Intensive Lipid Lowering by Statin Therapy Does Not Improve Vasoreactivity in Patients With Type 2 Diabetes

Ronald W. van Etten, Eelco J.P. de Koning, Marina L. Honing, Erik S. Stroes, Carlo A. Gaillard, Ton J. Rabelink

Abstract—Cardiovascular disease is the most important cause of morbidity and mortality in patients with type 2 diabetes. Endothelial dysfunction predicts cardiovascular outcome. Type 2 diabetes is characterized by endothelial dysfunction, which may be caused by dyslipidemia. Statin therapy restores endothelial function in hyperlipidemic patients. Therefore, we hypothesize a beneficial effect of atorvastatin on NO-dependent vasodilation in patients with type 2 diabetes and mild dyslipidemia (low density lipoproteins >4.0 mmol/L and/or triglycerides >1.8 mmol/L). We evaluated the effect of intensive lipid lowering (4 weeks of 80 mg atorvastatin once daily) on vasoreactivity in 23 patients with type 2 diabetes by using venous occlusion plethysmography. Twenty-one control subjects were matched for age, sex, body mass index, blood pressure, and smoking habits. The ratio of blood flows in the infused (measurement [M]) and noninfused (control [C]) arm was calculated for each recording (M/C ratio), and M/C% indicates the percentage change from the baseline M/C ratio. Serotonin-induced NO-dependent vasodilation was significantly blunted (52±30 versus 102±66 M/C%, P<0.005), and nitroprusside-induced endothelium-independent vasodilation was modestly reduced (275±146 versus 391±203 M/C%, P<0.05) in patients with type 2 diabetes compared with control subjects. Despite significant reduction of total cholesterol, low density lipoproteins, and triglycerides (5.8±1.0 to 3.2±0.6 [P<0.0001], 4.1±1.1 to 1.8±0.7 [P<0.0001], and 2.2±1.3 to 1.4±0.5 [P<0.05] mmol/L, respectively), no effect on NO-dependent (59±44 M/C%) and endothelium-independent (292±202 M/C%) vasodilation was demonstrated. These data suggest that intensive lipid lowering by atorvastatin has no effect on NO availability in forearm resistance arteries in type 2 diabetic patients. Other factors, such as hyperglycemia, may be a more important contributing factor regarding impaired vasoreactivity in this patient group. (Arterioscler Thromb Vasc Biol. 2002;22:799-804.)

Key Words: plethysmography ■ nitric oxide ■ type 2 diabetes ■ dyslipidemia ■ atorvastatin

Type 2 diabetes is associated with high morbidity and mortality caused by the early development of atherosclerosis.1–3 Dyslipidemia is a characteristic feature of patients with type 2 diabetes and has been implicated in the pathogenesis of cardiovascular complications in these patients.4–7 Lipid-lowering therapy has been shown to be of major importance in reducing cardiovascular risk in diabetic patient groups.8,9 The endothelium has emerged as a first-line defense mechanism against atherosclerosis. It has been shown that endothelial dysfunction predicts outcome in cardiovascularly compromised patient groups.10–12 In type 2 diabetes, endothelial dysfunction is characterized by an impaired availability of NO,13–16 which may be caused by dyslipidemia.17–20 In addition, impaired endothelium-independent vasoreactivity has also been shown,14,15 suggesting impaired smooth muscle responsiveness to NO.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibition is an effective lipid-lowering therapy that restores endothelial dysfunction in patients with hyperlipidemia.21–23 Statins have been shown to upregulate endothelial NO synthase (eNOS) expression and activity independent of LDL levels,24–28 potentially augmenting the availability of NO. Therefore, we hypothesize a beneficial effect of intensive lipid-lowering therapy by atorvastatin on NO-dependent vasoreactivity in patients with type 2 diabetes and mild dyslipidemia.

Methods

Study Design
Patients with type 2 diabetes were treated with atorvastatin (80 mg once daily) for 4 weeks. Vasoreactivity was assessed 3 times in this group (at the initiation [week 0], after 4 weeks of atorvastatin treatment [week 4], and after stopping atorvastatin for 4 weeks) to demonstrate a potential reversibility of changes in vasoreactivity induced by statin therapy (week 8); this is considered an A-B-A scheme. Using this open-label prospective A-B-A design, a patient serves as his own control.
Vascular function in a nondiabetic, matched, control group was assessed once (1) to compare the vasoreactivity between diabetic and nondiabetic subjects and (2) to serve as a reference for the potential beneficial effect on vasoreactivity caused by the intervention.

Subjects

Twenty-five patients with type 2 diabetes and mild hyperlipidemia (LDL >4.0 mmol/L and/or triglycerides >1.8 mmol/L) and 21 control subjects matched for age, sex, body mass index, blood pressure, and smoking habits were recruited for the present study. Two patients were withdrawn from the study before the initiation of the vascular assessments (1 patient was lost to follow up, and 1 patient was withdrawn because of technical difficulties of cannulation of the brachial artery). Twenty-three patients began the study. The median duration of diabetes was 8 years (range 1 to 24 years). Diabetes was treated by insulin in 11 patients, by oral hypoglycemic drugs in 8 patients, and by insulin plus oral hypoglycemic drugs in 4 patients. Medical treatment was not changed throughout the study. None of the patients or control subjects had evidence of clinical macrovascular disease. Assessments were performed at least 4 weeks after the cessation of confounding vasoactive medication, such as lipid-lowering medication, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates, estrogens, NSAIDs, and vitamin supplementation.

One patient stopped after the first assessment and 1 patient stopped after the second assessment because of discomfort during the procedure. Twenty-one patients with type 2 diabetes and all matched control subjects completed the present study.

All subjects gave written informed consent. The local research ethics committee of the University Medical Center Utrecht approved the protocol. All studies were performed in accordance with local institutional guidelines in our Good Clinical Practice (GCP)-certified unit.

Forearm Plethysmography

All subjects abstained from alcohol, tobacco, and caffeine-containing drinks and fasted for at least 12 hours before the measurements were performed. Measurements were performed in a quiet room with a constant normal temperature (22°C to 24°C) and were begun at 10:00 AM. Forearm blood flow (FBF) was measured in both arms by venous occlusion mercury strain-gauge plethysmography (Hokanson EC-4) as described previously. A microcomputer-based R-wave–triggered system for online monitoring was used. Upper arm cuffs were inflated automatically to 40 mm Hg during a time interval of 4 heartbeats, 4 times a minute during the last 3 minutes of every measurement. Wrist cuffs were inflated to 200 mm Hg or at least 40 mm Hg above systolic blood pressure to exclude the hands from circulation. FBF measurements were recorded during the last 2-minute period of infusion of saline or drug, at 5-minute intervals. The brachial artery of the nondominant arm was cannulated with a 20-gauge, flexible, polyurethane catheter (Arrow Int Inc). Saline (0.9%, Baxter Healthcare Ltd) was infused for at least 45 minutes before intra-arterial administration of vasoactive drugs. All drugs were administered at a constant infusion rate of 90 mL/h. Serotonin (5-HT, Sigma Chemical Co) was infused into the brachial artery in increasing doses of 0, 0.6, 1.8, and 6.0 ng per 100 mL forearm volume per minute. This protocol has previously been shown to cause a dose-dependent increase in NO-dependent vasodilation. Sodium nitroprusside (Merck) was infused in increasing doses of 0, 6, 60, 180, and 600 ng per 100 mL forearm volume per minute to assess endothelium-independent vasodilation. Infusions of the 2 drugs were in random order. All infuses were prepared in a pharmacy in accordance with Good Manufactory Practice (GMP) guidelines.

Laboratory Assessments

Fasting plasma glucose (FPG), hemoglobin A1c, total cholesterol, HDL, LDL, triglycerides, apoA-I, and apoB were assessed at week 0 in control subjects and in patients with type 2 diabetes with the use of standard methods. FPG was measured at weeks 4 and 8, and lipids and lipoproteins were measured at weeks 2, 4, and 8 in patients with type 2 diabetes.

Statistical Analysis

The FBF recordings made in the first 30 seconds after wrist-cuff inflation were not used for analysis. Average values of the FBF of the measurement arm (cannulated) and control arm were obtained from the last 4 to 6 recordings of each measurement period. The ratio of blood flows in the infused (measurement [M]) and control ([C]) arm was calculated for each recording (M/C ratio). The average value of the M/C ratio was calculated from these 4 to 6 M/C ratios. This M/C ratio provides an internal control by excluding systemic factors for influencing the results. The results are expressed as M/C ratio and as percentage change from baseline M/C ratio (M/C%). Only the responses (M/C ratio and M/C%) to the maximal serotonin and nitroprusside infusions are mentioned in the text. Differences in forearm reactivity of diabetic patients and matched control subjects and the effects of atorvastatin treatment on forearm reactivity, with the use of M/C% values as parameters, were analyzed by repeated-measures ANOVA. When a significant difference was revealed by this analysis, comparisons at each drug infusion level were made by use of unpaired (patients versus control subjects) and paired (before versus after atorvastatin treatment) 2-tailed t tests. Group comparisons with respect to clinical characteristics and laboratory results were made by unpaired t tests. The effect of treatment on biochemical parameters was analyzed by paired t tests. In the case of nonnormal distribution, a Wilcoxon signed rank test or a Mann-Whitney rank sum test was used. Statistical significance was taken at the 5% level. Data from the group of patients with type 2 diabetes was analyzed according to the intention-to-treat principle. All results are expressed as mean±SD.

The present study was designed to detect an increase of M/C ratio of 0.4 at the highest dose of serotonin after statin therapy. We needed 20 subjects to show this difference with an α error of 0.05 (2-sided) and 80% power based on a standard deviation of 0.6 (M/C ratio) in our prior studies. Results

Subjects

Subject characteristics at week 0 are shown in Table 1. Baseline FBFs (alone and expressed as M/C ratios) were similar in patients and in control subjects. As expected, serum levels of FPG (P<0.0001), hemoglobin A1c (P<0.0001), total cholesterol (P<0.05), LDL (P<0.05), triglycerides (P<0.01), and apoB (P<0.0001) were significantly higher in diabetic patients. The level of HDL (P<0.01) was significantly lower in diabetic patients. ApoA-I levels were not significantly different in diabetic patients and control subjects.

All lipid parameters decreased significantly after 4 weeks of treatment with atorvastatin (Table 2). Total cholesterol was lowered by 45% (P<0.0001), LDL was lowered by 57% (P<0.0001), triglycerides were lowered by 40% (P<0.01), apoA-I was lowered by 25% (P<0.0001), and apoB was lowered by 45% (P<0.0001). Interestingly, HDL was also significantly lowered by 20% (P<0.01). Four weeks after the termination of atorvastatin treatment, lipid concentrations had returned to baseline values, although LDL and apoA-I were still significantly lower than the baseline values (Table 2). No effect on blood pressure by atorvastatin was found (data not shown).

Serotonin-Induced and Sodium Nitroprusside–Induced Vasodilation in Patients With Type 2 Diabetes and Matched Control Subjects

Serotonin-induced vasodilation was severely impaired in patients with type 2 diabetes compared with control subjects.
TABLE 1. Baseline Characteristics in Patients With Type 2 Diabetes and in Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>DM2</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>58±8</td>
<td>58±9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>8/15</td>
<td>7/14</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85±15</td>
<td>84±14</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30±5.1</td>
<td>28±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>151±2</td>
<td>145±19</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>90±8</td>
<td>90±10</td>
<td></td>
</tr>
<tr>
<td>Smokers, n</td>
<td>6 (26%)</td>
<td>4 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.8±1.0</td>
<td>4.9±1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>2.2±1.2</td>
<td>1.3±0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>4.1±1.2</td>
<td>3.2±0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.2±0.3</td>
<td>1.5±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ApoA-1, g/L</td>
<td>1.4±0.3</td>
<td>1.6±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>1.3±0.3</td>
<td>0.9±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinin, μmol/L</td>
<td>77±11</td>
<td>74±11</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.6±1.3</td>
<td>5.8±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>8.9±2.5</td>
<td>5.1±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline FBF, ml · 100 mL</td>
<td>3.4±1.2</td>
<td>2.7±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline M/C ratio</td>
<td>1.2±0.3</td>
<td>1.3±0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (percent).

(M/C ratio from 1.2±0.3 to 1.8±0.6 [increase 53±30 M/C%] versus M/C ratio from 1.3±0.4 to 2.5±0.8 [increase 102±66 M/C%], respectively; P<0.005; Figure 1). Nitroprusside-induced vasodilation was also reduced in diabetic patients compared with control subjects (M/C ratio from 1.2±0.4 to 4.3±2.1 [increase 275±146 M/C%] versus 1.3±0.4 to 5.9±2.2 [increase 391±203 M/C%], respectively; P<0.05; Figure 2).

Effect of Atorvastatin on Serotonin-Induced and Sodium Nitroprusside-Induced Vasodilation in Patients With Type 2 Diabetes

Atorvastatin had no effect on baseline M/C ratio in patients with type 2 diabetes (1.2±0.3 versus 1.1±0.3 M/C ratio for week 0 versus week 4, P=NS; Figure 1). Four weeks of atorvastatin treatment had no effect on NO-dependent vasodilation (M/C ratio from 1.2±0.3 to 1.8±0.6 [increase 53±30 M/C%] before treatment versus M/C ratio from 1.1±0.3 to 1.7±0.5 [increase 59±44 M/C%] after treatment, P=NS; Figure 1) or on endothelium-independent vasodilation (M/C ratio from 1.2±0.4 to 4.3±2.1 [increase 275±146 M/C%] before treatment versus M/C ratio from 1.2±0.4 to 4.2±1.9 [increase 292±202 M/C%] after treatment, P=NS; Figure 2).

At week 8, after atorvastatin was withheld for 4 weeks, NO-dependent vasodilation (M/C ratio from 1.1±0.2 to 1.6±0.4 [increase 46±28 M/C%]) and endothelium-independent vasodilation (M/C ratio from 1.1±0.2 to 3.5±1.5 [increase 213±113 M/C%]) were not significantly different from NO-dependent and endothelium-independent vasodilation at week 0 (Figures 1 and 2).

Discussion

The main outcome of the present study is that despite intensive lipid lowering, high-dose atorvastatin does not

TABLE 2. Lipids, Lipoproteins, and Glucose Levels in Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L</td>
<td>8.9±2.5</td>
<td>9.9±3.0</td>
<td>9.6±3.2</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.8±1.0</td>
<td>3.5±0.9‡</td>
<td>3.2±0.6‡</td>
<td>5.6±1.0</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>4.1±1.2</td>
<td>2.1±0.9‡</td>
<td>1.8±0.6‡</td>
<td>3.8±1.0*</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.2±0.3</td>
<td>1.1±0.3*</td>
<td>1.0±0.2†</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.2±1.2</td>
<td>1.4±0.7†</td>
<td>1.3±0.5§</td>
<td>2.3±1.2</td>
</tr>
<tr>
<td>ApoA-1, g/L</td>
<td>1.4±0.3</td>
<td>1.2±0.4</td>
<td>1.1±0.3§</td>
<td>1.2±0.3*</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>1.3±0.3</td>
<td>0.8±0.2‡</td>
<td>0.7±0.2‡</td>
<td>1.3±0.3</td>
</tr>
</tbody>
</table>

After 4 weeks of treatment with atorvastatin, all lipid and lipoprotein concentrations were significantly lower compared with week 0. After stopping the atorvastatin treatment for 4 weeks, lipid and lipoprotein concentrations returned to baseline at week 8. LDL and ApoA-1 still were significantly lower at week 8 compared with week 0.

*P<0.05, †P<0.01, ‡P<0.0001.
endothelial NO production, 42 and uncouples eNOS, which paired NO-dependent vasodilation in forearm resistance arteries. 

Figure 2. Change in M/C ratio after sodium nitroprusside-induced endothelium-independent vasodilation. Endothelium-independent vasodilation is modestly reduced in patients with type 2 diabetes (open square) compared with matched control subjects (open circle). *P<0.05. Atorvastatin has no effect on endothelium-independent vasodilation in patients with type 2 diabetes (solid square). 

improve NO-dependent vasodilation in patients with type 2 diabetes.

Consistent with most studies evaluating vascular reactivity in patients with type 2 diabetes, 13–16 we demonstrated impaired NO-dependent vasodilation in forearm resistance arteries. As demonstrated by others, 14,15 endothelium-independent vasodilation was also impaired in patients with type 2 diabetes. However, this impairment was modest compared with the disturbance in the NO-mediated vasoreactivity. It should be noted that the present data cannot determine whether the lack of improvement in vasoreactivity during atorvastatin therapy is due to a lack of restoration of endothelium-derived second-messenger signaling (such as NO) or due to a defect in smooth muscle responsiveness.

Patients with type 2 diabetes are almost inevitably characterized by the presence of concomitant cardiovascular risk factors, such as hypertension, dyslipidemia, hyperglycemia, and overweight, which may negatively affect vascular responses. The diabetic patients studied are representative of the general type 2 diabetic population with different treatment regimens. We simultaneously assessed vascular function in a control group matched for age, sex, body mass index, smoking habits, and blood pressure. This allowed us to exclude these matched concomitant cardiovascular risk factors as a major cause for the difference between diabetic and control subjects in the present study.

The patients in the present study showed diabetes-related dyslipidemia. Endothelial dysfunction, which is characterized by impaired NO availability, has been demonstrated in coronary and peripheral arteries in patients with hyperlipidemia. 21,34–36 Diabetic dyslipidemia and, more specifically, increased levels of (oxidized) LDL and, to a lesser degree, increased levels of triglycerides and decreased levels of HDL have been put forward as factors causing endothelial dysfunction in patients with type 2 diabetes. 17–20,37 LDL reduces the expression and activity of eNOS in human platelets 38 and endothelial cells. 24,39,40 enhances NO degradation, 41 reduces endothelial NO production, 42 and uncouples eNOS, which results in increased superoxide production. 43 Also, hypercholesterolemia, per se, increases vascular superoxide production, which can be normalized by cholesterol lowering in rabbits. 44,45

By reducing cholesterol and LDL, atorvastatin could have a beneficial effect on NO-dependent vasodilation in type 2 diabetes. Furthermore, atorvastatin metabolites have antioxidant properties, protecting lipids from oxidation. 46 By inhibiting the geranylgeranylation of Rho GTPase, 25 statins have been shown to upregulate the expression and function of eNOS in endothelial cells and platelets of humans and other species. 24–28 Despite a reduction in total LDL of almost 60%, we did not show a beneficial effect of atorvastatin on NO-dependent vasodilation in the present study. The patients served as their own controls in the study design that was used, ensuring similar patient characteristics at all assessments.

In addition to dyslipidemia, hyperglycemia was the other major difference between the diabetic patients and control subjects in the present study. Hyperglycemia causes increased formation of endothelial oxygen radicals 47 and eNOS dysfunction. 48 In forearm vascular studies, hyperglycemia, per se, induces endothelial dysfunction. 49,50 Therefore, it is likely that in the present study, hyperglycemia contributed to impaired vasoreactivity and blunted any potential beneficial effects of lipid lowering on NO-dependent vasodilation. In the present study, diabetes therapy was not modified, and glycemic control remained unchanged throughout the study, as measured by fasting glucose concentrations at test visits.

Impaired smooth muscle responsiveness could also be an explanation for our observations. No change in nitroprusside-induced vasodilation was observed in patients on and off therapy, suggesting no beneficial effects of atorvastatin on the vascular smooth muscle response to signaling by exogenous NO. Recently, we have shown that infusion of 5-methyltetrahydrofolate, the active form of folic acid, improves NO-mediated vasodilation, whereas endothelium-independent vasodilation is not affected by folic acid in this type 2 diabetic patients. 35 Because 5-methyltetrahydrofolate restores the function of eNOS, these data suggest that NO-dependent improvement in vasoreactivity can be achieved in our patient group. 51–53

In patients with type 2 diabetes, the use of a different technique to assess endothelial function (high resolution ultrasonography of the brachial artery during ischemia-induced hyperemia) produced conflicting results for lipid-lowering therapy by statins. 54,55 Tsunekawa et al 54 reported that cerivastatin improved flow-mediated vasodilation in elderly subjects with type 2 diabetes. One important difference between the present study and the study by Tsunekawa et al is the vascular tissue bed studied. Although venous occlusion plethysmography is used to study forearm resistance vessels, high-resolution ultrasonography of the brachial artery during ischemia-induced hyperemia is used to study a conduit vessel. Because the extent of NO release from conduit vessels is different from extent of NO release from resistance vessels, less blunting of NO from conduit arteries in the study by Tsunekawa et al could explain the difference between our studies. Alternatively, glycemic control in the older patients with type 2 diabetes in the study by Tsunekawa...
et al was better than that in our patient group. Improved glycemic control has been shown to improve endothelial function. In contrast, Sheu et al demonstrated no effect on flow-mediated dilation (FMD) after 24 weeks of treatment with simvastatin in 21 patients with type 2 diabetes. The authors describe glycemic control in their patient group as “less than satisfactory.” These data suggest that beneficial effects of statins on endothelial function may partly depend on appropriate glycemic control.

The beneficial effect of statin therapy in type 2 diabetes patients, observed in subgroup analyses of large secondary prevention trials, may be mediated via other antiatherosclerotic pathways, independent from lipid lowering. These beneficial vascular effects of statins include increased fibrinolytic activity by release of tissue plasminogen factor and decreased synthesis of plasminogen activator inhibitor. Inhibition of tissue factor, inhibition of vascular smooth muscle cell proliferation, and reduction of inflammation and of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression.

In summary, we did not show an effect of atorvastatin on NO-dependent vasodilation in forearm resistance arteries of patients with type 2 diabetes. It is likely that despite intensive lipid lowering, other factors, such as hyperglycemia, may be an important causal factor for this impaired vasoreactivity. Furthermore, NO-independent actions of statin therapy may be of importance in the improved cardiovascular outcome in patients with type 2 diabetes.

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References


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