Sperm Abnormalities in Retinitis Pigmentosa

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Purpose. To determine the fatty acid composition of erythrocytes and sperm, along with the functional characteristics of sperm, in patients with retinitis pigmentosa. Sperm and retinal cells share important homologies. Both are rich in the highly polyunsaturated fatty acid, docosahexaenoic acid (DHA, 22:6[n-3]), and both contain a structural component called the axoneme. Low concentrations of DHA in the retina of monkeys are known to cause visual impairment. Because blood levels of DHA in retinitis pigmentosa patients are less than normal, reduced DHA in the retina might contribute to the visual impairment characteristic of this disease. This study was conducted on the hypothesis that the sperm of retinitis pigmentosa patients might be abnormal and that these abnormalities might infer similar lipid and structural abnormalities of the retina.

Methods. The lipid composition of erythrocytes and sperm (fatty acids and sterols) and sperm function were analyzed in 26 patients with retinitis pigmentosa and in 8 healthy men.

Results. The sperm of patients with retinitis pigmentosa had a much lower DHA concentration, a lower desmosterol-to-cholesterol ratio, reduced motility, abnormal structure, and lower sperm counts compared with that in normal subjects. Usher's II patients exhibited the most pronounced reductions of DHA in sperm. Sperm DHA concentration was positively correlated to sperm motility, to sperm count, and to the desmosterol-to-cholesterol ratio. Lower erythrocyte DHA was also observed in retinitis pigmentosa patients.

Conclusions. These results indicate that the sperm of patients with retinitis pigmentosa, particularly those with Usher’s II, have an abnormal lipid composition that is associated with reduced motility. The possibility exists that these patients might have similar abnormalities in the DHA biochemistry of the retina. Sperm biochemistry and function may be a marker for this disease. A clinical trial of DHA in retinitis pigmentosa is suggested for future study. Invest Ophthalmol Vis Sci. 1997;38:2619–2628.

Retinitis pigmentosa is the most common cause of blindness in children and in young adults in the United States. This genetically based disease has an estimated prevalence of 1 in 4000.2–8 One and a half million people throughout the world are affected.

This disease includes genetically determined disorders that produce degeneration of the retina, initially involving the photoreceptors. Autosomal recessive, autosomal dominant, and X-linked types occur. In addition, retinitis pigmentosa is seen in the context of many other syndromes, including Usher’s syndrome (congenital deafness and retinitis pigmentosa) and abetalipoproteinemia. In most forms, retinal degeneration is generally slow but ultimately results in complete loss of useful retinal function. Thus, the disease progresses from night blindness initially, to loss of peripheral vision, and eventually to loss of central visual acuity.9–17

The retina contains a high concentration of a highly polyunsaturated, long-chain fatty acid, docosahexaenoic acid (DHA), which has six double bonds and is 22 carbons in length 22:6(n-3). (The first number indicates the chain length, the second digit indi-
fore, knowledge of the status of these fatty acids in effects, retinal dysfunction, degeneration, and eventually, blindness. Thus, membrane lipids, especially DHA in the retina, seem essential to the health and function of the photoreceptors. A defect in the synthesis or catabolism of this important fatty acid could lead to retinal dysfunction, cell death, and perhaps, a picture similar to that of retinitis pigmentosa. Therefore, knowledge of the status of these fatty acids in the retina in the various forms of retinitis pigmentosa could give new insights into the pathogenesis of this group of disorders. However, for clinical and practical reasons, this information is difficult to obtain in the human retina, and more accessible tissues have been sought.

Several investigators have found lowered concentrations of DHA in erythrocytes and plasma in affected patients and have suggested that an abnormality of DHA metabolism might be present in retinitis pigmentosa. Recently, Schaefer et al reported that mean DHA concentrations of phosphatidylethanolamine fatty acids from the erythrocyte of several genetic types of retinitis pigmentosa were reduced. In human infants and in monkeys, the DHA content in erythrocytes has been positively correlated with visual functions and retinal DHA content, respectively. These data suggest the possibility that the low DHA content of the membranes may contribute to the pathogenesis of retinitis pigmentosa. However, alterations in plasma and erythrocyte DHA levels from normal values have not been notable, and other approaches may be needed to provide more definitive information about DHA concentrations and metabolism in retinitis pigmentosa patients.

In men, sperm may provide a better surrogate tissue for the retina, because it is the only other tissue in the body besides retina and brain that contains a very high content of DHA, approximately 20% of total fatty acids. Such high concentrations occur in monkey and human sperm. In our previous studies, monkeys fed an n-3-deficient diet had drastically decreased DHA concentrations in retina, erythrocytes, plasma, and sperm. Such parallel changes in DHA concentrations in these tissues further suggests that sperm DHA levels might well reflect retinal concentrations.

Along with similarly high DHA contents, another homology between retina and sperm is that both have axonemes (organelles composed of microtubules). In the retina, axonemes may play a role in development and maintenance of photoreceptor outer segments. In sperm, axonemes are critical to motility. Previous studies of sperm from patients with X-linked recessive retinitis pigmentosa and Usher’s syndrome with retinitis pigmentosa have shown morphologic abnormalities. However, to date, there have been no studies of fatty acid or lipid composition of sperm in the various forms of retinitis pigmentosa.

In view of the common characteristics between retina and sperm, we hypothesized that sperm DHA levels in retinitis pigmentosa might be abnormal. If so, this deficiency might reflect a similar deficiency in the retina of these patients. To test this hypothesis, we have compared sperm fatty acid, sterol composition, and sperm function in patients with retinitis pigmentosa with those factors in control subjects.

METHODS

Twenty-six men with retinitis pigmentosa were identified in the Oregon Retinitis Pigmentosa Center. All had extensive pedigrees, Goldmann perimetry, and fundus photographs, with examination of other family members whenever indicated and feasible, so that the type of retinitis pigmentosa had been determined to the most complete degree possible. Electroretinograms were obtained in only some of the patients. Through a collaborative effort with Dr. Edwin M. Stone, DNA from peripheral whole blood had been
screened for mutations of the genes for rhodopsin, peripherin/RDS, and ROM1. The study subjects included five autosomal dominant (including a father and son with a mutation of Rho Arg 133 Trp), two autosomal recessive, five X-linked recessive, six Usher’s II, two Usher’s I, and six unclassified (simplex or multiplex) patients.

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Human Ethics Committee of Oregon Health Sciences University and was explained carefully to each of the patients who volunteered for the study; informed consent was obtained from each participant.

Eight healthy men of ages comparable to the patients with retinitis pigmentosa provided semen for comparative purposes. The secondary sex characteristics of all patients, including testicular size, were determined by physical examination and were found to be normal.

Patients collected semen by masturbation. Semen parameters, sperm count, structure, and motility were determined on a 20-ml semen sample within 1 hour of sample collection. The rest of the collection was diluted with three volumes of saline and centrifuged at 500g for 20 minutes. The resulting sperm pellet was washed twice with saline. The lipids of the sperm pellet were extracted by the method of Folch et al., and butylated hydroxytoluene was added as an antioxidant. Sperm lipids were saponified with alcoholic potassium hydroxide, and the sterols were extracted with hexane. Sperm fatty acids were recovered by acidifying the aqueous phase and reextracting with hexane. Sterols were derivatized to form trimethylsilyl derivatives and the sterol content was determined by gas-liquid chromatography (model 8500; Perkin-Elmer, Norwalk, CT) on a 30-m SE-30 capillary column. The temperatures of column, detector, and injection ports were 260°C, 300°C, and 300°C, respectively. Helium was used as the carrier gas. Cholestane was used as the internal standard.

Sperm fatty acids were transmethylated with boron trifluoride–methanol and analyzed by gas–liquid chromatography on an instrument equipped with a hydrogen flame ionization detector (model Sigma 3B; Perkin-Elmer) and a 30-m SP-2330 fused silica capillary column (Supelco, Bellefonte, PA). The temperatures of column, detector, and injection ports were 260°C, 300°C, and 300°C, respectively. Helium was used as the carrier gas; the inlet pressure was 80 psi.

### TABLE 1. The Fatty Acid Composition of Sperm From Patients With Retinitis Pigmentosa (RP) and Control Subjects (Medians and Interquartile Ranges)

<table>
<thead>
<tr>
<th>Fatty Acids</th>
<th>Non-Usher’s RP (n = 18)</th>
<th>Usher’s II (n = 6)</th>
<th>Control (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated</td>
<td>49.2 ± 5.8</td>
<td>51.5 ± 4.3</td>
<td>47.8 ± 1.4</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>14.1 ± 8.2</td>
<td>23.3 ± 7.0</td>
<td>20.2 ± 5.9</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>31.7 ± 10.0</td>
<td>16.3 ± 9.8*</td>
<td>34.0 ± 6.2</td>
</tr>
<tr>
<td>14:0</td>
<td>1.7 ± 1.9</td>
<td>3.7 ± 2.2</td>
<td>2.1 ± 1.4</td>
</tr>
<tr>
<td>16:0</td>
<td>30.5 ± 7.1</td>
<td>30.7 ± 3.8</td>
<td>31.0 ± 2.4</td>
</tr>
<tr>
<td>18:0</td>
<td>14.4 ± 2.6</td>
<td>12.2 ± 2.6</td>
<td>13.5 ± 1.0</td>
</tr>
<tr>
<td>20:0</td>
<td>0.2 ± 0.3</td>
<td>0.5 ± 0.4†</td>
<td>0.0 ± 0.01</td>
</tr>
<tr>
<td>22:0</td>
<td>0.2 ± 0.6</td>
<td>1.2 ± 0.4*</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>24:0</td>
<td>0.2 ± 0.5</td>
<td>0.2 ± 0.6</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td>16:1(n-7)</td>
<td>2.7 ± 2.0</td>
<td>6.6 ± 1.0†</td>
<td>3.4 ± 2.5</td>
</tr>
<tr>
<td>18:1(n-9)/(n-7)</td>
<td>12.3 ± 3.1</td>
<td>13.7 ± 7.5†</td>
<td>10.0 ± 1.9</td>
</tr>
<tr>
<td>Trans 18:1(n-9)</td>
<td>0 ± 0.8</td>
<td>0.9 ± 2.0†</td>
<td>0 ± 0.2</td>
</tr>
<tr>
<td>18:2(n-6)</td>
<td>6.8 ± 2.2†</td>
<td>4.8 ± 1.6</td>
<td>5.7 ± 1.5</td>
</tr>
<tr>
<td>20:3(n-6)</td>
<td>2.9 ± 1.9</td>
<td>1.6 ± 1.3†</td>
<td>2.7 ± 1.5</td>
</tr>
<tr>
<td>20:4(n-6)</td>
<td>2.6 ± 2.0</td>
<td>1.5 ± 0.7†</td>
<td>2.7 ± 1.3</td>
</tr>
<tr>
<td>22:4(n-6)</td>
<td>0.5 ± 0.6</td>
<td>0.3 ± 0.2</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Total n-6</td>
<td>16.0 ± 2.9</td>
<td>10.8 ± 3.2§</td>
<td>13.5 ± 3.3</td>
</tr>
<tr>
<td>18:3(n-9)</td>
<td>0.1 ± 0.2</td>
<td>0.03 ± 0.05</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>20:5(n-3)</td>
<td>0.1 ± 0.2</td>
<td>0.1 ± 0.3</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>22:5(n-9)</td>
<td>0.7 ± 0.8</td>
<td>0.6 ± 0.4</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>22:6(n-3)</td>
<td>12.8 ± 8.6§</td>
<td>4.7 ± 6.3§</td>
<td>19.2 ± 6.4</td>
</tr>
<tr>
<td>Total n-3</td>
<td>15.5 ± 3.4</td>
<td>5.9 ± 7.4†</td>
<td>20.2 ± 5.9</td>
</tr>
</tbody>
</table>

* P < 0.005 vs control.
† P < 0.01 vs control.
‡ P < 0.05 vs control.
§ P < 0.001 vs control.
The split ratio was 1:170. The retention time and area of each peak were measured by an HP-3390 integrator, and a computer (HP85; Hewlett Packard, Palo Alto, CA) was used to identify and quantify each fatty acid. A mixture of fatty acid standards was run daily.

Blood samples were collected in tubes containing EDTA from 26 patients with retinitis pigmentosa and 8 control subjects. Plasma and erythrocytes were separated immediately by centrifugation. The erythrocytes were washed three times with saline. The lipids of the erythrocytes were extracted by the procedure of Rose and Oklander of using chloroform and isopropanol, because the use of isopropanol in place of methanol avoids extracting heme pigment. Butylated hydroxytoluene (5 mg/100 ml) was added as an antioxidant. The fatty acids of the erythrocytes were determined by gas–liquid chromatography in a manner similar to that in the procedure described for determining sperm fatty acids.

Study participants completed a 40-question dietary survey entitled the Diet Habit Survey. On the basis of answers from the survey, participants were classified into one of four dietary groups: 37% fat (typical American intake), 30% fat, 25% fat, and 20% fat. Patients were asked to base their answers on their dietary habits for the previous month.

Statistical Analysis
Nonparametric statistics were used for all comparisons, because the data did not satisfy normality assumptions. All data are reported as medians and interquartile ranges. The interquartile range is defined as the difference between the 25th and 75th percentiles of a given variable. Differences between groups in erythrocyte fatty acid concentrations, sperm biochemistry, structure, and motility were compared, using the Kruskal–Wallis test. The Wilcoxon signed rank test was used for paired comparisons. Tests for linear trend were made, using linear regression analysis. All computations were made with the SAS statistical package (Statistical Analysis Systems, Cary, NC).

RESULTS
The most striking finding was the low concentration of the n-3 fatty acid DHA in sperm from Usher’s II patients and in sperm from all other patients with retinitis pigmentosa (Table 1 and Fig. 1). The Usher’s II patients had a sperm DHA content of 4.7% of total fatty acids compared with 19.2% in normal subjects (P < 0.001). The Usher’s II sperm DHA concentration was only 24% of normal. The sperm of non-Usher’s retinitis pigmentosa patients also had a lower content of DHA compared with the sperm from control subjects (12.8 versus 19.2%, P < 0.001).

The sperm of the Usher’s II group was also lower in n-6 fatty acids. Arachidonic acid (20:4[n-6]) was 1.5% in Usher’s II patients versus 2.7% in normal subjects. Reduced levels of n-3 and n-6 sperm fatty acids were offset by higher levels of monounsaturated and saturated fatty acids in the Usher’s II group (see Table 1).

In addition to differing from that in normal control subjects, the sperm of the Usher’s II group was significantly different from that of the non-Usher’s group. Sperm of Usher’s II patients was lower in DHA than that of non-Usher’s patients (4.7% versus 12.8%, P < 0.05) and was lower in total n-3 fatty acids (5.9% versus 15.5%, P < 0.001).

Similarly, many n-6 fatty acids were lower in Usher’s II than in non-Usher’s patients. Linoleic acid (18:2[n-6]) was 4.8% in Usher’s II versus 6.8% in non-Usher’s patients (P < 0.001). Arachidonic acid followed the same pattern as its precursor linoleic acid; it was 1.5% in Usher’s II and 2.6% in non-Usher’s patients (P < 0.05).

The monounsaturated fatty acid 16:1(n-7) was higher in Usher’s II (6.6%) than in non-Usher’s patients (2.7%, P < 0.001). Finally, two saturated fatty acids were significantly higher in Usher’s II patients, 14:0 (3.7% versus 1.7%, P < 0.05) and 22:0 (1.2% versus 0.2%, P < 0.005).

The DHA concentrations in sperm from the five subgroups of retinitis pigmentosa patients are shown in Figure 1. Although the DHA content in the sperm from different forms of retinitis pigmentosa patients varied, in all of them, DHA was lower than the 19.2%
TABLE 2. The Sterol Composition of Sperm From Patients With Retinitis Pigmentosa (RP) and Control Subjects (Medians and Interquartile Ranges)

<table>
<thead>
<tr>
<th>Sterols (µg/10⁹ cells)</th>
<th>ALL RP (n = 26)</th>
<th>Usher's II (n = 6)</th>
<th>Control (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>209.3 ± 559.6*</td>
<td>1764.6 ± 3100.7†</td>
<td>111.3 ± 58.3</td>
</tr>
<tr>
<td>Desmosterol</td>
<td>44.4 ± 39.7</td>
<td>44.4 ± 105.3</td>
<td>34.3 ± 7.4</td>
</tr>
<tr>
<td>Desmosterol/cholesterol</td>
<td>0.22 ± 0.17†</td>
<td>0.025 ± 0.18†</td>
<td>0.50 ± 0.09</td>
</tr>
</tbody>
</table>

*P < 0.01 vs control.  †P < 0.05 vs control.

observed in normal sperm. The DHA concentrations were 4.7% in Usher’s II patients, 10% in autosomal recessive, 11.2% in X-linked, 16.1% autosomal dominant, and 16.4% in the sperm of Usher’s I patients. The DHA values in autosomal dominant and Usher’s I patients were not significantly lower than those in control subjects. The father and son with a mutation of Rho Arg 133 Trp showed similar DHA concentrations in sperm (12% to 13%) and in erythrocytes (both 3%). The biochemical abnormalities were not more marked in the father, even though the father’s disease was more advanced.

The sperm sterol composition (cholesterol and desmosterol) of retinitis pigmentosa patients differed from that of normal subjects (Table 2 and Fig. 2). Sperm contain two sterols, cholesterol and desmosterol. Sperm is a unique tissue, because it has a high content of desmosterol, a sterol not found elsewhere in the body. Desmosterol is the last step in cholesterol biosynthesis and does not accumulate in any other tissue. The ratio of desmosterol to cholesterol in the sperm of retinitis pigmentosa patients was lower than that in control sperm (0.22 versus 0.30, P < 0.05). This difference occurred mainly from a higher content of cholesterol in the sperm of retinitis pigmentosa patients (209 µg/10⁹ cells versus 111 µg/10⁹ cells in control subjects). Similar to the DHA concentration, sterol differences between retinitis pigmentosa patients and normal subjects were even more prominent in the sperm of Usher’s II patients.

Composite data on all subjects (normal and retinitis pigmentosa patients) were subjected to linear regression analysis. This analysis indicated that the DHA concentration in the sperm was positively correlated to sperm counts (r = 0.635, P < 0.001) and to sperm motility (r = 0.531, P < 0.001; Fig. 3). The desmosterol-to-cholesterol ratio was positively correlated to sperm motility (r = 0.473, P < 0.002). Cholesterol in sperm was negatively correlated with DHA in sperm (−0.73204, P = 0.0001). Desmosterol in sperm was not significantly correlated with DHA in sperm (−0.28632, P = 0.1121). The desmosterol-to-choles-

FIGURE 2. The sterol composition of sperm from retinitis pigmentosa patients and control subjects (*compared with control, P < 0.02 to P < 0.01).

FIGURE 3. Coefficient of correlation between the docosahexaenoic acid (DHA) concentration in the sperm and sperm motility.
TABLE 3. Morphologic and Functional Characteristics of Sperm From Patients With Retinitis Pigmentosa (RP) and Control Subjects (Medians and Interquartile Ranges)

<table>
<thead>
<tr>
<th></th>
<th>ALL RP (n = 26)</th>
<th>Usher's II (n = 6)</th>
<th>Control (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells/ml X 10^6</td>
<td>70.0 ± 89.4f</td>
<td>32.6 ± 51.3†</td>
<td>154.5 ± 194.6</td>
</tr>
<tr>
<td>Total cells X 10^6</td>
<td>171.8 ± 359.0§</td>
<td>86.4 ± 141.1†</td>
<td>647.1 ± 291.2</td>
</tr>
<tr>
<td>Total oval and motile cells X 10^6</td>
<td>90.7 ± 203.7§</td>
<td>57.7 ± 67.4‡</td>
<td>343.5 ± 175.3</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>60.3 ± 16.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade of forward progression*</td>
<td>2.5 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sperm tail abnormalities (%)</td>
<td>20.5 ± 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headless sperm (%)</td>
<td>2.5 ± 3.0f</td>
<td>1.5 ± 1.5</td>
<td>0 ± 2.0</td>
</tr>
</tbody>
</table>

* 1 = no progression; 4 = highly progressive.
† P < 0.01 vs control.
‡ P < 0.05 vs control.
§ P < 0.001 vs control.
|| P < 0.005 vs control.

The terol ratio was positively correlated with DHA in sperm (0.63453, P = 0.0001).

Besides differences in chemical composition, there were morphologic and functional differences between the sperm of retinitis pigmentosa patients and that of control subjects (Table 3). Retinitis pigmentosa patients produced fewer sperm per ejaculate (172 million cells versus 647 million cells in control subjects) and had a lower sperm concentration (70 million cells/ml versus 155 million cells/ml of semen in control subjects). The patients also had sperm with a higher incidence of tail abnormalities (20.5% versus 10% in control subjects), and pinhead forms (2.5% versus 0% in control subjects). Functionally, sperm of retinitis pigmentosa patients had reduced motility (60% versus 74% in control subjects).

Docosahexaenoic acid was lower in the erythrocyte fatty acids of retinitis pigmentosa patients versus that in the erythrocyte fatty acids of control subjects (Table 4). However, the difference was much less than the sperm DHA differences.

On average, there were no differences between the dietary habits of retinitis pigmentosa patients and control subjects. Both groups consumed a typical American diet of 37% fat. Although antioxidant intake was not specifically measured, the intakes of grains, beans, fruits, and vegetables, and sources of antioxidants in foods were not different among retinitis pigmentosa patients and control subjects.

**DISCUSSION**

The results of this study suggest further homologies between sperm and the retina. Sperm and retinal cells are normally high in DHA, an important phospholipid membrane component. Both contain a structural component in common, the axoneme. A decade ago, Hunter et al reported bizarre structure of sperm in patients with retinitis pigmentosa. In the current study, sperm from patients with retinitis pigmentosa had a low content of DHA, abnormal motility, and anomalous shapes. These data suggest, indirectly, that the concentration of DHA in retinal cells may also be low, which could affect their function, as will be discussed subsequently.

Abnormal levels of DHA in sperm of patients with retinitis pigmentosa were much more pronounced than the reduced concentrations of DHA in plasma and erythrocytes previously reported in such patients. Similarly, sperm DHA concentrations were markedly lower than erythrocyte DHA concentrations in the current study. The sperm of our non–Usher’s group of retinitis pigmentosa patients contained DHA reduced to 67% of normal (see Table 1). The erythrocyte DHA for the same group was 78% of normal.
(see Table 4). The Usher's II patients had the lowest content of DHA in sperm of all patients: 24% of normal values.

Recent studies by Hoffman et al in human infants indicate an association between levels of DHA in erythrocytes and the cone electroretinogram response parameters. In monkeys, the DHA concentrations in erythrocytes were also positively correlated with the DHA content in retina and brain. Abnormalities in the metabolism of DHA may be a component of and may contribute to the phenotype of retinitis pigmentosa.

In the literature, data about the sterol and fatty acid composition of human sperm are scanty. No quantitative determinations of human sperm sterols have been reported, and the fatty acid compositions of normal human sperm have been reported in only two studies before this one. Both of these analyses were carried out with packed gas-liquid chromatographic columns that poorly separate DHA in comparison to modern capillary columns. In contrast, the sperm of rhesus monkey has been extensively studied.

The biochemistry of sperm is characterized by a high content of desmosterol and DHA. Desmosterol is the direct precursor of cholesterol in the synthetic pathway and contains one additional double bond. Docosahexaenoic acid contains six double bonds. These characteristics may confer greater membrane fluidity to the motile sperm. Interestingly, in a recent study, we found that the high amounts of DHA and desmosterol in sperm were concentrated in the sperm tail, the locus of sperm motility and axonemes.

With our lipid data, we had the unique opportunity to demonstrate that the motility of human sperm is associated with its membrane lipid composition. Sperm with higher concentrations of DHA, a higher desmosterol-to-cholesterol ratio, or both had a greater percentage of motile cells and a higher value for forward progression.

Previous studies in vitro have demonstrated the effects of changes in phospholipid fatty acid composition on membrane physical properties and function. Studying the sperm and seminal plasma from normospermic, oligospermic, and azospermic men, Sebastian et al suggested that there was a positive correlation between seminal phospholipids and fertility. Unfortunately, the fatty acid composition of sperm phospholipids in that study was not reported.

The low DHA levels in retinitis pigmentosa could be caused by one or several metabolic defects. Poor absorption of DHA or its precursors—n-3 fatty acid, linoleic acid, and eicosapentaenoic acid—or inadequate dietary intake of DHA or other n-3 fatty acids could account for the low plasma and erythrocyte levels of DHA reported by previous investigators. Reduced synthesis of DHA from precursor fatty acids (for example, linolenic acid, 18:3[n-3]) is another possibility. The activities of the desaturase enzymes (delta-6 and delta-5 desaturases) could be abnormal in retinitis pigmentosa patients or there could be a problem in the elongation of n-3 fatty acids. Recently, Voss et al proposed a new pathway to form DHA from 22:5(n-3) with elongation to 24:5, desaturation to 24:6, and beta oxidation to 22:6. Analyzing the fatty acid profile of erythrocytes, Hoffman and Birch suggested that a metabolic defect in fatty acid chain elongation mechanism exists in retinitis pigmentosa patients. Finally, because of its polyunsaturated structure, DHA is prone to oxidation. Peroxidation could be increased in retinitis pigmentosa patients, perhaps because of low tissue stores of antioxidants, thus accounting for lower concentrations of DHA.

The lower content of DHA in the sperm of retinitis pigmentosa patients is probably not the result of a dietary deficiency of DHA and its precursor fatty acid, linolenic acid, which is widely obtainable in foods. Adults can synthesize DHA from linolenic acid and therefore do not require a dietary source of DHA. The sources of DHA in the American diet are fish and chicken, with the chicken's diet containing fish meal. Our retinitis pigmentosa patients were consuming the typical American diet, which contains adequate n-3 fatty acids. Because our patients were from the Pacific Northwest, many consumed fish in their diets, especially salmon, a rich source of DHA and other n-3 fatty acids.

The abnormal fatty acid composition of sperm in patients with retinitis pigmentosa observed in our study suggests that their retinal membranes might also have abnormal phospholipid molecular species. The molecular species composition of membrane phospholipids is associated with membrane fluidity and the functions and activity of membrane-bound enzymes. In our previous studies, our results demonstrated that the membranes of sperm, brain, and retina each have a distinctive composition of the phospholipid molecular species. Diets deficient in n-3 fatty acids not only drastically changed the phospholipid molecular species composition of these tissues but they also affected the function of retina and brain. Therefore, abnormal phospholipid molecular species could be the cause of or the result of abnormal n-3 fatty acid metabolism. Further study is needed to delineate these possibilities.

An underlying assumption of this report is that a primary defect in the metabolism of DHA in the retina...
and sperm may be responsible for some of the features seen in this disease. There are certainly morphologic abnormalities of the sperm and of the retinal cells that could result from the abnormal metabolism of DHA. However, another point of view would be that a common genetic factor produces the cellular abnormalities and the decreased DHA content. To some extent, the decreased DHA in sperm may occur in part because of morphologic abnormalities in retinitis pigmentosa. Only further studies will answer these questions.

If the retinas of retinitis pigmentosa patients have reduced content of DHA, as do their sperm and erythrocytes, then the results of studies in monkeys with dietary n-3 fatty acid deficiency may offer some promise. These monkeys have impaired vision, abnormal electroretinogram findings, and a low content of DHA in the retina, reduced to 7.1% of total fatty acids with a normal retinal value of 36.4%. When deficient monkeys received supplementary DHA in their diets, concentrations in plasma and erythrocytes increased greatly, and the retinal concentration was restored to normal. When these composite data are considered in light of the low content of DHA in the sperm and erythrocytes of retinitis pigmentosa patients, it is suggested that dietary supplements of DHA from fish oil should be studied further as a possible intervention in the inevitable downhill course of this disease.

**Key Words**
docosahexaenoic acid, desmosterol-cholesterol, erythrocyte fatty acids, sperm fatty acids, sperm motility

**References**


Sperm Abnormalities in Retinitis Pigmentosa


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