Review

Insights of hypercarotenaemia: A brief review

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SUMMARY

Carotenoids are generally 40-carbon tetraterpenoids responsible for most of the yellow, orange and red colours throughout the natural world. Pro-vitamin A carotenoids serve as the precursors of vitamin A. In addition to that, carotenoids exhibit range of important protective mechanisms in human health. Hypercarotenaemia is characterized by carotenodermia resulting in yellowing of the skin specially palms and soles. Hypercarotenaemia develops in subjects consuming high levels of carotenoid rich foods or β-carotene supplements (>30 mg day^{-1}) over a period of months. Less or normal intake of carotenoids very rarely gives rise to metabolic carotenaemia due to genetic defects of the enzyme 15-15′-carotenoid dioxygenase. Moreover, it is known that those with hypothyroidism and diabetes mellitus tend to develop hypercarotenaemia with the normal intake of carotenoid rich foods. Further, hypercarotenaemia has been reported in anorexia nervosa. However, recently some studies have been shown that there is no major correlation between carotenoid intake and hypercarotenaemia indicating that a genetic factor is at play in development of hypercarotenaemia. Therefore, the subjects appear to need to be genetically pre-disposed to hypercarotenaemia.

1. Introduction

Hypercarotenaemia is a benign condition characterized by carotenodermia caused by the deposition of carotenoids in the stratum corneum of the epidermis resulting in jaundice-like yellowing of the skin specially palms and soles and high plasma carotenoid concentrations [1,2]. However, fat bearing tissues are the main target of carotenoids, which is adipose tissue. The carotenoid in the serum is only small indications of the total carotenoids accumulated in the body. It is hypothesized that there may be an equilibrium of carotenoids in adipose tissue, serum and liver.

Hypercarotenaemia can be differentiated by jaundice because in hypercarotenaemia, sclera of the eye and buccal mucous membrane are not converted into yellow colour as they are mainly protein-based structures. Hypercarotenaemia spontaneously recovers when the dosage is reduced or after cessation of intake. 'Canthaxanthin retinopathy' a known toxic manifestation of carotenoid intake has been reported from European countries due to large doses of canthaxanthin. Under this condition, a reversible deposition of pigmented granules in the retina had been occurred with some loss in night vision [3].

2. Occurrence of carotenoids

Carotenoids are a widespread group of natural plant pigments responsible for most of the yellow, orange and red colours throughout the natural world. They are found in the plant kingdom, providing brilliant colours to fruits, vegetables and flowers. Carotenoids are invariably found in all green plant tissues. In leaves, they are located in chloroplasts as photosynthetic pigment—protein complexes and in mature fruits and flowers within chromoplasts. In green tissues although the colour of carotenoids is masked by that of the remarkably high green pigment of chlorophyll, colour appears during maturation of fruits and in leaves with the onset of autumn or leaf fall which is associated with the degradation of chlorophyll [4].

Ripening of fruits accompanies the conversion of chloroplasts into chromoplasts with the disappearance of photosynthetic organelles. In this conversion carotenoids are concentrated in distinct structures, which can be defined as crystalline, fibrillar, tubular, membranous and globular [5].

Annual de-novo production of carotenoids in nature is about 100 million tons by all higher plants along with some bacteria, algae, yeast and fungi. It is estimated that more than 600 of different carotenoids excluding cis and trans isomers are widely distributed and they have now been identified. This number includes the

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extensive diversity of carotenoids in algae bacteria and fungi. Animals are incapable of synthesizing carotenoids. But, fewer amounts of these pigments have been encountered in some animal foods as a result of selectively or non-selectively absorbed carotenoids from their diet. This is known to be deposited unchanged or transformed to keto or hydroxy derivatives [6,7].

3. The structure of carotenoid

Carotenoids are generally 40-carbon tetraterpenoids, which are formed by joining eight 5-carbon isoprene units ($-CH_2-C(CH_3)=CH-CH_2-$) in a head-to-tail manner except at the center where there is a tail-to-tail linkage. As a result, the sequence is reversed at the center, which provides a symmetrical and linear basic molecule. Lateral methyl groups of this molecule are separated by six carbon atoms from the center of the molecule and five carbon atoms elsewhere in the molecule. The basic linear carotenoid structure may be subject to processes such as hydrogenation, dehydrogenation, cyclization, double bond migration, chain shortening or extension, introduction of oxygen functions, rearrangement, isomerization or any combination of these modifications resulting 'in a myriad of structures' [6]. The carotenoids mainly found in plant foods are given in Fig. 1.
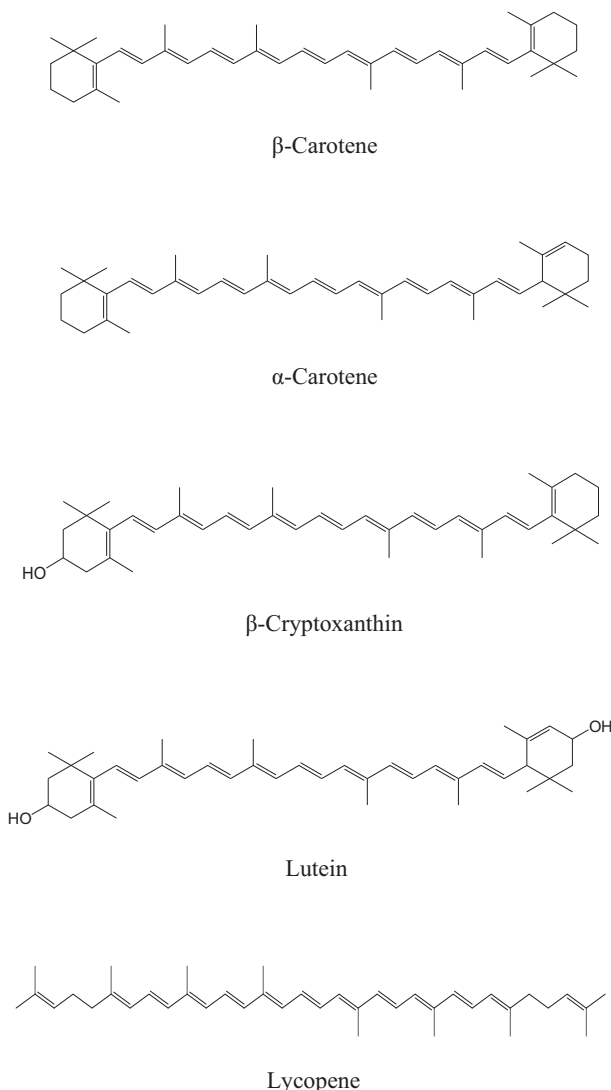

β-Carotene

α-Carotene

β-Cryptoxanthin

Lutein

Lycopene

Fig. 1. Some main carotenoids found in plant foods.

4. Biological functions of carotenoids

Though more than 600 carotenoids have been found in the nature, α-carotene, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, lycopene and canthaxanthin have been detected predominantly in human blood [4]. Biological functions of carotenoids mainly include its pro-vitamin A activity. The pro-vitamin A carotenoids act as the precursor of vitamin A. Vitamin A has many health benefits and it is mainly involved with vision, cell differentiation and maintenance of cell membranes, embryogenesis and immuno-enhancement [2]. In addition to that, carotenoids exert their antioxidant activity by singlet oxygen quenching and free radical scavenging effects thereby they possess a range of important protective mechanisms for human health. This involves protection against the pathogenesis of degenerative diseases especially coronary heart diseases, cancers and an array of other free radical-mediated conditions [8–10]. Lutein and zeaxanthin are important in prevention of age-related macular degeneration [11].

5. Bioconversion of carotenoids

The proportion that is converted into retinol from the absorbed pro-vitamin A carotenoids is known as 'bioconversion'. The cleavage is catalyzed by the cytosolic enzyme 15-15′-carotenoid dioxygenase and the key enzyme is β-carotene-15-15′-dioxygenase. The central cleavage occurs at the central 15:15′ double bond and in the case of β-carotene the yield would be two molecules of retinal [12,13]. This can be either be reduced to retinol or oxidized to retinoic acid. The reaction takes place primarily in the intestinal mucosa and enzyme activity is also found in tissues such as the liver. Though central oxidative cleavage is the major pathway asymmetric cleavage is also possible [14]. Asymmetric cleavage would produce apo-carotenal intermediates that could be converted to apo-carotenoic acids, which subsequently can be converted into retinoic acid [15]. Alternative metabolic products of β-carotene by central and eccentric cleavage path ways are given in Fig. 2.

6. Biochemical basis of hypercarotenaemia

Hypercarotenaemia develops due to intake of high doses of β-carotene or carotenoid rich foods such as carrot, pumpkin, orange, tomato or β-carotene supplements (>30 mg day^{-1}) over a period of months. When carotenoids are ingested in excess for extended periods, the pro-vitamin A carotenoids are not converted into retinol if vitamin A level in the body is satisfactory. This self-limiting conversion is important in prevention of hypervitaminosis. This leads to an increase carotenoid concentration in the serum with resultant hypercarotenaemia [1,2]. On the other hand, failure to split pro-vitamin A carotenoids into retinal due to genetic defects of the enzyme 15-15′-carotenoid dioxygenase also can lead to metabolic carotenaemia under less or normal intake of carotenoids, but this is very rare [16].

Vitamin A and retinoids are metabolized in the liver. In this case liver cytochrome P_{450} plays a role to enhance the polarity of the metabolites. It is assumed that the carotenoid degradation process is likely to be similar to that of vitamin A and retinoids. Therefore, taking part of cytochrome P_{450} system in carotenoid metabolism is possible. Due to inefficient absorption, some carotenoids exit in the faeces probably via bile. The final metabolites of carotenoids excreted are still unknown [1].

It is also shown that those with hypothyroidism tend to develop hypercarotenaemia with the normal intake of carotenoid rich foods. The thyroxine and hyperthyroidism can enhance the conversion of β-carotene which is a pro-vitamin A carotenoid in to two molecules of vitamin A (retinol). Therefore, the characteristic
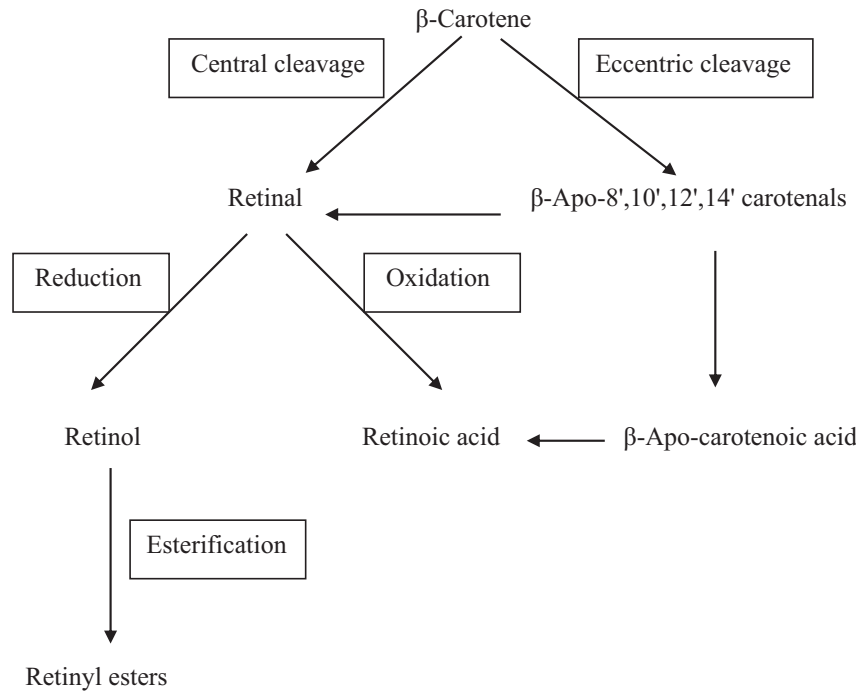
Fig. 2. Alternative metabolic products of β-carotene by central and eccentric cleavage.

yellowish discolouration of the skin in hypothyroidism is due to elevated level of β-carotene in the blood. Aktuna et al. carried out a study on 36 patients with thyroid dysfunction. This study indicated that in the hypothyroid subjects the serum level of β-carotene was markedly higher compared to the euthyroid controls, whereas the hyperthyroid subjects showed an obvious lower level of β-carotene. Further, this study had been carried out by using 16 hyperthyroidism, 8 hypothyroidism, and 12 euthyroid subjects showed that the β-carotene level in serum of hypothyroid group was significantly higher compared to euthyroid controls (p < 0.05). The mean serum β-carotene level of hypothyroid and euthyroid controls were 1.1 and 0.6 μg/mL, respectively. However, hyperthyroid group had showed that significantly lower serum β-carotene level which was reported as 0.3 μg/mL. Furthermore, authors mentioned that, there was no significant different in retinol levels in all 3 groups surprisingly the hyperthyroid group showed a slightly lower value i.e., 0.6 μg/mL than the mean value for other groups which was 0.7 μg/mL [17]. Moreover, it has been reported that frequently elevated serum carotene levels in the subjects with diabetes mellitus due to impaired conversion of pro-vitamin A carotenoids in to vitamin A. But yellowish discolouration of the skin had developed only in 10% of cases [18].

In addition to that, the findings of Robboy et al., has been shown that in patients with anorexia nervosa there is a statistically significant elevation in serum α-carotene (p < 0.001), retinyl ester (p < 0.001), retinol (p < 0.01) and retinoic acid (p < 0.02) levels. The authors suggested that possible reason for development of hypercarotenaemia in anorexia nervosa may be due either to enhanced carotene and vitamin A ingestion or an acquired defect in the utilization or metabolism of vitamin A [19]. A retrospective case–control study conducted by Boland et al., revealed that out of 101 female patients with anorexia nervosa, 62% of patients had been developed hypercarotenaemia with an obvious elevation of serum β-carotene compared to control group. The authors had been mentioned that hypercarotenaemia is a common finding in anorexia nervosa patients [20].

7. Over consumption of carotenoid rich foods and hypercarotenaemia

Several studies have been shown that hypercarotenaemia is caused by excessive intake of carrot, orange, pumpkin and tomato [1,2,21–25], where tomato being the cause for lycopenaemia. According to Mazzone and Cantona, 23-year old woman having yellow-orange discolouration of skin had been excluded from jaundice as her sclera was not yellowish coloured and her serum bilirubin concentration was normal. In addition to that, other conditions such as hyperlipidaemia, diabetes mellitus, hypothyroidism and porphyria which could lead to hypercarotenaemia had been excluded. Marked elevation of serum β-carotene level had been shown by high-performance liquid chromatography (HPLC). However, the patient was a vegetarian and the diet comprised of low-calorie with high content of orange juice, pumpkin and carrots [21].

Another case study indicated that there was a 32-year-old female with yellowish discolouration of the skin for three years. Initially she had been noted that yellowing of her palms, followed by yellowing of soles. The intensity of the yellowish discolouration had been increased gradually with lightening of her original black negroid colour. During this period, she had no any complain regarding related diseases that can develop hypercarotenaemia. But her diet history revealed that excessive eating of oranges, sweet potatoes and spinach especially, during orange season eating of at least a dozen of oranges daily. Her blood investigations showed that normal liver function tests, thyroid function tests and renal function tests and she was diagnosed to have diet related carotenaemia [24]. A 40-year-old woman with orange discolouration of both palms who was excluded from jaundice had a history with eating of tomatoes and tomato-based dishes approximately 5 times per week for 3 years, on average 1.4–1.8 kg of tomatoes weekly. Tomato is a rich source of lycopene which is a hydrocarbon carotenoid. The discolouration was diagnosed as lycopenaemia. The patient was advised to decrease the ingestion of tomato. The follow-up

examination done after 2 weeks revealed that the discolouration had faded and by 4 weeks it had been totally disappeared [25].

Priyadarshani et al. carried out a study on hypercarotenaemia in Sri Lankan infants/children age ranged from 9 months to 2.5 years. In this study hypothyroidism had been excluded from all the subjects by estimating serum thyroid-stimulating hormone (TSH) level. None of them were jaundiced and not on any medication. This study indicated that according to the case histories boiled, homogenized carrot and papaw were the main carotenoids rich food fed to these infants. Boiled pumpkin has also given but with less frequency. The authors highlighted that carrot might be the main causative agent for hypercarotenaemia in the study group [22]. This finding is supported by the carotenoid profile and content of carrot variety found in Sri Lanka which is known as 'New kuroda'. The carrot variety 'New kuroda' is very rich in pro-vitamin A carotenoids, β-carotene and α-carotene which has been indicated in Table 1 [26]. *In-vitro* bioaccessibility studies indicated that boiled carrot (pulp) had bioaccessible β-carotene and α-carotene of 301.0 ± 65.6 and 119.3 ± 10.77 $\mu g\ g^{-1}$ on the basis of dry weight, respectively. It was a percentage of 73 (for β-carotene) and 60.6 (for α-carotene) when compared to the amounts present in the boiled carrot (pulp) on the basis of dry weight. These results indicated that boiled carrot pulp has a very good *in-vitro* bioaccessible β- and α-carotenes as a result of the heat treatment and reduced particle size in this preparation [27]. In addition to that according to the study carried out in Sri Lanka, β-carotene level of papaw is ranged from 9.9 to 79.2 $\mu g\ g^{-1}$ on the basis of dry weight [28]. Further, pumpkin varieties found in Sri Lanka are very rich sources of pro-vitamin A carotenoids, which is indicated in Table 2 [26]. However, when consider the β-carotene levels of carrot, papaw and pumpkin it is not surprising that the major carotenoid is β-carotene in the development of hypercarotenaemia in the study population as consumption pattern showed that carrot, papaw and pumpkin were mostly consumed [22].

Above finding was supported by another study carried out in Sri Lanka, indicating that hypercarotenaemia (n = 35) is due to excessive ingestion of carrot, pumpkin and papaw. This study further detailed that the serum α- and β-carotenes varied from

trace to 119 g/dL and from trace to 149 g/dL, respectively. The mono-hydroxy metabolites were varied from non-detectable level to 214 g/dL where as poly-hydroxy metabolites from 7.0 to 823 g/dL. In this study carotenoid metabolites have been identified only by HPLC retention time and the structures had not been deduced by the authors. In addition to that, α- and β-carotenes were not detected in the feces of the hypercarotenaemic patients (n = 5) but they were present in the feces of the non-hypercarotenaemic subjects (n = 8) as determined by HPLC [23].

Despite patients coming from Colombo, Sri Lanka, where red-fleshed papaw is common but no lycopene was detected in the serum. Reasons for this can be many. Firstly, it is possible that parents do not feed their children red-fleshed papaw. It is also possible that lycopene, which plays a role as a good antioxidant [29] may be subject to faster metabolism.

The study carried out on prevalence of hypercarotenaemia in Western province of Sri Lanka indicated that among 780 of nursery/kindergarten children only 615 of children had been feed with high carotenoid diet and the quantity is similar to the amount eaten by hypercarotenaemic children. Out of 615 children only 287 children had received vitamin A mega dose. From the children who had received vitamin A mega dose only 4 had experienced with hypercarotenaemia. Further one among them had a sibling, though he had a similar carotenoid diet there was no any clinical feature of hypercarotenaemia [30].

However, among all the subjects investigated, twelve (n = 12) had developed hypercarotenaemia.

The prevalence of hypercarotenaemia among children fed high quantity of carotenoid foods (n = 615) was 2%, while the group fed with vitamin A mega dose and not fed vitamin A mega dose were 1.4% and 2.5%, respectively. Thus, the prevalence of hypercarotenaemia among high carotenoid eaters is 2%. When considering the high carotenoid bearing food/fruits eaters, 47% had taken the vitamin A mega dose while the other 53% had not. From the group who had taken vitamin A mega dose, 1.4% experienced hypercarotenaemia, while this was 2.5% in the non-vitamin A mega dosed group [30].

Further, authors stated that most of the children do not develop hypercarotenaemia though they were fed with the same amount of carotenoid bearing foods as given to hypercarotenaemics. This indicates that no major correlation between carotenoid intake and hypercarotenaemia clearly showing that a genetic factor is at play, the subjects appear to need to be genetically pre-disposed to hypercarotenaemia. However, it seems that this remained as a problem to be proven with more experimental data in the future. Likewise, the mega dosing with vitamin A also has had no major effect on development of the condition. The authors had been proposed a genetic effect that is probably recessive, especially in the absorption or the metabolism of carotenoids in hypercarotenaemics. And finally, they concluded that the prevalence of hypercarotenaemia to be <2%, irrespective to the amount of

Table 1
Carotenoid content of raw *Daucus carota*.

Carotenoid	Carotenoid content[a] ($\mu g\ g^{-1}$)	
	FW	DW
β-Carotene	43.8 ± 5.6	456.3 ± 58.3
α-Carotene	20.5 ± 1.7	213.5 ± 17.7
Lutein	3.8 ± 0.4	39.6 ± 4.2

FW-fresh weight.
DW-dry weight.
Quantification has been carried out by HPLC.
[a] Mean ± SD in six specimens each in duplicate.

Table 2
Carotenoid content of *Cucurbita maxima* varieties found in Sri Lanka.

Pumpkin variety	Carotenoid content[a] ($\mu g\ g^{-1}$) FW		
	β-Carotene	α-Carotene	Lutein
Arjuna	50.9 ± 5.7 (332.7 ± 37.3)	27.3 ± 3.1 (178.4 ± 20.3)	39.1 ± 4.7 (255.6 ± 30.7)
Ruhunu	8.7 ± 1.2 (113.0 ± 15.6)	6.2 ± 1.0 (80.5 ± 13.0)	8.2 ± 1.2 (106.5 ± 15.6)
Meemini	6.2 ± 2.1 (53.4 ± 18.1)	11.8 ± 3.1 (101.7 ± 26.7)	30.8 ± 4.7 (265.5 ± 40.5)
Janani	3.0 ± 0.9 (26.8 ± 8.0)	1.2 ± 0.3 (10.7 ± 2.7)	31.2 ± 2.8 (278.6 ± 25.0)
Samson	5.1 ± 0.8 (44.0 ± 6.9)	2.0 ± 0.4 (17.2 ± 3.4)	45.8 ± 4.8 (394.8 ± 41.4)

Carotenoid content in $\mu g\ g^{-1}$ on the basis of dry weight is given in parenthesis.
FW-fresh weight.
Quantification has been carried out by HPLC.
[a] Mean ± SD in six specimens each in duplicate.

Table 3
Clinical presentation, carotenoid consumption/serum carotenoids associated with hypercarotenaemia.

Reference	Number of subjects (n) and clinical presentation	Carotenoid rich food intake/serum carotenoids
Mazzone and Canton, 2002 [21]	n = 1, Yellow-orange discolouration of the skin with no yellowish colour sclera	Marked elevation in serum β-carotene
Bari, 2009 [24]	n = 1, Yellowish discolouration of the skin with no related diseases that can develop hypercarotenaemia	Excessive intake of carotene-rich food such as oranges, sweet potatoes and spinach
Shaw,2009 [25]	n = 1, Lycopenaemia	Excessive ingestion of tomatoes and tomato-based dishes
Priyadarshani et al., 2009 [22]	n = 8, Hypercarotenaemia	Excessive ingestion of boiled, homogenized carrot and papaw
Wageesha et al., 2011 [23]	n = 35, Hypercarotenaemia	Excessive ingestion of carrot, pumpkin and papaw. Elevated serum α- and β-carotenes which varied from trace to 119 g/dL and from trace to 149 g/dL, respectively
Svensson and Vahlquist, 1995 [35]	n = 1, Yellow discolouration of skin with no increased ingestion of carotenoid rich foods and excluded from jaundice	Genetic defect in the metabolism of carotenoids
Boland et al., 2001 [20]	n = 110, Anorexia nervosa	Significantly higher mean serum β-carotene level in anorexia nervosa patients than in controls
Robboy et al., 1974 [19]	n = 8, Anorexia nervosa	A significant elevation in serum α-carotene (p < 0.001) compared to control group
Aktuna et al., 1993 [17]	n = 8, Hypothyroidism	A marked increase in serum β-carotene compared to euthyroid controls (p < 0.05)

carotenoids ingested and vitamin A mega dose [30]. Table 3 summarizes the clinical presentation, carotenoid consumption/serum carotenoids associated with hypercarotenaemia.

Above finding was supported by the study carried out by Wageesha et al. on Wistar rats and ICR mice [31]. The study indicated that excess feeding of carrot for 2½ months i.e., an average of 6 g carrot per day with butter did not show outward signs of hypercarotenaemia. In addition, serum had not been shown detectable amounts of carotenoids and their metabolites. The authors suggested that this could be due to rapid metabolism of absorbed carotenoids. Further adipose tissue, liver, digesta in rats and bile in the mice had not been shown any detectable level of carotenoids. Contrast to that faeces contained high levels of α- and β-carotenes as evidenced by thin layer chromatography (TLC) and HPLC. The authors concluded that this observation indicates that there may be a control of developing of hypercarotenaemia at the level of intestinal absorption of carotenoid [31].

8. The structures of carotenoid metabolites

According to the study carried out by Khachik et al., thirty-four carotenoids including 13 geometric isomers and 8 carotenoid metabolites had been identified in the breast milk and serum of three lactating mothers by high-performance liquid chromatography (HPLC)-photodiode array (PDA) detection-mass spectrometry (MS). Among the metabolites there were two and four metabolites which had been derived from lycopene and lutein/zeaxanthin, respectively because of the oxidation. Other two metabolites had been resulted from lutein by dehydration of lutein under the acidic condition. These metabolites are namely, 2,6-cyclolycopene-1,5-diol-I, 2,6-cyclolycopene-1,5-diol-II, (3R,6′R)-3-hydroxy-2′3′-didehydro β,ε-carotene, (3R,6′R)-3-hydroxy-3′4′-didehydro-β,γ-carotene, 3-hydroxy-ε,ε-carotene-3-one, 3-hyroxy-β,ε-carotene-3-one, ε,ε-carotene-3-3′-dione and (3R,3′S,6′R)-lutein or 3′-epilutein [32]. These had been identified by their HPLC–UV/visible-MS profiles with fully characterized (^{1}H and ^{13}C NMR spectroscopy) synthetic compounds. It is difficult to stipulate a typical pathway for carotenoid catabolism in humans as the pathway may depend on the type of carotenoid involved and the other conditions such as pH where carotenoid in.

It was noted that according to the Khachik et al., the hydroxy groups in all the serum carotenoid metabolites are inserted on the rings of the carotenoid molecule [32]. This finding is supported by the spectral characteristics of the hexane extract of the serum from hypercarotenaemic patients which is carried out by Priyadarshani

et al., [22]. These spectra showed that smooth characteristic three peeks of carotenoid indicating serum carotenoids and their metabolites having the same chromophore and hydroxylation has been taken place on the ring which is outside the chromophore of the molecule.

According to the study carried out by Priyadarshani et al., six to eight metabolites (retention times varied from 5 to 8 min) were found in the serum of typical hypercarotenaemic patients. This is due to progressive hydroxylation of the β-ionone ring of the carotenoid molecule. Nevertheless, hydrophilicity of these suspected metabolites had been identified only by low retention times in HPLC. Lutein, which is present in pumpkin and cannot be verified, as other di-hydroxy derivatives from the metabolites of the carotenoids interfere with the lutein peak [22].

The same study highlighted that though yellow-fleshed papaw is a good source of β-cryptoxanthin, estimation of β-cryptoxanthin in the serum of the hypercarotenaemic patients by HPLC chromatogram was difficult because the normal β-carotene metabolites are known to have very similar structures as β-cryptoxanthin. Hence, the dissymmetric β-cryptoxanthin peak which had been appeared on the HPLC chromatogram is probably due to mixing of β-cryptoxanthin and mono-hydroxy derivatives of β-carotene. However, the chemical structures of these carotenoid metabolites have not been deduced by the authors [22].

9. Hypercarotenaemia and enzyme defects

According to Priyadarshani et al., out of eight hypercarotenaemic patients six cases appear to be typical hypercarotenaemia. In these typical cases vitamin A levels were normal, which varied from 32 to 61 μg dL^{-1}. The author concluded that there was no defect in the activity of 15-15′ dioxygenase enzymes and their control. The carotenoid metabolites also appeared to be normal and collectively di, tri, poly-hydroxy metabolites had been ranged from 22.5 to 282.1 μg dL^{-1}. In one atypical case vitamin A was 75.2 μg dL^{-1} [22], which is very close to the upper level of normal of the vitamin A level for this age category (81 and 84 μg dL^{-1} for males and females, respectively) [33]. In this case a second sharp peak had been appeared in the HPLC chromatogram at a lower retention time than retinol at 325 nm and if this was retinoic acid it could cause a serious problem. But, the authors had not been confirmed this peak as the retinoic acid. The same case had low β-carotene (3.5 μg dL^{-1}) and no mono-hydroxy metabolites and β-cryptoxanthin but normal di, tri and poly-hydroxy metabolites were present (128.2 μg dL^{-1}). The reason why this

condition was observed could have been due to the high carotenoid diet being discontinued for some time before venesection. In the case of vitamin A level, a question arises over the possibility of inadequate control of 15-15′ dioxygenase enzyme [22].

In the other atypical case, there is a definite defect in the metabolism of β-carotene, as an unusual peak appeared on HPLC chromatogram between β-carotene and mono-hydroxy peak. According to the reaction scheme this could be a usual epoxide where the next enzyme (3-mono-hyrdoxylase) appeared to be absent. Alternatively, this could be an unusual epoxide. As a result, it is not surprising that further hydroxylation enzymes do not recognize such an epoxide. Exact identification of this unusual peak remained as a limitation of this study. Controls with non-hypercarotenaemics showed there were no detectable levels of carotenoids and its metabolites (detection limit >0.01 µg dL^{-1}) [22].

Lindqvist et al. reported an important finding regarding carotenoid 15,15′-monooxygenase which is the enzyme that catalyzes the first step of the conversion of pro-vitamin A carotenoids to vitamin A in the small intestine. The authors identified that one heterozygous T170M missense mutation in the carotenoid 15,15′-monooxygenase gene in a subject with hypercarotenaemia and mild hypovitaminosis A. Further, *in-vitro* studies showed that 90% reduction of the carotenoid 15,15′-monooxygenase activity with the replacement of a highly conserved threonine with methionine. Therefore, according to the findings of Lindqvist et al., haploinsufficiency of the carotenoid 15,15′-monooxygenase enzyme may cause hypercarotenaemia and hypovitaminosis A in subjects who consume carotenoid-containing but vitamin A-deficient diet [34].

Another study reported that a 3-year old girl with long-standing yellow discolouration of her skin. This patient had no history of increased ingestion of carotenoid rich foods and showed usual blood chemistry. The patient had no diabetes mellitus or hypothyroidism. The jaundice had been ruled out by showing normal liver function tests with clear sclerae and oral mucosa. There was no maternal carotenaemia as well. The authors explained that in this case hypercarotenaemia was probably due to the defect of carotene dioxygenase enzyme which is responsible for conversion of pro-vitamin A carotenoids to vitamin A [18,35].

10. Conclusion

Hypercarotenaemia is known to be due to excessive intake of carotenoid rich foods over a period of months. Rarely, failure to split pro-vitamin A carotenoids into retinal due to genetic defects of the enzyme 15-15′-carotenoid dioxygenase can lead to metabolic carotenaemia under less or normal intake of carotenoids. It has been also shown that those with hypothyroidism and diabetes mellitus tend to develop hypercarotenaemia with the normal intake of carotenoid rich foods. According to recent findings the subjects appear to need to be genetically pre-disposed to hypercarotenaemia as some children do not develop hypercarotenaemia though they were fed with the same amount of carotenoid bearing foods as given to hypercarotenaemics.

Conflicts of interest

The author declares that there are no conflicts of interest.

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