PLASMA LEVELS OF THIOBARBITURIC ACID REACTIVE SUBSTANCES (TBARS) OF THE EMPLOYEE WITH TYPE 2 DIABETES MELLITUS WITH MULTIPLE LACUNAR LESIONS

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Summary

The multiple lacunar lesion is one of the most common atherosclerotic vasculopathy in diabetics. However, the increased incidence of multiple lacunar lesions experienced by diabetics is not fully explained by conventional risk factors for atherosclerosis. To determine if serum lipid peroxide levels are relevant to these observations, levels of thiobarbituric acid reactive substances (TBARS), an accepted index of intravascular free radicals, were measured in 335 type 2 diabetics in the employee who received screening examination by magnetic resonance imaging (MRI) (excluding patients with symptomatic cerebral infarction, intracranial hemorrhage, recent brain trauma or known demyelinating disease). Of these diabetics, 136 patients had multiple lacunar lesions, and 199 patients had no these lesions. The TBARS levels of the patients with multiple lacunar lesions were significantly higher than those without the lesions (4.0 ± 1.4 vs 3.5 ± 1.0 µmol/ml, p<0.001). When serum TBARS levels (nmol/dl) were corrected to an arbitrary reference level of 100 mg/dl for serum lipid and lipoprotein, TBARS: total-cholesterol (p<0.01), TBARS: LDL-cholesterol (p<0.01), TBARS: HDL-cholesterol (p<0.01), TBARS: apoB (p<0.01), TBARS: apoAI (p<0.01) ratios were higher in diabetics with multiple lacunar lesions than in those without these lesions (Table 3).

Multivariate regression analysis of continuous variables showed that serum TBARS levels were closely and independently associated with serum triglyceride (F-value=52.1, P=0.0001). Hemoglobin A1c, smoking years, fasting blood glucose and insulin secretion after oral glucose load were not associated with lipid peroxide values.

In order to confirm the relationship between serum TBARS and serum lipids in diabetics with multiple lacunar lesions, the 56 diabetics with hyperlipidemia received 400 mg of slow-release bezafibrate (2-[4-2-(4-chlorobenzenamido) ethyl] phenoxy-2-methylpropionic acid) daily for four weeks. Serum TBARS levels, serum triglyceride levels, serum cholesterol levels tended to decrease significantly (p<0.0001). Overall the degree of the improvement of serum TBARS and serum triglyceride levels were significantly intercorrelated (r=0.449, p<0.001). These studies indicate that lipid peroxides may be important in the pathogenesis of the multiple lacunar lesions in diabetics and also suggest that the strict control of lipid levels has a beneficial effect in the lowering of the lipid peroxide levels in type 2 diabetics.

(Key words) Thiobarbituric acid reactive substances, Type 2 diabetes mellitus, Multiple lacunar lesions

Introduction

Membrane damage of endothelial cell is thought to be an early event leading to atherosclerosis and thrombosis and may be initiated by several factors including lipid peroxidation\(^5\). Reactive oxygen species such as hydrogen peroxide, superoxide and hydroxy radicals attack biomembrane, and induce peroxidation of lipids, leading to an increase in cell permeability and loss of endothelial integrity\(^6\). Our recent reports have shown an increased release of lipid peroxide from the erythrocyte membranes of diabetic patients during conditions of increased oxidative stress and a decreased erythrocyte content of reduced glutathione (GSH). The latter protects the cell against free radicals, hydrogen peroxide and organic peroxides and depressed GSH levels have been associated with enhanced lipid peroxidation.
peroxidation as a result of decreased scavenging of free radicals. Other previous reports have shown that increased levels of lipid peroxides (measured as thiobarbituric acid reactive substances (TBARS)) have been observed in the serum of diabetic subjects, especially in the presence of an atherosclerotic vascular disease. Some authors proposed the attractive hypothesis of a possible involvement of the oxidative stress in the development of atherosclerosis in the diabetes.

Recently new diagnostic devices such as magnetic resonance imaging (MRI) of the brain have become a recognized and increasingly popular diagnostic modality. Multiple lacunar lesions are frequently identified on MRI, and increase with advancing age and with risk factors for strokes. It has been suggested that multiple lacunar lesions especially in the cerebral white matter are important causes of stroke and dementia. However, predictive factors for such lesions have not been definitely established.

In the present study, we addressed the question of whether the serum TBARS level is useful as an indicator of multiple lacunar lesions in type 2 diabetes mellitus. Finally, we investigated the correlation between serum TBARS level and serum lipid levels.

Research design and methods

Clinical characteristics and laboratory data of subjects are shown in Table 1. We retrospectively evaluated 335 patients with type 2 diabetes mellitus in the employees who were seen in the Bibai Rosai Hospital from 1997 to 2000 and diagnosed as having multiple lacunar lesions from their clinical signs, symptoms and brain images. We excluded patients with recent brain trauma or known demyelinating disease. All patients received a neurological examination by the same neurologist on the same day as MRI examination. The ages ranged from 51 to 76 yr (mean ± SD, 63 ± 10yr). The duration of diabetes was ranked from 5 to 28 yr (mean ± SD, 13 ± 9). 75 were controlled with diet alone, 164 were controlled with oral hypoglycemic agents, and 96 were treated with insulin injection. None of them had hepatic or autoimmune disease. The duration of diabetes denotes from the patient was diagnosed as diabetes.

Magnetic resonance imaging was performed by using 1.5-T MR imaging system (Magnetom SP, Siemens-Asahi Medical, Japan). The imaging procedures were a T2-weighted spin-echo pulse sequence with TR=3500 ms, TE=93 ms and two acquisitions, and a T1-weighted gradient-echo pulse sequence with TR=640 ms, TE=15 ms, flip angle=70 degrees and two acquisitions. Transaxial planes parallel to the orbitomeatal line covering almost the entire brain were obtained with slice thickness of 5 mm. The lesions have increased multiple high intensity areas of the T2W1 coincided with the low intensity areas of the T1W1, and are identified by two investigators. These lesions were considered to be multiple lacunar lesions in this study.

Peripheral venous blood was collected after an overnight fast for measurement of concentration of serum blood glucose, serum total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, apolipoprotein Al (apoAI) and B (apoB), hemoglobin A1c (HbA1c), and TBARS. Samples for the TBARS assay were allowed to clot and separated within 1 hour and 1 ml of serum was treated with disodium EDTA, final concentrations 34 mmol l⁻¹, respectively and stored at −70°C for up to one week until analysed.

TBARS were estimated by a modification of Yagi’s fluorometric method. Serum was mixed with 1 ml 12N sulphuric acid in an Eppendorf tube and 0.5 ml 10% phosphotungstic acid added. After standing at room temperature for five minutes the mixture was centrifuged at 4000 rpm for five minutes. The supernatant was discarded and the sediment thoroughly mixed with 1 ml 12N sulphuric acid and the centrifugation was repeated. The sediment was then resuspended in fresh thiobarbituric acid reagent (1 ml of a solution of 0.67% acqueous thiobarbituric acid in 0.5 M trometamol (TRIS) buffer adjusted to pH 3.2–3.8 with glacial acetic acid); mixed thoroughly, and heated at 95°C for one hour in an boiled bath, cooled, and extracted with 4 ml n-butanol. After centrifugation at 2,000 x g for 20 minutes, supernatant was removed for fluorometric measurement (515 nm excitation, 553 nm emission) in a Perkin-Elmer luminescence spectometer. A standard was obtained by 0.5 nmol malondialdehyde bis (diethy lacetal) 98% (Sigma) with thiobarbituric acid reagent. All serum samples were assessed in duplicate. Serum concentration of TBARS being expressed in terms of malondialdehyde equivalents (µ mol/l). Fasting plasma glucose (FPG) was assayed enzymatically using an autoanalyzer (Glucose Auto and Stat, GA-1122, Kyoto Daiichi Kagaku, Co., Ltd. ). Serum HbA1c was determined using an autoanalyzer (HLC-723Gh, Tokyo Soda Manufacturing Co.,
Ltd.) coupled with high-performance liquid chromatography. Serum total cholesterol (TC) and triglyceride (TG) were determined enzymatically using an autoanalyzer (The Paralled, American Monitor Co., Ltd.). High density lipoprotein cholesterol (HDL-C) was measured using commercially available kit (HDL-C-2 DAIICHI, Daiichi Chemical Co., Ltdf.). Serum Apo AI, Apo B and apo E were determined using an autoanalyzer. The concentration of serum low density lipoprotein cholesterol (LDL-C) was estimated by the formula: LDL-C = TC-HDL-C-TG/5[17]. Response of insulin after a glucose challenge was analysed according to the criteria for the 75g oral glucose tolerance test (GTT) of the Japanese Diabetes Society. Body mass index was calculated as weight/height[kg/m²].

Blood pressure was measured with a standard clinical sphygmomanometer (cuff 25 × 12 cm). Data are presented as means ± SD. Statistical evaluation was performed by unpaired t test and by multiple regression analysis. Since there were no significant sex-or age-related differences in the clinical and biochemical data used in the present study, both male and female patients were treated as a single group.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics and laboratory data of diabetics with and without silent lacunar lesions</th>
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<tbody>
<tr>
<td></td>
<td>Total diabetic patients</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>335</td>
</tr>
<tr>
<td>M:F</td>
<td>146/189</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 10</td>
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<tr>
<td>Diabetic duration (years)</td>
<td>13 ± 9</td>
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<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>158 ± 54</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 ± 7.3</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>137 ± 4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 ± 5</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>241 ± 3.5</td>
</tr>
<tr>
<td>Ischemic heart disease (n)</td>
<td>49</td>
</tr>
<tr>
<td>Retinopathy (n)</td>
<td>102</td>
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<tr>
<td>Neuropathy (n)</td>
<td>59</td>
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<tr>
<td>Proteinuria (n)</td>
<td>123</td>
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<tr>
<td>Mode of therapy (n)</td>
<td></td>
</tr>
<tr>
<td>Diet alone</td>
<td>75</td>
</tr>
<tr>
<td>Oral hypoglycemic agent</td>
<td>164</td>
</tr>
<tr>
<td>Insulin</td>
<td>96</td>
</tr>
</tbody>
</table>

Values are means ± SD
HbA1c reference range 4.0-6.0%
*p<0.001 vs uncomplicated diabetic patients

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Serum lipid, apolipoprotein, thiobarbituric acid reactive substances</th>
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<tbody>
<tr>
<td></td>
<td>Diabetic patients</td>
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<tr>
<td></td>
<td>Uncomplicated</td>
</tr>
<tr>
<td>N</td>
<td>199</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>134 ± 20</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>212 ± 41</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>55 ± 16</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>131 ± 35</td>
</tr>
<tr>
<td>Apo AI (mg/dl)</td>
<td>134 ± 32</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>107 ± 30</td>
</tr>
<tr>
<td>Apo E (mg/dl)</td>
<td>6.6 ± 29</td>
</tr>
<tr>
<td>Apo B: APO AI</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>TBARS (nmol/ml)</td>
<td>3.5 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SD
Statistical significance was determined by unpaired t test
*p<0.05, **p<0.01, ***p<0.001 vs uncomplicated diabetic patients
Results

HbA1c, fasting blood glucose, body mass index, sex had no significant influence on TBARS concentrations. The median age and diabetic duration of patients with multiple lacunar lesion were higher than those without multiple lacunar lesions (67 ± 9 vs 61 ± 10 μmol/ml, p<0.001). Systolic blood pressure was significantly higher in diabetics with multiple lacunar lesions than those without the lesions (146 ± 5 vs 128 ± 4 mmHg, p<0.001) (Table 1). Serum TBARS levels were significantly higher in diabetics with multiple lacunar lesions than those without the lesions (4.0 ± 1.4 vs 3.5 ± 1.0 nmol/ml, p<0.001). Triglyceride (p<0.01), total cholesterol (p<0.05), and LDL-cholesterol (p<0.001), apoB (p<0.001) concentrations and apoB: apoAI ratio (p<0.001) were significantly higher and HDL cholesterol (p<0.01) were significantly lower in diabetics with multiple lacunar lesions than in those without these lesions (Table 2).
To exclude the potential influence of serum lipids on serum lipid peroxidation products, TBARS levels (nmol/dl) were corrected to an arbitrary reference level of 100 mg/dl for serum lipid and lipoprotein. The obtained TBARS: HDL-cholesterol (p<0.01), TBARS: LDL-cholesterol (p<0.01), TBARS: total-cholesterol (p<0.01) ratio were higher in diabetics with multiple lacunar lesions than in those without these lesions (p<0.01) (Table 3).

In the total 335 diabetic subjects, stepwise regression analysis of continuous variables with TBARS as dependent variable showed positive associations between TBARS and triglyceride (F=52.1, p=0.0001), total cholesterol (F=8.0, p=0.0002). Hemoglobin A1c, smoking years, fasting blood glucose and insulin secretion after oral glucose load were not associated with lipid peroxide values.

In order to confirm the relationship between serum TBARS levels and serum triglyceride levels, the 56 diabetics with hyperlipidemia received 400 mg of slow-release bezafibrate (2-[2-(4-chlorobenzamido) etyl] phenoxy-2-metylpropionic acid) daily for four weeks. Bezafibrate is a homologue of clofibrate that has been shown to reduce serum triglyceride levels and increase high density lipoprotein cholesterol levels in patients with various types of hyperlipidemia [188-20]. The levels of serum TBARS, serum triglyceride, serum cholesterol, serum LDL cholesterol, apoB, apoE and apoB: apoA ratio stended to decrease significantly (p<0.0001).

Overall the degree of the improvement of serum TBARS and serum triglyceride levels were significantly intercorrelated (r=0.449, p<0.001). Overall the degree of the improvement of serum TBARS and serum triglyceride levels were significantly intercorrelated (r=0.449, p<0.001) (Figure 1).

Table 5  Mean levels of thiobarbituric acid reactive substances, lipid, lipoprotein, and apolipoprotein concentrations in hyperlipidemic diabetics with multiple lacunar lesions before and after 4 weeks of bezafibrate administration.

<table>
<thead>
<tr>
<th></th>
<th>before treatment</th>
<th>during treatment</th>
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<tbody>
<tr>
<td>TBARS (nmol/ml)</td>
<td>4.1 ± 1.3</td>
<td>3.7 ± 1.0***</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>230 ± 39</td>
<td>202 ± 37***</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>52 ± 17</td>
<td>55 ± 16*</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>156 ± 46</td>
<td>150 ± 52.0***</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>139 ± 39</td>
<td>142 ± 40</td>
</tr>
<tr>
<td>Apo AI (mg/dl)</td>
<td>123 ± 35</td>
<td>103 ± 23***</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>8.1 ± 3.5</td>
<td>6.0 ± 1.3***</td>
</tr>
<tr>
<td>Apo B : Apo A ratio</td>
<td>0.9 ± 0.3</td>
<td>0.8 ± 0.3***</td>
</tr>
</tbody>
</table>

Abbreviations: Apo, apolipoproteins
Values are mean ± SD.
*p<0.01, **p<0.001, ***p<0.0001 vs serum levels before bezafibrate administration.

Fig. 1  Correlation between the degree of improvement in serum TBARS level and serum triglyceride level
Discussion

Estimation of lipid peroxidation is complicated by the large number of potential peroxidation products and by the reactivity of these metabolites. The most common technique for measuring lipid peroxide involves the use of thiobarbituric acid-reactive substances (TBARS) in serum. The assay has been discussed critically for lack of specificity and sensitivity, but many of these problems have been found to have inconsiderable effects when Yagi’s method is used\(^1\). Furthermore good correlation has been found between the results obtained by Yagi’s method and those determined with high performance liquid chromatography.

Increased levels of serum TBARS have been previously reported in patients with peripheral arterial disease, ischemic heart disease, hypertension, and diabetes mellitus\(^1\).\(^2\).

In the present study, we demonstrated elevated TBARS levels in the plasma of diabetic patients with multiple lacunar lesions, although these associations do not indicate whether the relationship is causal. It is suggested that serum TBARS level is one of the indicators of multiple lacunar lesions seen in diabetic patients.

In diabetic patients the effect of blood glucose control on lipid peroxide concentration is controversial\(^5\),\(^21\),\(^22\). The interaction between glycosylation and oxidative changes is unclear. Some studies have suggested that glycosylated proteins might themselves act as sources of free radicals, in which case a clear association between lipid peroxides and HbA1c might be expected\(^23\). High levels of serum TBARS have been found in patients with poor blood glucose control in one study, although no correlation between HbA1c and free radical activity was recorded in another. In the present study, there was no significant correlation between HbA1c and TBARS. In addition, there was no independent association between HbA1c and TBARS on multiple regression analysis. This may be influenced by the rapidly changing glucose levels in the diabetics, which are for the most part dependent on the time since their last insulin action. Longitudinal studies are necessary in order to evaluate clearly whether there is any genuine effect of blood glucose control on serum lipid peroxide levels in diabetes mellitus.

The relationship between lipids and TBARS concentrations still remains a matter of controversy. In the present study serum total cholesterol and triglyceride were significantly increased in the diabetics with multiple lacunar lesions as compared with those without the lesions (\(p<0.05\) and \(p<0.01\) respectively). However, when serum TBARS were adjusted to those of serum lipid fractions, the obtained ratios for both serum TBARS: total cholesterol resulted in still higher values in diabetics with multiple lacunar lesions than those without, thus indicating that the rise in serum TBARS in diabetic patients is not only the results of the hyperlipidemia, but may express the enhanced oxidative stress as a result of depressed scavenging for free radicals.

Vascular disease remains the most common cause of mortality and morbidity in diabetics\(^24\). Although the process leading to macroangiopathy in diabetes is poorly understood, it may be associated with increased free radical activity which produces atherosclerosis. Oxidized LDL-cholesterol has been involved in atherosclerosis by means of its cytotoxicity on endothelial cells, its enhanced uptake in macrophages through the scavenger LDL receptor, favouring the generation of foam cells, and by inducing adhesion of monocytes to the arterial intima, their differentiation into resident macrophages\(^25\),\(^26\). However, others believe that damage due to peroxidation occurs within the arterial wall and serum peroxides are not involved\(^27\).

In the present study, stepwise regression analysis suggested that serum TBARS concentrations were closely associated independently with triglyceride rather than total cholesterol. Serum triglyceride may be an important risk factor for atherosclerotic disease such as cerebrovascular disease. An increased rate of superoxide anion production in mononuclear cells has been demonstrated in patients with hypertriglyceridermia\(^28\). In turn, lipid peroxidase inhibits lipoprotein lipase activity and, thereby, serum triglyceride hydrolysis\(^29\). The positive correlation between serum triglycerides and TBARS values proved in this study might provide a pathogenic relationship between molecules containing both apoB and triglyceride and atherosclerosis. Increased unsaturation of triglyceride would also promote lipid peroxide formation, but it is unlikely that diabetes would have different levels of unsaturated lipids.

Serum lipid peroxide is involved in prostaglandin synthesis both stimulating cyclooxygenase in favor of thromboxane A\(\text{2}\) synthesis, and simultaneously inhibiting prostaglandin synthesis, thereby increasing platelet aggregability\(^30\),\(^31\). In addition, TBARS can decrease thrombin-neutralizing activity of antithrombin III which may contribute to
thrombotic events. Therefore, by these mechanisms, TBARS may affect as a potential vascular risk factor by the relation with a thrombotic tendency. Accelerated production of lipid peroxide, along with enhanced synthesis of thromboxane A2 synthesis, might promote the advance of diabetic vasculopathy. Although attention has focused on oxidized LDL-cholesterol, it is quite possible that oxidation of the proteins, especially very low density lipoprotein, may be of importance in silent lacunar lesions in diabetes.

To conclude, this study suggests that lipid peroxides (measured by thiobarbituric acid-reactive substances) are elevated in type 2 diabetics with multiple lacunar lesions, and related to the abnormal lipoprotein profile observed in subjects with the lesions. Further studies are planned to investigate the oxidation of these specific lipoprotein fractions and to determine if plasma lipid peroxidation correlates prospectively with cerebrovascular disease.

Reference

多発ラクナ脳梗塞を合併した2型糖尿病の勤労者における
血清チオバルビタール酸反応物質（TBARS）値の検討

藤原 豊
美眼労災病院内科

キーワード
チオバルビタール酸反応物質、2型糖尿病、多発ラクナ脳梗塞

多発ラクナ脳梗塞は糖尿病における代表的動脈硬化性
疾患の一つである。しかしながらその発症要因について、
既存の動脈硬化因子について十分解明されていないのが
現状である。そこで、MRIでスクリーニング検査をうけ
た勤労者335名を対象に、血管内の活性酸素のマーカー
とされる過酸化脂質を血清チオバルビタール酸
（TBARS）にて測定し、その発症との関連を検討した。
対象からの多発ラクナ脳梗塞、脳出血、脳変性疾患は除外
した。対象のうち136名は多発ラクナ脳梗塞を合併し、
199名は多発ラクナ脳梗塞を合併していなかった。
血清TBARS値は合併群では非合併群より有意に高かった
（4.0 ± 1.4 vs 3.5 ± 1.0 µmol/ml, p < 0.001)。血清
TBARS値を血清脂質およびリポ蛋白で補正したところ、
TBARS: total-cholesterol（p < 0.01）、TBARS: 
LDL-cholesterol（p < 0.01）、TBARS: HDL-cholesterol
(p < 0.01)、TBARS: apoB（p < 0.01）、TBARS: apoA1
(p < 0.01) ratioは多発ラクナ脳梗塞合併群で有意に高
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LDL-cholesterol（p < 0.01）、TBARS: HDL-cholesterol
(p < 0.01)、TBARS: apoB（p < 0.01）、TBARS: apoA1
(p < 0.01) ratioは多発ラクナ脳梗塞合併群で有意に高
かった。

値は血清中性脂肪の独立
した危険因子であった（F-value = 52.1, p = 0.0001)。
ヘモグロビンA1c、喫煙年数、空腹時血糖値、糖負荷後
のインスリン値は、血清TBARSと相関しなかった。
さらに、多発ラクナ脳梗塞を有する糖尿病における血
清TBARSと血清脂質との関連を検討するため、多発ラ
クナ脳梗塞合併症を有する56名を無作為に抽出し、脂
質降下剤であるslow-release bezafibrate (2-[4-2-(4-
chlorobenzamido)ethyl]phenoxy-2-methylpropionic acid)
400mgを4週間投与し、血清TBARS値と脂質パラメー
タの変動を検討した。血清TBARS、コレステロール、
中性脂肪は有意に低下した（p < 0.0001)。血清TBARS
値と血清中性脂肪は有意に相関した（r = 0.449, p <
0.001)。

これらの結果は多発ラクナ脳梗塞を合併した糖尿病に
おいいて過酸化脂質がその発症に関与していることを示唆
しており、過酸化脂質と関連する血清脂質の厳格な管理
の重要性を示している。