Dear Sir,

Atherosclerosis is reported to be accelerated in patients with chronic renal failure treated by hemodialysis [1]. Risk factors for it would include impaired lipoprotein metabolism and altered blood coagulation-fibrinolysis status. Some recent studies have shown that patients with chronic renal failure have an elevated plasma level of lipoprotein Lp(a) [2, 3], a low-density-lipoprotein-like lipoprotein having an additional protein component called Apo(a) [4]. An increased Lp(a) level is regarded as an independent risk factor for atherosclerosis in the general population [4]. High homology between Apo(a) and the kingle 4 domain of plasmin-ogen [5] may account for the proposed thrombogenic and atherogenic nature of Lp(a) [6]. Theoretically, Lp(a) competitively inhibits plasmin-mediated fibrinolysis [4]. So far, however, such a predicted suppression of fibrinolysis has not been clinically demonstrated in hemodialysis patients. To address this issue, we measured Lp(a) and coagulation-fibrinolysis parameters in hemodialysis patients before and after oral administration of niceritrol, a nicotinic acid analogue, which is known to lower Lp(a) concentration in nonuremic subjects [7].

The subjects were 17 (7 male and 10 female) nondiabetic hemodialysis patients. They were all Japanese. The mean (± SE) age was 58 ± 3 years and duration of hemodialysis treatment was 90 ± 15 months, respectively. The body mass index was 21.1 ± 0.5 kg/m². They received niceritrol (Pery-cit®, Sanwa Kagaku Kenkyusho Co. Ltd., Nagoya, Japan),
750 mg/day, for 4 weeks. Lp(a) was measured by ELISA [TintElize® Lp(a), Biopool, Umeå, Sweden]. The thrombin-antithrombin (TAT) complex concentration was measured by ELISA (Enzygnost® TAT, Hoechst Japan Co. Ltd., Tokyo, Japan) as a sensitive index of blood coagulation. D-dimer, which is one of the degradation products of cross-linked fibrin, was measured by ELISA (Asserachrom® D-Di, Boehringer Mannheim Yamanouchi Co. Ltd., Tokyo, Japan) as a molecular marker for secondary fibrinolysis. Lipoproteins were assayed by ultracentrifugation as described elsewhere [8]. Blood samples were drawn after an overnight fast before starting hemodialysis.

After treatment

<table>
<thead>
<tr>
<th></th>
<th>p value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>114.4 ± 5.8</td>
<td>80.2 ± 6.3</td>
</tr>
<tr>
<td></td>
<td>0.0001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 1 gives the results. Following the treatment, Lp(a) decreased by 33%. Niceritrol did not change the TAT plasma level, whereas it significantly increased D-dimer by 15%. TAT and D-dimer showed a positive correlation both at baseline and after niceritrol treatment, suggesting a dynamic balance between coagulation and secondary fibrinolysis (fig. 1). Interestingly, the slope of the regression line became greater after niceritrol treatment. The difference between the two slopes was statistically significant ($t = 2.234, \text{d.f.} = 30, p < 0.05$).

One of the postulated mechanisms for accelerated atherogenesis by Lp(a) is that Lp(a) could be a competitive inhibitor for plasmin as shown in vitro [4]. Previous studies failed to
to show such an influence of Lp(a) on secondary fibrinolysis in a clinical setting [9]. In the present study, the 4-week administration of niceritrol was followed by a decrease in Lp(a), an increase in D-dimer and no change in TAT levels. Importantly, Lp(a) reduction by niceritrol treatment shifted the dynamic balance between coagulation and secondary fibrinolysis. Although there is still a possibility that niceritrol directly affected the blood coagulation system, our data can be interpreted to indicate that lowering Lp(a) attenuated the Lp(a)-mediated suppression of secondary fibrinolysis. Our observations clinically support the current concept that elevated Lp(a) interferes with the coagulation-fibrinolysis system, at least in hemodialysis patients.

References


Lp(a) and Coagulation-Fibrinolysis Status in HD Patients
Nephron 1997;77:112-113