Thrombospondin-1 and blood pressure in 7 to 8-year-old children born low birth weight and small for gestational age

Marlyn Malonda, Adrian Umboh, Stefanus Gunawan

Abstract

Background Thrombospondin-1 (TSP-1) is associated with endothelial damage, glomerular impairment, and hypertension. Low birth weight (LBW) and small for gestational age (SGA) children have higher risk of morbidity and mortality.

Objective To assess for a possible association between TSP-1 level and blood pressure in children who were born low birth weight and small for gestational age.

Methods We conducted a cross-sectional study from March to May 2015. Inclusion criteria were children who were born LBW and SGA in 2007-2008 at Prof. Dr. R. D. Kandou General Hospital, resided in Manado, North Sulawesi, had complete medical records, and whose parents consented to their participation. Exclusion criteria were children who were in puberty, obese, had renal disease, taking medications that affect blood pressure, or who were admitted to the hospital in the 2 weeks prior to enrollment. Data were analyzed using regression and simple correlation tests to assess for associations between TSP-1 and birth weight, as well as TSP-1 and blood pressure.

Results Subjects' mean TSP-1 level was 257.95 ng/dL. There was a strong negative correlation between TSP-1 and birth weight (r=-0.784; P<0.0001). In addition, there were strong positive correlations between TSP-1 level and systolic blood pressure (r=0.718; P<0.0001) as well as TSP-1 and diastolic blood pressure (r=0.670; P<0.0001).

Conclusion Higher TSP-1 is associated with higher systolic and diastolic blood pressure in 7 to 8-year-old children who were LBW and SGA at birth. Also, TSP-1 and birth weight have a strong negative correlation. [Paediatr Indones. 2017;57:269-73; doi: http://dx.doi.org/10.14238/pi57.5.2017.269-73 ].

Keywords: thrombospondin-1; blood pressure; low
pathophysiology of SGA pregnancies. The TSP-1, an inhibitor of angiogenesis, is a cellular matrix protein that was identified during cell injury. This TSP-1 is present in vascular circulation and binds to cellular receptors and other proteins in the vascular structure.  

Few studies have been done to determine a direct relationship between TSP-1 level, birth weight, and blood pressure in animals, especially in children born LBW and SGA. Therefore, the objective of this study was to assess for possible associations between TSP-1 level and birth weight, as well as TSP-1 and blood pressure in 7 to 8-year-old children who were born LBW and SGA.

Methods

We conducted a cross-sectional study from March to May 2015 in Manado. The study was approved by the Ethics Committee of Sam Ratulangi University Medical School.

Subjects were healthy children who were born LBW and SGA seven to eight years prior to the study (2007-2008) in Prof. Dr. R.D. Kandou Hospital, had complete medical records, resided in Manado, North Sulawesi, and whose parents consented to participation. We excluded children who were in puberty, obese, had renal disease, taking medications that affect blood pressure, or who were admitted to the hospital in the two weeks prior to enrollment. Subjects underwent physical examination as well as anthropometric and blood pressure measurements. Body weight was measured using a platform beam balance scale. Blood pressure was measured in a quiet room in the subject’s house, with the subject in a resting position, using a standard sphygmomanometer with an appropriately-sized cuff. Subjects underwent three readings, taken in five-minute intervals. The three readings were averaged to obtain a mean value.

The onset of the first Korotkoff phase was used to determine systolic blood pressure, and the onset of the fifth Korotkoff phase was used to determine diastolic blood pressure. Blood specimens were drawn with aseptic technique. Thrombospondin-1 levels were measured and analyzed using Human TSP-1 by Quantikinine R&D Systems.

The correlation between TSP-1 level and blood pressure was analyzed using regression and simple correlation tests. The minimum required sample size was calculated to attain 90% power, and P values < 0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows version 22.0.

Results

During the study period, 128 LBW and SGA children were identified. However, 30 children’s families could not be reached by phone, 26 had moved away, and 10 parents refused to participate. Hence, the eligible study population was 62 children, but 17 of these were excluded due to lack of cooperation (2), illness (5), and obesity (10). Therefore, 45 subjects were recruited into the study.

Table 1 shows the subjects’ baseline characteristics. Subjects’ mean birth weight are 2,000 was 1,980g and mean TSP-1 level was 257.95 ng/dL.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n(%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (60)</td>
</tr>
<tr>
<td>Age, n(%)</td>
<td></td>
</tr>
<tr>
<td>7 years</td>
<td>29 (64.4)</td>
</tr>
<tr>
<td>8 years</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>Mean birth weight (SD), g</td>
<td>1,980 (148.24)</td>
</tr>
<tr>
<td>Mean TSP-1 (SD), ng/dL</td>
<td>257.95 (67.13)</td>
</tr>
<tr>
<td>Mean systolic BP (SD), mmHg</td>
<td>102.89 (9.91)</td>
</tr>
<tr>
<td>Mean diastolic BP (SD), mmHg</td>
<td>68.56 (8.02)</td>
</tr>
</tbody>
</table>

Figures 1, 2, and 3 show the relationships between TSP-1 levels and birth weight, as well as TSP-1 and systolic and diastolic blood pressures, respectively. There was a strong negative correlation between TSP-1 level and birth weight (r=-0.784; P<0.0001), a strong correlation between TSP-1 level and systolic blood pressure (r=0.718; P<0.0001), and a strong correlation between TSP-1 level and diastolic blood pressure (r=0.670; P<0.0001) in children with a history of LBW and SGA.
To the best of our knowledge, this is the first study to investigate TSP-1 levels and blood pressure in children with a history of LBW and SGA. A previous study in an animal model determined that blood pressure increased due to several factors, including arterial tone, and increased TSP-1 expression. Our findings suggest that the higher TSP-1 levels correlate to higher systolic and diastolic blood pressures. Strong positive correlations between TSP-1 level and systolic blood pressure \((r=0.718; P<0.0001)\) and diastolic blood pressure \((r=0.670; P<0.0001)\) were statistically significant. Our findings are consistent with those of Bauer et al.\(^8\) They measured blood pressure with a transducer implanted in the tails of mice and found a positive correlation between TSP-1 level and blood pressure. Circulating TSP-1 inhibits endothelial nitric oxide synthase (eNOS) activation in endothelial cells. TSP-1-null mouse endothelial cells have inherently greater eNOS activity. Thus, TSP-1 limits production of the diffusible vasodilator nitric oxide (NO). Addition of intravenous TSP-1 to TSP-1-null mice stimulated vasoconstriction that can increase blood pressure. Higher TSP-1 circulating in blood correlated with increased blood pressure.\(^8\)

Another study reported that in a rat model, TSP-1 level could increase diastolic blood pressure and mean arterial pressure (MAP). The integrity of the capillary wall was influenced by the level of TSP-1 circulating in blood. This result demonstrated for the first time that a matricellular protein acutely regulated blood pressure and cardiovascular responses to stress. Therefore, TSP-1 might act either as a direct vasoconstrictor or as an inhibitor of an endogenous vasodilator such as NO.\(^9\)

Circulating TSP-1 is related to the risk of renal disease, especially hypertension in later life, along with other possible mediators that may disturb biomarker pathways (related to oxidative stress, endothelial dysfunction, angiogenesis, capillary rarefaction, and transforming growth factor \(\beta1\)). The TSP-1 enhances fibrosis and renal damage by its interaction with the biomarkers mentioned above. This TSP-1 is expressed in glomerulopathies and is considered an early marker of inflammation and fibrosis. Increased TSP-1 can inhibit NO, that in turn causes vasoconstriction, significantly increased glomerulosclerosis, glomerular matrix accumulation, podocyte injury, renal infiltration with inflammatory cells, and altered renal function parameters.\(^{10-15}\)

Nevertheless, a comparison between human and animal models of TSP-1 levels and blood pressure should be viewed cautiously since TSP-1 levels and blood pressure in animal models may differ from human models.

We also found that TSP-1 levels in children with history of LBW and SGA were high, as well as
a negative correlation between TSP-1 level and birth weight ($r = -0.784; P < 0.0001$). Similarly, previous publications showed that birth weight was a risk factor for increased TSP-1 levels.\textsuperscript{16,17}

Isenberg \textit{et al}. reported that the expression of TSP-1 in wild type mice born SGA and aged between 14 to 18 months demonstrated greater degrees of ischemia in the glomeruli and tubulointerstitium of the kidney and formed atherosclerosis in the vessel walls. TSP-1 level was related to birth weight. Also, TSP-1 increased in response to cellular injury. TSP-1 binding to CD47 receptors inhibits NO signaling by preventing cGMP synthesis and activation of its target cGMP-dependent protein kinase. The CD47 is a ubiquitously-expressed transmembrane protein that is present on all cardiovascular cell types and platelets. This potent antagonism of NO signaling allows TSP-1 to acutely constrict blood vessels, accelerate platelet aggregation, and if sustained, inhibit angiogenic responses.\textsuperscript{16}

Andraweera \textit{et al}. found that increased TSP-1 levels in SGA infants increase the risk of cardiovascular and renal disease in later life. They noted TSP-1 to be a prothrombotic and anti-angiogenic glycoprotein expressed in blood vessels. A single nucleotide polymorphism in the TSP-1 gene (TSP-1 2210A/G) was reported to be a significant risk factor for familial premature myocardial infarction, hypertension, and renal disease, which was associated with SGA, suggesting that TSP-1 polymorphism may be associated with the risk of vascular disorders across the course of life.\textsuperscript{17}

In a rat study, TSP-1 expression was more prominent, especially in peritubular interstitial space. The percentage of glomeruli with positive intraglomerular TSP-1 staining was 19.3 (SD4.5) %; ($P < 0.0001$). Tubulointerstitial TSP-1 expression in the cortex was 8.8 (SD 4.2) tubules/mm$^2$. TSP-1 has been shown to both inhibit endothelial cell proliferation and accelerate endothelial cell death (apoptosis). In addition, Kang \textit{et al}. found that age-related TSP-1 expression was increased in both glomeruli and interstitium in rat kidneys. The increased TSP-1 expression strongly correlated with the degree of glomerulosclerosis, tubulointerstitial fibrosis, and glomerular hypertension.\textsuperscript{18}

Accumulations of TSP-1 in vascular tissue may increase the blood pressure at a younger age, especially in children with a history of LBW and SGA, as related to intrauterine retardation. Even from the time of conception, TSP-1 may affect inhibition of vascular vasodilation and apoptosis of glomerular membrane.\textsuperscript{5,7,9,15}

A limitation of this study was that the blood pressure measurements were performed on only one occasion. A 24-hour ambulatory measurement of blood pressure would be more accurate. Another limitation was that TSP-1 was measured only once, hence, further study is needed to monitor the TSP-1 levels in subjects.

In conclusion, 7 to 8-year-old children who were low birth weight and small for gestational age at birth have negatively correlated birth weight and TSP-1 level. Also, higher TSP-1 level is associated with higher blood pressure.

\textbf{Acknowledgements}

We were very grateful to Prof. Dr. Julius Lolombulan, MS, for his assistance with statistical analysis.

\textbf{Conflict of Interest}

None declared.

\textbf{References}

Marlyn Malonda et al: Thrombospondin-1 and blood pressure in low birth weight and small for gestational age