Relationship Between Plasma Glutathione Levels and Cardiovascular Disease in a Defined Population

The Hisayama Study

Haruki Shimizu, MD; Yutaka Kiyohara, MD; Isao Kato, MD; Takanari Kitazono, MD; Yumihiro Tanizaki, MD; Michiaki Kubo, MD; Hirofumi Ueno; Setsuro Ibayashi, MD; Masatoshi Fujishima, MD; Mitsuo Iida, MD

Background and Purpose—Glutathione (GSH) appears to have marked antioxidant activities and therefore may prevent cardiovascular disease (CVD). However, there are very few reports on this subject. In a community-based case–control study, we tested the hypothesis that low levels of plasma GSH are closely associated with CVD and its clinical types.

Methods—The association between fasting plasma total GSH (tGSH) levels and CVD were assessed using conditional logistic regression analysis among 134 CVD cases and 435 age- and sex-matched healthy control subjects.

Results—Mean tGSH concentrations were lower in all CVD cases than in the control subjects (3.06 versus 3.71 \(\mu\)mol/L; \(P=0.0001\)). Among the CVD types, both the cerebral infarction cases (2.98 versus 3.59 \(\mu\)mol/L; \(P=0.001\)) and cerebral hemorrhage cases (2.51 versus 3.43 \(\mu\)mol/L; \(P=0.0027\)) had significantly lower tGSH levels than the corresponding control groups had. The same tendency was observed for cases of subarachnoid hemorrhage (3.45 versus 3.83 \(\mu\)mol/L; \(P=0.36\)) and myocardial infarction (3.65 versus 3.77 \(\mu\)mol/L; \(P=0.69\)), but these differences were not statistically significant. After adjustment for other confounding factors, the risk of CVD was significantly lower in the third (adjusted odds ratio, 0.40; 95% CI, 0.21 to 0.77) and the fourth quartiles (adjusted odds ratio, 0.25; 95% CI, 0.12 to 0.51) than in the first. This association was most prominent in patients with lacunar infarction or cerebral hemorrhage.

Conclusions—These findings suggest that reduced plasma tGSH levels are a risk factor for CVD, especially for cerebral small vessel disease. (Stroke. 2004;35:2072-2077.)

Key Words: cardiovascular diseases ■ cerebral hemorrhage ■ lacunar infarction ■ risk factors

Oxidative stress appears to play a major role in the development of cardiovascular disease (CVD).\(^1\) Several endogenous substances, including homocysteine, which may be involved in the production of oxygen radicals in vessel walls, are reported to promote atherosclerotic disease by causing oxidative vascular injury.\(^2\) Conversely, antioxidants such as vitamin C, vitamin E, and carotene may have protective effects against the development of CVD.\(^3\)

Glutathione (GSH), a sulfhydryl (SH)-containing tripeptide, has several major physiological functions: it maintains SH groups of proteins in a reduced state, participates in amino acid transport, detoxifies foreign compounds, enzymatically degenerates endogenous peroxides, forms bioactive molecules, and acts as a coenzyme in several enzymatic reactions.\(^2\) GSH has also been demonstrated to play a role in detoxifying oxygen radicals and therefore may prevent cellular damage from oxidative stress.\(^2\) Several clinical case–control studies have shown that patients under chronic disease states such as heart disease,\(^4\) arthritis,\(^4,5\) diabetes,\(^4,5\) and malignancies\(^6\) have lower plasma levels of GSH than control subjects, suggesting that GSH has a protective role against such diseases. As for CVD, only a few studies have associated GSH levels in plasma or red blood cells with coronary heart disease.\(^7,8\) Thus far, no study has shown an association with stroke.

Since 1961, we have been performing a cohort study of CVD in the town of Hisayama, a suburban community of \(\approx7500\) residents on Kyushu Island in Japan. The present report describes this population-based retrospective case–control study, which was designed to investigate the relationship between plasma total GSH (tGSH) levels and clinical types of CVD (namely, type-specific stroke and myocardial infarction) in the community of Hisayama.

Subjects and Methods

Patients and Control Subjects

Throughout the course of the Hisayama study, information concerning newly developed cases of CVD among residents was collected through weekly visits to local practitioners and major hospitals in

Received February 5, 2004; final revision received June 4, 2004; accepted June 22, 2004.

From the Department of Medicine and Clinical Science (H.S., Y.K., I.K., T.K., Y.T., M.K., S.I., M.F., M.I.), Graduate School of Medical Sciences, Kyushu University, Fukuoka City, Japan; and the Saga Research Institute of Ohtsuka Pharmaceutical Co, Ltd (H.U.), Saga, Japan.

Correspondence to Dr Haruki Shimizu, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka City, 812-8582 Japan. E-mail haru-sz@d7.dion.ne.jp

© 2004 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000138022.86509.2d

2072
and around town. Regular health checks were performed biennially to residents aged 40 years or older to obtain information about any new cardiovascular events missed by the monitoring network. Whenever a new cardiovascular event was suspected, one of the study physicians neurologically and physically examined the subject (ultimately including the majority of subjects) and collected clinical information, including that regarding the course of the disease, as soon as possible.

Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours and was classified as cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, or an undetermined type. Morphological examinations by several imaging techniques or autopsy, or both, were performed on almost all stroke cases encountered. Cerebral infarction was further subdivided into 4 clinical categories: lacunar infarction, atherothrombotic infarction, cardioembolic infarction, and undetermined subtypes, according to the criteria established previously and described in detail elsewhere.

Diagnosis of myocardial infarction was based on detailed clinical information and at least one of the following findings: electrocardiographic evidence of myocardial infarction; elevated cardiac enzymes; or a morphological finding including echocardiographic, scintigraphic, and angiographic abnormalities compatible with myocardial injury. From June to October 1996, we enrolled all of the town’s prevalent cases of CVD, for a preliminary total of 176 patients with a history of stroke or myocardial infarction. Excluding cases with severe disability or with undetermined stroke type, a total of 134 cases (69 men and 65 women; mean age, 72.0 ± 4.6 years; range, 46 to 91 years) were eligible for the present study. The mean interval from the onset of CVD to blood sampling for plasma tGSH measurement was 7.5 years (range, 3 months to 30 years). The patient group included 75 cases of cerebral infarction, 28 cases of cerebral hemorrhage, 14 cases of subarachnoid hemorrhage, 21 cases of myocardial infarction, and 4 cases of simultaneous cerebral and myocardial infarctions. The 75 cerebral infarction cases were subdivided into 43 cases of lacunar infarction, 24 of atherothrombotic infarction, and 8 of cardioembolic infarction. As a control group, Hisayama residents who were healthy and free from both stroke and myocardial infarction, and who had participated in the 1996 health checkup, were randomly selected. For each CVD case, there were 1 to 5 sex- and age-matched (±2 years) controls. The control group consisted of 435 individuals (246 men and 189 women; mean age, 67.9 ± 2.4 years; range, 46 to 91 years).

**Laboratory Measurement**

During the screening period in 1996, blood samples were obtained from all cases and control subjects in an overnight fasting state. Plasma GSH and total homocysteine levels in the collected samples of CVD cases and controls were measured, using the high-performance liquid chromatography method described previously by Toyo’oka et al at the Saga Research Institute of Ohtsuka Pharmaceutical Co, Ltd, with no awareness of the case–control status or of clinical information. Plasma vitamin B12 concentrations were also determined using high-performance liquid chromatography with fluorescence detection. A chemiluminescent immunoassay was used to measure plasma folate and vitamin B12. Serum cholesterol levels were measured enzymatically, and total protein levels were determined by the Biuret method. Diabetes mellitus was determined by either a 75-g oral glucose tolerance test (the 1998 WHO criteria), casual blood glucose levels (>11.1 mmol/L), or a medical history of diabetes. Height and weight were measured in light clothes without shoes, and the body mass index (kg/m²) was calculated. Sitting blood pressure was measured 3 times on the right upper arm using a sphygmomanometer after a rest of at least 5 minutes. The average of the 3 measurements was used for the analysis. Hypertension was defined as a systolic blood pressure reading ≥ 140 mm Hg, a diastolic blood pressure reading ≥ 90 mm Hg, or the current use of antihypertensive drugs. Questions on personal smoking habits and alcohol consumption were asked, and the subjects were categorized as either current users or not.

**Statistical Analysis**

The mean age was compared using the Student t test, as was the frequency of male gender using the χ² test. Age- and sex-adjusted mean values of relevant factors were calculated using the covariance method. Differences in the parameters between CVD cases and controls were assessed by the Student t test, and trends in the parameters among the tGSH quartiles were assessed by multiple linear regression analysis. The age- and sex-adjusted frequencies were calculated by the direct method, then compared by the Cochran–Mantel–Haenszel χ² test using 10-year age groupings with the total subjects as a standard. The odds ratio (OR) and 95% CI of CVD and its clinical types were calculated by the distribution of tGSH tertiles or quartiles using conditional logistic regression analysis. A value of P < 0.05 was considered statistically significant.

**Ethical Considerations**

This study was conducted with the approval of the Human Ethics Review Committee of the Kyushu University Graduate School of Medical Sciences. Written informed consent for medical research was obtained from all participants.

**Results**

The clinical characteristics of CVD cases and control subjects are demonstrated in Table 1. Because there were fewer control subjects in the elderly than in the younger case–control sets, especially in the case of females, the mean age and proportion of women were higher in the CVD group than in the control group. Thus, comparisons for other variables were performed after adjusting for age and sex. Mean systolic blood pressure and the frequency of hypertension and diabetestes were significantly higher among CVD cases than among control subjects. CVD patients had lower body mass index, serum cholesterol, and total protein levels. Although the plasma folate concentration was the same between CVD patients and controls, the former presented lower plasma vitamin B12 and higher vitamin B12 levels than the latter. The mean total homocysteine levels were significantly higher in

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of the Study Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex, % male</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
<tr>
<td>Diabetes, %</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
</tr>
<tr>
<td>Total protein, g/L</td>
</tr>
<tr>
<td>Folate, mmol/L</td>
</tr>
<tr>
<td>Vitamin B12, nmol/L</td>
</tr>
<tr>
<td>Vitamin B12, pmol/L</td>
</tr>
<tr>
<td>Total homocysteine, μmol/L</td>
</tr>
<tr>
<td>Drinking, %</td>
</tr>
<tr>
<td>Smoking, %</td>
</tr>
</tbody>
</table>

All variables except for age and sex were adjusted for age and sex. Values are expressed as means ± SE (for age, SD) and percentages. *P<0.01, †P<0.05 vs controls.
The mean value or frequency of each relevant factor was then
significantly lower tGSH levels than those of the respective
types, cases of cerebral infarction or hemorrhage had signifi-
cantly decreased with elevating tGSH levels, whereas the frequency of
diabetes significantly decreased with elevating tGSH levels. Although the body mass index was the
same across tGSH levels, serum cholesterol levels signifi-
cantly decreased with elevating tGSH. Individuals who were
included in the first quartile of tGSH had low mean serum
total protein and vitamin B12 levels, whereas plasma folate and
vitamin B12 levels were the same across all tGSH levels.
There was no correlation between tGSH and total homocys-
teine levels. The frequency of alcohol consumption significa-
antly decreased with increasing tGSH levels, although no
such trend was seen in the frequency of smoking habits.

To further evaluate the association of CVD with tGSH
levels, crude and multivariate-adjusted ORs were calculated
by quartiles of tGSH levels (Table 4). Compared with the first
quartile, in the third and fourth quartiles the risk of CVD
decreased with elevating tGSH and was significantly lower in the
third (crude OR, 0.41; 95% CI, 0.23 to 0.72) and the fourth (crude OR, 0.24; 95% CI, 0.12 to 0.46) quartiles. A similar pattern was observed for cerebral infarction and
cerebral hemorrhage, but not for subarachnoid hemorrhage or
myocardial infarction. The magnitude of the effect of tGSH
on each type of CVD, except for cerebral hemorrhage in the
fourth quartile, was not found to be attenuated substantially
from quartile to quartile, even after adjustment for other
confounding factors such as systolic blood pressure, diabetes,
body mass index, cholesterol, total protein, folate, vitamin B12,
vitamin B12, total homocysteine, smoking habits, and alcohol
consumption.

### TABLE 2. Comparison of Age- and Sex-Adjusted Mean
Values±SE of Fasting Total Plasma Glutathione Concentrations
Between Cases With Cardiovascular Disease and Controls

<table>
<thead>
<tr>
<th>CVD Cases and Controls</th>
<th>Plasma Glutathione (µmol/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n=134)</td>
<td>3.06±0.12</td>
<td></td>
</tr>
<tr>
<td>Control (n=435)</td>
<td>3.71±0.06</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n=75)</td>
<td>2.98±0.16</td>
<td></td>
</tr>
<tr>
<td>Control (n=248)</td>
<td>3.59±0.08</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n=28)</td>
<td>2.51±0.27</td>
<td></td>
</tr>
<tr>
<td>Control (n=121)</td>
<td>3.43±0.13</td>
<td>0.0027</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n=67)</td>
<td>3.83±0.17</td>
<td>0.36</td>
</tr>
<tr>
<td>Control (n=67)</td>
<td>3.65±0.29</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case (n=21)</td>
<td>3.77±0.13</td>
<td>0.69</td>
</tr>
<tr>
<td>Control (n=95)</td>
<td>3.77±0.13</td>
<td></td>
</tr>
</tbody>
</table>

CVD cases than in the control subjects. Alcohol consumption
was significantly less frequent in CVD patients than in the
control subjects, whereas the frequency of smoking habits
was the same between the 2 groups.

The age- and sex-adjusted mean values of plasma tGSH
levels were significantly lower among CVD cases overall
than among the control subjects (Table 2). Among CVD
types, cases of cerebral infarction or hemorrhage had signifi-
cantly lower tGSH levels than those of the respective
responding control groups. A similar tendency was observed
in cases of subarachnoid hemorrhage or myocardial
infarction, although the differences were not statistically
significant.

CVD patients and control subjects were combined into 1
group, then divided into quartiles based on their tGSH levels.
The mean value or frequency of each relevant factor was then
compared among the 4 groups (Table 3). Individuals who
were included in the fourth quartile of tGSH were younger,
but the proportion of men did not differ among the quartiles.
The levels of systolic and diastolic blood pressures decreased
with increasing tGSH levels, whereas the frequency of
ehypertension did not significantly differ among the 4 groups.
The frequency of diabetes significantly decreased with elevating tGSH levels. Although the body mass index was the
same across tGSH levels, serum cholesterol levels signifi-
cantly decreased with elevating tGSH. Individuals who were
included in the first quartile of tGSH had low mean serum
total protein and vitamin B12 levels, whereas plasma folate and
vitamin B12 levels were the same across all tGSH levels.
There was no correlation between tGSH and total homocys-
teine levels. The frequency of alcohol consumption significa-
antly decreased with increasing tGSH levels, although no
such trend was seen in the frequency of smoking habits.

To further evaluate the association of CVD with tGSH
levels, crude and multivariate-adjusted ORs were calculated
by quartiles of tGSH levels (Table 4). Compared with the first
quartile, in the third and fourth quartiles the risk of CVD
decreased with elevating tGSH and was significantly lower in the
third (crude OR, 0.41; 95% CI, 0.23 to 0.72) and the fourth (crude OR, 0.24; 95% CI, 0.12 to 0.46) quartiles. A similar pattern was observed for cerebral infarction and
cerebral hemorrhage, but not for subarachnoid hemorrhage or
myocardial infarction. The magnitude of the effect of tGSH
on each type of CVD, except for cerebral hemorrhage in the
fourth quartile, was not found to be attenuated substantially
from quartile to quartile, even after adjustment for other
confounding factors such as systolic blood pressure, diabetes,
body mass index, cholesterol, total protein, folate, vitamin B12,
vitamin B12, total homocysteine, smoking habits, and alcohol
consumption.

### TABLE 3. Age- and Sex-Adjusted Mean Values or Frequencies of Cardiovascular Risk Factors
According to Quartiles of Total Glutathione Levels

<table>
<thead>
<tr>
<th>Factors</th>
<th>&lt;2.53 (n=142)</th>
<th>2.53–3.41 (n=143)</th>
<th>3.41–4.4 (n=143)</th>
<th>&gt;4.4 (n=141)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70±9</td>
<td>69±9</td>
<td>70±9</td>
<td>67±9</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>61</td>
<td>52</td>
<td>53</td>
<td>56</td>
<td>0.39</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>142±2</td>
<td>141±2</td>
<td>135±2</td>
<td>133±2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78±1</td>
<td>79±1</td>
<td>77±1</td>
<td>74±1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>54</td>
<td>62</td>
<td>47</td>
<td>49</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>15</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.0±0.3</td>
<td>22.4±0.3</td>
<td>22.3±0.3</td>
<td>21.4±0.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.1±0.1</td>
<td>5.2±0.1</td>
<td>5.3±0.1</td>
<td>5.4±0.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Total protein, g/L</td>
<td>70±0.4</td>
<td>72±0.4</td>
<td>73±0.4</td>
<td>72±0.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>Folate, nmol/L</td>
<td>6.4±0.3</td>
<td>6.4±0.3</td>
<td>6.5±0.3</td>
<td>6.5±0.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Vitamin B12, nmol/L</td>
<td>68.2±2.2</td>
<td>74.1±2.2</td>
<td>92.9±2.2</td>
<td>82.3±2.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Vitamin B12, pmol/L</td>
<td>728±26</td>
<td>649±23</td>
<td>674±24</td>
<td>692±24</td>
<td>0.55</td>
</tr>
<tr>
<td>Total homocysteine, µmol/L</td>
<td>11.7±0.4</td>
<td>11.4±0.4</td>
<td>11.7±0.4</td>
<td>11.0±0.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Drinking, %</td>
<td>41</td>
<td>34</td>
<td>29</td>
<td>29</td>
<td>0.008</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>27</td>
<td>19</td>
<td>25</td>
<td>24</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Age and sex were not age- and sex-adjusted. Values are expressed as means±SE (for age, SD) and percentages.
We further divided the combined group of patients with cerebral infarction and the corresponding control subjects into tertiles by tGSH levels and estimated the OR of each subtype of cerebral infarction (Table 5). The risk of lacunar infarction was significantly lower in the second and third tertiles than in the first. In the case of atherothrombotic infarction or cardioembolic infarction, however, the risk decreased with elevating tGSH levels. However, these trends were not statistically significant. Because there were no cases of cardioembolic infarction in the second tertile, we could not estimate OR for this tGSH level.

**Discussion**

The major new finding of the present study is that CVD cases had much lower levels of plasma tGSH than control subjects did. The risk of CVD continuously decreased with increasing

### TABLE 4. Crude and Adjusted Odds Ratios of Cardiovascular Disease and its Types in Each Quartile of Total Glutathione Distribution

<table>
<thead>
<tr>
<th>Subtype of Cerebral Infarction</th>
<th>Quartiles of Glutathione (µmol/L)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>&lt;2.53 (95% CI)</td>
<td>1.0 (0.54)</td>
<td>0.41 (0.23–0.72)</td>
<td>0.24 (0.12–0.46)</td>
</tr>
<tr>
<td></td>
<td>2.53–3.41 (95% CI)</td>
<td>1.0 (0.57)</td>
<td>0.41 (0.21–0.77)</td>
<td>0.25 (0.12–0.51)</td>
</tr>
<tr>
<td></td>
<td>3.41–4.4 (95% CI)</td>
<td>1.0 (0.55)</td>
<td>0.29 (0.12–0.69)</td>
<td>0.19 (0.07–0.52)</td>
</tr>
<tr>
<td></td>
<td>≥4.4 (95% CI)</td>
<td>1.0 (0.59)</td>
<td>0.22 (0.15–0.32)</td>
<td></td>
</tr>
</tbody>
</table>

**OR indicates odds ratio.**

*Adjusted for age, sex, systolic blood pressure, diabetes, body mass index, cholesterol, total protein, folate, vitamin B₆, vitamin B₁₂, total homocysteine, smoking, and drinking.

### TABLE 5. Crude and Adjusted Odds Ratios of Subtypes of Cerebral Infarction in Each Tertile of Total Glutathione Distribution

<table>
<thead>
<tr>
<th>Subtype of Cerebral Infarction</th>
<th>Tertile of Glutathione (µmol/L)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar infarction</td>
<td>&lt;2.9 (95% CI)</td>
<td>1.0 (0.35)</td>
<td>0.33 (0.14–0.76)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>2.9–4.1 (95% CI)</td>
<td>1.0 (0.22)</td>
<td>0.23 (0.09–0.65)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>≥4.1 (95% CI)</td>
<td>1.0 (0.49)</td>
<td>0.46 (0.15–1.38)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
</tbody>
</table>

**OR indicates odds ratio; NA, not available.**

*Adjusted for age, sex, systolic blood pressure, diabetes, body mass index, cholesterol, total protein, folate, vitamin B₆, vitamin B₁₂, total homocysteine, smoking, and drinking.
tGSH levels and was not attenuated even after adjustment for other confounding factors. Thus, the reduced level of plasma tGSH may be an independent risk factor for the development of CVD.

Among the clinical types of CVD, the risk of lacunar infarction and cerebral hemorrhage significantly decreased with elevating tertiles of tGSH. A similar tendency was observed for atherothrombotic, cardioembolic, and myocardial infarctions, although for these groups the difference was not statistically significant. It is well-known that arteriosclerotic lesions of the perforating intracerebral arteries induced mainly by chronic arterial hypertension contribute to the development of lacunar infarction and cerebral hemorrhage. However, both atherothrombotic infarction and myocardial infarction are the consequences of atherosclerosis of large cerebral and coronary arteries, and rupture of an intracranial saccular aneurysm is the most common cause of subarachnoid hemorrhage. γ-glutamyl transpeptidase, produced in the first step of the breakdown of GSH, is contained in larger quantities with much higher enzyme activity in the endothelium of capillaries than in that of larger vessels in the brain. This suggests that the concentration of GSH in the brain is apt to decrease more in capillaries than in large arteries; consequently, cerebral small arteries may be more sensitive to fluctuation in levels of plasma GSH. However, atherothrombotic and myocardial infarctions are associated with major risk factors—such as hypertension, diabetes, and smoking—that carry greater exposure to oxidative stresses and therefore may be associated with tGSH deficiency. In addition, the sample size of atherothrombotic, cardioembolic, and myocardial infarction was insufficient to draw a conclusion. Thus, our findings imply that plasma tGSH offers a strong defense mechanism at least against arteriosclerosis of small cerebral arteries, whereas its preventive effects on atherosclerosis of large vessels are inconclusive.

Several mechanisms by which GSH may prevent cerebrovascular damage have been suggested. Harlan et al showed that depletion of GSH by buthionine sulfoximine, an inhibitor of glutathione synthesis, augmented the endothelial damage caused by hydrogen peroxide released from activated neutrophils. Thus, GSH may have marked protective effects against oxidative damage by means of its direct antioxidative effects. GSH has been reported also to play a role in the maintenance of SH groups and other cellular antioxidants in a reduced state, thereby maintaining their antioxidative effects. In addition, Thomas et al showed that both GSH and GSH-dependent selenoperoxidase protect cells against the damage induced by oxidized low-density lipoprotein. Presumably, this protection may be the result of detoxification of lipid hydroperoxides and the reduced formation of free radical intermediates with greater reactivity.

Several limitations of our study should be discussed. The primary limitation is that our data were derived from a retrospective case–control study. Thus, we cannot exclude the possibility that decreased tGSH was a consequence of CVD or related conditions. Vegetarians were reported to have higher plasma levels of tGSH than nonvegetarians, and healthy men receiving ascorbic acid-deficient diets had lower plasma tGSH levels than control subjects. Thus, it is possible that changes in lifestyle after CVD onset, such as decreased dietary intake of vegetables and vitamins, may be related to or contribute to the decreased plasma tGSH levels in our patients. We did not examine dietary intake in this case–control study. However, the plasma concentrations of vitamin B12 and folate in our CVD patients were higher than or approximately equal to those of the controls, suggesting that the CVD patients did not have vitamin-deficient diets. The secondary limitation is that our study lacked information on drug use, which could affect plasma tGSH levels. Although the effects of drug use on tGSH levels have been scarcely studied, it has been reported that antihypertensive agents, long-acting nitrates, and aspirin, which are frequently used in CVD patients, did not affect plasma tGSH levels. Thus, a bias from this source is unlikely. The third limitation is that our sample size of CVD patients is relatively small for subtype analysis, especially for myocardial infarction and the subtypes of stroke. Further study with a larger sample size is needed to establish more definitive conclusions.

In conclusion, a reduced level of tGSH may be an important risk factor for the development of CVD, and especially of lacunar infarction and cerebral hemorrhage. There is evidence that orally administered GSH increases its plasma concentrations in animals and humans. Thus, it is anticipated that oral administration of GSH is a possible therapeutic strategy for the prevention of CVD, although further studies, including randomized, double-blind, and placebo-controlled trials, are essential to confirm the preventive effects of GSH against CVD.

Acknowledgments

The authors thank the residents of Hisayama Town, for their participation in the survey, and the staff of the Division of Health and Welfare of Hisayama Town, for their cooperation in this study. This study was supported in part by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

References


Relationship Between Plasma Glutathione Levels and Cardiovascular Disease in a Defined Population: The Hisayama Study
Haruki Shimizu, Yutaka Kiyohara, Isao Kato, Takanari Kitazono, Yumihiro Tanizaki, Michiaki Kubo, Hirofumi Ueno, Setsuro Ibayashi, Masatoshi Fujishima and Mitsuo Iida

Stroke. 2004;35:2072-2077; originally published online July 15, 2004;
doi: 10.1161/01.STR.0000138022.86509.2d
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/9/2072

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/