Relationship of Serum Cholesterols and Vitamin E to Depressive Status in the Elderly

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Various relationships of serum cholesterols and \( \alpha \)-tocopherol in the blood to depressive status as assessed by a short version of the Geriatric Depression Score (GDS) were cross-sectionally and longitudinally investigated in the elderly using multivariate analysis. Subjects comprised 504 residents (195 men and 309 women) aged 65 years and over in a rural community. Neither cholesterols nor \( \alpha \)-tocopherol significantly related to depressive status in either sex, adjusted for age and educational attainment in cross-sectional analysis. However, both total cholesterol and \( \alpha \)-tocopherol at baseline significantly prevented a 4-year longitudinal progression of depressive status in men alone, adjusted for age, education, and the GDS score at baseline. LDL+VLDL cholesterol related in the same fashion as total cholesterol, whereas HDL cholesterol did not significantly relate to the progression of depressive status.

\[ J \text{ Epidemiol, 1999 ; 9 : 261-267.} \]

depressive status, community elders, serum cholesterols, alpha-tocopherol, longitudinal study

The relationship of low serum cholesterol to a death of violence has been observed in both observational and intervention studies \(^1,2\). Muldoon and his colleagues demonstrated that meta-analysis of six representative intervention trials for reducing coronary heart disease by lowering cholesterol resulted in an increase of overall mortality due to excess death from violence including suicide. Further, Morgan and his colleagues documented that low plasma cholesterol was associated with the prevalence of depressive status in the elderly and a linear inverse relationship between plasma cholesterol and the score of depression adjusted for age and other variables \(^3\). Mechanisms of low cholesterol upon violence including suicide and depressive status have been recently investigated \(^4-7\). However, there have been opposing views concerning the association between low cholesterol and depressive status \(^8\). Furthermore, what component of the various lipoprotein cholesterols plays what role has not yet been examined.

The association of nutritional status with mental health or functional capacity in the aging process has been recently raised \(^9\). High intakes or high levels in blood samples of antioxidants have been reported to have favorable effects on cognitive function. Vitamin E as one antioxidant is likely to slow progression of cognitive impairment \(^15\). However, the association between antioxidants and depressive status has not been addressed. Cognitive ability and depressive status are well associated, at least cross-sectionally, in the older population \(^9\). We felt it necessary to deal with vitamin E in the blood in relation to depressive status in a representative elderly sample. The present study investigated relationships of serum total, HDL, and LDL+VLDL cholesterols, and \( \alpha \)-tocopherol to development of depressive status on both cross-sectional and longitudinal basis in a representative sample of the community elderly.

MATERIALS AND METHODS

In 1991, Tokyo Metropolitan Institute of Gerontology launched a new longitudinal interdisciplinary study on aging (TMIG-LISA) which was designed to run until 2001. TMIG-LISA comprised disciplines of medical sciences, psychology,
For medical sciences, two study areas of different environments enrolled: one was Koganei City, a suburb of Tokyo, and another was Nangai Village, in Akita Prefecture, in the northeast of Japan. Since traits of study areas and sampling methods have been described elsewhere, only necessary points will be briefly described here. Subjects for the present study were the cohort investigated in Nangai Village. Baseline survey for TMIG-LISA project was undertaken in 1992. All residents aged 65 years or over living at home with the exception those with bedridden status were regarded as eligible. As shown in Table 1, 79.6% of eligible residents responded to the baseline survey. The survey consisted of medical examinations and interviews, and respondents underwent both or either of them. Follow-up surveys were carried out in 1994 and 1996. The present study dealt with longitudinal data set between the baseline and 1996. The response rate to the follow-up survey was sufficiently high, and the data of 504 subjects were used for the analysis of the present study because those with missing data were excluded (Table 1).

### MEASUREMENTS

The baseline survey of 1992, all eligible subjects were invited to undergo medical examinations, and interview surveys were undertaken by door-to-door method. In the follow-up survey in 1996, the same instruments and procedures as in the baseline survey were adopted with the exception that interview surveys were carried out on a different day from that of the medical examinations. Only in the case of disabled subjects who were not able to visit the allocated place, were home visits made by interviewers to administer the questionnaire.

In the baseline survey, Geriatric Depression Scale (GDS) was employed as one of the interview surveys; however, in the follow-up survey a short version of GDS was employed. Therefore, the data of the short version GDS were used in the present analysis. GDS has been validated in several populations over the last decade.

Educational attainment was inquired into as one of the interview surveys. As one of the medical examinations, casual blood samples were taken from cubital veins. Serum total cholesterol (TC) was measured by enzymic method, and high density lipoprotein cholesterol (HDL-C) was measured by enzymic method after precipitation of LDL+VLDL cholesterol with MgCl2 and dextran. α-tocopherol was measured by the method of high pressure liquid chromatography.

|               | 1992  | 1996 |
|---------------|-------|------|
|               | Men   | Women| Total |
| Eligible      | 377   | 563  | 940   |
| Respondents   | 300   | 448  | 748   |
| Response rate (%) | 79.6 | 79.6 | 79.6 |
| deceased      | 40    | 39   | 79    |
| in hospitals or institutions | 10   | 15   | 25    |
| move out of the village | 1    | 1    | 2     |
| long-term absence | 0    | 3    | 3     |
| refusal       | 1     | 0    | 0     |
| no. of subjects used for analysis | 195  | 309  | 504   |
ANALYTICAL METHODS

Cross-sectional and longitudinal analyses were performed in order to examine the relationship of serum cholesterols or \( \alpha \)-tocopherol to the score of the short version GDS using multiple regression analysis. For cross-sectional analysis, relationships of TC, HDL-C, or LDL+VLDL cholesterol to the score of the short version GDS at baseline was examined adjusted for age and education level. LDL+VLDL cholesterol was calculated by subtracting HDL-C from total cholesterol. Age and values of cholesterols were dealt with as continuous variables. Level of education was dichotomized into low and high: completing primary school or below was regarded as low, and the rest were regarded as high. The relationship of \( \alpha \)-tocopherol to GDS score at baseline was also analysed using the same procedure as for cholesterols.

For the dependent variable for longitudinal analysis, \( \Delta \)GDS was calculated for each subject by subtracting the score at baseline from that of 1996. \( \Delta \)GDS was compared according to tertile of TC and \( \alpha \)-tocopherol at baseline, adjusted for age, education, and GDS score at baseline. Also, multiple regression analysis was performed between \( \Delta \)GDS score and serum cholesterols or \( \alpha \)-tocopherol at baseline, adjusted for the above confounding variables.

RESULTS

Table 2 shows the distribution of variables at baseline in 1992. Both values of serum total cholesterol and \( \alpha \)-tocopherol were significantly higher in women than in men, whereas there was no significant sex difference in age, education level, or a short version GDS score. Correlation matrix of baseline variables and GDS score of 1996 is shown in Table 3. In both sexes, high correlations were found between serum total cholesterol and \( \alpha \)-tocopherol. Correlation of GDS score between baseline and 1996 was significant, but not markedly high either in men or women. Table 4 indicates 4-year longitudinal changes of GDS and the values of differences between 1992 and 1996(\( \Delta \)GDS) as dealt with for the dependent variables of the present study. \( \Delta \)GDS shows no significant difference between men and women. In cross-sectional multiple regression analysis among baseline variables, neither serum total cholesterol nor \( \alpha \)-tocopherol significantly related to GDS

| Table 2. Distribution of variables at baseline in 1992. |
|---------------------------------|------------------|------------------|
|                                | Men (n=195)      | Women (n=309)    |
| Age (year)                     | 70.7 ±4.7        | 71.5 ±4.9        |
| Education low                  | 174 (89.2%)      | 285 (92.2%)      |
| high                           | 21 (10.8%)       | 24 ( 7.8%)       |
| GDS score (max=15)             | 2.98±2.41        | 3.35±2.31        |
| Serum total cholesterol (mmol/l)| 4.56±0.85        | 5.15±0.84**      |
| \( \alpha \)-tocopherol (\( \mu \)mol/l) | 16.71±5.57      | 19.03±6.49**     |

** sex difference \( p<0.01 \)

**=p<0.1 *p<0.05 **=p<0.01

| Table 3. Correlation matrix of variables. |
|-------------------------------------------|------------------|------------------|
|                                           | Men (n=195)      | Women (n=309)    |
| Age (1992)                                | .021             | .192**           |
| Education (1992)                          | .003             | -.125^           |
| GDS (1992)                                | .029             | -.366**          |
| GDS (1996)                                | .129*            | -.194**          |
| Serum total cholesterol                   | .011             | -.034            |
| \( \alpha \)-tocopherol                   | -.013            | .455**           |

Women (n=309)
score in either sex. Longitudinal relationships of TC and α-tocopherol at baseline to ΔGDS (GDS score of 1996 - GDS score of 1992) are shown in Table 5 and 6, respectively. The relationship of TC was inverse in both sexes and significant in men (Table 5). This implies that the higher TC was at baseline, the less GDS score longitudinally rose. Although it is not diagrammed, the relationship of HDL cholesterol at baseline was different from that of LDL+VLDL cholesterol when each was entered into the model in place of TC. LDL+VLDL cholesterol had a significantly inverse relationship to ΔGDS; however, the relationship of HDL cholesterol did not reach significant level. As shown in Table 6, the inverse relationship of α-tocopherol at baseline to ΔGDS reached significant level in men alone as observed in the relation of TC (Table 5). Thus, both serum cholesterols and α-tocopherol had preventive effects on progression of depressive status in the male elderly.

### DISCUSSION

Morgan and his colleagues demonstrated an association of depressive status with low serum cholesterol in older people.

Table 4. Longitudinal changes of GDS score between baseline in 1992 and the follow-up in 1996 (Mean±SD).

|          | 1992     | 1996     | ΔGDS      |
|----------|----------|----------|-----------|
|          | (values in 1996 - values in 1992) |          |           |
| Men(n=195)| 2.95±2.41 | 3.33±2.70 | 3.35±2.89 |
| Women(n=309)| 3.35±2.31 | 4.04±2.98** | 0.70±3.18 |

**longitudinal change p<0.01

Table 5. Relationship of serum total cholesterol (TC) at baseline in 1992 to the longitudinal change in GDS score (ΔGDS), adjusted for age, education, and GDS score at baseline.

|          | ΔGDS       | β       |
|----------|------------|---------|
|          | adjusted mean±SE |         |
| Men (n=195) | 1st tertile | 0.64±0.32 | -0.157* |
|   | 2nd tertile | 0.64±0.31 |         |
|   | 3rd tertile | -0.21±0.31 |         |
| Women (n=309) | 1st tertile | 0.75±0.28 |         |
|   | 2nd tertile | 0.94±0.28 | -0.036 |
|   | 3rd tertile | 0.40±0.28 |         |

TC (mmol/l) tertile: < 4.11, 4.11 ≤< 4.92, 4.92 ≤< 5.53, 5.53 ≤in Men,
< 4.79, 4.79 << 5.39, 5.39 << 5.71, 5.71 <in Women
*p<0.05

Table 6. Relationship of α-tocopherol at baseline to the longitudinal change in GDS (ΔGDS), adjusted for age, education, and GDS score at baseline.

|          | ΔGDS       | β       |
|----------|------------|---------|
|          | adjusted mean±SE |         |
| Men (n=195) | 1st tertile | 0.72±0.32 | -0.193** |
|   | 2nd tertile | 0.36±0.32 |         |
|   | 3rd tertile | -0.001±0.31 |         |
| α-tocopherol at baseline |
| Women (n=309) | 1st tertile | 0.75±0.29 |         |
|   | 2nd tertile | 0.85±0.28 | -0.060 |
|   | 3rd tertile | 0.49±0.28 |         |

α-tocopherol (μmol/l) tertile: < 13.69, 13.69 ≤< 17.87, 17.87 ≤in Men,
< 16.01, 16.01 ≤< 20.19, 20.19 ≤in Women

**p<0.1
however MacCallum and his colleagues did not find that association. Thus, there has been disagreement in terms of the linkage between serum cholesterol and depressive status in epidemiological observations of the community elderly. The present study yielded a predictive significance of low serum cholesterol for depressive status in the longitudinal observation in men alone. We found association neither of the cross-sectional observation in men or women, nor the longitudinal observation in women. First, we should note this sex difference observed in the present study. Although at present we cannot sufficiently elucidate the cause of this sex difference, it may be linked with a significantly lower level of serum cholesterol in men than in women (Table 2). Morgan and his colleagues enrolled men alone for study subjects, while MacCallum and his colleagues analysed the data of men and women combined by entering sex for an independent variable. This difference in the sampling nature and method of analysis between the two preceding studies may have brought about the difference in findings regarding the linkage between serum cholesterol and depressive status. When dealing with significantly different biological data between sexes, analysis should be separately performed for each sex.

We should also note that the data obtained by MacCallum and his colleagues was on the basis of a cross-sectional observation. The association is likely to be more prominent in a longitudinal observation than in a cross-sectional observation as recognized in the present study. Strandbeg and his colleagues reported different results from the present study showing that low HDL cholesterol and high triglyceride related to depressive status at baseline. To the contrary, in a longitudinal observation of men, HDL cholesterol inversely related, and triglyceride directly related to progression of depressive status.

Despite the small number of epidemiological studies and the existing disagreement among them, research into the mechanism between low serum cholesterol and depressive status has progressed. Engelberg hypothesized that reduction in serum cholesterol may decrease brain-cell membrane cholesterol, lower lipid microviscosity, and decrease the exposure of protein serotonin receptors on the membrane surface, resulting in a poorer uptake of serotonin from the blood and less serotonin entry into brain cells.

Also clinically, drugs that selectively increase serotonin neurotransmission proved to be effective antidepressants. Smith and his colleagues examined whether lowering brain serotonin activity by depletion of its amino acid precursor, triptophan, could provoke a short-term relapse of clinically significant symptoms in women vulnerable to major depressive disorder. They concluded that the lowering brain serotonin function could precipitate clinical depressive symptoms. On the other hand, Penttininen proposed a new hypothesis in terms of the mechanism of depression. He postulated a common cause between atherosclerosis and depression, because death from coronary heart disease is likely to correlate with suicide. He hypothesized that oxidized low density lipoprotein activates a cell-mediated immune reaction, resulting in the production of interleukin-2. Interleukin-2 causes a decrease of serum cholesterol, especially HDL cholesterol, and an increase of serum triglycerides. It causes a suicidal tendency through the suppression of melatonin. His idea is of great interest. However, the favorable effect of HDL cholesterol on the progress of depressive status was not longitudinally shown in either study by Strandberg and his colleagues or us; rather high HDL cholesterol was likely to be deleterious in the former study.

Depressive status is significantly linked with low functional capacity. Further, functional capacity is also associated with low serum cholesterol. Snowdon and his colleagues found that reduced functional capacity as assessed by basic activities of daily living was significantly associated with low lycopene and low LDL cholesterol, the predominant carrier of lycopene, in the blood among old women. We found that a higher level of functional capacity as assessed by the TMIG Index of Competence was more likely to decline over time in the elderly with low serum total cholesterol. Serum cholesterol thus relates to mental health and competence in the elderly. Further investigation is warranted to document this and to look into the mechanisms behind it. Vitamin E in terms of both intake and levels in blood has been investigated in relation to cognitive functioning in the elderly. However, there has been little research available concerning association between vitamin E and depressive status. This is curious because cognitive function is strongly associated with depressive status, at least cross-sectionally. Therefore, the relationship between cognition and vitamin E should be adjusted for depressive status as a confounder. The lack of that adjustment may be due to the virtually rare availability of both measurements of cognition and depressive status. In the present study, dementia being clinically identified, no scale for assessing cognitive function was employed because of the limitation of time. The causal relationship between α-tocopherol and depressive status found in the present study may be confounded by cognitive function. Further investigation is necessary in order to clarify this. The literature has documented a positive association between malnutrition and a variety of cognitive and behavioral deficits across the life span. However, serum albumin did not predict depressive status in the present subjects as far as the cross-sectional data were concerned. Relevant nutritional factors relating to mental health may differ according to socio-demographic and nutritional backgrounds of subjects investigated.

ACKNOWLEDGMENTS

The present study was done as part of a research project "Tokyo Metropolitan Institute of Gerontology, Longitudinal Interdisciplinary Study on Aging, TMIG-LISA." The authors
are grateful to the collaboration of participants in this project.

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