Plasma HDL Levels Highly Correlate With Cognitive Function in Exceptional Longevity

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Background. Families of centenarians have high levels of plasma high-density lipoprotein (HDL) cholesterol, which may have neurological as well as cardiovascular protective effects during aging. Because plasma HDL level declines progressively with aging, we examined whether centenarians with higher plasma HDL levels have better cognitive function.

Methods. Total plasma cholesterol, low-density lipoprotein (LDL) cholesterol, HDL, triglycerides, and apolipoprotein levels were measured in a group of centenarians ($n = 139$; older than 95 years) and were correlated with their cognitive function (measured by Mini-Mental State Examination [MMSE]).

Results. Plasma HDL levels correlated significantly with MMSE ($r = .32; p < .0001$). Each decrease in plasma HDL tertile ($74.9 \pm 2.1$, $50.6 \pm 0.5$, and $36.8 \pm 1.0$ mg/dl) was associated with a significant decrease in MMSE ($23.4 \pm 1.8$, $17.7 \pm 1.8$, and $12.4 \pm 1.8$; $p < .04$ for each plasma HDL tertile). As expected, increased plasma apolipoprotein A-I and decreased plasma triglyceride levels were also correlated with a significantly superior cognitive function. Biological markers of hydration and nutritional status did not differ between the groups with the higher or lower plasma HDL or MMSE.

Conclusions. These data demonstrate that cognitive dysfunction in centenarians is associated with a progressive decline in plasma HDL concentrations. This underscores the protective effects of increased plasma HDL and its role in maintaining superior cognition in longevity.

Centenarians have approximately double the life expectancy of their cohort. They have escaped a variety of age-related diseases, and the causes of their deaths are often undetermined (1). Moreover, various studies suggest that while the effect of genetics on life span is minimal across ages, this is not the case with centenarians. Siblings of centenarians have been shown to be at approximately four- to fivefold the ‘risk’ to have longevity (2), suggesting that genetic factors have a strong role in determining longevity in this population. In fact, Puca and colleagues (3) recently performed linkage analysis of affected centenarians’ siblings and revealed a few common loci, most impressive the one on chromosome 4. These facts have promoted our search for a measurable inherited biological factor that is unique to this population.

A search for a candidate biological factor for longevity is limited by the fact that centenarians are at the end of their lives, and a factor that could have sustained their health until recently may be on the decline. To overcome such a possibility, we have collected data from offspring of centenarians and their spouses, as a control population. We reasoned that if a significant longevity factor is inherited, it might be more apparent in the offspring of centenarians. Indeed, we have reported that plasma high-density lipoprotein (HDL) was markedly and significantly increased in offspring of centenarians (4). Although a prospective study showed that plasma HDL levels decrease with aging (5), plasma HDL levels in centenarians were similar to that of a control population that is approximately 30 years younger. Thus, we reasoned that centenarians may have had higher plasma HDL levels through much of their lives and may be losing the protection provided by plasma HDL when they reach such exceptional longevity.

Among the many effects of plasma HDL, it recently became apparent that it protects from decreased cognitive function associated with Alzheimer’s disease (6) and other forms of dementia (7,8). Thus, we hypothesized that centenarians who have elevated levels of plasma HDL also have superior cognitive function (defined by Mini-Mental State Examination [MMSE]) (9). Such a positive correlation demonstrates a putative role that plasma HDL might have, not only in longevity, but also in a parallel preservation of cognitive function.

Methods. One hundred and thirty-nine centenarians (we use this term because all of our study population was older than 95 years), 95–107 years of age (103 women, age 97.7 ± 0.2 and 37 men, age 97.6 ± 0.4), were recruited to participate in the study. The participants’ ages were defined by their birth certificates or date of birth as stated in their passports. We chose to study a population of Ashkenazi Jews, who originate from relatively few founders. Ashkenazi Jewish founders lived in the 16th to 17th centuries in the “Pale of Settlement” of eastern and central Europe. They were subjected to isolation, inbreeding, and then rapid expansion.

There is much evidence to support the use of this unique population as a resource to discover important genes. For example, three specific mutations in a cancer gene were subjected to isolation, inbreeding, and then rapid expansion. There is much evidence to support the use of this unique population as a resource to discover important genes. For example, three specific mutations in a cancer gene were subjected to isolation, inbreeding, and then rapid expansion.

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statistically with MMSE (r = .32; p < .0001). Figure 1

Plasma levels of HDL in centenarians correlated signifi-

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higher plasma HDL concentrations compared to the cente-

Table 1. Mini-Mental State Examination Score

Table 2. Plasma HDL Levels in Female and Male Centenarians

Note: HDL = high-density lipoprotein; MMSE = Mini-Mental State Examination; Apo A-I = apolipoprotein A-I; LDL = low-density lipoprotein; BMI = body mass index.

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Figure 1. Average Mini-Mental State Examination (MMSE) scores in centenarians grouped according to plasma high-density lipoprotein (HDL) tertiles (1 = 74.9 ± 2.1, 2 = 50.6 ± 0.5, and 3 = 36.8 ± 1.0 mg/dl). *p < .05 versus all.

Table 2. Plasma HDL Levels in Female and Male Centenarians With High (25–30) and Low (<25) MMSE Scores

Note: HDL = high-density lipoprotein; MMSE = Mini-Mental State Examination.

the early-onset breast cancer among Ashkenazi women (BRCA genes). However, this population is comparable to non-Jewish populations, in regard to longevity, prevalence of atherosclerotic cardiovascular diseases, and dementia.

Subjects were recruited by word of mouth and through advertisements in Jewish aging centers and homes. Informed written consent was obtained in accordance with the policy of the Committee on Clinical Investigation of the Albert Einstein College of Medicine. A single nurse practitioner administered the MMSE test (9) to all participants in the morning hours. Seven subjects were excluded because they were blind or deaf.

Venous blood was obtained from all subjects as described elsewhere (10) for plasma SMA-20 (including albumin and blood urea), total plasma triglycerides, HDL, low-density lipoprotein (LDL), and apolipoprotein A-I (Apo A-I) concentrations. Biochemical tests were performed at the laboratories of Montefiore Medical Center-Moses Division.

Statistical analysis of the data was performed using PROC MIXED in SAS System Version 6.12 (SAS Institute, Cary, NC). Because the distribution of MMSE was not normal, we used a nonparametric test (Mann-Whitney test) for comparisons. The Bonferroni correction was applied for comparisons between three categories (plasma HDL tertiles). Pearson’s correlation coefficient was used to express the correlation between plasma HDL values and MMSE scores.

RESULTS

Characteristically, there are more female than male centenarians, as reflected in our population (2.81:1 female: male ratio). As is specifically seen at younger ages as well, women had higher plasma HDL levels than men in our study (plasma HDL levels 55.7 ± 1.8 for women and 50.0 ± 3.1 mg/dl for men), though in our sample, this difference was not statistically significant.

Plasma levels of HDL in centenarians correlated significantly with MMSE (r = .32; p < .0001). Figure 1 demonstrates the average MMSE scores in centenarians grouped according to HDL tertiles (74.9 ± 2.1, 50.6 ± 0.5, and 36.8 ± 1.0 mg/dl), and Table 1 depicts the decline of MMSE scores across the tertiles of HDL. p values refer to results of Bonferroni corrected t tests. Furthermore, we examined whether the subjects with the higher MMSE score (25–30) also have higher plasma HDL concentrations compared to the centenarians with a moderate MMSE score (<25). Indeed, a statistically significant difference was noted between plasma HDL concentrations between those groups, both in men and women (Table 2).

The association of MMSE and HDL levels was of equal strength in both men and women, as demonstrated by an analysis of covariance, including gender and gender-HDL interaction as covariates. Details are found in Table 3.

To control for possible confounding effects of plasma Apo A-I and triglyceride levels, we carried out multiple regression analysis of MMSE scores against plasma HDL concentrations plus these two covariates, the results of which appear in Table 4. The effects of Apo A-I and triglycerides were not significant, and HDL remained the only independent predictor of MMSE in this analysis.

To control for possible confounding effects of nutritional status or dehydration, we reasoned that a poor nutritional status would be associated with lower body mass index and lower LDL levels in the lower cognitive function group. As
obstructive pulmonary disease, cancer, and death in a 7-year follow-up of 65-year-old men and women, implicating plasma HDL in variety of age-related diseases.

Several lines of evidence suggest that decreased plasma HDL/Apo A-I levels are associated with a decline in cognitive function of demented patients. Initial reports from Japan suggested that low levels of Apo A-I and A-II are markedly decreased in Alzheimer’s disease (7) and senile dementia (8). This has been confirmed by Merched and colleagues (6) in a ~75-year-old population diagnosed as having Alzheimer’s disease. This study has shown that both Apo A-I and plasma HDL were significantly lower in the sick population. The positive relationship in our study between plasma HDL concentrations and the cognitive function implicates plasma HDL’s role not only in early-onset of Alzheimer’s disease, but also in protecting cognitive function with aging per se.

Interestingly, nearly 80% of centenarians are women (18), although in this study, we successfully recruited more men than their expected ratio in a centenarian population. While levels of plasma HDL tended to be lower in male than in female centenarians, the levels in men (~50 mg/dl) were relatively higher compared to the levels seen in younger men (~45 mg/dl) (19). This underscores the notion that lower average plasma HDL already places men at a longevity disadvantage, allowing fewer men than women to enter the centenarian stage. While the correlation of plasma HDL levels to the cognitive function in centenarians was also similar in both genders, it should be noted that relatively more men have reached excellent MMSE scores with lower plasma HDL levels.

It could be argued that lower cognitive function can lead to a decline in plasma HDL; however, it does not seem to be the case here. Decreased plasma HDL/Apo A-I can be seen in prolonged nutritional deprivation, as might happen in demented patients. In such a case, body mass index, as well as the levels of plasma LDL and plasma albumin, are also expected to be decreased, which was not the case here. While our population has a clinically insignificant increase in blood urea nitrogen (the upper limit of the laboratory normal), it was similar in all plasma HDL tertiles. These data support an independent effect of plasma HDL on cognitive function.

What are possible mechanisms by which plasma HDL/Apo A-I protects from the onset of dementia, as well as other age-related diseases? First, mounting evidence suggests that even in classical Alzheimer’s patients, vascular and endothelial functions are impaired, in a similar mechanism to that described for cardiovascular disease (20). Furthermore, plasma HDL has been shown to modulate pathways involved in thrombosis (21), oxidation (22), and inflammation (23). Finally, increasing levels of Apo A-I/plasma HDL induce the formation of Apo J complexes, which affect the blood–brain barrier transport, maintaining intact brain cell function (24).

This study demonstrates a significant role for lipid metabolism in preservation of cognitive function. Furthermore, implicating plasma HDL levels in the initial cognitive decline at the end of life may lead to the development of specific strategies to prevent this unfavorable condition.

Table 3. Analysis of Variance of MMSE Against HDL With Adjustment for Gender and Gender × HDL Interaction

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>Sum of Squares</th>
<th>F Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1</td>
<td>610.9716</td>
<td>4.43</td>
<td>.0372</td>
</tr>
<tr>
<td>HDL</td>
<td>1</td>
<td>1736.8783</td>
<td>12.59</td>
<td>.0005</td>
</tr>
<tr>
<td>Gender × HDL</td>
<td>1</td>
<td>9.1248</td>
<td>0.07</td>
<td>.7974</td>
</tr>
</tbody>
</table>

Note: MMSE = Mini-Mental State Examination; HDL = high-density lipoprotein.

Table 4. Multiple Regression of MMSE Against HDL, Apolipoprotein A-I, and Triglyceride Levels (R^2 = .12)

<table>
<thead>
<tr>
<th>Term</th>
<th>Coefficient</th>
<th>SE</th>
<th>t Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>8.28</td>
<td>7.08</td>
<td>1.17</td>
<td>.2453</td>
</tr>
<tr>
<td>HDL</td>
<td>0.223</td>
<td>0.11</td>
<td>1.99</td>
<td>.0489</td>
</tr>
<tr>
<td>Apo A-I</td>
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<td>0.06</td>
<td>-0.13</td>
<td>.8952</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.02</td>
<td>0.02</td>
<td>-0.95</td>
<td>.3424</td>
</tr>
</tbody>
</table>

Note: MMSE = Mini-Mental State Examination; HDL = high-density lipoprotein; Apo A-I = apolipoprotein A-I.

seen in Table 1, these measurements were not different among the groups. In addition, plasma albumin level did not appreciably differ among the tertiles of HDL (3.89 ± 0.48, 3.73 ± 0.46, and 3.73 ± 0.50 mg/dl). Furthermore, albumin level was not correlated with MMSE score. In addition, urea nitrogen, as a proxy measure of hydration status, was similar in all tertiles of HDL (25 ± 1, 28 ± 2, and 29 ± 2 mg/dl) and was not correlated with MMSE scores.

**DISCUSSION**

We have shown that plasma HDL levels were positively and significantly associated with high cognitive function (defined by MMSE) in centenarians (Table 1). Apo A-I is the main apolipoprotein constituent of HDL, while triglyceride levels are negatively correlated with plasma HDL levels. Thus, although plasma HDL exhibited the best statistical relationship to MMSE, we cannot rule out the possibility that either Apo A-I or triglycerides are the most biologically important determinants of cognitive function. These relationships between the metabolic characteristics and cognitive function were independent of gender or of other markers, indicating hydration or nutritional status.

The possibility that plasma HDL plays a role in longevity derives primarily from the knowledge of the relationship between certain diseases and plasma HDL. Most noted are studies over many years that have shown that high plasma HDL levels play a major role in prevention and protection against coronary heart disease (11–15). It is proposed that HDL’s antiatherogenic function is through reverse cholesterol transport, clearing cholesterol from the arteries to the liver for secretion through the biliary system. These result in decreased cholesterol content in arteries obtained from humans (16). Recently, Burke and colleagues (17) have demonstrated that a 2–3% increase in plasma HDL at basal is associated with decreased cardiovascular disease, chronic
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