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Editor’s Note: For many years, this journal has, on the recommendation of numerous statistical consultants, discouraged the use of correlation coefficients in method-comparison studies. We request that authors include the standard error of the estimate (S\(_{xy}\)) as an indication of the scatter about the regression line (see, e.g., reference 2).

Measurement of Serum Transferrin Receptors in Screening for Hemochromatosis

To the Editor:

One major problem in identifying hereditary hemochromatosis at an early stage is the lack of specific biochemical or genetic markers for the disorder. Thus, a battery of tests aimed to quantify the patient’s iron status is applied to potentially affected subjects.

Measurement of serum transferrin receptors (s-TfR) is reportedly important in assessing several hematological disorders, particularly in identifying mild iron deficiency of recent onset (1, 2). On the other hand, in states of iron overload, s-TfR is decreased in rats but normal in humans (3, 4).

In an ongoing study of hemochromatosis, our laboratory measured s-TfR in 882 healthy men (ages 18-22 years) reporting to a military base nearby. The assay was performed to investigate whether s-TfR might complement the battery of tests commonly used in screening studies and might help identify individuals with a potential iron-overload problem. In individuals with serum iron (s-Fe) >25 μmol/L (n = 81), we determined serum ferritin (s-Fe), s-TfR, and total iron-binding capacity (TIBC). The mean ± SD s-TfR of this group (3.99 ± 9.3 mg/L, n = 81) was slightly less than in those with s-Fe <25 μmol/L (3.50 ± 9.1 mg/L, n = 81, P = 0.048).

The relationship between s-TfR, transferrin saturation (TS%), and s-Fe in the group of 81 was examined more closely. After dividing the group into five subgroups according to their TS% (Table 1), we noted a negative correlation between mean s-TfR and mean TS%, but not between mean TS% and mean s-Fe of the subgroups. Analysis of variance revealed a significant (P = 0.003) contrast in the group means of s-TfR, confirming the trend of decreasing s-TfR with increasing TS%. By comparison, the contrast in group means of s-Fe was not significant (P = 0.3).

Among the 81 individuals with s-Fe >25 μmol/L, only 19 had a TS% >60%. Of these individuals, 13 had an s-Fe <100 μmol/L, whereas only 3 had an s-Fe >100 μmol/L. The mean s-TfR of those individuals with TS% >60% and s-Fe >25 μmol/L was significantly less than in those having an s-Fe <25 μmol/L (P = 0.0008) and also less than in those with an s-Fe >25 μmol/L but TS% <60% (P = 0.006).

If s-TfR reflects the rate of erythropoiesis, then a low s-TfR may reflect a low rate of erythropoiesis. When this is combined with an increase in TS%, the rate of iron accumulation in the liver will increase. Under such conditions, the concentrations of hepatic iron in young individuals may not yet have reached a stage where s-Fe is suspiciously high. Even though a positive diagnosis has not yet been confirmed (e.g., by determination of iron in liver biopsy specimens) in any of the 19 candidates for hereditary hemochromatosis, our results suggest that, in screening studies of young persons, determinations of s-TfR may be more valuable than determinations of s-Fe in combination with TS%. We recommend further evaluation of s-TfR in population studies for early detection of iron overload.

References

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Fish-Oil Supplementation Reduces Lp(a) Concentrations in Type III Dysbeta10lipoproteinemia

To the Editor:

Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein similar in structure to low-density lipoprotein (LDL) with an additional apolipoprotein [apo (a)] bound to apo B by disulfide bridges (1). Reduction of plasma Lp(a) concentrations by dietary and pharmacological treatment has been largely unsuccessful, probably because of the strong

Table 1. Distribution of TS%, s-TIR, and s-Fe in 81 Individuals with s-Fe >25 μmol/L

<table>
<thead>
<tr>
<th>TS% range</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>38 ± 1</td>
<td>4.58 ± 1.68</td>
<td>100 ± 114</td>
<td>3</td>
</tr>
<tr>
<td>40-49</td>
<td>45 ± 3</td>
<td>3.55 ± 0.98</td>
<td>63 ± 27</td>
<td>32</td>
</tr>
<tr>
<td>50-59</td>
<td>53 ± 3</td>
<td>3.23 ± 0.73</td>
<td>71 ± 35</td>
<td>27</td>
</tr>
<tr>
<td>60-69</td>
<td>64 ± 3</td>
<td>3.10 ± 0.83</td>
<td>68 ± 68</td>
<td>10</td>
</tr>
<tr>
<td>&gt;69</td>
<td>83 ± 10</td>
<td>2.40 ± 0.46</td>
<td>92 ± 45</td>
<td>9</td>
</tr>
</tbody>
</table>

* Mean ± 2 SD for the 811 individuals with s-Fe <25 μmol/L: 3.50 ± 1.62 mg/L. The range of values obtained in 10 healthy male laboratory workers was 3.31-4.53 mg/L (s).

Note: **Mean ± 2 SD for the 811 individuals with s-Fe <25 μmol/L: 3.50 ± 1.62 mg/L. The range of values obtained in 10 healthy male laboratory workers was 3.31-4.53 mg/L (s)."
genetic control of plasma Lp(a) concentrations. A recent study indicated that apo(a) is also associated with very-low-density lipoprotein (VLDL) in type III and type IV hypertriglyceridemia (HTG) (2).

This prompted us to examine the possible relationship between VLDL apo B reduction and plasma Lp(a) variation in individuals with type III or type IV HTG during treatment with fish oil. We studied 18 subjects; 9 had type III dysbetalipoproteinemia, which was defined by elevated concentrations of triglycerides (TGs) (>2 g/L), the apo E2/2 phenotype by isoelectric focusing, and the presence of a β-VLDL on agarose gel electrophoresis. The other 9 subjects had endogenous HTG characterized by elevated concentrations of TG (>2 g/L) and low concentrations of LDL cholesterol (<1.6 g/L) on repeated measurements. There were no secondary causes of hyperlipidemia, and no subject was using any drug that affects lipid metabolism. Participants received 6 g/d of ω3 fatty acids (Promega, Parke-Davis of Warner Lambert Canada Inc. Scarborough, Ontario) for 12 wk. Total and LDL apo B concentrations were measured by immunodensitometry in total plasma and on the density >1.006 g/mL ultracentrifugation fraction; Lp(a) was measured by a noncompetitive enzyme-linked immunosorbent assay (3).

Before treatment, the mean plasma Lp(a) difference between the two measurements was 5.5 (±13.5) mg/L, which corresponds to a variation of 4.4% from the mean plasma concentration. Table 1 summarizes the mean changes in VLDL apo B, LDL apo B, and Lp(a) concentrations for each group. The reduction in VLDL apo B (−35%, P <0.01) was associated with a clear decrease in Lp(a) (−30%, P <0.0001) and with no effect on LDL apo B (+7%, NS) in the type III subjects. In endogenous HTG the reduction in VLDL apo B (−65%, P <0.0001) was associated with a significant increase in LDL apo B (+33%, P <0.005) and with no significant change in Lp(a) (−16%, NS) concentrations. There was no statistically significant correlation between VLDL apo B reduction or LDL apo B variation and Lp(a) changes after treatment, which suggests an independent effect of fish oil on these particles. The Lp(a) decrease was clear in type III subjects (all subjects had lower plasma Lp(a) concentrations after treatment than at baseline), whereas more scatter was observed in the response of type IV individuals (two subjects had higher plasma Lp(a) levels after treatment). The reasons for these discrepancies are unknown. However, a previous study showed that, after a fat meal, apo(a) was found in the chylomicron-VLDL plasma density fraction (4). Because fish oil supplementation reduces chylomicron and VLDL remnant concentrations that accumulate in the plasma of type III hyperlipidemic individuals (5), we suggest that the observed decrease in Lp(a) in type III subjects is related to the decrease in the remnant particles. An alternate explanation is that fish oils decrease the secretion of Lp(a)-associated apo B, therefore reducing Lp(a) production by the liver. This explains the similar trend in Lp(a) reduction in type III and type IV hyperlipidemic subjects.

References
2. Selinger E, Dallongeville J, Davignon J. Lp(a) is present in plasma of density >1.006 g/mL in hypertriglyceridemia. Circulation 1990;82:III–90.
4. Berson TP, Innerarity TL, Pitts RE, Rall SC, Weisberger KR, Mahley RW. Fat feeding in humans induces lipoproteins of density less than 1.00 that are enriched in apolipoprotein(a) and that cause lipid accumulation in macrophages. J Clin Invest 1986;77:622–30.

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A Positive Control for Acetylcholinesterase Electrophoresis

To the Editor:

Preparation of a positive control for qualitative gel-electrophoresis analysis for acetylcholinesterase (ACHE; EC 3.1.1.7) in amniotic fluid (AF), mixing cerebrospinal fluid (CSF) with AF, was recently described (1). This control has no qualitative difference in band characteristics from those of AF known to be positive for neural-tube defect (NTD). Our laboratory has been studying ACHE since 1981 (2), and we have always used this control when AF positive for NTD was not available. However, we have found that the concentration of CSF before mixing does not generally appear to be necessary.

We wish to make two points: First, even CSF minimally contaminated with blood must be excluded; if it is not excluded, several cholinesterase bands appear on electrophoresis. Second, we found a second electrophoretic band in the CSF of Guillain-Barre syndrome patients (3). These CSF specimens must also be excluded. Nevertheless, CSF-AF sample mix or AF sample from NTD as control must be used routinely in ACHE

Table 1. Plasma Lipoprotein Apo B and Lp(a) Concentrations before and after 4 and 12 Wk of ω3 Fatty Acid Treatment

<table>
<thead>
<tr>
<th>Type</th>
<th>Before Treatment</th>
<th>4 wk</th>
<th>12 wk</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 wk</td>
<td>12 wk</td>
</tr>
<tr>
<td>Type III (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL apo B (mg/L)</td>
<td>680 (65)</td>
<td>500 (50)</td>
<td>430 (40)</td>
</tr>
<tr>
<td>LDL apo B (mg/L)</td>
<td>780 (100)</td>
<td>760 (120)</td>
<td>810 (130)</td>
</tr>
<tr>
<td>Lp(a) (mg/L)</td>
<td>95</td>
<td>51 (23 - 295)</td>
<td>78 (15 - 234)</td>
</tr>
<tr>
<td>Type IV (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL apo B (mg/L)</td>
<td>820 (60)</td>
<td>240 (60)</td>
<td>260 (50)</td>
</tr>
<tr>
<td>LDL apo B (mg/L)</td>
<td>860 (140)</td>
<td>1140 (160)</td>
<td>1130 (150)</td>
</tr>
<tr>
<td>Lp(a) (mg/L)</td>
<td>54</td>
<td>49</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>(31 - 252)</td>
<td>(30 - 183)</td>
<td>(22 - 174)</td>
</tr>
</tbody>
</table>

* Apo B concentration is mean (SD); Lp(a) is median (range).
* Difference from baseline, paired Student's t-test, P <0.01.
* Difference from baseline, signed-rank test, P <0.01.
* Difference from baseline, paired Student's t-test, P <0.0001.