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## Serum vitamin A concentration is elevated in idiopathic intracranial hypertension

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**Article abstract**—*Objective:* The primary purpose was to investigate whether serum vitamin A concentration is associated with idiopathic intracranial hypertension (IIH). The secondary aim was to obtain pilot data regarding the amount of vitamin A ingested by patients and controls. *Background:* Vitamin A is an attractive candidate mediator of IIH as many of the symptoms and signs of hypervitaminosis A mimic those of IIH. *Methods:* We prospectively determined serum retinol and retinyl ester concentration in 16 women with IIH and 70 healthy young women. Using a survey instrument, we also determined the average daily vitamin A ingestion in a convenience sample of patients and controls. *Results:* Serum retinol concentration was significantly higher in the patient group (median 752 ug/L) compared with the control group (median 530 ug/L), even after adjusting for age and body mass index ( $p < 0.001$ ). Retinyl ester concentration, however, was similar in the patient (median 48 ug/L) and control (median 41 ug/L) groups ( $p = 0.32$ ). There was no significant correlation between serum retinol concentration and body mass index in the patients ( $r = 0.16$ ) or controls ( $r = -0.02$ ). Finally, there was no significant difference in the amounts of vitamin A ingested by the patients or controls, although the small number of subjects in both groups reduced the power of this conclusion. *Conclusions:* Elevated serum retinol concentration is associated with IIH. Obesity, by itself, does not explain these higher levels. Patients may ingest an abnormally large amount of vitamin A, metabolize it abnormally, or be unusually sensitive to its effects. Alternatively, elevated level of serum retinol may reflect an epiphenomenon of another variable we did not measure or a nonspecific effect of elevated retinol binding capacity. **Key words:** Idiopathic intracranial hypertension—Vitamin A—Retinol—Obesity.

NEUROLOGY 1999;53:1114-1118

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Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri or benign intracranial hypertension, usually occurs in otherwise healthy overweight women of childbearing age.<sup>1,2</sup> These attributes suggest that a hormonal or metabolic agent of women who are overweight and young is important in the pathogenesis of this condition. Whereas many exogenous agents and endogenous metabolic disturbances have been implicated in caus-

ing increased CSF pressure, those factors have been reported in single case reports or small uncontrolled series that often involved patients who failed to fulfill a modern case definition of IIH.<sup>3</sup> Moreover, no single disease or toxin has been identified as significantly associated with IIH using a case-control analysis.<sup>3,4</sup>

Vitamin A is an attractive candidate mediator of IIH. Many reports confirm vitamin A intoxication

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Received January 8, 1999. Accepted in final form June 7, 1999.

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produces symptoms and signs indistinguishable from IIH.<sup>5,6</sup> Intoxication has resulted from excessive ingestion of vitamin A supplements,<sup>7-11</sup> foods rich in vitamin A content,<sup>12-13</sup> and therapeutic retinoid derivatives.<sup>14-17</sup> Hypervitaminosis A has also been implicated in IIH associated with chronic renal failure.<sup>18</sup>

If hypervitaminosis A is indeed important in the development of typical IIH, then one could hypothesize that either affected patients ingest excessive amounts of this nutrient or that their metabolism of it is somehow altered. The primary purpose of our investigation was to investigate whether serum vitamin A concentration is associated with IIH. A secondary aim was to obtain pilot information to determine if there are differences in the amount of dietary vitamin A ingested by patients with IIH and control subjects.

**Methods.** This was a prospective cross-sectional survey conducted in three phases. The first phase of the investigation was to establish a reference range for serum vitamin A in young women. The next phase of the investigation—based on sample size estimation derived, in part, from results of the first phase—involved prospective recruitment of patients with IIH. Finally, a convenience sample of patients and controls was investigated using a survey instrument to obtain pilot data in order to compare the amounts of dietary vitamin A ingestion in both groups. The procedures outlined in the following were reviewed and approved by the Institutional Review Boards of the participating institutions. All participating subjects and patients provided written informed consent after the nature of the procedures had been explained to them.

**Control subjects.** Control subjects were prospectively recruited in order to establish reference values for serum vitamin A concentration and to obtain dietary information regarding vitamin A ingestion. All of the control subjects recruited for vitamin A determination were enrolled by the principal investigator (D.M.J.). We identified potential control subjects by advertising our interest in periodicals distributed to employees at our institution and women receiving dietary counseling. Interested participants underwent formal screening for entry criteria by trained research study coordinators. Only women between the ages of 18 and 45 years were enrolled. Because of the demographic composition of the referral region of the principal investigator's institution, and not by design, only white women were enrolled. Potential subjects were excluded from enrollment if they had been diagnosed with IIH at any time or if they experienced daily headaches, transient visual obscurations, diplopia, pulsatile intracranial noises, or focal neurologic symptoms. Subjects were not enrolled if they were pregnant, had delivered a baby within the last 2 months, or were breast-feeding. Subjects receiving retinoid medication, eating more than one serving of liver per week, or receiving more than 5,000 IU or 800 ug retinol equivalent daily were excluded from enrollment, as these conditions would contribute to hypervitaminosis A. The presence of renal disease, liver disease, diabetes, hypertension, or daily alcohol use also constituted exclusion from enrollment as these conditions alter vitamin A metabolism. Finally, a potential subject was excluded if receiving

more than 200 IU of vitamin D daily or more than 8 mg of  $\alpha$ -tocopherol equivalents daily, as some pharmaceutical preparations of those substances have been observed to contain retinol. Subjects who fulfilled all entry criteria were paid \$10.00 for participating.

In addition to submitting a blood sample for vitamin A determination, each control subject also had her weight (in kilograms) and height (in meters) measured by a trained research study coordinator. Body mass index (BMI) was then calculated as weight divided by height squared.

Initial recruitment efforts occurred without regard to targeted BMI. Because we did not know if an association existed between serum vitamin A concentration and BMI, our goal was to enroll subjects who represented a full range of BMI values. Following interim analyses during the enrollment phase, subjects with certain BMI values were more specifically targeted in order to achieve our goal. Before recruitment started, we determined that a sample size of 84 subjects was required in order to detect a correlation between serum vitamin A concentration and BMI of 0.3 with 80% power.

Additional obese white women between the ages of 18 and 45 years who did not have IIH were recruited from the outpatient practices of the investigators in order to obtain dietary information regarding vitamin A ingestion (see following). Their heights and weights were recorded. Obesity was defined as BMI greater than 30.<sup>19</sup> The same entry criteria described earlier were applied to these subjects.

**Patients.** To ensure a valid comparison with the controls, cases were prospectively recruited and studied using standardized methods. Only white women between the ages of 18 and 45 years with IIH characterized by fulfillment of the modified Dandy criteria<sup>2</sup> were asked to participate. Potential patients were excluded if their symptoms had been present for more than 3 months or if they were receiving treatment, including diuretic, corticosteroid, or supervised weight reduction. The other exclusion criteria applied to control subjects were also applied to potential patients. We recorded the duration of symptoms, papilloedema grade using a standardized grading scheme,<sup>20</sup> qualitative pattern of visual field loss, and opening pressure measured at the time of diagnostic lumbar puncture.

Based on review of control data and retrospective cases, we determined that the study required at least 13 patients to provide 90% statistical power for the comparison of cases and controls (two-sided test with  $\alpha = 0.05$ ). The study was conservatively planned to allow up to 20 patients to be enrolled. Reevaluation of sample size assumptions after enrolling 16 patients showed power exceeding 90% and enrollment was terminated.

**Vitamin A assays.** Serum samples from 20-mL specimens of clotted blood were frozen promptly after separation of the clots, protected from light exposure, and sent packed with dry ice to the analytic laboratory (R.D.E.). Two or more samples with masked labeling were separated from each specimen for evaluation of analytic precision, verification of the sensitivity of the analyses, and second (duplicate) analysis on a second day. Each specimen sample was stored in a  $-70^{\circ}\text{C}$  freezer between analyses.

The fat-soluble vitamins were extracted from the serum samples with isopropyl alcohol and heptane; control sera and a saline blank were treated in the same way. The retinol and retinyl esters were quantified by ultraviolet

absorbance using a high-pressure liquid chromatography (HPLC) system. The HPLC system was calibrated with purified retinol and retinyl palmitate (Sigma Chemical Company, St. Louis, MO) dissolved in heptane. Because beta-carotene co-chromatographed with retinyl esters, the system was also calibrated with beta-carotene. The retinol and retinyl esters were quantified according to absorbances at 325 nm. Beta-carotene absorbs sufficiently at 325 nm to cause significant error in the quantitation of retinyl esters. Therefore, a correction for the beta-carotene absorbance at 325 nm was determined by measuring the beta-carotene absorbance at 325 nm for each specimen, and the beta-carotene absorbance at 450 nm; the ratio of absorbances at 450 nm and 325 nm as observed with the beta-carotene standard were used in the calculation of the retinyl ester values.

The HPLC system included a spectrophotometric detector set to monitor the column effluent continuously at 325 nm and 450 nm. The chromatographic column (micro-Bondapak, Waters Corporation, Milford, MA) was packed with 5- $\mu$ m particles coated with octadecyl units, and the system was operated isocratically with a mixture of acetonitrile 75% and methanol 25%.

**Vitamin A questionnaire.** We searched Nutritionist IV version 1.0 (N-Squared Computing, Salem, OR), a nutrition-specific computerized database, to identify the vitamin A content of food items. We then selected specific food items from each of the major categories of food groups for inclusion in our survey instrument based on high concentration of vitamin A and high frequency of expected use. We assigned a reference portion for each of the 36 foods included in our survey instrument. Subjects were asked to indicate their eating frequency of each of the items by selecting never or indicating the number of times per day, week, or month they ate the reference portion. Pictures of the food and reference portions were available for many of the survey items to assist subjects in defining their eating frequencies. For each item, the retinol equivalent per day was calculated by multiplying the retinol equivalent per reference portion by the eating frequency. The total retinol equivalents per day was then calculated by summing the total retinol equivalents per day of each of the food items.

**Statistical analyses.** Assays for retinol and retinyl esters for individual serum samples were replicated, and sample medians over the replicates were used for analysis. The primary statistical analyses were based on nonparametric procedures owing to the non-normal (skewed) distributions of the response variables. Comparisons of patient and control results were based on the Wilcoxon rank-sum procedure, and associations between variables were assessed with Spearman rank correlations. The comparisons of patient and control results for retinol and retinyl ester were adjusted for age and BMI in a general linear model (i.e., analysis of covariance) after log transformation of the ester values.

**Results.** The table summarizes the main results of our comparisons between patients with IIH and control subjects. We enrolled 70 control subjects, ranging in age from 18 to 45 years and with a median (mean) age of 36 (34) years. Their BMI ranged from 17 to 53, with a median (mean) value of 27 (31). The serum retinol levels of the controls ranged from 293 to 990  $\mu$ g/L with a median

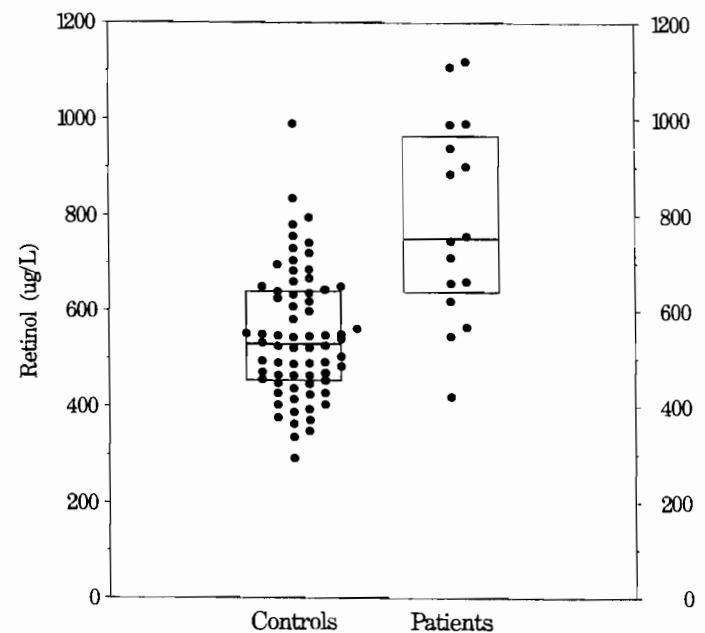
**Table** Comparison of major variables in patients with idiopathic intracranial hypertension and control subjects

Variable	Patients (n = 16)	Controls (n = 70)
Age (y), range	18-42	18-45
Median, mean ( $p = 0.003$ )	28, 28	36, 34
Body mass index ( $\text{kg}/\text{M}^2$ ), range	27-68	17-53
Median, mean ( $p = 0.047$ )	32, 35	27, 31
Serum retinol ( $\mu\text{g}/\text{L}$ ), range	421-1,120	293-990
Median, mean ( $p < 0.001$ )	751, 789	530, 547
Serum retinyl esters ( $\mu\text{g}/\text{L}$ ), range	8-154	9-142
Median, mean ( $p = 0.32$ )	48, 55	41, 46
Vitamin A ingestion (retinol equivalents/d)*	266-9,883	626-13,347
Median, mean ( $p = 0.95$ )	2,308, 2,785	1,542, 3,816

\* Data from 13 patients and 10 controls contributed to the vitamin A ingestion comparison.

(mean) of 530  $\mu$ g/L (547  $\mu$ g/L) (figure 1). Their serum retinyl ester levels ranged from 9 to 142  $\mu$ g/L with a median (mean) of 41  $\mu$ g/L (46  $\mu$ g/L) (figure 2).

We also enrolled 16 patients with IIH, ranging in age from 18 to 42 years of age and with both a median and mean age of 28 years. The duration of IIH ranged from 1 to 13 weeks (median 6 weeks). Papilledema in the worse eye was grade 1 in 12%, grade 2 in 37%, grade 3 in 25%, grade 4 in 6%, and grade 5 in 19% of patients. The predominant visual field pattern of both eyes in the patients included isolated blind spot enlargement in 26 eyes, inferior arcuate



**Figure 1.** Scattergram shows individual values of serum retinol concentration for controls and patients. The upper and lower sides of the rectangle represent the 75th and 25th percentile values. The horizontal bar within the rectangle represents the median value, which differs significantly between the two groups. Note that, despite the overlap of patient and control values, the majority of patient values are greater than the median control value.

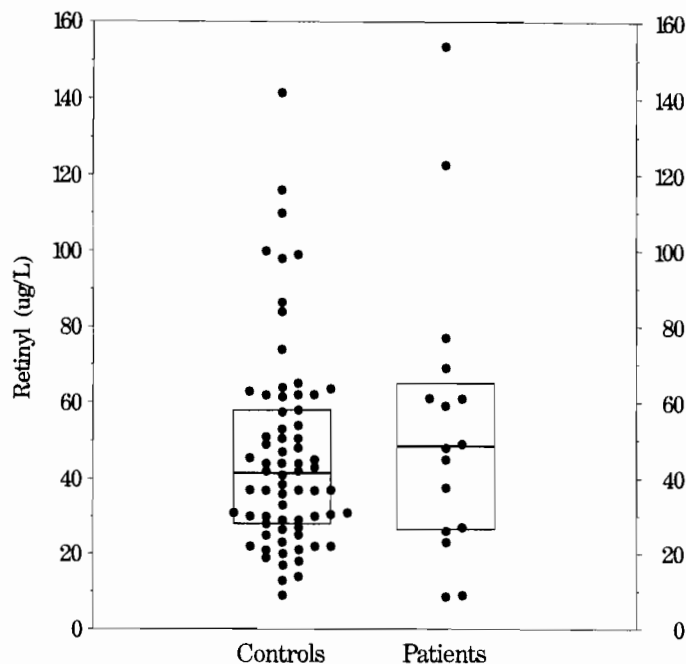


Figure 2. Scattergram shows individual values of serum retinyl ester concentration for controls and patients. The upper and lower sides of the rectangle represent the 75th and 25th percentile values. The horizontal bar within the rectangle represents the median value, which does not differ significantly between the two groups.

loss in 5 eyes, and severe superior and inferior nasal arcuate loss in 1 eye. Opening CSF pressures during diagnostic lumbar puncture ranged from 220 to 500 mm CSF, with a median (mean) value of 355 mm CSF (361 mm CSF).

The BMI of patients with IIH ranged from 27 to 68 with a median (mean) value of 32 (35), and was somewhat greater than the BMI of control subjects ( $p = 0.047$ ; see table). Controls were significantly older than patients ( $p = 0.003$ ; see table 1), but the ranges in age were very similar. The serum retinol concentrations of patients ranged from 421 to 1120 ug/L with a median (mean) of 751 ug/L (789 ug/L). The difference in serum retinol between controls and patients was statistically significant ( $p < 0.001$ ), and remained significant after adjusting for age and BMI ( $p < 0.001$ ; see figure 1, table). The serum retinyl ester concentrations of patients ranged from 8 to 154 ug/L with a median (mean) of 48 ug/L (55 ug/L). There was no significant difference in retinyl ester levels between controls and patients ( $p = 0.32$ ; see figure 2, table).

There was no significant correlation between serum retinol level and age in the control ( $r = -0.19$ ,  $p = 0.11$ ) or patient ( $r = 0.24$ ,  $p = 0.37$ ) groups. Likewise, there was no significant correlation between serum retinol level and BMI in either the control ( $r = -0.02$ ,  $p = 0.89$ ) or patient ( $r = 0.16$ ,  $p = 0.54$ ) group. Finally, there was no significant correlation between patient serum retinol concentration and duration of their symptoms ( $r = -0.06$ ,  $p = 0.82$ ), or papilledema grade ( $r = 0.12$ ,  $p = 0.66$ ) of their more severely affected eye.

There was no significant difference in amounts of vitamin A ingestion between the 10 controls (median, 1,542 retinol equivalents per day) and 13 patients (median, 2,308 retinol equivalents per day) who completed the nutrition survey instrument ( $p = 0.95$ ). However, the small num-

bers of subjects provide relatively little statistical power for this comparison. A sample size calculation, using a log scale to correct for the skewed distribution, indicated that we would need at least 110 individuals per group to provide a power of 80% in a two-tailed test ( $p$  value = 0.05) to identify a true difference of 800 retinol equivalents per day, if one existed.

**Discussion.** We found that serum concentrations of vitamin A, in the form of retinol, are significantly higher in patients with IIH than in healthy controls. There was no association between serum retinol level and BMI in the control or patient populations. This suggests that obesity, although well documented as strongly associated with IIH, is not, by itself, the patient characteristic responsible for causing higher levels of vitamin A in affected individuals. The pilot data from our dietary survey do not suggest that elevated retinol concentrations in patients result from abnormally greater ingestion of dietary vitamin A. However, this conclusion must be tempered by the fact that the small number of patients and controls lowers the statistical power of this comparison.

How might excessive circulating vitamin A produce increased intracranial pressure? When specifically bound, circulating retinol and retinyl esters are not toxic. Intoxication in humans occurs when the capacity for hepatic storage or binding to retinol binding protein is exceeded.<sup>21,22</sup> At that level of hypervitaminosis A, the proportion of the circulating retinyl esters increases. Increased plasma levels of retinol and retinyl esters then circulate nonspecifically bound to lipoproteins. As such, the excessive retinol and retinyl esters can interact with cell membranes and produce damage by membranolytic surface-active properties. If increased circulating retinol interacted nonspecifically with cellular membranes of the arachnoid granulations to disrupt cell membrane integrity, then CSF outflow would be impaired.<sup>23-25</sup> The elevation of intracranial pressure that resulted from this process could then produce typical symptoms and signs of IIH in a predisposed individual.

Some reported cases of human hypervitaminosis A had elevated circulating retinyl esters that correlated with symptoms of toxicity better than retinol concentrations.<sup>9,12,26-28</sup> Our patients, on the other hand, had normal levels of retinyl esters. The minimal level to which serum retinol concentrations were elevated in patients with IIH differs markedly from the toxic levels reported in patients with hypervitaminosis A, and probably explains why retinyl ester levels were normal in our patient group.

It is unlikely that the elevated serum retinol concentration in patients with IIH was the result of reduced hepatic or retinol binding protein binding capacity for several reasons. None of our patients had malnutrition, liver disease, renal disease, or proteinuria, or was taking medication (e.g., glucocorticoid) that can alter metabolism or affect binding

capacity of retinol binding protein. The concentration of retinyl esters, the vitamin A fraction usually elevated when retinol binding protein capacity is exceeded, was not significantly different between patients and controls. This suggests that elevated retinol in patients with IIH is an epiphenomenon or a nonspecific effect of altered vitamin A metabolism. Indeed, Selhorst et al.<sup>29</sup> found that the concentration of retinol binding protein was abnormally elevated in a greater number of patients than controls.

Despite our positive results, it seems unlikely that retinol toxicity, by itself, is directly related to the pathogenesis of IIH for several reasons. Many patients with IIH had serum retinol values that overlapped with control values (see figure 1). In many patients, the retinol value was below the upper control limit. Serum retinyl ester levels were not significantly greater than control values. However, it remains possible that mild elevation of serum retinol is one factor that contributes to elevated intracranial pressure in predisposed women.

Vitamin A may cause or contribute to the development of IIH in several ways: Patients may ingest an abnormally large amount of it, metabolize it abnormally, or be unusually sensitive to its effects. Alternatively, elevated level of serum retinol in patients with IIH may reflect an epiphenomenon of a variable we did not measure or a nonspecific effect of elevated retinol binding capacity. Our results provide testable hypotheses for future investigations of these possibilities.

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