proliferation [70], eosinophilia [71], chemokine secretion [53, 72], inflammatory responses [52, 67], retinoid signaling [73], thymic stromal lymphopoietin (TSLP) production [53] and bacterial colonization [74] are regulated by RAR and RXR pathways and are also severely dysregulated in atopic dermatitis (table 1).

Due to the high variety of nutritionally relevant carotenoids, we expect that besides the axis: β -carotene → retinal → ATRA (fig. 2), other carotenoid metabolites could exist to activate the wide array of nuclear hormone receptors binding and being activated by ATRA, e.g. RAR α , RAR β , RAR γ , RXR α , RXR β , RXR γ and PPAR β [75–78]. All these nuclear hormone receptors also obtain an important function during atopy development and we postulate that carotenoids and PUFA metabolites may exist, which can more selectively activate and mediate the signalling via specific nuclear hormone receptor subtypes.

The RAR subtypes RAR α , RAR β and RAR γ are of great interest and are present in the human immune system and in human skin [54, 79, 80]. Gene knockout (KO) studies using epidermal specific KO mutants display that each of these RAR subtypes obtains a different spatial/temporal distribution within the skin and a different function in the skin and in the immune system. Unfortunately, receptor-specific retinoids are neither known nor have they been detected in the human organism/human skin. Novel, more sensitive and more specific analytical techniques will help to find and elucidate more complex pathways within the human organism responsible for more selective nuclear receptor activation.

It has been found that retinoid signaling, along with the expression of the various target genes involved, is generally much lower in the skin of patients with chronic atopic dermatitis than in that of healthy volunteers (ta-

ble 2) [73]. Of note is the low expression of retinaldehyde dehydrogenase 1 (RALDH1), the enzyme mainly responsible for ATRA synthesis. Skin levels of ATRA and retinol are also much lower, while serum levels of both substances are comparable (table 2). The physiological significance of these results remains unknown.

'Antioxidants'

In many studies, derivatives like vitamin A and carotenoids are classified as antioxidants [81, 82]. Recent studies show that this antioxidant concept is controversial because of the relatively high carotenoid concentrations (not physiologically relevant) needed to elicit these antioxidant effects. An excellent review was written by Erdman et al. [83] in 2009 that calculated radical concentrations and correlated them with local carotenoid concentrations.

The modern view is that carotenoids and vitamin A display antioxidant activity in higher concentrations mainly in nonbiological assays; this antioxidant concept has never convincingly been described in the *in vivo* situation [83, 84]. The antioxidant effects seem to be related to the nuclear receptor-activation potential of bioactive carotenoid metabolites [85–87]. NRF2, NFκB, PPAR and RAR activation pathways seem to be the key steps for these observed antioxidant effects in various organs [87–89]. We propose that carotenoids (pro-vitamin A carotenoids as well as non-pro-vitamin A carotenoids) are metabolized under radical/oxidative conditions to bioactive carotenoid metabolites which can activate RAR- and/or PPAR-mediated signalling and thereby block/ameliorate NFκB signalling and possibly other pro-oxidant and pro-inflammatory pathways as previously described for lycopene [90]. Another example is the recently identified apolycopenoids which display this potent anti-inflammatory potential [32].

The Western Diet and Carotenoid Patterns in Different Countries

In the Western diet, various nutrients are present in high concentrations like sugar, fat, n6-PUFAs, vitamin A and pro-vitamin A carotenoids (table 3) [40, 91, 92], while other nutrients like n3-PUFAs and non-pro-vitamin A carotenoids are less abundant [40]. Carotenoids are the nutritional biomarkers of consumed foods that contain them in high concentrations [7, 20]. Examples are the increased concentrations of lycopene after tomato (tomato-based products) consumption, β-carotene after the consumption of carrot juice and lutein after the consumption of spinach [93]. The previously mentioned mechanism of action of bioactive carotenoid metabolites is also depen-

Table 2. Summary of ATRA levels in the serum and skin of adults and in the serum of children

Concentration ng/ml or ng/g	Nonatopics	Atopics	Significance
<i>Adults</i>			
ATRA	2.8	2.9	–
in human serum	(n = 6)	(n = 6)	
ATRA	0.7/1.2	0.4/0.5	–
in human skin samples	(n = 2)	(n = 2)	
<i>Children</i>			
ATRA	1.6	1.6	–
in human serum	(n = 62)	(n = 24)	

Data are based on studies from Mihaly et al. [73] and Grüber et al. [26]. Significance = Calculated statistical significance in previous studies with a result that was either significant or nonsignificant (–).

Table 3. Summary of calculated dietary intakes in mg/person/day of vitamin A and carotenoids in former West and East Germany

	East Germany		West Germany	
	1986	1993	1986	1993
Retinol	0.86	1.73	1.43	1.43
β-Carotene	1.20	2.17	2.11	2.15

Figures are based on male individuals of 25–50 years of age. Data are extracted from Gericke et al. [92].

dent on various other factors like fats and oils that are ingested.

Interaction of dietary fat and dietary β-carotene has been determined in various studies [94]. β-Carotene and fat intakes in a Western diet are much higher and result in strongly increased β-carotene concentrations in the human organism, and increased ATRA concentrations are also highly likely. The exact mechanism of this interaction and the clinical and nutritional relevance for atopic diseases remains elusive.

The high ingestion of β-carotene in Western society can be explained by: (1) the frequent consumption of natural foods high in β-carotene like various tropical fruits and vegetables, and (2) the consumption of convenient foods fortified with β-carotene as pro-vitamin A and as a natural antioxidant or food colorant. We discuss the relevance of these details in the chapter 'Ethnicity, atopy and nutrition'.

Table 4. Average of serum concentrations from various carotenoids, ATRA and the ratio of pro-/non-pro-vitamin A carotenoids determined in nonatopic and atopic children

Concentration in ng/ml	Nonatopics	Atopics	Significance
Lycopene	13	9	*
Lutein	61	50	–
β-Carotene	77	66	–
ATRA	1.6	1.6	–
Ratio of pro-/non-pro-vitamin A carotenoids	1.3	1.7	p = 0.086

Values from the studies of Rühl et al. [25] and Grüber et al. [26].

Significance = Calculated statistical significance in previous studies with a result that was either significant (*), nonsignificant (–) or with the exact determined p value.

Carotenoids and Vitamin A in Breast Milk

There is a controversial discussion as to whether the intake of breast milk protects against allergies. Various factors are involved in allergic sensitization and a clear statement cannot be drawn based on current knowledge [95, 96]. The concentration of carotenoids and retinoids in breast milk seems not to be homeostatically regulated like the retinol levels in human serum [12, 13, 97]. Various reports clearly display that an increased maternal consumption of vitamin A results in an increased amount of vitamin A in breast milk [14, 98–100]. Increased maternal consumption of β-carotene increases the amounts of it in breast milk [6, 14, 16, 97, 101, 102], but also the amount of vitamin A [103]. In addition, milk samples rich in fat also have a particularly high content of vitamin A and β-carotene (reviewed in [104]).

These nutritional facts seem to correlate and may make a potential contribution to the increased atopy prevalence in Western countries [105]. Unfortunately, it appears very complicated or even impossible to obtain a direct correlation between the increased consumption of vitamin A, pro-vitamin A carotenoids and fat and an increased prevalence of atopy. Dozens of children must be examined when the first 'start signs' of the atopic march appear [106–108] and the individual nutrition and day-by-day carotenoid/retinoid/bioactive carotenoid metabolite levels as well as the atopy and inflammation markers must be examined and correlated with systemic and topical atopy markers. In terms of an ethical and financial base, an acceptable study in this field with selected children who are developing atopy seems to not be feasible.

Retrospective evaluations of cohort studies are already in progress and will deliver hints but no direct conclusions about the connection: high dietary β-carotene → high ATRA concentrations → increased atopy markers. Mouse studies are not feasible, because mice display a different carotenoid transport and metabolism [109]. In contrast to humans, the carotenoids in mice are mainly cleaved in the intestine and are rarely transported and stored within the organism.

Carotenoids, Retinoids and Atopy Risk in Cohorts of Children

The levels of retinoids and carotenoids have been determined in some studies, and in others, only those of selected vitamin A derivatives and carotenoids, which makes the comparison of studies difficult. Some studies have focused on adults with/without atopy [110–115], and here again, it is difficult to compare these with the situation in children, in whom atopy is developing. Additional information also stems from children studies, where vitamin A supplements were used, are summarised [116–118].

Different Studies Measuring Carotenoid and Vitamin A Levels in Children in Relation to Atopy

In general, β-carotene and various other carotenoids are lower in the serum of atopics (table 4) [25]. This fact can be explained by two alternatives which can be considered accumulative. (1) In atopic disease, there is a high chronic inflammatory background resulting in higher amounts of free radicals, and carotenoids with a long conjugated double-bound system can be destroyed with lower serum levels as a result [81]. (2) Various studies have reported that the dietary intake of carotenoids and fruits/vegetables is, in general, lower in children with atopy [111, 119–125]. In addition, lower serum vitamin A alcohol (retinol) levels have been found in asthmatic children [126–128].

In adults with established and chronic atopy, carotenoids are in general lower [112, 129]. In the study by Nagel et al. [115], a calculated higher intake of β-carotene is associated with an increased risk of hay fever. β-Cryptoxanthin and α-carotene intakes have been inversely associated with allergic skin sensitization [111]. In studies by Riccioni et al. [113, 130], serum lycopene levels were lower in subjects with stable asthma.

A general problem is that studies are performed mainly after the allergic phenotypes have been detected and

are already established. Measurements in children during allergic sensitization or who develop atopy later have not been performed. In addition, reduced serum concentrations of carotenoids and vitamins are, to some extent, of questionable relevance, because serum concentrations are maintained via homeostatic regulation and, in chronic inflammation, various factors in lipid homeostasis are downregulated as in the case of retinol-binding protein [8–10, 131] and lipoproteins [132].

There are also studies that misinterpret various terms in an unusual way, e.g. ‘vitamin A is an antioxidant’ and ‘carotenoids are vitamin A precursors’ [91, 133, 134]; these terms are not valid or are only valid for specific nonbiological systems. More care should be taken when discussing carotenoids, retinoids, vitamin A and antioxidants, in order to interpret scientific data and suggest dietary guidelines for atopy prevention with respect to ‘antioxidants’.

Carotenoids, and especially vitamin A, are claimed to be potential antioxidants, while it is rarely mentioned that they are also precursors of highly potent and potential toxic derivatives. Retinoic acids, in particular, have a potent ability to strongly promote atopy and inflammatory processes. Supplementation with ‘antioxidants’ for atopy prevention, claimed to be beneficial by various groups [129, 133], may in fact result in increased atopy prevalence, as has been already negatively experienced in cancer prevention trials, using healthy ‘antioxidants’ for smokers, that resulting in adverse effects with an elevated risk for cancer [46].

Studies on Vitamin Supplementation in Children

There have been interesting approaches where the potential beneficial ‘antioxidants’ and vitamins were supplemented to animal models [11, 52, 71, 135], human adults [65, 93] or children [116–118, 136]. In such studies, it was observable that atopy prevalence and skin parameters were negatively affected and that supplementation, particularly with vitamin A, may result in an increased prevalence of atopic diseases.

DNA Polymorphism, Carotenoids and Atopy

DNA polymorphisms are a key hint for additional information about the involvement of carotenoids in atopy. Three proteins have been associated with carotenoid attraction and cellular incorporation. (1) SR-BI is a transporter protein which is normally associated with cholesterol incorporation [137]. Novel studies describe this pro-

tein as being involved in lycopene and lutein/zeaxanthin transport and cellular uptake [138]. The main sites of SR-BI expression are the adrenal cortex (www.biogps.org), which is also an important site of carotenoid accumulation [139], but not in the allergy-relevant immune competent cells and the lung. One publication pointed out that SR-BI is expressed in cultured human keratinocytes and the mouse epidermis and its involvement in epidermal barrier maintenance [140]. (2) GSTP1 (glutathione S-transferase Pi-isoform) was described as a binding protein for zeaxanthin (possibly also for lutein) in the human organism [141]. A connection between GSTP1 expression in the human retina and the lutein/zeaxanthin accumulation was recently described [142]. (3) A study by Li et al. [143] determined additional STARD3 (steroidogenic acute regulatory lipid transfer domain protein 3) as a lutein-binding protein in the macula of primates, which has high expression levels in the lungs (www.biogps.org).

Various other studies have focused on the function of the GSTP1 polymorphism and its association to atopic diseases. GSTP1 polymorphism has been associated with asthma incidence and partly with a risk for atopic dermatitis [144–146]. GSTP1 is highly expressed in the bronchial epithelial cells, monocytes, B lymphocytes and the thymus (www.biogps.org). No direct association of GSTP1 polymorphism → zeaxanthin uptake/concentrations → asthma/atopic dermatitis risk has been identified yet, but this association seems to be possible. Protective effects of zeaxanthin in the lungs (bronchial epithelial cells) and the skin may be a key step in enabling/preventing allergic sensitization in these organs. The involvement of zeaxanthin in atopy prevention and how this is mediated mechanistically is still unknown.

In summary, with regard to the association of carotenoid transporter-proteins, polymorphisms and local carotenoid levels with atopy prevention, let us conclude that the carotenoids lutein/zeaxanthin and lycopene may be important for atopy development and atopy prevention in specific non-pro-vitamin A carotenoid-accumulating target tissues.

Ethnicity, Atopy and Nutrition

Excellent hints for different nutrition/lifestyle and their connection to atopy rates are to be found among migrants or different ethnicities with traditional low atopy rates living in countries with high atopy rates [147–149]. Atopy rates are usually high in Western-lifestyle-based countries and lower in poorer/developing countries

Table 5. Average of serum concentrations from various carotenoids, ATRA and ratio of pro-/non-pro-vitamin A carotenoids and allergy rates of Turkish and German children living in Germany based on various studies and on our preselected study cohorts

	German children	Turkish children	Significance
a Average of serum concentrations, ng/ml			
Lycopene ¹	9	14	*
Lutein ¹	48	64	*
β-Carotene ¹	89	62	*
ATRA ²	1.9	1.4	*
Ratio of pro-/non-pro-vitamin A carotenoids ¹	2.0	1.2	*
b Allergy rates, %			
Cohort ³	18.3	9.7	n.d.
Cohort ⁴	36.7	24.7	*
Cohort ¹	49	23	n.d.
Cohort ²	53	12	n.d.

n.d. = Not determined. * Significant.

¹ Values from Rühl et al. [25]. ² Values from Grüber et al. [26].

³ Values from Grüber et al. [151]. ⁴ Values from Kabesch et al. [147].

[150]. It has been suggested that besides genetic factors, environmental factors might mainly account for these differences in atopy prevalence between different ethnic groups.

We present three examples which all indicate that nutrition, with a special focus on vitamin A and carotenoids, is a major factor which is different in these high- or low-risk atopy populations. Various other lifestyle and sociodemographic factors are also known to differ between these groups. We focus here on Turkish and German children growing up in Germany, Roma/Gypsy and Czech children growing up in the Czech Republic and German children from former East and West Germany.

Situation between Turkish and German Children Growing Up in Germany

Turkish migrant children who grow up in Germany display much lower atopy rates than their German peers (table 5b) [147, 151]. This phenomenon is mainly attributed to lifestyle factors like family history of atopy, lower socioeconomic status, direct or indirect exposure to tobacco smoking, number of siblings, housing conditions and pet ownership. Grüber et al. [151] also demonstrated that cultural adaptation of Turkish migrants resulted in increased atopy prevalence comparable to their German peers.

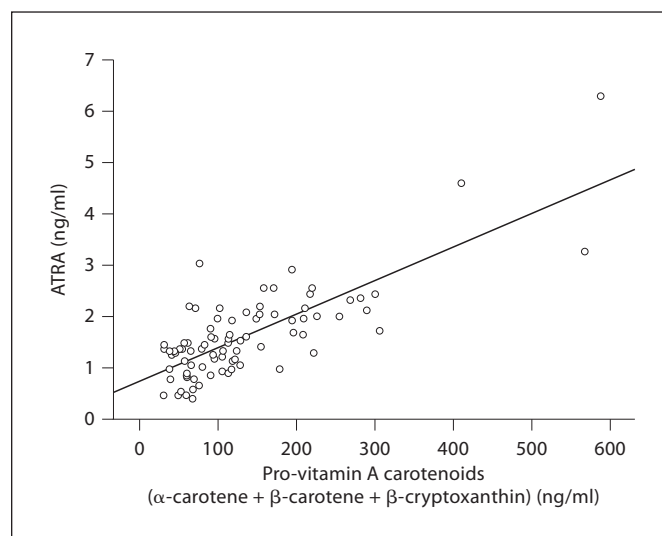


Fig. 3. Correlation of serum concentrations of ATRA and pro-vitamin A carotenoids (α-carotene + β-carotene + β-cryptoxanthin) based on Turkish and German children (see [26]; reproduction permission was obtained).

We also focused on nutritional factors like retinoids and carotenoids. In this study [25], we classified the carotenoids in non-pro-vitamin A carotenoids and pro-vitamin A carotenoids because of the known effect of the pro-vitamin A carotenoid metabolite ATRA on the immune and skin phenotype of atopy (table 1). Lower ratios of pro-vitamin A carotenoids were observed in Turkish children than in German children. The pro-vitamin A carotenoids α-carotene and β-carotene, in particular, were significantly lower in Turkish children [25], while the non-pro-vitamin A carotenoids lutein and lycopene were significantly higher (table 5). In the same study, the children were stratified for atopics versus nonatopics, and we determined that only the non-pro-vitamin A carotenoid lycopene was significantly lower in atopics (table 4) [25].

We conclude from this study that, in German children, altered nutrition rich in pro-vitamin A carotenoids might be a potential risk for atopy prevalence in specific stages during their development. In a later study determining the bioactive pro-vitamin A carotenoid metabolite ATRA, we observed a correlation of the pro-vitamin A carotenoid and ATRA serum levels (fig. 3) and significantly lower ATRA levels in Turkish migrant children in comparison to German children (table 5) [26]. We conclude that altered nutrition may also be a critical point in

explaining atopy prevalence differences in children with different ethnicity living in the same environment.

Czech and Gypsy Children in the Czech Republic

Interesting studies were conducted when examining local Czech and Gypsy/Roma children in the Czech Republic. Gypsy children display almost no atopic diseases (1.5% asthma, 3% rhinitis and 0% atopic dermatitis), and the prevalence of atopy among Czech children is slightly lower than in other European countries (9% asthma, 8% allergic rhinitis and 9% atopic dermatitis) [152]. The incidence of various infectious diseases like influenza, bronchitis, pneumonia, otitis media and intestinal infections was significantly higher in Gypsy children [152]; some of these were connected with low intake and levels of vitamin A [153]. Rambouskova et al. [154] compared the nutritional and health status of Czech and Gypsy children. They determined that Gypsy women had significantly lower blood concentrations of retinol (360 ng/ml) and β -carotene (230 ng/ml) than Czech mothers (460 ng/ml retinol and 360 ng/ml β -carotene). These 2 studies also point towards an important effect of carotenoids and retinoids on atopy prevalence.

The Situation in Former West and East Germany

Fortunately, we can also partly compare and draw conclusions between the populations of former West Germany and East Germany, which possess a comparable genetic background, but in the East Germans a lower socioeconomic background and different lifestyle and nutritional behavior [92, 155–157]. Children in the former East Germany had a lower atopy prevalence than their West German counterparts [158–160]. The general food intake of West versus East Germans was different in many aspects; these facts, mainly related to PUFA and vitamin intake, have been reported (table 3) [92].

The estimated consumption of pro-vitamin A carotenoids of former East Germans during the process of reunification between 1986 and 1993 has increased remarkably. Whether lower consumption of β -carotene in the former East German population was partly associated with lower atopy sensitization rates remains elusive because retrospective analytical examinations are no longer possible, due to the lack of available serum/blood data banks from before German reunification in 1990.

Lower Socioeconomic Lifestyle and Atopy Protection

In conclusion, we could determine that lifestyle factors, especially nutrition, are different in different ethnicities growing up in the same macroenvironment. Low-

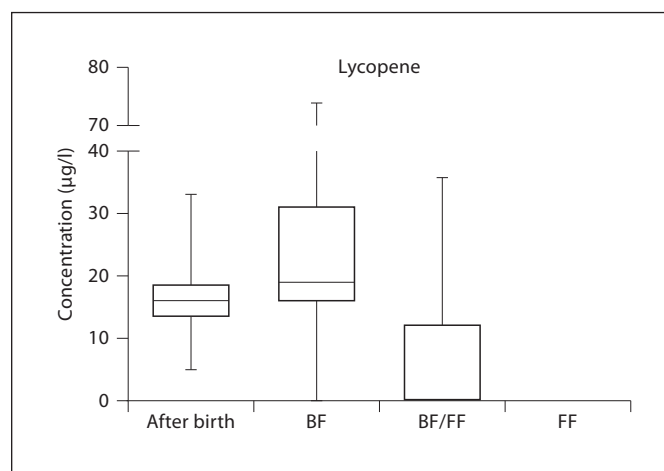


Fig. 4. Lycopene levels in children after birth, breast-fed children (BF), formula-fed children (FF) and the two combined (BF/FF) (see [166]; reproduction permission was obtained).

er socioeconomic lifestyle indicated possibly by a higher intake of certain fruits and vegetables might lower atopy sensitization rates (reviewed in [91]), while a nutrition high in vitamin A and pro-vitamin A carotenoids might be one important factor for higher atopy prevalence in populations with a higher socioeconomic background.

What Is New and What to Do?

What Is New?

It is a new concept that non-pro-vitamin A and pro-vitamin A carotenoids are potentially involved in atopy development. It has not been directly and conclusively proven [51], but many arguments provided in this review support this connection. Populations with higher β -carotene intake and proven higher β -carotene concentrations in the organism possess an increased risk for atopy prevalence, but a linear correlation between β -carotene and atopy markers like serum IgE levels has not been obtained [25].

In addition, it seems that the non-pro-vitamin A carotenoid lycopene is associated with protection against atopy development [111, 130, 161–163]. Lycopene is in general not supplemented in infant nutrition, and so levels of it in the serum of children being fed fortified food are almost absent in comparison to breast-fed children (fig. 4). In contrast to the pro-vitamin A carotenoids, which are precursors of the highly active ATRA, the non-pro-vitamin A carotenoids lutein/zeaxanthin and lycopene

	Traditional lifestyle	Western lifestyle
Nutrition		
Vitamin A	low	high
Pro-vitamin A carotenoids	low	high
Non-pro-vitamin A carotenoids	high	low
Breast milk		
Pro-vitamin A carotenoids	low	high
Vitamin A	low	high
Serum levels in children		
Non-pro-vitamin A carotenoids	high	low
Pro-vitamin A carotenoids	low	high
ATRA levels	low	high
Atopy prevalence	low	high

Fig. 5. Summary of a traditional versus a Western lifestyle, showing retinoids and carotenoids in nutrition and breast milk, serum levels in children and atopy prevalence.

pene are associated with low serum and organ ATRA levels. The mechanism of non-pro-vitamin A carotenoid-mediated protective effects still needs to be examined more deeply in healthy volunteers and in atopic patients. Lutein/zeaxanthin and lycopene can also obtain potential optimized radical-scavenger effects in membranes and these effects may ameliorate atopy risk.

Figures 5 and 6 show the following connection. High dietary β -carotene intake $\rightarrow$ high β -carotene concentrations in the organism $\rightarrow$ high ATRA concentration in the organism $\rightarrow$ high activation of RAR-dependent target genes $\rightarrow$ high activation of atopy-relevant target genes $\rightarrow$ higher susceptibility of atopic diseases. This connection is not yet fully confirmed.

Non-pro-vitamin A versus pro-vitamin A carotenoids in breast-fed children with atopy development has never been investigated. Therefore, no connection can be drawn and this topic still needs further investigation. Few studies have been conducted examining the involvement of nutritionally relevant carotenoids in atopy development. Today, β -carotene and (only in selected infant formula) the non-pro-vitamin A carotenoids lutein and/or lycopene are present [47, 48, 164–166], while the other carotenoids α -carotene, β -cryptoxanthin and zeaxanthin are not present at all.

Nutritional products for older children after weaning are mainly based on fruits, vegetables and grain products

[48, 167]. The major source of infant nutrition is carrots, which are a rich source of β -carotene [168], in addition to various other carotenoids which are also present in these infant food products because of the great variety of different fruits and vegetables used. In some products, the pro-vitamin A part of carotenoids comprises 76%, while non-pro-vitamin A carotenoids comprise only 24% [48]. Publications from the 1950s and even earlier describe carrots as the major source of infant nutrition [169, 170]; recent studies are not available as to the beneficial value and the usage of carrots.

We would like to point out that the consumption of pro-vitamin A and the nutritional supply of vitamin A in Western societies are currently more than optimal in comparison to periods between, before or even shortly after the Second World War [104].

It is highly questionable whether or not nutritional guidelines drawn up 60 years ago or prior to that are still valid; they could actually be detrimental and should be carefully investigated. Such guidelines are, however, still used as references by major market leaders without acknowledgement of the altered, much-improved and optimized dietary supply of valuable nutrients at the present time.

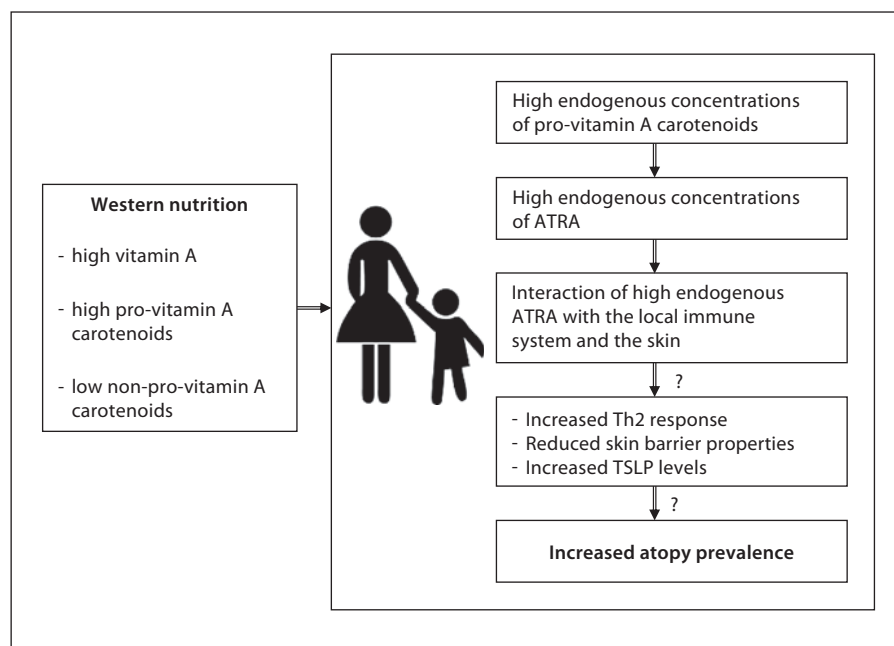
In summary (fig. 5 and 6): (1) in Western European society, β -carotene intake and serum β -carotene concentrations are higher [25], (2) increased serum concentrations of β -carotene result in increased serum ATRA concentrations [5, 26], (3) ATRA induces a Th1 $\rightarrow$ Th2 shift in immune responses [52, 66, 68, 171] and (4) an increased Th2 immune response leads to atopy development [107, 172]. Each of these single steps has been conclusively documented and accepted; however, a direct link between (1) increased β -carotene intake to (4) increased atopy risk has not yet been established and further conclusive studies are needed.

What to Do?

With the consideration that non-pro-/pro-vitamin A carotenoids are of relevance for atopy development, it would appear that we need an improved balance of non-pro-vitamin A versus pro-vitamin A carotenoid levels in children. This could be achieved by improved infant, child and maternal nutrition. This improved nutrition should aim at a more balanced carotenoid supply including less pro-vitamin A carotenoids.

Without it having been conclusively shown that non-pro-/pro-vitamin A carotenoids are important for atopy development, more experimental supplementation studies are needed in animals and humans, to either conclude that

Fig. 6. Summary of the influence of Western nutrition on carotenoid and retinoid levels with regard to atopy prevalence.



there is no connection between dietary carotenoids and atopy sensitization rates in the Western nutrition or to explain which factors in 'Western nutrition' coincide with low non-pro-vitamin A versus pro-vitamin A carotenoid ratios in population with higher atopy sensitization rates.

Our summary clearly shows that the carotenoid lycopene, in particular, seems to have beneficial effects with regard to atopy and its development, and that maybe a higher dietary intake of lycopene or lycopene-containing foods may be a strategy to prevent increased atopy sensitization rates (fig. 4).

Where Is More Knowledge Needed?

Development of Atopic Disease in Humans

To understand the involvement of carotenoids and retinoids in the development of atopy, we must have a closer understanding of this development in humans. The involvement of local epidermal inflammation and epidermal integrity disturbances in the skin seems to be the initial step for the start of the 'atopic march' [107, 108]. The involvement of TSLP, a cytokine generated in inflamed skin, is an initial step in the later systemically relevant Th1 → Th2 shift of immune responses [53, 72, 173].

This 'inside-outside' theory of atopy development [174] and the 'atopic march' occur mainly in children at various time points. The starting point of atopy develop-

ment seems to be in the skin, with an initial local inflammation, and later in the activated immune system, with an altered Th1/Th2-balanced immune response [107]. The involvement of food and thereby of carotenoids, retinoids and their bioactive metabolites during epidermal integrity and barrier development of the skin and during Th1 → Th2 shift has, in part, been established, mainly in in vitro, ex vivo and animals studies. Atopic disease development in humans has not been investigated in 'real time' because of the ethical restrictions to investigating 'real-time' targets like retinoids/carotenoids/bioactive carotenoid- and retinoid-metabolites/eicosanoids and immune parameters in the skin and in various regions where an atopy-relevant immune response occurs.

The Association of Food Intake with Bioactive Metabolite Concentration

Linking food intakes directly with the generation of bio-active metabolites which activate selectively specific nuclear hormone receptor pathways poses a problem. These selective nuclear hormone-specific, nutrition-related activators can influence the epidermal integrity, epidermal inflammation and Th1/Th2 development in the human organism via activation of specific pathways. The time- and the organ-specific metabolic activation of food components are not well understood and have not been exactly determined in humans, especially during childhood.

Mice experiments with carotenoid treatments are difficult to interpret and experiments with humans are ethically and financially highly restricted. The use of appropriate animal models for atopy development and an appropriate comparable carotenoid metabolism to that in humans are needed and may provide more details about the involvement of food intakes estimated by determining carotenoids, retinoids and bioactive carotenoid and retinoid metabolites during the development of atopy.

Establishment of Biomarkers for Atopy and for Specific Diets

To evaluate human intervention or cohort studies, we need appropriate biomarkers for atopy and for specific diets. These biomarkers must be localized in the serum and, if available, in disease-specific target tissues like the immune system and the skin. Ideally, these food biomarkers overlap with the atopy markers. The correlation of food biomarkers between different groups with and without sensitization/initial dermal inflammation/a higher atopy risk/atopy should be compared.

Contribution of Infant Nutrition Containing Lutein and Lycopene on Atopy Markers

Products for infant nutrition containing the carotenoids β -carotene, lutein and lycopene have been developed for the US market [47, 164, 175]. These should be examined more deeply in clinical supplementation studies in lactating mothers and their children, in order to establish if they have positive effects on atopy prevalence.

Recommendations for the Development of Infant Nutrition Based on Retinoids and Carotenoids for Atopy Prevention

Can Better Milk Formula Lead to Improved Health Status?

Based on this review, lutein/zeaxanthin and lycopene are needed in infant nutrition. A more balanced carotenoid supply based on 'real' life conditions should be aimed for. The relationship between non-pro-vitamin A versus pro-vitamin A carotenoids and the concentration of these carotenoids in the food are still unknown variables and need to be determined supplementation studies in animals as well as in humans. In addition, the exact rationale as to why different carotenoids should be supplemented should be studied more deeply.

Can Improved Milk Formula Result in Lower Atopy Sensitization Rates?

Mouse studies cannot be performed because of the different carotenoid kinetics in comparison to the human situation. Human supplementation studies using carotenoid supplements are difficult and expensive to perform. Before we can provide a conclusive answer to this question, more appropriate animal studies using β -carotene, lutein/zeaxanthin and lycopene supplementation are needed in appropriate animal models like gerbils, ferrets or pigs.

The general answer on this question remains: If pro-vitamin A carotenoids and bioactive retinoids are increased, and non-pro-vitamin A carotenoids are too low in 'Western nutrition' and an altered nutritional behavior is involved in atopy development, then an optimization of the dietary intake of the above-mentioned may lead to lower atopy sensitization rates by using optimized alternative food products.

The prerequisite for future recommendations is: We need more experimental supplementation studies and more companies who are interested in the production of improved infant milk formula and infant nutrition based on retinoids and carotenoids, with the aim of reducing the potential for atopy sensitization.

Micronutrients and Atopy: Other Options

Various other nutritional components have been connected with an increased or ameliorated atopy sensitization risk. Besides retinoids and carotenoids, prebiotics, probiotics, trace elements, n3-poly-unsaturated fatty acids, minerals and 'antioxidants' have also been associated with lower risks of atopy [91, 134].

The discussion about vitamin D is controversial and ongoing; while various studies have determined lower vitamin D levels in atopics (reviewed in [176, 177]), other studies in children and lactating mothers may indicate that higher vitamin D serum concentrations are associated with higher atopy rates [178]. It is suggested that only specific windows during allergic sensitization might be vulnerable to higher vitamin D levels which might explain the different outcome of such studies [179].

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