Effect of the Angiotensin II Receptor Antagonist Telmisartan on Lipoprotein Lipase Mass in Preheparin Serum

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Aim: Lipoprotein lipase protein exists in preheparin serum (preheparin LpL mass), even though lipoprotein lipase activity is rarely detected. Recent clinical studies have clarified that low preheparin LpL mass concentration is an important coronary risk factor. The aim of this study was to clarify the effect of telmisartan, which is an angiotensin II receptor antagonist with partial peroxisome proliferator-activated receptor-γ agonist activity, on preheparin LpL mass concentration in the serum of patients with hypertension.

Methods: Fifty untreated hypertensive patients were treated with telmisartan 40 mg/day for 12 weeks and the subjects were divided into two groups by their mean value of preheparin LpL mass concentration at baseline (cut-off level: Male 55 ng/mL, Female 65 ng/mL).

Results: Before telmisartan therapy, low preheparin LpL mass concentration was closely associated with the pathogenesis of insulin resistance and the presence of coronary atherosclerosis. Preheparin LpL mass concentration significantly increased after telmisartan therapy in subjects with a low preheparin LpL mass concentration (baseline/12 weeks after, 46 ± 12 ng/mL/54 ± 14 ng/mL, p = 0.001).

Conclusion: This finding indicated that telmisartan could prevent the occurrence of coronary events in subjects with hypertension by increasing the preheparin LpL mass concentration.


Key words: Telmisartan, Preheparin serum lipoprotein lipase mass, Hypertension, Peroxisome proliferator-activated receptor-γ

Introduction

Lipoprotein lipase (LpL) is a key enzyme catalyzing the hydrolysis of triglyceride in circulating lipoproteins, which are very low density lipoprotein or chylomicron. LpL is produced mainly in adipocytes and skeletal muscle cells, and is believed to be transported to the surface of endothelial cells. Recently, a sensitive immunoassay system using specific monoclonal antibody against LpL demonstrated the presence of LpL protein in preheparin serum (preheparin LpL mass). Furthermore, some clinical studies have clarified that a low preheparin LpL mass concentration is closely associated with the progression of coronary atherosclerosis and recently, an increase of preheparin LpL mass concentration is considered one of the important targets of drug therapy in preventing cardiovascular events.

It is well known that blood pressure control is the first step in the prevention of cardiovascular events in subjects with hypertension; however, researchers have noted that beyond blood pressure control effects, reduction of insulin resistance is especially important to prevent cardiovascular events. Some studies have shown that pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, improves insulin sensitivity and decreases the risk of atherosclerosis. PPAR-γ is one of the most important activators of adipose tissues and the production of LpL in adipose tissues is regulated by PPAR-γ. Shirai et al. reported that troglitazone, another PPAR-γ agonist, increased preheparin LpL mass concentration in subjects with type II diabetes. On the other
hand, recent in vitro and in vivo studies have indicated that telmisartan, unlike other ARBs, acts as a partial PPAR-γ agonist at concentrations that are achievable with oral doses recommended for the treatment of hypertension\(^{29, 30}\), suggesting that telmisartan may reduce insulin resistance and increase preheparin LpL mass concentration. In this study, we examined the clinical significance of preheparin LpL mass concentration and the effect of telmisartan on preheparin LpL mass concentration in subjects with hypertension.

### Methods

#### Study Population

The study population consisted of 50 patients who were beginning hypertensive therapy for the first time (office systolic blood pressure ≤ 140 mmHg and/or diastolic blood pressure ≤ 90 mmHg) and were prescribed 40 mg of telmisartan once-daily for 12 weeks. The subjects were divided into Group L (subjects with low preheparin LpL mass concentration) or Group H (subjects with high preheparin LpL mass concentration) by their mean value of preheparin LpL mass concentration at baseline (cut-off level: Male 55 ng/mL, Female 65 ng/mL); their clinical characteristics and effects of telmisartan on preheparin LpL mass concentration were compared. All subjects were asked not to change their medications, nor to exercise habits during the study. Informed consent was obtained from all participants, and the study was approved by the local ethics committee.

#### Estimation of Coronary Risk Factors

Age, sex, blood pressure, diabetes mellitus, obesity, smoking, serum lipid concentrations, and insulin resistance were examined as potential risk factors for coronary disease. Diabetes mellitus was defined as a history of diabetes mellitus or fasting blood glucose levels ≥ 126 mg/dL. Obesity was defined as a body mass index ≥ 25 kg/m\(^2\). Smoking was defined as positive if there was a current or past history of cigarette smoking. On the other hand, coronary artery disease was defined as angiographical ≥ 75% diameter stenosis, estimated by the American Heart Association reporting system\(^{31}\).

#### Blood Sampling

Blood biochemical examination, including preheparin LpL mass concentration, was performed once before telmisartan administration and again 12 weeks after. Blood samples were collected in the morning after an overnight fast. Total cholesterol (TC) and triglycerides (TG) were measured enzymatically using a kit from Nippon Shoji (Osaka, Japan) and an autoanalyzer (Hitachi 7150 from Hitachi Tokyo, Japan). High density lipoprotein cholesterol (HDL-C) was measured by the selective inhibition method (Daiichi Pure Chemicals, Tokyo). The concentration of low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald’s formula (Total cholesterol—high density cholesterol—triglycerides/5)\(^{32}\). Plasma glucose was measured using the glucose oxidase method and serum insulin concentration was measured using an enzymatic immunoassay. Insulin sensitivity was quantified using HOMA-IR (glucose (mg/dL) × insulin (μU/mL)/405)\(^{33}\).

#### Preheparin LpL Mass Assay

Serum was separated within 1 hour and samples for LpL mass measurement were frozen at −80°C. Preheparin LpL mass was measured by sandwich enzyme-linked immunosorbent assay using a specific monoclonal antibody against lipoprotein lipase, as described elsewhere\(^5\). A commercial kit from Daiichi Pure Chemicals (Tokyo) was used in this study. For the assay system, a linear response was observed from 5 ng/mL to 400 ng/mL. The within-run coefficient of variation was 2.8%. The between-day coefficient of variation was 4.3%.

#### Estimation of Abdominal Fat

At baseline, we calculated the abdominal fat area at the umbilical levels by computed tomography. The abdominal visceral fat areas and subcutaneous fat areas were determined using a computed tomography scanning technique\(^34\).

#### Statistical Analysis

A commercially available statistical software program (Stat View-J 5.0; HULINKS Inc., Tokyo, Japan) was used for all statistical analyses. Data were expressed as the mean value ± standard deviation. Between-group comparisons were performed using Student’s \(t\)-test or Mann-Whitney \(U\) test and the correlation coefficient was estimated by Spearman’s rank correlation analysis. Multivariate analysis was performed using multiple regression analysis. A \(p\) value of less than 0.05 was considered significant.

### Results

#### Patient Characteristics

Patient characteristics are shown in Table 1. There were no differences in age, sex or blood pressure between the two groups. More subjects were obese in Group L than in Group H. Furthermore, subjects in

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**Table 1.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Preheparin LpL Mass Concentration</th>
<th>Blood Pressure</th>
<th>Diabetes</th>
<th>Obesity</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Low</td>
<td>Systolic</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>H</td>
<td>High</td>
<td>Diastolic</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 1. Baseline clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group H</th>
<th>Group L</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 ± 9</td>
<td>61 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/12</td>
<td>12/13</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (systole, mmHg)</td>
<td>155 ± 13</td>
<td>158 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (diastole, mmHg)</td>
<td>91 ± 7</td>
<td>92 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (32)</td>
<td>9 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 25 kg/m²)</td>
<td>4 (16)</td>
<td>10 (40)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Visceral fat area (cm²)</td>
<td>92 ± 42</td>
<td>129 ± 68</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Subcutaneous fat area (cm²)</td>
<td>130 ± 64</td>
<td>170 ± 84</td>
<td>NS</td>
</tr>
<tr>
<td>History of CAD</td>
<td>2 (8)</td>
<td>12 (48)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The subjects were divided into Group L (subjects with low preheparin LpL mass concentration) or Group H (subjects with high preheparin LpL mass concentration) by their mean value of preheparin LpL mass concentration at baseline (cut-off level: Male 55 ng/mL, Female 65 ng/mL). BMI: body mass index CAD: coronary artery disease Data are expressed as the mean ± SD ( ): %

Table 2. Comparisons of blood biochemical parameters in two groups

<table>
<thead>
<tr>
<th></th>
<th>Group H</th>
<th>Group L</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preheparin LpL mass (ng/mL)</td>
<td>72 ± 11</td>
<td>46 ± 12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>211 ± 34</td>
<td>205 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>128 ± 23</td>
<td>122 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>82 ± 31</td>
<td>151 ± 85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>66 ± 17</td>
<td>52 ± 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Administration of statin</td>
<td>3 (12)</td>
<td>5 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>103 ± 12</td>
<td>110 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>6.2 ± 3.4</td>
<td>8.7 ± 3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.6 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LpL: lipoprotein lipase LDL: low-density lipoprotein HDL: high-density lipoprotein HOMA-IR: homeostasis model assessment-insulin resistance Data are expressed as the mean ± SD ( ): %

Group L had a significantly larger area of visceral fat than those in Group H even though there were no significant differences between them in subcutaneous fat area. On the other hand, a larger number of subjects had a history of coronary artery disease in Group L. Blood biochemistry data are shown in Table 2. Mean preheparin LpL mass concentration was significantly lower in Group L, but there were no significant differences between the two groups in TC concentration, LDL-C concentration or fasting blood glucose concentration. However, TG concentration, insulin concentration and HOMA-IR value were significantly higher in Group L than in Group H. HDL-C concentration was significantly lower in Group L.

Multivariate Analysis of Preheparin LpL Mass Concentration Before Telmisartan Therapy

To clarify which factor shows an independent association with a low preheparin LpL mass concentration at baseline, we performed multiple regression analysis to investigate the factors related to preheparin LpL mass concentration. A history of coronary artery disease and TG concentration were found to be independent variables for low preheparin LpL mass concentration as the subordinate factor (t value = 2.4, 2.1, p = 0.01, p < 0.05, respectively, Table 3).

Changes in Different Parameters After Telmisartan Therapy

A significant decrease of blood pressure was observed in both groups after telmisartan therapy for 12 weeks (Table 4). TG concentration and HOMA-IR levels were significantly decreased in Group L but not in Group H. In Group L, the preheparin LpL mass concentration increased significantly compared with its baseline value (baseline/12 weeks after, 46 ± 12 ng/mL/54 ± 14 ng/mL, p = 0.001); however, there were no significant changes in Group H (baseline/12 weeks after, 72 ± 11 ng/mL/75 ± 11 ng/mL, p = NS) (Fig. 1).

Correlation between the Change in Each Parameter and that in Preheparin LpL Mass Concentration in Group L

There was no significant correlation between the change in systolic or diastolic blood pressure and the change in preheparin LpL mass concentration (Table 5). On the other hand, the change in preheparin LpL
Table 4. Changes in each parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group H</th>
<th>Group L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58 ± 8</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.4 ± 2.8</td>
<td>22.4 ± 2.9</td>
</tr>
<tr>
<td>Blood pressure (systole, mmHg)</td>
<td>155 ± 13</td>
<td>135 ± 6 **</td>
</tr>
<tr>
<td>Blood pressure (diastole, mmHg)</td>
<td>91 ± 7</td>
<td>80 ± 7 **</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>211 ± 34</td>
<td>202 ± 33</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>128 ± 33</td>
<td>120 ± 28</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>82 ± 31</td>
<td>80 ± 35</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>66 ± 16</td>
<td>65 ± 20</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>103 ± 12</td>
<td>101 ± 12</td>
</tr>
<tr>
<td>Insulin (µg/mL)</td>
<td>6.2 ± 3.4</td>
<td>5.7 ± 4.9</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.6 ± 0.8</td>
<td>1.4 ± 1.1</td>
</tr>
</tbody>
</table>

*p < 0.05 vs baseline, **p < 0.0001 vs baseline
Data are expressed as the mean ± SD (): %
Abbreviations as in Table 2

mass concentration showed a significant correlation with the change in TG concentration, HDL-C concentration, insulin concentration and HOMA-IR ($r = -0.39, 0.55, -0.43, -0.41, p < 0.05, < 0.01, < 0.05, < 0.05$, respectively).

Discussion

Blood pressure was similar in the two groups at baseline; however, subjects with a low preheparin LpL mass concentration reflected the pathogenesis of insulin resistance. Furthermore, a low preheparin LpL mass concentration was closely associated with the presence of coronary atherosclerosis. Telmisartan therapy increased the preheparin LpL mass concentration in subjects with a low preheparin LpL mass concentration at baseline and the increase significantly correlated with changes in TG concentration, HDL-C concentration and HOMA-IR as a marker of insulin resistance.

Significance of a Low Preheparin LpL Mass Concentration in Subjects with Hypertension

Some researchers have reported a relation between low preheparin LpL mass concentration and insulin resistance. Actually, in this study, subjects with low preheparin LpL mass concentration showed a high

![Fig. 1. Changes in preheparin LpL mass concentration.](image)

Preheparin LpL mass concentration significantly increased in Group L, however, there were no significant changes in Group H. Data are expressed as the mean ± SD
*p = 0.001 vs baseline

Table 5. Correlation between change in each parameter and change in preheparin LpL mass concentration in Group L

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔBlood pressure (systole, mmHg)</td>
<td>-0.13</td>
<td>NS</td>
</tr>
<tr>
<td>ΔBlood pressure (diastole, mmHg)</td>
<td>-0.24</td>
<td>NS</td>
</tr>
<tr>
<td>ΔTotal cholesterol (mg/dL)</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>ΔLDL-cholesterol (mg/dL)</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>ΔTriglyceride (mg/dL)</td>
<td>-0.39</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ΔHDL-cholesterol (mg/dL)</td>
<td>0.55</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ΔFasting blood glucose (mg/dL)</td>
<td>-0.19</td>
<td>NS</td>
</tr>
<tr>
<td>ΔInsulin (µg/mL)</td>
<td>-0.43</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ΔHOMA-IR</td>
<td>-0.41</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2
HOMA-IR value at baseline and a significant correlation between the change in preheparin LpL mass concentration and that in HOMA-IR after telmisartan therapy, suggesting that low preheparin LpL mass concentration indicates insulin resistance in vivo. However, multiple regression analysis revealed that low preheparin LpL mass concentration was an independent variable for the presence of coronary artery disease after adjustment for HOMA-IR as a marker of insulin resistance. Therefore, low preheparin LpL mass concentration is considered not only a marker of insulin resistance but is also an important target for the prevention of coronary events, which cannot be prevented by blood pressure control in hypertensive subjects. Insulin resistance is known to affect the physiology of various organs, including skeletal muscles, adipose tissue and liver. Furthermore, recent basic and clinical studies have described the direct effects of insulin resistance at the level of the vessel wall. LpL is known to exist in endothelial cells, showing activity, and LpL was also reported to exist on the coronary lumen surface. Therefore, low preheparin LpL mass concentration may reflect insulin resistance that is not detectable by HOMA-IR, at the level of the vessel wall, especially in coronary arteries.

Endothelial dysfunction is one of the most important factors involved in the progression of coronary atherosclerosis and it is well known that nitric oxide (NO) activity affects coronary endothelial function. In addition, lipoprotein lipase is reported to increase NO production in cultured macrophages. We previously reported that low preheparin LpL mass concentration was closely associated with coronary endothelial dysfunction, as estimated by intracoronary administration of acetylcholine. Those findings suggested that low preheparin LpL mass concentration reflected decreased NO production in coronary arteries, providing further evidence of the linkage between low preheparin LpL mass concentration and coronary atherosclerosis in subjects with hypertension.

It is useful to have plain cut-off levels of preheparin LpL mass concentration in clinical research or daily practice. Clinical studies have been performed concerning the preheparin LpL mass concentration in hypertensive subjects; however, no data show an appropriate definition of low preheparin LpL mass concentration. In this study, by dividing subjects into two groups, low and high, by the mean value of preheparin LpL mass concentration, the pathogenesis of insulin resistance or the presence of coronary atherosclerosis was reflected. Therefore, these values (men, 55 ng/mL; women, 65 ng/mL) may be useful cut-off levels to predict the occurrence of cardiovascular disease in hypertensive treatment.

Effects of Telmisartan Therapy on Preheparin LpL Mass Concentration

In this study, telmisartan therapy decreased TG concentration in subjects with low preheparin LpL mass concentration, and there was a significant inverse correlation between the changes in both parameters. Previous studies have shown that telmisartan decreases TG concentration in hypertensive patients. On the other hand, it is well known that LpL plays a central role in triglyceride metabolism. Although the precise mechanism is not fully understood, our results may indicate that the decrease of TG concentration by telmisartan therapy can be explained to some degree by the increase of LpL activity. Indeed, there was a significant correlation between the increase in preheparin LpL mass concentration and the increase in HDL-C concentration after telmisartan therapy in subjects with low preheparin LpL mass concentration at baseline, despite the low increase of HDL-C concentration. Low HDL-C concentration is one of the most important coronary risk factors; therefore, telmisartan may prevent coronary events in some patients by increasing HDL-C concentration and preheparin LpL mass concentration. Some reports have clarified that small dense LDL-C is involved in the pathogenesis of insulin resistance, and this type of LDL is often associated with coronary artery disease. Shirai et al. reported that troglitazone increased LDL particle size and preheparin LpL mass concentration. In addition, Saiki et al. reported that valsartan, another ARB, increased both preheparin LpL mass concentration and LDL particle size and that there was a significant relation between them. In this study, we did not examine LDL particle size; however, telmisartan, which is an ARB with PPAR-γ agonist activity, is expected to enlarge LDL particle size through an increase of preheparin LpL mass concentration, and thereby contribute to the prevention of coronary events.

It is notable that the increase of preheparin LpL mass concentration by telmisartan therapy expressed the degree of PPAR-γ effects in addition to class effects of ARBs. Shirai et al. reported that therapy with troglitazone at a dose of 400 mg/day resulted in a 68% increase of preheparin LpL mass concentration from baseline and we confirmed that pioglitazone at a dose of 15 mg/day also resulted in a 40% increase of preheparin LpL mass concentration in vivo. On the other hand, Saiki et al. reported that valsartan increased...
preheparin LpL mass concentration by 17%, which was almost the same increase found in our study. Mori et al.\textsuperscript{40} reported that switching to telmisartan (40 mg/day) from candesartan (8 mg/day) did not result in a significant increase of preheparin LpL mass concentration. Valsartan and candesartan were reported to exert very little PPAR-\( \gamma \) effects compared to telmisartan in a basic study\textsuperscript{50}, thus, it is unclear whether the increase of preheparin LpL mass concentration by telmisartan reflects the degree of PPAR-\( \gamma \) effects in addition to class effects of ARBs \textit{in vivo}. However, our results included subjects with coronary artery disease with few diabetes subjects were small compared to Saiki \textit{et al.} or Mori \textit{et al.} These differences in the study population may explain the difference in the increase of preheparin LpL mass concentration; therefore, further studies are needed to compare other ARBs with telmisartan regarding their effect on preheparin LpL mass concentration in various study populations.

In our study, the visceral fat area was significantly larger in subjects with low preheparin LpL mass concentration than in those with high preheparin LpL mass concentration at baseline. Kobayashi \textit{et al.}\textsuperscript{11, 55} also reported a link between the increase of visceral fat volume and low preheparin LpL mass concentration. These findings suggest that therapy to reduce visceral fat volume can be expected to lead to an increase of preheparin LpL mass concentration. Activation of PPAR-\( \gamma \) is considered to decrease visceral fat area by decreasing adipose cell size\textsuperscript{56, 57}. Very recently, Shimabukuro \textit{et al.}\textsuperscript{58} reported that telmisartan significantly reduced visceral fat, as estimated by computed tomography, whereas amlodipine, which is a calcium channel blocker, increased visceral fat area. Unfortunately, we did not evaluate visceral fat after telmisartan therapy; however, the mechanism of increase of preheparin LpL mass concentration in our study can be partly explained by a decrease of adipose cell size through PPAR-\( \gamma \) activation by telmisartan.

\textbf{Limitations}

The study population was small and this was a cross-sectional study concerning the relation between preheparin LpL mass concentration and coronary artery disease; therefore, a prospective study involving a larger population is needed to evaluate low preheparin LpL mass concentration as a coronary risk factor in subjects with hypertension. The precise mechanism for the increase of preheparin LpL mass concentration by telmisartan therapy is not fully understood. Multifarious studies are expected to clarify the significance of telmisartan therapy from the viewpoint of preheparin LpL mass concentration.

\textbf{References}

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