IS THERE A THERAPEUTIC EFFECT OF VITAMIN A SUPPLEMENTATION ON RETINITIS PIGMENTOSA: A LITERATURE REVIEW

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ABSTRACT

Retinitis Pigmentosa is a hereditary disease with no known cure. It has been suggested that high doses of vitamin A supplements can retard the progression of this disease. This paper is a literature review presenting studies that both support and contradict this hypothesis. The most recent study has been the most controversial, but its recommendation to supplement retinitis pigmentosa patients with high doses of vitamin A has been endorsed by various ocular agencies. Even the studies that support the use of vitamin A show some subjects that do not respond to this therapy. The evidence is strong, however, that people with retinitis pigmentosa have low serum levels of vitamin A. It seems, therefore, that even people that do not show a visual improvement when placed on vitamin A therapy can at least replenish their body levels. Vitamin A is a fat soluble vitamin and, therefore, can have toxic effects on the body when taken in large doses. If supplements are taken under the supervision of a physician, however, the risks are reduced and the benefit may be a delay in the progression of retinitis pigmentosa.

INTRODUCTION

Retinitis pigmentosa cannot be considered a common disease, but it is definitely devastating to those who incur it. It is a progressive, hereditary disease in which there is presently no known cure. Low vision aids and protective filters are often prescribed to patients with retinitis pigmentosa in an attempt to produce the best vision possible, but no treatment has been discovered that even retards the progression of the disease. A recent study[1], however, has made the claim that supplements of vitamin A may beneficially affect the course of retinitis pigmentosa. This is a statement which may give hope to sufferers of the disease, but whether it is true or false hope has yet to be determined. The purpose of this paper is to review the literature on the effects of vitamin A on retinitis pigmentosa in an attempt to determine how much merit this statement has. First, a description of retinitis pigmentosa will be given, as well as a discussion of the role of vitamin A in the visual system. This will be followed by a review of the literature on vitamin A and retinitis pigmentosa and a discussion on possible toxic effects of vitamin A supplementation. Finally, concluding statements on the topic will be made.

RETINITIS PIGMENTOSA

Retinitis pigmentosa is actually the name applied to a group of inherited retinal degenerative diseases with a prevalence of approximately 1 in 4000 worldwide.[1,2] It is typically characterized by night blindness and constricted visual fields.[2] Eventually, almost all will lose central vision as well.[3]

Retinitis pigmentosa is usually a bilateral, asymmetrical retinal dystrophy which affects both rods and cones, but predominantly rods.[2] Age of onset, rate of progression, and amount of eventual visual loss usually depend on the mode of inheritance of the disease.[2] The modes

of inheritance are autosomal recessive, autosomal dominant, and X-linked recessive.[2] Autosomal recessive is the most common type of inheritance.[2] The least common type is X-linked recessive which only occurs in males, and is the most severe type.[2] Autosomal dominant is the second most common type and the least severe of the three.[2] Other atypical and associated types of retinitis pigmentosa also exist.[2]

The clinical picture of retinitis pigmentosa consists of a classic triad of retinal pigmentary changes, arteriolar attenuation, and waxy disc pallor.[2] The intraretinal pigment accumulates in a jet black, bone spicule appearance around retinal vessels in the midretinal periphery.[2] As the disease progresses, these pigmentary changes on the retina extend both posteriorly and anteriorly.[2]

The diagnosis of retinitis pigmentosa is usually confirmed by electrodiagnostic evaluation including dark adaptometry, electro-oculography, and electroretinography. In retinitis pigmentosa, dark adaptometry thresholds are elevated, especially in the rod portion of the curve; electro-oculogram measures will be reduced; and the electroretinogram (ERG) will be very low in amplitude or even completely absent.[2] Patients with retinitis pigmentosa can actually be detected early in life on the basis of an abnormal ERG, even in the absence of typical ophthalmoscopic irregularities.[3]

As the disease progresses, characteristic changes in visual fields occurs. It begins with an absolute "ring scotoma".[2] A group of separate scotomas 20° to 25° from fixation coalesce to form an eventual ring. The outer edge of the ring rapidly extends peripherally while the inner edge slowly contracts towards fixation. Often,the entire peripheral field disappears and a small island of central vision remains.[2]

THE ROLE OF VITAMIN A IN VISION

Vitamin A is a very important component of the retinal visual pigment known as rhodopsin. Rhodopsin is a light sensitive pigment used for vision in dim light.[4] Rhodopsin is composed of a lipoprotein called opsin attached to a chromophore molecule called 11-cis retinaldehyde.[4] Eleven-cis retinaldehyde is a product of vitamin A oxidation and isomerization.[3]

There is actually a term called the visual cycle which is used to describe all the metabolic reactions of vitamin A that are known to occur in the retina.[4] After vitamin A is ingested and then absorbed, it is stored by the liver. In order for it to be mobilized, it must be bound to a specific retinol binding protein (RBP).[3] It is then delivered to target cells which contain specific receptor cells for the RBP. The pigment epithelium of the retina contains such receptor cells, and once this vitamin A - RBP complex is received by the pigment epithelium, vitamin A is esterified and stored again.[3] On demand, vitamin A is hydrolysed and transported to the photoreceptor outer segments and along the way, the oxidation and isomerization of vitamin A to 11-cis retinaldehyde occurs.[3] In a dark adapted state, the 11-cis retinaldehyde combines with opsin to form rhodopsin and allows for "night vision".[4] In the light, 11-cis retinaldehyde is isomerized to all-trans retinaldehyde and, thus, rhodopsin is broken down to free molecules of opsin and all-trans retinaldehyde resulting in visual excitation.[3]

It is obvious, therefore, that vitamin A is an essential component for vision, especially in the dark. It was mentioned that decreased night vision is a symptom of retinitis pigmentosa. As the following literature review will recite, patients with retinitis pigmentosa have decreased serum levels of vitamin A. These two factors are what led to the hypothesis that supplementing retinitis

pigmentosa patients with vitamin A could be beneficial. Let us now review the literature on the natural course of retinitis pigmentosa, the relationship between vitamin A serum levels and retinitis pigmentosa, and the therapeutic trials of vitamin A supplementation on patients with retinitis pigmentosa.

LITERATURE REVIEW

NATURAL COURSE OF RETINITIS PIGMENTOSA

If the benefits of a possible therapeutic substance are to be studied, it is important to know what the natural course of the disease would be if the treatment was never implemented. Berson et al (1985)[5] did a three year study on 94 patients with retinitis pigmentosa ranging from 6 to 49 years of age. This included patients with autosomal dominant, recessive, X-linked, and isolated forms of the disease in approximately equal numbers. No significant difference in progression of the disease was found between the autosomal recessive, X-linked, or isolated groups, but the autosomal dominant group showed less progression than the other groups. The full field ERG decreased significantly in 77% of the total number of patients, and they lost 16 to 18 1/2 % of remaining ERG amplitude per year. The group lost an average of 4 1/2 % of remaining visual field area per year and bone spicule pigmentation increased in 54% of the patients over the three year period. Visual acuity and dark adaptation thresholds remained relatively stable throughout the study. The steady loss of ERG amplitude prompted the authors of this study to conclude that the ERG could be useful in planning interventions for retinitis pigmentosa.

VITAMIN A SERUM LEVELS IN RETINITIS PIGMENTOSA

Campbell and Tonks (1962)[6] studied a series of patients ranging from 9 to 65 years of age with retinitis pigmentosa, some for as long as twelve years. They found that retinitis pigmentosa patients had a persistently low level of vitamin A in the blood. The mean value was well below that of normal subjects in 91% of the adults studied and in all of the children. The authors suggested that the very low levels of plasma vitamin A found in affected children was related to the early symptom of night blindness in children. The authors also indicated some possible reasons for the vitamin A deficiency. These included defective absorption of vitamin A; defective transport or storage mechanisms of vitamin A in the liver; the vitamin circulating in a form which the retina could not use; or a metabolic defect in the retina itself in the early stages of the disease.

Campbell et al (1964)[7] continued on to state that a low level of vitamin A in children is a normal feature, but in cases of untreated retinitis pigmentosa, it does not rise to a normal value in adult life. They also stated that loss of visual function in retinitis pigmentosa may arise from a lack of the appropriate enzymes which produce the conversion of vitamin A to rhodopsin in the retina.

THERAPEUTIC TRIALS OF VITAMIN A ON RETINITIS PIGMENTOSA

As mentioned, there is evidence that patients with retinitis pigmentosa have lowered systemic levels of vitamin A. Now let us explore what the effects are of supplementing vitamin A to these patients.

Negative Studies

Chatzinoff et al (1968)[8] did a double blind study on 88 retinitis pigmentosa patients for three years. The treatment group received 100000 units of 11-cis vitamin A intramuscularly, twice per week. The control group received identical dosages of all-trans vitamin A. Visual fields, visual acuity, and dark adaptometry were measured during the study. Only three people in the treatment group showed improvement, 28 regressed, and four remained the same. The authors, therefore, concluded that 11-cis vitamin A was not of value in treatment of retinitis pigmentosa.

Sandberg et al (1977)[9] studied two vitamin A deficient patients with chronic alcoholism and night blindness. When supplemented with vitamin A, these patients regained normal plasma vitamin A, normal rod thresholds, and normal rod and cone ERG amplitudes. In patients with retinitis pigmentosa, on the other hand, the authors of this study stated that elevations of rod psychophysical thresholds were linearly correlated with the amount of rhodopsin remaining as measured by retinal densitometry. This suggested to them that the deficiency in retinitis pigmentosa centered around the whole rhodopsin molecule (opsin + chromophore), rather than a specific lack of the vitamin A aldehyde chromophore. Therefore, the conclusion from this study was that hereditary retinitis pigmentosa does not involve a local deficiency of vitamin A in the retina.

Bergsma and Wolf (1977)[10] gave 47 retinitis pigmentosa patients a 500000 IU dose of oral vitamin A per day for 28 days. At the end of this 28 day trial, they found no significant change in dark adaptation, cone thresholds, color vision, or ERG measures. They also found no significant improvement in visual acuity and no patient reported any striking subjective improvement in vision. These authors

also suggested that there was no beneficial effect of supplementing retinitis pigmentosa patients with vitamin A.

Positive Studies

Two studies indicating beneficial effects of vitamin A on retinitis pigmentosa involve retinitis pigmentosa associated with Bassen - Kornzweig syndrome, also known as abetalipoproteinemia. This is a hereditary disorder characterized by gastrointestinal symptoms, haemotological disorders, neuromuscular disturbances, and retinitis pigmentosa, all appearing in the first decade of life.[11] Untreated patients with abetalipoproteinemia have very low circulating levels of vitamins A and E.[11] Vitamin E is a component of photoreceptors and plays an essential role in preventing autooxidation of polyunsaturated fatty acids.[11]

Gouras et al (1971)[12] gave two abetalipoproteinemia patients doses of up to 200000 IU of vitamin A and found that visual thresholds and ERG improved. They suggested that the vitamin A deficiency and the resultant deterioration of retinal function could be reversed by vitamin A therapy.

Bishara et al (1982)[11] studied eight patients with abetalipoproteinemia. These patients were administered 50000 IU of vitamin A twice per week and 100 mg/kg/day of vitamin E to a maximum dose of 3000 mg daily. Treatment was started as early as the first day of life to as old as 26 years of age, and patients were followed from two to six years. Electroretinograms and electro-oculograms were measured, and the ophthalmoscopic features were monitored. The combined therapy was found to have a stabilising effect in preventing deterioration both in fundus and in electrophysiological functions of the retina. These authors, therefore, advocated the simultaneous administration of vitamins A and E in patients suffering from

abetalipoproteinemia.

Campbell et al (1964)[7] did therapeutic trials with vitamin A alone, vitamin E alone, and vitamins A and E combined on retinitis pigmentosa patients, and compared their results to an untreated group. The dosages used were 24000 IU daily of vitamin A and 50 mg two times per day of vitamin E. Patients were followed for as long as six years. The results showed that a significant number of patients had improved visual fields, and improved rod and cone thresholds with all three types of treatment. The percentages of patients who improved were similar among the three treatment groups. The study found that the level of vitamin A in the blood could easily be raised, and maintained at a normal level by any one of the vitamins used, but it fell within a few weeks after cessation of treatment. The authors stated that vitamin E probably had the effect of "saving" the vitamin A available in the body from the diet. The conclusion of this study was that it is possible to "alleviate the disease in man, and to delay the onset of blindness" by therapeutic administration of vitamin A and/or E in suitable doses.

There was a considerable time period with no research on this topic until a very recent study by Berson et al (1993).[1] They did a randomized, controlled, double masked trial with a 2 x 2 factorial design with a duration of four to six years. They used 601 patients with retinitis pigmentosa aged 18 to 49 years and 95% of these patients completed the study. The patients were assigned to one of four treatment groups receiving 15000 IU per day of vitamin A, 15000 IU per day of vitamin A plus 400 IU per day of vitamin E, trace amounts of both vitamins, or 400 IU per day of vitamin E. Electroretinograms, visual field area, and visual acuity were measured annually. The results indicated that the two groups receiving 15000 IU per day of vitamin A had, on average, a slower rate of decline of

retinal function (based on cone ERG amplitude) than the two groups not receiving this dosage. The two groups receiving this dosage of vitamin A were 32% less likely to have a decline in amplitude of 50% or more from baseline in a given year than those not receiving this dosage. On the other hand, the two groups receiving 400 IU per day of vitamin E were 42% more likely to have a decline in amplitude of 50% or more from baseline. The visual field results were not statistically significant but the trend was similar in that the vitamin A group showed the smallest rate of loss per year and the vitamin E group the largest. This prompted the authors to state that they anticipated that patients receiving vitamin A at dosages of 15000 IU per day would show a slower rate of decline of visual field area over the long term than those not receiving this dosage. Visual acuity declined about one letter per year in all groups so the data did not predict a beneficial effect of vitamin A on the rate of decline of visual acuity over the long term. The authors stated that their conclusions were based on group averages so they could not provide assurance that a specific patient would benefit from this treatment. They also found no evidence that the beneficial effect of vitamin A was confined to one or another genetic type. Based on their findings, therefore, the authors recommended that "most adult patients with the common forms of retinitis pigmentosa take a supplement of vitamin A, 15000 IU/d, under the supervision of an ophthalmologist and avoid the use of high dose supplements of vitamin E."

The aforementioned statement prompted many responses from concerned readers.[13] In particular, Massof and Finkelstein (1993)[14] wrote an editorial on the Berson group's study. They commended the group for the design and execution of the study, but they had three major concerns. One concern was that they felt the study did not

demonstrate significant benefit for any measure of visual function. They contended that the ERG is not a direct measure of visual function, but visual fields and visual acuities are and these two measures showed no significant differences in the study. The authors of the study countered by stating that a significant relationship does exist between ERG amplitude and the capacity to perform visual activities.[15] They based this on the frequency of responses on a questionnaire given to the patients before the study began. This questionnaire demonstrated that patients with smaller amplitudes were less likely to drive, walk unaided at night, or be employed than were patients with larger amplitudes.

Another concern of Massof and Finkelstein was that the significant effect observed with the cone ERG may have had additional explanations not related to slowed disease progression. They stated that ERG signals contain background noise. A patient could have a reduced ERG but it may not appear that way if the background noise is picked up in the ERG signal. They suggested, therefore, that the ERG results may be misleading and not proper evidence to support a beneficial effect of vitamin A on retinitis pigmentosa.

Their final concern was that the long term systemic and/or toxic effects of supplemented vitamin A are unknown. They stated that although the investigators saw no toxic or systemic effects in their patients over the study period, they were concerned about it because young and pregnant patients were specifically excluded. The Berson group indicated in their study that they chose a dosage of 15000 IU per day because they had no evidence that more than 18380 IU per day would provide any greater benefit. Also, they had reports that 25000 IU per day or greater was associated with potentially dangerous side effects. They, therefore, felt safe with their choice of dosage.

TOXIC EFFECTS OF VITAMIN A

Since vitamin A is a fat soluble vitamin, the potential for toxicity exists if much more is ingested than the body requires. As mentioned above, Massof and Finkelstein were concerned about this when critiquing the Berson et al study. Thus, let us explore this topic a little further.

The recommended daily allowances for vitamin A as defined by the Food and Nutrition Board of the National Research Council are 1500 IU/d for infants (12 months old and younger), 2500 IU/d for children (younger than 4 years old), 5000 IU/d for adults and children 4 years and older, and 8000 IU/d for pregnant or lactating women.[16] This indicates that the studies reviewed in this paper were using doses of at least three times the recommended daily allowances. None of the studies reported any patients developing effects of vitamin A toxicity, but based on these recommendations the concern for potential toxicity seems legitimate.

Signs and symptoms of acute and chronic vitamin A toxicity are listed in Tables 1 and 2 respectively. Hathcock et al (1990)[16] stated that a consumption of 25000 to 50000 IU/d of vitamin A for periods of several months or more could produce multiple adverse effects such as those listed in the tables. They reported that the lowest intakes causing toxicity have occurred in people with liver function compromised by drugs, viral hepatitis, or protein-energy malnutrition. Also, children and pregnant women were reported as especially vulnerable groups for vitamin A toxic effects. A study by Geubel et al (1991)[17] corroborated the notion that a dosage of 25000 IU/d or more of vitamin A should be avoided. They found that the smallest continuous daily consumption leading to cirrhosis was 25000 IU during a six year period.

TABLE 1

Signs and symptoms of acute vitamin A toxicity

Children	Adults
Anorexia	Abdominal pain
Bulging fontanelles	Anorexia
Drowsiness	Blurred vision
Increased intracranial pressure	Drowsiness
Irritability	Headache
Vomiting	Hypercalcemia
	Irritability
	Muscle weakness
	Nausea, vomiting
	Peripheral neuritis
	Skin desquamation

Reference 16

TABLE 2

Signs and symptoms of chronic vitamin A toxicity

Children

Alopecia, anorexia, bone pain and tenderness, bulging of fontanelles, craniotabes, fissuring at lip corners, hepatomegaly, hyperostosis, premature epiphyseal closure, photophobia, pruritis, pseudotumor cerebri, skin desquamation, skin erythema

Adults

Alopecia, anemia, anorexia, ataxia, bone pain, bone abnormalities, brittle nails, chelitis, conjunctivitis, diarrhea, diplopia, dryness of mucous membranes, dysuria, edema, elevated CSF pressure, epistaxis, exanthema, facial dermatitis, fatigue, fever, headache, hepatomegaly, hepatotoxicity, hyperostosis, insomnia, irritability, menstrual abnormalities, muscular stiffness and pain, nausea, negative nitrogen balance, nervous abnormalities, papilledema, petechiae, pruritis, pseudotumor cerebri, skin desquamation, skin erythema, skin rash, skin scaliness, splenomegaly, vomiting, weight loss

Reference 16

CONCLUSIONS

With the amount of research that has been done on the therapeutic effect of vitamin A on retinitis pigmentosa, there is still no definite conclusion that can be made. Some studies indicate the effect is beneficial, and some suggest that it is not. One thing that is for certain is that even in the studies where there is found to be a beneficial effect, it is not so for every individual in the study. Regardless of this fact, the evidence must be compelling enough, as the Data Safety and Monitoring Committee, the public affairs office of the National Eye Institute, and the Retinitis Pigmentosa Foundation Fighting Blindness have all endorsed the recommendation by the Berson study group that adults with retinitis pigmentosa take supplements of vitamin A.[15] Since it cannot, as yet, be predicted which individuals will receive a beneficial effect from vitamin A treatment, it seems that the recommendation was made for all adults with retinitis pigmentosa to try to help as many people as possible.

In my own opinion, I agree that patients with retinitis pigmentosa should take supplements of vitamin A. I do not believe that the evidence is strong enough to suggest that vitamin A improves the symptoms of retinitis pigmentosa, nor am I entirely convinced that it retards the progression of the disease. What I do believe, however, is that patients with retinitis pigmentosa have decreased levels of vitamin A in their body. It seems obvious, therefore, that these people should be supplemented enough to at least bring their body levels of vitamin A to normal. If by doing this, some people receive a beneficial effect to their visual symptoms, it is a positive result for those particular individuals. For those who do not receive a beneficial effect visually, at least they have replenished their serum levels so that vitamin A can perform its other functions

required by the human body. This is assuming that no toxic effects occur, and I do not believe that this is a major concern especially if supplements are taken under the supervision of a physician. Retinitis pigmentosa patients have low levels of vitamin A to begin with, and supplementation of levels lower than 25000 IU per day have not proven to cause toxic effects in otherwise healthy individuals. Therefore, supplementation at the 15000 IU per day dosage that has been recommended, should be enough to bring body levels of vitamin A to normal, give any kind of therapeutic effect that it may produce, and be safe at the same time.

It does not appear that it is just a decreased level of serum vitamin A that is the cause of the symptoms of retinitis pigmentosa, otherwise all patients would improve when treated with vitamin A. It is possible that some patients with this condition have a decreased ability to retain vitamin A in the retina due to impaired rods and cones, or that they have some carrier protein that is abnormal so that vitamin A is not efficiently transported from the serum to the retina.[1] If this is the case, it would seem that no matter how much vitamin A is placed into the body's circulation, the retina would not be able to receive it in a usable form. However, the actual mechanisms leading to retinitis pigmentosa are still unknown. Each case may be different and there may be different degrees of the disease where some retinas may have a better ability than others to accept vitamin A from the blood if enough is made available. Until the disease is fully understood, more research is necessary.

Vitamin A is known to be an essential nutrient to the body and, thus, it is a natural type of therapy. As uncertain as the evidence may be as to whether vitamin A actually improves the symptoms of the condition, I see no reason why a person with retinitis pigmentosa should not, under supervision, take supplements of vitamin A.

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