MINIREVIEWS

Relevance of ADAMTS13 to liver transplantation and surgery

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Abstract

A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 (ADAMTS13) specifically cleaves unusually-large von Willebrand factor (VWF) multimers under high shear stress, and down-regulates VWF function to form platelet thrombi. Deficiency of plasma ADAMTS13 activity induces a life-threatening systemic disease, termed thrombotic microangiopathy (TMA) including thrombotic thrombocytopenic purpura (TTP). Children with advanced biliary cirrhosis due to congenital biliary atresia sometimes showed pathological features of TMA, with a concomitant decrease of plasma ADAMTS13 activity. Disappearance of their clinical findings of TTP after successful liver transplantation suggested that the liver is a major organ producing plasma ADAMTS13. *In situ* hybridization analysis showed that ADAMTS13 was produced by hepatic stellate cells. Subsequently, it was found that ADADTS13 was not merely responsible to development of TMA and TTP, but also related to some kinds of liver dysfunction after liver transplantation. Ischemia-reperfusion injury and acute rejection in liver transplant recipients were often associated with marked decrease of ADAMTS13 and concomitant formation of unusually large VWF multimers without findings of TMA/TTP. The similar phenomenon was observed also in patients who underwent hepatectomy for liver tumors. Imbalance between ADAMTS13 and VWF in the hepatic sinusoid might cause liver damage due to microcirculatory disturbance. It can be called as "local TTP like mechanism" which plays a crucial role in liver dysfunction after liver transplantation and surgery.

Core tip: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 (ADAMTS13) is a cleaving protease of von Willebrand factor (VWF). The deficiency of this molecule is known to cause thrombotic thrombocytopenic purpura (TTP). Recent studies revealed that ADAMTS13 might have functional relevance to pathogenesis of various liver disease separately from the development of TTP. Imbalance between ADAMTS13 and VWF in the hepatic sinusoid might cause liver damage due to microcirculatory disturbance. It can be called as "local TTP like mechanism" which plays a crucial role in liver dysfunction after liver transplantation and surgery including ischemia reperfusion injury and acute rejection.

INTRODUCTION

The liver produces a variety of coagulation and fibrinolytic proteins, which are essential to create the hemostatic network on a basis of coagulation cascade[1,2]. In contrast, plasma von Willebrand factor (VWF) plays a pivotal role in primary hemostasis by anchoring platelets onto the denuded vascular subendothelial matrices under high shear stress generated in microvasculatures. VWF is produced exclusively in vascular endothelial cells as unusually large VWF multimers (UL-VWFM) and the secreted into circulation. Before secretion, VWF is cleaved into the smaller multimers by a specific plasma protease, termed a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 (ADAMTS13), at the peptide bond between Tyr1605 and Met1606 within the VWF-A2 domain[3,4]. The lack of ADAMTS13 induces excess activity of UL-VWFM and may results in microcirculatory disturbance with formation of thrombi in microvasculatures.

The *ADAMTS13* gene is located on chromosome 9q34, and the enzyme consists of 1427 amino acid residues with a multi-domain structure[5]. The initial northern blotting studies indicated that ADAMTS13 mRNA is exclusively expressed in the liver[6], and the subsequent immunological studies with *in situ* hybridization analyses revealed that ADAMTS13 is unambiguously produced in hepatic stellate cells (Itoh cells)[7]. However, ADAMTS13 was also identified in platelets[8], vascular endothelial cell[9], and kidney podocytes[10]. Therefore, an important question has been arisen which organ is most responsible for maintaining the plasma levels of ADAMTS13 activity. In this regard, we found that pediatric patients with advanced biliary cirrhosis due to bile duct atresia often showed pathological features resembling to thrombotic microangiopathy (TMA) which shows microangiopathic hemolytic anemia, destructive thrombocytopenia, and organ dysfunction caused by platelet thrombi. Further, these patients usually had a significantly low plasma level of ADAMTS13 activity, and interestingly their clinical and laboratory findings rapidly improved after a successful liver transplantation (our original data). These results strongly suggested that the liver is a major organ producing plasma ADAMTS13. In the absence of ADAMTS13, UL-VWFM released from vascular endothelial cells left uncleaved, which induce platelet hyperagglutination under high shear stress and generate platelet thrombi in organ microcirculation[3,4,11-13], typically shown in thrombotic thrombocytopenic purpura (TTP), a life-threatening generalized disease and a phenotype of common pathological features of TMA.

Subsequently we have reported that the decrease of plasma ADAMTS13 activity correlates with the disease progression of various chronic liver diseases including hepatitis C-associated liver cirrhosis[14], the ischemia-reperfusion injury and acute rejection in liver transplant recipients[15], and hepatic dysfunction after hepatectomy for liver tumors[16]. The hepatic sinusoid is the narrowest vascular structure within the liver and is the principal site of blood flow regulation. The anatomical location of hepatic stellate cells, which embrace the sinusoids, provides a favorable arrangement for sinusoidal constriction, and for control of sinusoidal vascular tone and blood flow[17]. Because of this specific microanatomical environment, it is suspected that hepatic stellate cell is a key player in regulating hepatic sinusoidal blood circulation. From this point of view, this review is showing the dynamics of ADAMTS13 activity and its clinical relevance to the pathogenesis of liver dysfunction after liver transplantation and surgery.

ENDOTHELIAL CELL INJURY AND ADAMTS13 IN CIRRHOTIC LIVER

The mechanism of thrombocytopenia in patients with liver cirrhosis provides suggestion to relevance of ADAMTS13 to development of liver dysfunction due to microcirculatory disturbance. It has been speculated that thrombocytopenia in liver cirrhosis is caused by hypersplenism and impaired synthesis of thrombopoietin in the liver[18,19]. However, Uemura et al[14,20] provided an evidence of increase of UL-VWFM in patients with severe liver cirrhosis. Thrombocytopenia may be enhanced by platelet aggregation increased UL-VWFM

under high shear stress. Their data showed a significant reduction of plasma ADAMTS13 activity in patients with advanced liver cirrhosis mainly caused by hepatitis C virus infection[20]. The results are consistent with reports by Mannucci *et al*[21] and Feys *et al*[22]. Severity of decreased ADAMTS13 activity was parallel to impaired hepatic functional reserve[20]. The plasma ADAMTS13 activity in Child-Pugh classification (Child) C patients was significantly lower than those in patients with Child A and B. Among these, UL-VWFM-positive patients showed the lowest plasma ADAMTS13 activity, most impaired liver and renal function, and lowest Child-Pugh scores. These results indicate that severe cirrhosis may be prone to platelet aggregation. High susceptibility to thrombotic formation may be supported by high incidence of portal or hepatic venous thrombosis in patients with severe liver cirrhosis[23,24]. Even in the absence of clinically overt thrombotic events, microcirculation may be disturbed by formation of platelet microthrombi caused by the enzyme-substrate imbalance between ADAMTS13 and UL-VWFM.

Substantial increase of plasma VWF levels according to progression of liver diseases has been reported previously[25,26]. This is probably due to endothelial damage of the hepatic sinusoid caused by endotoxin and cytokines[25-28]. Hepatic cell necrosis and subsequent liver regeneration, and/or high shear stress due to portal hypertension in cirrhotic liver may play major roles in up-regulating VWF in hepatic sinusoidal endothelium. The mechanism responsible for the decrease of ADAMTS13 activity in advanced cirrhotic patients may include enhanced consumption due to a degradation of a large quantities of VWF[21], inflammatory cytokines[29,30], and/or ADAMTS13 plasma inhibitor[13,31]. These findings in patients with liver cirrhosis suggest that imbalance between ADAMTS13 and UL-VWFM can induce liver dysfunction due to microcirculatory disturbance.

It is well-known that ticlopidine, which is one of the most popular antiplatelet agents, can be a cause of severe deficiency of ADAMTS13 activity, the condition known as TTP[32]. The drug may induce inhibitor of ADAMTS13. Because the patients with cirrhosis are prone to deficiency of ADAMTS13 activity, the use of ticlopidine is better to be avoided as possible.

ASSAY SYSTEM OF ADAMTS13 AND UL-VWFM

The article contains some original data in the part of liver transplantation. ADAMTS13 and UL-VWFM were measured with the methods described below. Written informed consent was obtained in all patients in whom the blood samples were used for the assay.

Traditionally, the activity of plasma ADAMTS13 was measured by the multimer method using full length VWF as a substrate according to the method reported by Furlan *et al*[12], although we made slight modification to this method as described in our previous study[15].

The method required at least 3 d to assay the activity of ADAMTS13. Our newly developed method is enzyme-linked immunosorbent assay (ELISA) using a specific murine monoclonal antibody to Tyr1605 residue of VWF-A2 domain which is generated by ADAMTS13 cleavage. Rrecombinant GST-VWF73-His polypeptide is used as a substrate[33]. One of the advantages of this method is that the assay time is significantly shortened. This new method is more sensitive and more rapid than the traditional multimer method. This ELISA kit is available on commercial base now. Plasma UL-VWFM can be analyzed by vertical agarose gel electrophoresis as described[15].

IMPACT OF ADAMTS13 IN PATIENTS WITH LIVER TRANSPLANTATION

We have revealed significant decrease of ADAMTS13 activity in very sick children with advanced cirrhotic biliary atresia (BA) and full recovery of the activity after living-related liver transplantation (LRLT). This finding strongly suggested that the liver is the major source of ADAMTS13. Briefly, 8 pediatric patients with BA received LRLT from adult live donors, indicating that almost a normal size of liver was transplanted into the recipients (Table 1). Before LRLT, plasma ADMTS13 activity showed a significant decrease in 7 out of 8 patients, and the value for two patients (cases 1 and 8) was extremely low at 13% and 6% of the control, respectively. One to three months after successful LRLT, six patients showed an increase in ADAMTS13 activity. It is noteworthy that decreased ADAMTS13 activity restored by liver transplantation in the majority of patients (Figure 1). Table 1 and Figure 1 are original data of our research team. With regard to the increase in ADAMTS13 activity after LRLT, there were two possible explanations. One is simply that the liver is the major organ to synthesize ADAMTS13, like blood coagulation factors Ⅷ and Ⅸ previously shown in hemophiliacs who received liver transplantation[34-36]. Another explanation might be that liver dysfunction produces a harmful substance which may affect the systemic production or activity of ADAMTS13. However, the presence of a substance interfering with the enzyme activity is plausible, because no inhibitor of ADAMTS13 was detected in sick BA patients. While the site of ADAMTS13 synthesis still remained to be elucidated at the time of study about pediatric BA patients, the results strongly suggested that the liver is the critical organ in the synthesis of ADAMTS13. Following this finding, our research group performed *in situ* hybridization analyses of the liver, which revealed that stellate cells (Ito cells) of sinusoid of the liver produced ADAMTS13[7].

Subsequently, we experienced one noticeable adult patient who developed severe thrombocytopenia soon after LRLT because of advanced liver failure due to Budd-Chiari syndrome (Figure 2). The analysis of the thrombocytopenic mechanism in this patient gave a

Table 1 Profiles of patients who received living-related liver transplantation

	Recipient						Donor				
Case	Age	Sex	Underlying disease	ABO-Rh (D) blood group	SV (g)	Presence of schistocytes before LRLT	Relation to the recipient	Age	ABO-Rh(D) blood group	GV (g)	GV/SV ratio
1	9 mo	M	BA	A+	274	+	Father	35 yr	A+	290	1.06
2	1 yr 4 mo	F	BA	A+	245	+	Mother	38 yr	A+	314	1.28
3	12 yr	F	BA	A+	891	-	Mother	44 yr	A+	392	0.44
4	11 mo	F	BA	A+	259	+	Mother	35 yr	A+	306	1.18
5	8 mo	F	BA	O+	185	+	Father	36 yr	O+	263	1.42
6	1 yr	F	BA	A+	262	+	Mother	41 yr	O+	215	0.82
7	11 mo	F	BA	AB+	280	-	Mother	35 yr	A+	266	0.95
8	7 mo	M	BA	A+	226	-	Mother	30 yr	A+	228	1.01

LRLT: Living-related liver transplantation; SV: Standard liver volume; GV: Graft liver volume; BA: Biliary atresia; M: Male; F: Female.
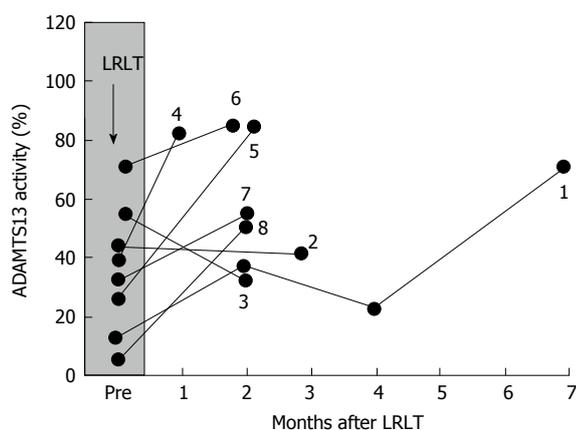

Figure 1 Plasma a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 activity before and after living-related liver transplantation. Predominantly decreased ADAMTS13 activity could be fully restored after living-related liver transplantation in 6 out of 8 sick children with advanced cirrhotic biliary atresia (cases 1, 4, 5, 6, 7 and 8). Pre: Before transplantation; LRLT: Living-related liver transplantation; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13.

paradigm shift, which closely linked the axis of VWF-ADAMTS13 reaction to liver transplantation. Briefly, during his uneventful clinical course in the early stage after liver transplantation, the platelet count decreased gradually from 83000/μL to 62000/μL until postoperative day 5, and decreased further to 25000/μL until day 7 (Figure 2, left). While the patient developed graft liver dysfunction due to acute rejection around day 7, no possible causes of thrombocytopenia were found from clinical findings and usual laboratory tests. To make a decision of platelet transfusion to this patient, plasma ADMTS13 activity was assessed. This was because it has been said that prophylactic platelet transfusion is better avoided to TMA-patients, who had no manifestations of overt bleeding[37]. The result of assay showed a remarkable decrease of ADAMTS13 activity to 3% from 108% before surgery. Presence of UL-VWFM in patient plasma was also identified apparently on day 1 and day 7 using SDS-agarose gel electrophoretic analysis (Figure 2, right panel). Transfusion of a large amount of fresh frozen plasma (FFP) as a treatment for TMA together with a high-dose steroid pulse therapy as treatment for

acute rejection resulted in recovery of thrombocytopenia and liver function, and substantial increase of ADMTS13. Thereafter, the ADAMTS13 activity finally recovered to 50%, corresponding to the lower limit of the normal range, until day 98. The UL-VWFM tended to diminish on day 15, but again became prominent on day 22 during the second episode of acute rejection, and became undetectable until day 45. Profound decrease of plasma ADAMTS13 is a specific finding of TMA which is known as a sporadic serious complication after solid organ transplantation with an estimated frequency of 0.5%-3.0%[38-41]. However, the patient never showed any apparent clinical features including renal dysfunction, neuro-psychological symptoms or hemolytic anemia, as typically seen in TMA[41]. Because the patient certainly had a remarkably increased plasma level of VWF, together with the presence of UL-VWFM, we have supposed that platelet transfusion might generate microcirculatory disturbance due to the enhanced micro-thrombi formation, initially localized to the transplant liver, but later could be expanded systematically. This idea came from the findings, in which liver transplantation often accompanies with the endothelial cell damage due to ischemia-reperfusion injury and acute rejection. In fact, the injured hepatic vascular endothelial cells may release a large quantity of VWF/UL-VWFM[42,43], which may induce a consumption of ADAMTS13 in plasma. Then we supposed new hypothesis that the initiation of pathological mechanism may occurs locally at the site of the transplanted liver.

Based on these findings, we have started analysis of ADAMTS13 activity and UL-VWFM in patients after liver transplant recipients. The results revealed that significant decrease of ADAMTS13 and up-regulation of UL-VWFM were commonly and frequently observed after liver transplantation without findings of usual systemic TMA or TTP[15]. These changes in ADAMTS13 activity and UL-VWFM were relevant to posttransplant liver dysfunction, including ischemia-reperfusion injury and acute rejection (Figure 3). Many of patients with decreased ADAMTS13 activity showed concurrent thrombocytopenia. The clinical manifestation was analogous with TMA, especially to TTP. However, different from TTP, the deterioration was restricted to the transplanted liver, without development
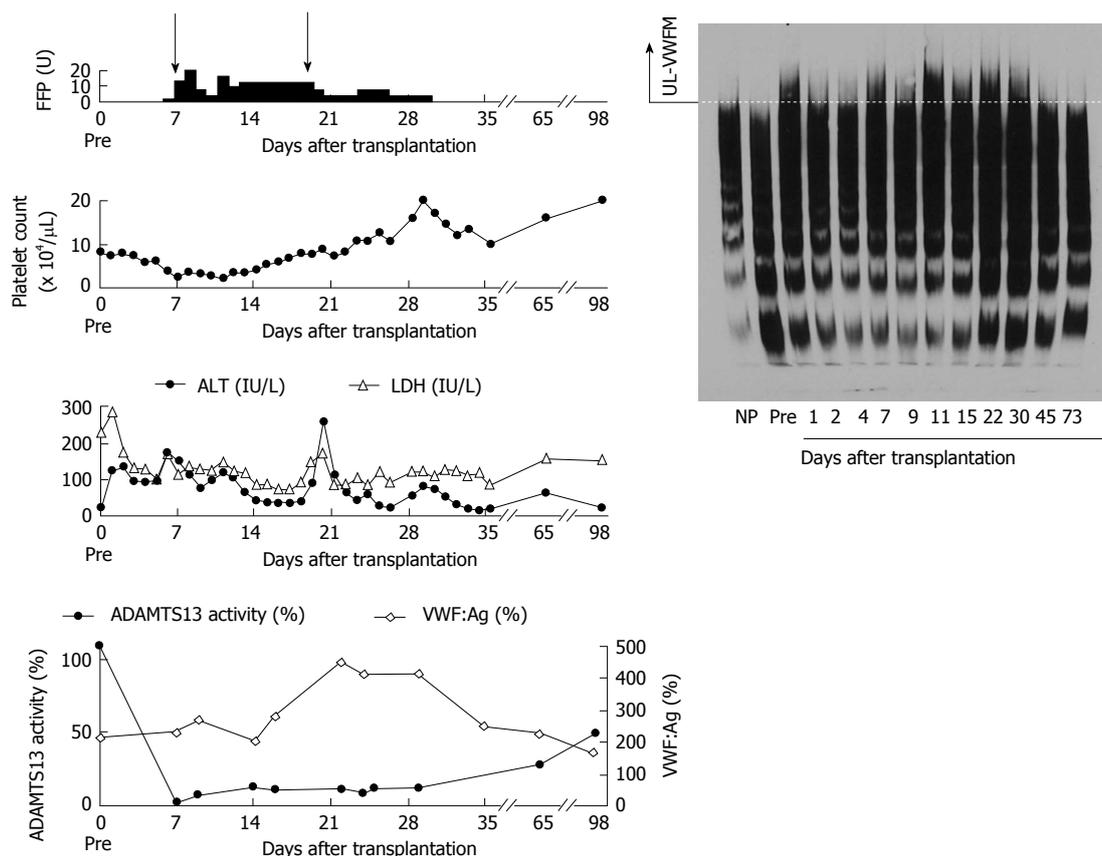
Figure 2 Clinical course of 27-year-old male with Budd-Chiari syndrome after liver transplantation. Serum ALT level mildly increased on days 1 and 2 because of ischemia-reperfusion injury, decreased thereafter, but rapidly increased again on day 7 due to acute rejection (left panel). The platelet count decreased gradually and reached a nadir on day 7, when ADAMTS13 activity decreased markedly to less than 3% from 108% before surgery. After the administration of fresh frozen plasma and bolus injection of methylprednisolone (arrow), ALT level decreased and the platelet count gradually increased. The ADAMTS13 activity increased to 22% on day 14. After the first episode of acute rejection, VWF:Ag increased further and reached 368% on day 21, when ALT again increased due to a second episode of acute rejection. Bolus injection of methylprednisolone (arrow) led to a rapid decrease of ALT and a gradual increase in the platelet count. VWF:Ag decreased gradually, and ADAMTS13 activity finally recovered to 50% until day 98. Plasma UL-VWFM was detectable on day 1 at the time of ischemia-reperfusion injury, thereafter diminishing gradually during days 2 to 4, and again becoming evident on day 7 when acute rejection developed (right panel). The UL-VWFM disappeared transiently on day 9, but reappeared on day 11, coinciding with a mild increase of transaminase. UL-VWFM tended to diminish on day 15, but again became prominent on day 22 during the second episode of acute rejection. Pre: Before transplantation; NP: Normal plasma control; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; FFP: Fresh frozen plasma; VWF: von Willebrand factor; UL-VWFM: Unusually large VWF multimers; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13.

of renal dysfunction or neurological disorders which were characteristic to usual TTP. Then we have advocated "local TTP like mechanism" for the first time as a pathogenesis of imbalance between plasma ADAMTS13 and UL-VWFM in liver transplant recipients[15].

It was reported that increased numbers of activated platelets and VWF expression were indicated in the hepatic sinusoidal endothelial cells of the re-perfused or cold-preserved liver[42,43]. VWF expression was increased significantly in the grafted liver with acute rejection due to allogenic immune response[43]. After up-regulation of VWF, formation of UL-VWFM on the vascular endothelial cells may induce platelet thrombi in the hepatic sinusoid. This may be the mechanism of microcirculatory disturbance due to imbalance between ADAMTS13 and UL-VWFM in liver transplant recipients. This hypothesis explains clearly why organ dysfunction restricts to the grafted liver in liver transplant recipients with low ADAMTS13 activity, distinct from systemic

organ disorders in patients with "classical TTP".

Recent report by Kobayashi *et al*[44] confirmed our findings by showing cross correlation between decrease of ADAMTS13 activity and thrombocytopenia in 81 liver transplant recipients. They also showed increased levels of VWF and up-regulated UL-VWFM. More recently, Hori *et al*[45] reported poor outcomes in patients who developed TMA like disorder after liver transplantation. Most of these patients showed marked decrease of ADAMTS13 activity, while they did not include ADAMTS13 activity in the diagnostic criteria of the disorder. Cross correlation between low ADAMTS13 activity and poor outcomes of the patients was shown in their study.

Following our study[15], another group also reported that a reduction of ADAMTS13 activity after liver transplantation[46]. They insisted that reduction of ADAMTS13 correlated to thrombotic complication by showing a patient with hepatic artery thrombosis. However, different from our findings, they failed to detect UL-VWFM in any
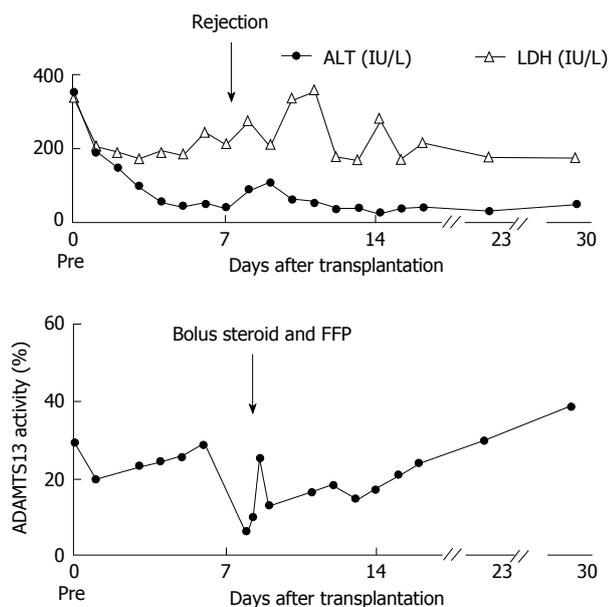
Figure 3 A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 activity before and after treatment for acute rejection in a liver transplant recipient. Decreased ADAMTS13 activity during acute rejection recovered after treatment for rejection. Pre: Before transplantation; FFP: Fresh frozen plasma; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13.

patients with decreased ADAMTS13 activity. The authors speculated that increased plasmin or other proteolytic enzymes cleaved UL-VWFM demonstrating increased plasma levels of tissue plasminogen activator in these patients[46,47]. However, if plasmin cleaves UL-VWFM effectively, thrombotic complications could be prevented. Actually, it has been accepted commonly that UL-VWFM is detected in patients with TTP[20,48]. This may suggest that the deficiency of ADAMTS13 can induce formation of UL-VWFM independently of plasmin and other proteolytic pathways. In addition, hepatic artery thrombosis is a complication crossly linked technical and anatomical implications at the arterial anastomotic site. Basically, ADAMTS13 relates to the formation of platelet thrombi at the "micro" vasculature. Thrombosis of peripheral arterial system as a consequence of microcirculatory disturbance of the graft liver and surgical hepatic arterial thrombosis at the anastomotic site should be distinguished strictly to elucidate the real correlation between ADAMTS13 and the development of thrombotic complications after liver transplantation.

Our experience in liver transplant recipients strongly emphasize the importance of monitoring plasma ADAMTS13 activity not only in diagnosing adverse events including ischemic injury and acute rejection, but also in the treatment of thrombocytopenia after liver transplantation. It should be stressed that platelet transfusion under the decreased activity of ADAMTS13 in liver transplant recipients may deteriorate graft microcirculatory disturbance due to further formation of platelet aggregates in the liver *via* the "local TTP"

mechanism[15]. Liver dysfunction with marked decrease of ADAMTS13 activity should be treated with a large amount of FFP or plasma exchange as indicated for TTP, even when the patient shows no clinical signs of usual TTP.

KINETICS OF ADAMTS13 AFTER HEPATECTOMY FOR LIVER TUMORS

Hepatectomy is mainly indicated for treatment of liver tumors. Because hepatic functional mass is reduced after hepatectomy, thrombo-hemostatsis related agents produced in the liver may decrease at least in the early phase before regeneration of the residual liver. Because ADAMTS13 is produced mainly by the hepatic stellate cells[7], production of ADAMTS13 may decrease after hepatetctomy. In addition, ischemia-reperfusion injury of the liver is an inevitable event in liver surgery due to manipulation of the liver and/or Pringle's maneuver which occludes hepatic blood inflow transiently to decrease bleeding during hepatic transection[49]. Therefore, hepatectomy may induce UL-VWFM in the hepatic sinusoid and result in microcirculatory disturbance *via* the "local TTP like mechanism" as mentioned in the liver transplantation section. Liver failure is a most serious complication after liver surgery. Microcirculatory disturbance may further deteriorate liver dysfunction after hepatectomy.

We reported that plasma ADAMTS13 decreased significantly after hepatectomy[16]. The activity of ADMTS13 showed marked and rapid drop from 67% ± 30.6% before surgery to 48% ± 24.6% (mean ± standard deviation) on day 1 after hepatectomy (n = 70, $P < 0.0001$)[16]. The decrease of ADAMTS13 activity was more profound in patients with major hepatectomy in comparison to those with minor hepatectomy[16]. Multivariate analysis revealed that patients with Pringle's maneuver for longer than 60 min induced most marked decrease of ADAMTS13 activity compared to those with shorter Pringle's maneuver and those without Pringle's maneuver (Figure 4). The severity of ADAMTS13 reduction was significantly correlated with the amount of resected liver mass and the severity of ischemic injury of the liver. ADAMTS13 activity on day 1 strongly correlated with the postoperative maximal levels of total bilirubin as an indicator of postoperative liver dysfunction[16]. These results suggested crucial roles of ADAMTS13 in liver dysfunction and liver failure after hepatectomy.

Figure 5 shows kinetics of ADAMTS13 and UL-VWFM in a patient who underwent major hepatectomy with long Pringle's maneuver. Interestingly, ADAMTS13 activity did not decrease during ischemia by Pringle's maneuver, and decreased very significantly after re-perfusion until the next day. UL-VWFM did not appear during ischemia, and significantly up-regulated after surgery. Induction of UL-VWFM and decrease of ADAMTS13 may develop in the reperfusion phase after ischemic events.
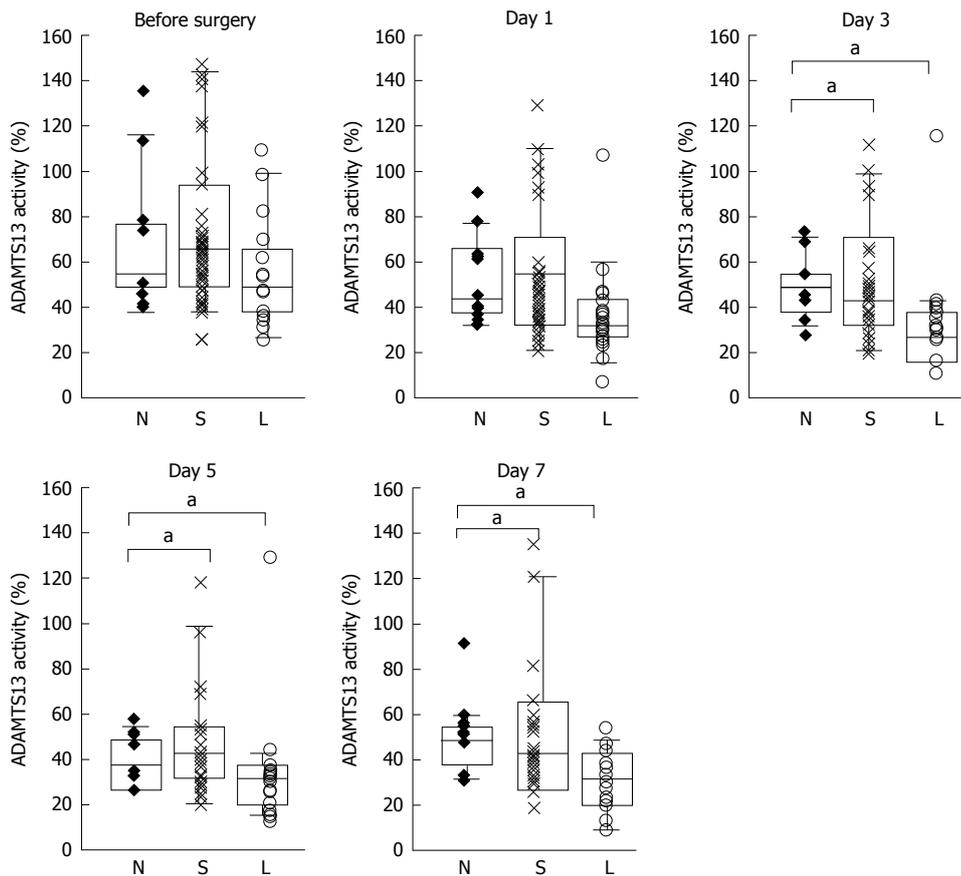
Figure 4 A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 activity according to blood occlusion time by Pringle's maneuver. Pringle's maneuver for long time (over 60 min: L) induced significantly profound decrease of ADAMTS13 activity, comparing to short (15-45 min: S) or no blood occlusion (N). The box shows the 25th-75th percentile, the bar indicates the median value, and the whiskers indicates the 5th-95th percentile. [a]*P* < 0.05 by ANOVA. ANOVA: Analysis of variance; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13.

Marked decrease of platelet count with unexplainable origin is often observed during the first postoperative week after hepatectomy. In our study, significant correlation was observed between ADAMTS13 activity and decrease of platelet count[16]. Reduction of ADAMTS13 synthesis by decreased hepatic functional mass after hepatectomy may be a cause of decreased plasma ADAMTS13 activity. Another possible mechanism of marked decrease of ADAMTS13 may be high share stress after major hepatectomy. Major hepatectomy increases relative amount of portal inflow of residual liver. Because UL-VWFM is stretched by high share stress, a large amount of ADAMTS 13 may be consumed (Figure 6). Decrease of ADAMTS13 may be a possible indicator of postoperative liver dysfunction. From our findings, 40% may be the safe line of ADAMTS13 activity after hepatectomy[16]. Replacement therapy for decreased ADAMTS13 may prevent postoperative liver dysfunction.

Recent study also reported decrease of ADAMTS13 after major hepatectomy[50]. The study showed correlation between increased VWF to ADAMTS13 ratio and thrombotic complication after major hepatectomy. Melloul *et al*[51] refered to the possible role of ADAMTS13 activity in development of pulmonary embolism after hepatectomy. Correlation between overt embolism and decreased activity of ADAMTS after hepatectomy is needs to be further elucidated.

THROMBOCYTOPENIA AND TRANSFUSION OF PLATELET CONCENTRATES

Various degrees of thrombocytopenia are commonly observed in cirrhotic patients and in those who received surgical interventions, such as liver transplantation and hepatectomy[52,53]. Before discovery of ADAMTS13, transfusion of platelet concentrates to these patients has been simply and routinely performed to prevent hemorrhagic events. But after discovery of ADAMTS13, the investigators have become cautious to platelet transfusions to such patients. This is because our groups of investigators have shown that a significant decrease of plasma ADMTS13 activity and vice versa a remarkably high plasma concentration of VWF, containing UL-VWFM, are both frequently observed in patients with various liver diseases including surgical interventions[15,16,20]. These circumstances generate an extremely high plasma ratio of VWF or UL-VWFM to ADAMTS13, that lead to an unstable condition forming platelet thrombi by UL-VWFM
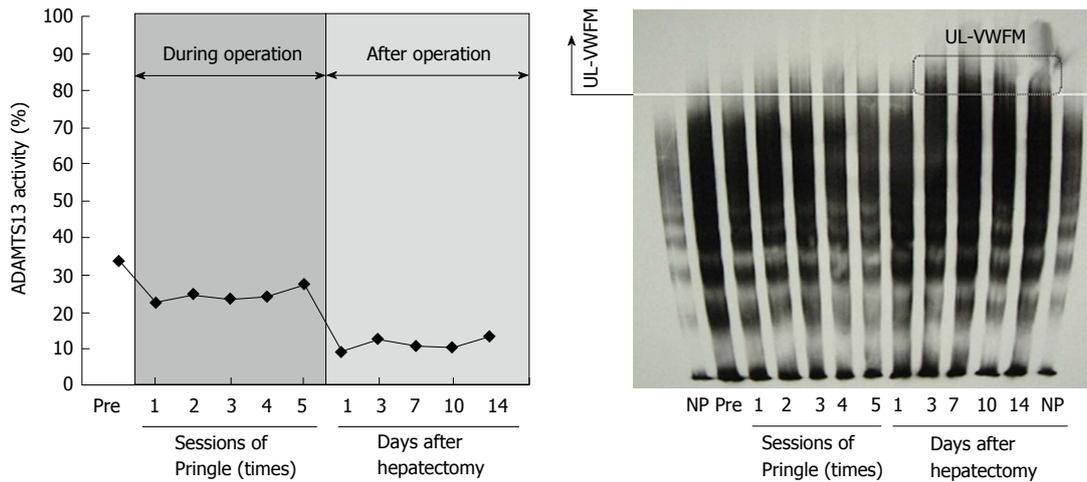
Figure 5 Perioperative changes of a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13 activity and unusually large von Willebrand factor multimers in a patient with large hepatectomy. The patient underwent long Pringles's maneuver (75 min). While ADAMTS13 did not decrease during hepatectomy even with long ischemic time by hepatic inflow occlusion, the activity markedly decreased until the next day. Consistently, UL-VWFM did not appeared during hepatectomy, and significantly up-regulated from day 3. Pre: Before transplantation; NP: Normal plasma controls; UL-VWFM: Unusually large von Willebrand factor multimers; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13.

Figure 6 Hypothesis about mechanism of liver dysfunction *via* the local thrombotic thrombocytopenic purpura like mechanism. UL-VWFM: Unusually large von Willebrand factor multimers; ADAMTS13: A disintegrin-like and metalloproteinase with thrombospondin type-1 motifs 13.
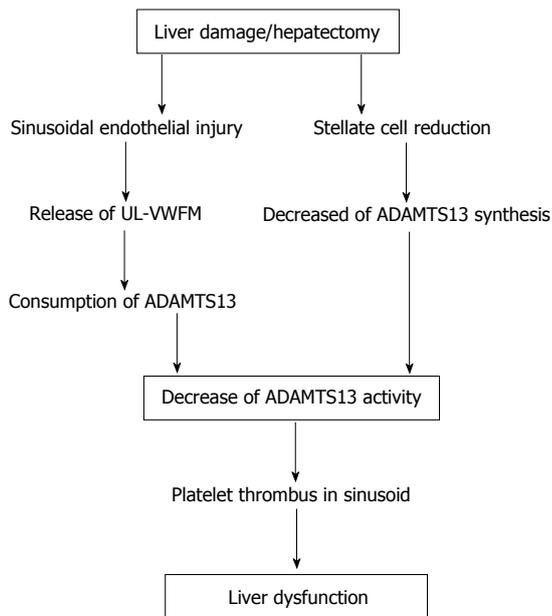
under high shear stress generated in microvasculatures, and may induce multiple organ failure resembling to TTP. Actually, porto-pulmonary hypertension exacerbated by platelet transfusion in a patient with ADAMTS13 deficiency due to platelet aggregation in microcirculation of the liver and lung, and the pulmonary arterial pressure fell after replacement of plasma ADAMTS13 by infusion of FFP[54]. Thus, our opinion is that the measurement of plasma ADAMTS13 activity is pre-requisite during the clinical course in these patients, and the prophylactic platelet infusion is better to be avoided or rather contraindicated. However, we also must emphasize

that platelet transfusions should be performed if overt bleeding once developed, supplying ADAMTS13 by infusion of FFP simultaneously.

CONCLUSION

ADAMTS13/UL-VWFM paradigm, which we advocated, is a new concept in the field of liver disease and surgery. The partnership between hematology and hepatology not only suggests a novel mechanism for thrombocytopenia, but also provides a useful diagnostic tool for the treatment of thrombocytopenia and liver dysfunction in patients with various liver diseases. Introduction of ADAMTS13 activity assay system as a routine clinical laboratory tests may help to prevent inadequate platelet transfusion. The efficacy of preemptive supplementation of ADAMTS13 activity by administrating FFP as a source of ADAMTS13 after liver surgery should be investigated in view of ADAMTS13/UL-VWF dynamics. We are particularly interested in developing recombinant ADAMTS13 preparations, which provides a new therapy for patients with hematologic and various liver diseases.

ACKNOWLEDGMENTS

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