

## Fibrinogen status in relapse and remission of childhood nephrotic syndrome

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### ABSTRACT

**Objective** To evaluate fibrinogen concentration of relapsing nephrotic syndrome (NS) in children, and to investigate relationship between fibrinogen with albumin and cholesterol.

**Methods** A cross-sectional study among NS patients admitted to pediatric outpatient clinic and pediatric ward at Sanglah Hospital, Denpasar, from November 1, 2003 to January 31, 2004. All patients were evaluated for clinical and laboratory findings of relapse and remission, including edema, proteinuria, serum albumin, total cholesterol, as well as total platelet count and fibrinogen concentration to evaluate coagulation parameters in nephrotic patients.

**Results** There were 36 patients with the mean age of 7.4 (SD 2.3) years included in this study. Mean fibrinogen concentration in relapse state was 671.8 (SD 102.7) mg/dl, while in remission state was 255.2 (SD 50.5 mg/dl); the mean difference was 416.6 mg/dl (95% CI 362.9;470.4;  $P<0.001$ ). Fibrinogen was inversely and strongly correlated with serum albumin concentrations ( $r=-0.91$ ;  $P<0.001$ ). Fibrinogen was positively and strongly correlated to total cholesterol ( $r=0.80$ ;  $P<0.001$ ). Using multiple regression analysis, it was shown that only relapse/remission status was significantly associated with fibrinogen concentration ( $P<0.001$ ).

**Conclusion** Fibrinogen status is significantly correlated with relapse and remission status of NS in childhood patients. [Paediatr Indones 2006;46:149-153].

**Keywords:** nephrotic syndrome, fibrinogen, children

**N**ephrotic syndrome (NS) is characterized by the presence of edema, massive proteinuria, hypoalbuminemia, and hypercholesterolemia. It is reported that the annual incidence of NS is between 2 and 7 per 100 000 children between the ages of 1 and 18 years.<sup>1</sup> Wirya<sup>2</sup> found the annual incidence of NS in Jakarta

of 6 per 100 000 children below age 14 years. Although the most common clinical manifestation of NS is generalized edema, patients are at risk of developing other problems, such as bacterial infections, electrolyte abnormalities, and thromboembolic complications.<sup>3</sup>

The association between hypercoagulability and thromboembolic complications in NS is well documented.<sup>4,5</sup> The reported incidence is 1.8% to 5.3% among children, and children with secondary NS have a higher incidence of thrombotic events than those with minimal change disease.<sup>6</sup> Thromboembolic complications include venous or arterial circulation, involving pulmonary vessels, inferior vena cava, renal vein, mesenteric artery with small bowel necrosis, femoral artery, retinal artery, and coronary artery. The frequency of renal vein thrombosis is 35%. Pulmonary embolism is the most serious complications, accounting about 8%.<sup>4</sup> Hypercoagulable state probably has multifactorial etiology. It is influenced by alterations in plasma concentration of many proteins involved in the regulation of clotting and fibrinolytic systems such as fibrinogen, AT-III, protein C, and protein S.<sup>7</sup> Hemocon-

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tration and hyperviscosity, relative immobilization, corticosteroid therapy, and diuretics may contribute to thromboembolism in nephrotic patients.<sup>8</sup>

Childhood NS, in contrast to the adult form of the disease, usually exhibits episodes of remission and relapse related to steroid therapy. However, attempts to find a relationship between aberrations in the hemostatic system and the activity of the nephrosis, the underlying renal histology, and the response to steroid therapy, produced conflicting results. Elidrissy *et al*<sup>9</sup> recorded increased concentrations of wide variety of clotting factors during the relapse and normalized with clinical remission. They concluded that these changes were determined by the response to steroid and not by the renal histology *per se*. On the other hand, Alkjaersig *et al*<sup>5</sup> reported elevated concentrations of fibrinogen in certain histological types of NS, and these changes normalized with remission. The aim of this study was to evaluate the fibrinogen status of relapse and remission of children with NS and to investigate the relationship between fibrinogen with albumin and cholesterol.

## Methods

A cross-sectional study was conducted in the pediatric outpatient clinic and pediatric ward from November 2003 through January 2004 at Sanglah Hospital, Denpasar. All subjects who fulfilled the criteria of NS were recruited. NS was defined by massive proteinuria (qualitative  $\geq +3$  or quantitative  $>40$  mg/m<sup>2</sup>/hour), hypoalbuminemia (serum albumin concentrations below 2.5 g/dl), edema, and hyperlipidemia. Remission was defined by protein-free urine (negative or trace dipstick) in 3 consecutive days. Relapse was defined by massive proteinuria for 3 consecutive days after history of remission. All patients having abnormal liver functions and bleeding disorders (investigated by history and clinical manifestation) were excluded from the study. The study has been approved by The Human Study Ethical Committee of Sanglah Hospital. The nature and purpose of the study was explained to the parents of all subjects, and informed consent was obtained before any subject was investigated.

All patients who fulfilled the criteria were evaluated for clinical and laboratory sign of relapse and remission, including edema, proteinuria, serum albumin,

total cholesterol, as well as clotting, and thrombotic parameters. Total platelet count and fibrinogen concentrations were measured to evaluate the coagulation state.

Qualitative proteinuria was determined using sulpho-salicylic acid (SSA) reagent which value ranges between (-) to (+4). Platelet count was measured with Cell-Dyn 3700 (Abbott). Serum albumin and total cholesterol levels were determined using Synchron CX System (Beckman Coulter). Fibrinogen was determined according to the Clauss method (Fibriquik, bioMerieux, France).

Independent *t*-test, correlation, and multiple regression analysis were used for statistical analyses and comparison of the results. Data were analyzed using SPSS 11.5 software for Windows, while the level of significance was considered as  $P < 0.05$ . Data were presented as confidence interval (CI) 95%.

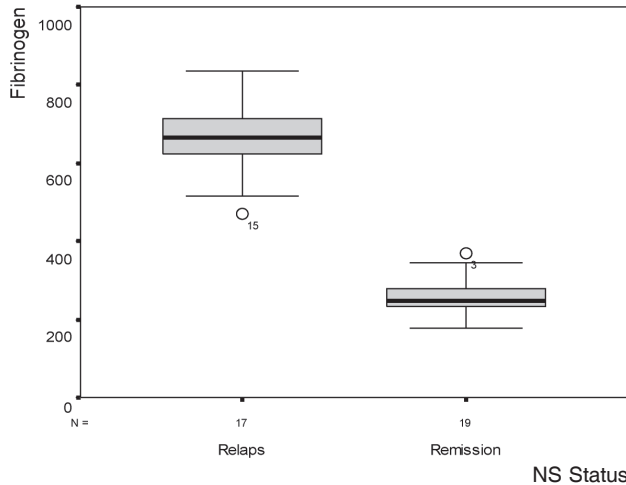
## Results

During the study period from November 1, 2003 to January 31, 2004, we found 36 patients with NS. Baseline characteristics of the patients were summarized in **Table 1**. Mean platelets count was 421.0 (SD 115.9) K/ $\mu$ l. The mean fibrinogen concentration of the nephrotic children was 451.9 (SD 224.9) mg/dl (above normal limits). Seven patients had fibrinogen concentrations above 700 mg/dl.

The results of the fibrinogen concentrations were compared between those with relapse and remission (**Figure 1**). Mean fibrinogen concentration in the relapse was 671.8 (SD 102.7) mg/dl, while in patients with remission was 255.2 (SD 50.5) mg/dl. Mean dif-

**TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS**

Characteristics	Value
Age, mean (SD) years	7.4 (2.3)
Sex n (%)	
Male	19 (53%)
Female	17 (47%)
Relapse	17 (47%)
Remission	19 (53%)
Blood pressure, mean (SD)	
Systolic (mmHg)	111.4 (11.1)
Diastolic (mmHg)	73.5 (11.9)
Albumin, mean (SD) g/dl	2.5 $\pm$ 1.5
Cholesterol, mean (SD) mg/dl	338.1 $\pm$ 181.1
Platelet, mean (SD) (K/ $\mu$ l)	421.0 $\pm$ 115.9
Fibrinogen, mean (SD) mg/dl	451.9 $\pm$ 224.9



**FIGURE 1.** FIBRINOGEN CONCENTRATIONS BETWEEN THOSE WITH RELAPSE AND REMISSION

ference between the two groups was significant [416.6 mg/dl, CI 95% (362.9; 470.4),  $P < 0.001$ ].

The correlations between changes in coagulation parameters and biochemical findings were also investigated. Fibrinogen was inversely and strongly ( $r = -0.91$ ;  $P < 0.001$ ) correlated with serum albumin concentrations (**Figure 2**) with regression equation  $y = 809.5 - 140.5x$  (albumin). Fibrinogen was positively and strongly correlated with cholesterol ( $r = 0.80$ ;  $P < 0.001$ ) with regression equation  $y = 115.8 + 0.99x$  (cholesterol) (**Figure 3**).

In order to analyze the association between some independent factors including relapse/remission status, serum albumin, or cholesterol and fibrinogen con-

centration as dependent factor, we use multiple regression analysis. Only relapse/remission was shown to be significantly associated with fibrinogen concentrations ( $P < 0.001$ ) (**Table 2**).

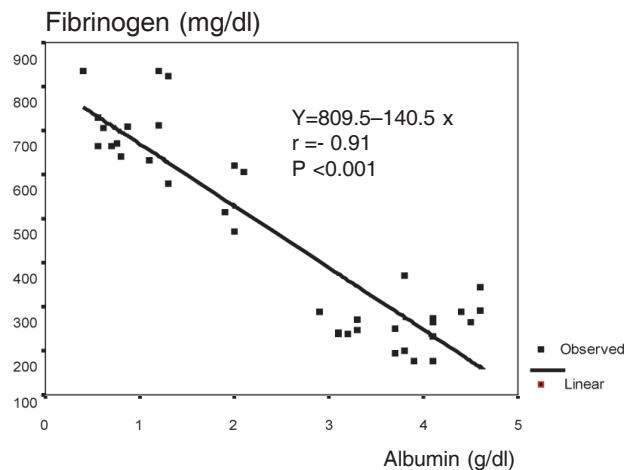
**TABLE 2.** RESULTS OF MULTIPLE REGRESSION

	B	SE	P	95% CI
Albumin	-35.448	27.619	0.208	-91.74 - 20.770
Cholesterol	7.392E-02	0.139	0.599	-0.21 - 0.357
Relapse/remission	-300.705	69.866	<0.001	-443.0 - -158.4

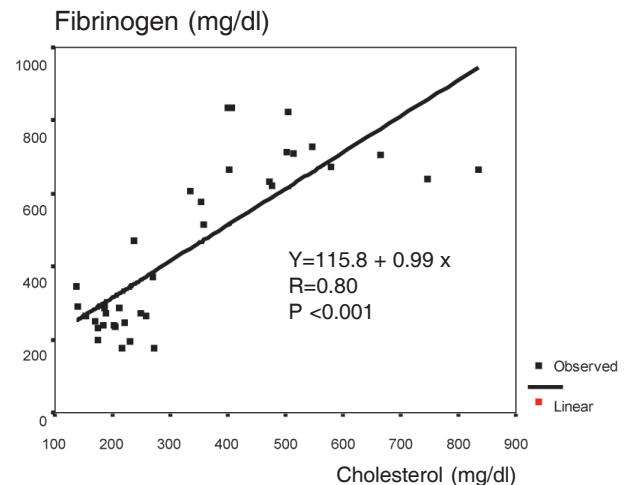
## Discussion

Patients with NS are at increased risk of thromboembolic complications. This risk has been attributed to a variety of intrinsic factors, such as coagulation protein abnormalities, impaired fibrinolysis, and increased platelet aggregation, as well as extrinsic factors such as dehydration, trauma, diuretic, and corticosteroid use.<sup>3,4,7</sup> The coagulation system in healthy individuals is dependent on a fine homeostatic balance between pro and antithrombotic factors. Therefore, a hypercoagulability state can result either from a decrease in thrombolytic or an increase in prothrombotic activity.<sup>10</sup>

Common coagulation abnormalities reported in association with NS include increased platelet aggregation and factors I, II, VII, VIII, and X, all of which can increase risk for thrombosis.<sup>4,7</sup> This, when coupled with a decrease in AT III, plasminogen, protein C, and protein S, all of which have an antithrombotic



**FIGURE 2.** THE RELATIONSHIP BETWEEN FIBRINOGEN AND SERUM ALBUMIN CONCENTRATIONS



**FIGURE 3.** THE RELATIONSHIP BETWEEN FIBRINOGEN AND TOTAL CHOLESTEROL CONCENTRATIONS

role, further increases the hypercoagulable state in nephrotic patients.<sup>7,10</sup> A coagulation abnormality in NS has generally been explained on the basis of urinary protein loss. High urinary loss of protein in NS is associated with increased synthesis of several proteins including coagulant factors, as compensatory response. The hypercoagulable state may result as consequences of these changes.<sup>4,6</sup> Increased hepatic protein synthesis is not sufficient to compensate for the renal loss of proteins with molecular weight (MW) below 70 000 daltons. However, it leads to a marked increase of plasma proteins with more than 100 000 daltons, which were not filtered in selective proteinuria. For proteins with MW between 70 000-100 000 daltons the urinary loss seems to be balanced by an increased rate of hepatic synthesis.<sup>11</sup>

Hoyer *et al*<sup>11</sup> found fibrinogen and a<sub>2</sub>-macroglobulin concentrations were inversely correlated with serum albumin, while AT-III correlated positively ( $P < 0.001$ ). These findings suggest an increasing risk for hypercoagulability when albumin is below 2 g/dl. Elidrissy *et al*<sup>9</sup> found fibrinogen concentrations were markedly elevated during the relapse of NS ( $P < 0.01$ ), and decreased slightly but remained above the control group in early and late remission. De Mattia *et al*<sup>12</sup> found that fibrinogen concentration was elevated at the onset of the disease, than decreased progressively near control values. Fibrinogen had positive correlation with cholesterol concentrations and negative correlation with albumin concentrations. AT III was only found to be decreased at the onset of the disease when proteinuria was elevated.

The plasma fibrinogen concentration is elevated at the relapse episodes. This can be explained as a manifestation of increased elevated hepatic protein synthesis, not balanced by urinary loss because of high molecular weight.<sup>8,11,12</sup> In this study, we found fibrinogen concentration was significantly high in the relapse episodes compared with remission.

Serum fibrinogen concentrations are elevated in response to hypoalbuminemia and proteinuria, and are known to cause sludging and thrombosis.<sup>5</sup> Our study showed significantly inverse relationship between serum fibrinogen and albumin concentrations among study subjects. Positive correlation was found between serum fibrinogen and cholesterol concentrations. Using multiple regression analyses, it was found that only relapse and remission status was significantly associated with fibrinogen concentrations.

While thromboembolic events are reported in adult with NS, they are much less commonly recognized in children. The incidence of thromboembolic events in children with NS has been reported to range from 1.8% to 5.3%. This discrepancy may be in part explained by the misclassification or underdiagnosis of such events.<sup>6,10</sup> Moreover, compared with adults, nephrotic children have increased amount of protein C and a<sub>2</sub>-macroglobulin (which has fibrinolytic activity), both of which may be protective against the development of thrombi.<sup>8,11</sup> Although the risk of thrombotic events in children with NS might be lower, there is evidence that the implications of such events are greater in children. Ulinski *et al*<sup>13</sup> in their reports found mesenteric thrombosis which was responsible for a 240 cm small bowel necrosis of a 7-year-old boy, necessitating bowel resection. In the study of Hoyer *et al*<sup>11</sup> in which 26 children with NS were evaluated with pulmonary ventilation and perfusion studies during remission, a surprising 26.9% had evidence of pulmonary embolism. It is possible that the use of angiography, Doppler ultrasonography, or pulmonary perfusion/ventilation isotope scanning more useful in detecting thromboembolic complications in NS.<sup>14</sup> It is worth mentioning that, beside hemostatic changes, other factors, such as hemoconcentration, immunological injury, diuretics, and steroid therapy can participate in the development of thrombosis in NS.<sup>12</sup>

Our study was limited by the method we used, i.e. cross sectional and small number of patients. By using cohort observational method, we will be able to see the coagulation changes in the clinical course from relapse to remission episodes of NS. Other limitation was, we only investigated fibrinogen concentrations, while platelet aggregation, AT-III, protein C, and protein S were not evaluated.

In conclusion, we have shown that the increase of fibrinogen correlated to the relapse and remission episodes of NS. The study has emphasized the importance of relapse and remission status in understanding the fluctuations in fibrinogen concentrations in childhood NS. If facilities are available, one should perform detailed coagulogram including proteins C and S, and AT-III concentrations. This study still has some limitations, so that further investigation is needed to shed more light on this coagulation abnormalities.

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