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Original Article

Obesity as a risk factor for dengue shock syndrome in children

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Abstract

Background Dengue hemorrhagic fever (DHF) leads to high morbidity and mortality if not be treated properly and promptly. Obesity may play a role in the progression of DHF to dengue shock syndrome (DSS) and could be a prognostic factor.

Objective To evaluate childhood obesity as a prognostic factor for DSS.

Methods We reviewed medical records of patients with DHF and DSS admitted to Department of Child Health, Dr. Sardjito Hospital, Yogyakarta between June 2008 and February 2011. Subjects were aged less than 18 years and fulfilled WHO criteria (1997) for DHF or DSS. The exclusion criteria were the dengue fever, a milder form of disease, or other viral infections. Risk factors for DSS were analyzed by logistic regression analysis.

Results Of 342 patients who met the inclusion criteria, there were 116 DSS patients (33.9%) as the case group and 226 DHF patients (66.1%) as the control group. Univariate analysis revealed that risk factors for DSS were obesity (OR=1.88; 95%CI 1.01 to 3.51), secondary infection type (OR=0.82; 95%CI 0.41 to 1.63), plasma leakage with hematocrit increase >25% (OR=3.42; 95%CI 2.06 to 5.65), platelet count <20,000/μL (OR=1.95; 95%CI 1.20 to 3.16), and inadequate fluid management from prior hospitalization (OR=9.11; 95% CI 1.13 to 73.66). By multivariate analysis, plasma leakage with hematocrit increase >25% was associated with DSS (OR=2.51; 95%CI 1.12 to 5.59), while obesity was not associated with DSS (OR=1.03; 95%CI 0.32 to 3.31).

Conclusion Obesity is not a risk factor for DSS, while plasma leakage with hematocrit increase >25% is associated with DSS. **[Paediatr Indones. 2013;53:187-92.]**

Keywords: *dengue hemorrhagic fever, dengue shock syndrome, obesity*

Dengue infection is a disease endemic to Indonesia, affecting an increasing number of patients.[1] It is a viral disease with high morbidity and mortality in children aged less than 15 years (86-95%), particularly in children aged 5-14 years.[2-4] The prevalence of morbidity and mortality of dengue hemorrhagic fever (DHF) varies across regions, mainly due to differences in age status of the population, vector density, spread rate of Dengue virus, Dengue viral serotype prevalence, and meteorological conditions.[5]

It is important for clinicians to recognize risk factors for dengue shock syndrome (DSS), in order to provide proper and prompt treatment, thus decreasing mortality due to DHF. Risk factors predicted to be associated with DSS were obesity,[6] platelet count <20,000/μL,[7] plasma leakage with hematocrit increase > 25%,[7] secondary infection,[8] and inadequate fluid management from prior hospitalization.[1,9]

Theoretically, increase production of interleukin (IL)-6, IL-8 and tumor necrosis factor- α (TNF-α) mediator in obese patients may have an association

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with DSS, due to progressive plasma leakage in DHF. Previous studies have reported that obesity contributes to the occurrence of DSS.[10-13] However, it is still unclear if obese children are at higher risk of developing more severe DHF, i.e. DSS, than non-obese children. The aim of this study was to evaluate obesity as a risk factor for DSS in children.

Methods

We assessed the possibility of obesity as a risk factor for disease severity in DSS and non-DSS patients. Subjects were aged less than 18 years, fulfilled WHO criteria (1997) for DHF or DSS and were admitted to the Department of Child Health at Dr. Sardjito Hospital, Yogyakarta from June 2008 to February 2011. We excluded patients with diagnoses of dengue fever or other viral infections.

Subjects were divided into two groups. The control group consisted of subjects with DHF grade I or II, positive tourniquet test, 2-7 days of fever, platelet count $<100,000/mm^3$, and positive signs of plasma leakage such as increased hematocrit, or having pleural effusion, or ascites. The case group included patients diagnosed with DHF grade III or IV, who met the above criteria of DHF grade I or II plus signs of shock, such as weak pulse, narrowing pulse pressure, poor tissue perfusion, clammy skin, and decreased urine output.

Sample size was calculated based on the formula for an unpaired case-control study,[14] in which the proportion of the effect on the control (P2) was 0.24;[6] clinically significant when odds ratios (OR) was 2; α was 0.05 ($Z\alpha = 1.96$) and β was 0,2 ($Z\beta = 0.842$). The minimum subjects required were 342 children.

Data was collected from medical records, clinical reports containing patients' data, parents, and disease history. Nutritional status was assessed by BMI (kg/m^2) for age, according to the WHO Growth Chart (2006).[15]

The determinant was obesity, whereas the outcome was dengue severity (DSS or DHF). Confounding factors were infection type, platelet count, fluid management during prior hospitalization, and plasma leakage. Children were classified as obese if their BMI for age was > 2 SD, and non-obese if BMI for age was ≤ 2 SD. Type of infection was classified as either primary or secondary infection. Primary infection was defined as having positive anti-dengue IgM. Secondary infection was defined as having positive anti-dengue IgM and IgG, or positive anti-dengue IgG alone. Mild thrombocytopenia was defined as having platelet count ≥ 20,000/uL. Severe thrombocytopenia was defined as having platelet count < 20,000/uL. Plasma leakage was defined as increased vascular permeability characterized by ascites, pleural effusion and increased hematocrit. Mild plasma leakage was defined as hematocrit increase ≤ 25%, while severe plasma leakage was defined as hematocrit increase >25%. Fluid management was classified as adequate at the previous hospital if the patient received the appropriate fluid requirement and fluid management protocol, while otherwise was classified as inappropriate.

Odds ratios with 95% confidence interval were calculated to assess an association between obesity and DHF severity. This study was approved by the Ethics Committee for Medical Research and Health, Gadjah Mada University Medical School.

Results

We included 342 subjects in this study, consisting of 116 (33.9%) children with DSS and 226 (66.1%) children without DSS. The basic characteristics of subjects of both groups are shown in **Table 1**.

Univariate and multivariate logistic regression analyses were performed to identify an association between obesity and DSS. Univariate analysis revealed that the significant risk factors for DSS were obesity, secondary infection type, platelet count <20,000/μL, plasma leakage with hematocrit increase > 25% and inadequate fluid management from prior hospitalization. For multivariate analysis, we included risk factors with P<0.25: obesity, low platelet count, plasma leakage with hematocrit increase >25% and inadequate fluid management from the prior hospitalization. Logistic regression analysis results are presented in **Table 2**.

Our results showed that obesity was not a risk factor for DSS (OR=1.025; 95% CI 0.32 to 3.31). However, plasma leakage with hematocrit increase > 25% was a risk factor for DSS (OR=2.51; 95% CI 1.12 to 5.59).

Table 1. Basic characteristics of subjects

Characteristics	DSS group (n=116)	non-DSS group (n=226)	Total (n=342)
Gender, n (%)			
Male	55 (47.4)	122 (54.0)	177 (51.8)
Female	61 (52.6)	104 (46.0)	165 (48.2)
Age, n (%)			
1-4 years	18 (15.5)	39 (17.2)	57 (16.6)
5-9 years	58 (50.0)	79 (35.0)	137 (40.1)
10-14 years	35 (30.2)	86 (38.1)	121 (35.4)
15-18 years	5 (4.3)	22 (9.7)	27 (7.9)
Nutritional status, n (%)			
Non-obese	93 (80.2)	93 (88.2)	294 (86.0)
Obese	23 (19.8)	23 (19.8)	48 (14.0)
Infection type, n (%)			
Primary	16 (13.8)	27 (11.9)	43(12.6)
Secondary	73 (62.9)	101 (44.7)	174 (50.9)
Missing data	27 (23.3)	98 (43.3)	125 (36.6)
Plasma leakage, n (%)			
Hct** increase > 25%	89 (76.7)	111 (49.1)	200 (58.5)
Hct** increase ≤ 25%	27 (23.3)	115 (50.9)	142 (41.5)
Pleural effusion, n (%)			
Yes	112 (96.6)	208 (92.1)	320 (93.6)
No	4 (3.4)	17 (7.5)	18 (5.3)
Missing data	0(0)	1 (0.4)	1 (0.3)
Ascites, n (%)			
Yes	97 (83.6)	86 (38.1)	183 (53.5)
No	19 (16.4)	139 (61.5)	158 (46.2)
Missing data	0 (0)	1 (0.4)	1(0.3)
Platelet count, n (%)			
< 20,000/µL	44 (37.9)	54 (23.9)	98 (28.7)
≥ 20,000/ µL	72 (62.1)	172 (76.1)	244 (71.3)
Previous fluid management, n (%)			
Adequate	56 (48.3)	51 (22.6)	107 (31.3)
Inadequate	10 (8.6)	1 (0.4)	11 (3.2)
Missing data	50 (43.1)	174 (77.0)	224 (65.5)
Bleeding manifestations, n (%)			
Yes	30 (25.9)	52 (23.0)	82 (24.0)
No	86 (74.1)	173 (76.6)	259 (75.7)
Missing data	2 (0.9)	1 (0.4)	1 (0.3)
Complications, n (%)			
Encephalopathy	15 (12.9)	1 (0.4)	16 (4.7)
DIC*	2 (1.7)	2 (0.9)	4 (1.2)
Septicemia	4 (3.4)	0 (0)	4 (1.2)
Prolonged shock	9 (7.8)	0 (0)	9 (2.6)
Lung edema	6 (5.2)	1 (0.4)	7 (2.0)
None	80 (69.0)	222 (98.3)	302 (88.3)

*DIC=disseminated intravascular coagulation

**Hct=hematocrit

Table 2. Univariate and multivariate analysis of risk factors for DSS

Risk factors	Univariate		P value	Multivariate*	
	OR	95% CI		OR	95% CI
Obesity	1.88	1.01 to 3.51	0.07	1.03	0.32 to 3.31
Secondary infection type	1.22	0.61 to 2.43	0.69	-	-
Plasma leakage with hematocrit increase >25%	3.42	2.06 to 5.65	0.00	2.51	1.12 to 5.59
Platelet count < 20,000/µL	1.93	1.20 to 3.16	0.01	0.95	0.44 to 2.07
Inadequate fluid management from prior hospitalization	9.12	1.13 to 73.66	0.02	8.10	0.98 to 66.70

* logistic regression analysis

Discussion

Based on our univariate and multivariate analyses, obesity was not a risk factor for DSS in our subjects (OR = 1.03; 95% CI 0.32 to 3.31), similar to several other studies.[1,6,9,16,17,18] However, in contrast to our results, Chuansumrit *et al*. showed that children with >50th percentile body weight for age were more likely to have grade III and IV DHF than those with lesser body weight (P=0.039).[19] Mongkalangoon found that obesity in children increased the risk of DSS (OR=3; 95% CI 1.2 to 7.48).[20]

Theoretically, obesity may affect the severity of dengue infection due to the increased production of white adipose tissue (WAT) which causes increased mediator production. Subsequently, progressive plasma leakage leads to higher risk of DSS. In keeping with the above hypothesis, excess fat tissue in obese patients should be measured using skin fold thickness, theoretically a more direct measure of adipose tissue compared to BMI for age. Not using skin fold as an indicator for obesity in our study may be the reason for the insignificant association between obesity and DSS. Mediators (IL-6, IL-8 and TNF-α) have also been thought to increase capillary permeability and may underlie the process of progressive and severe plasma leakage. However, Hung *et al*., in a study on interferon-γ and TNF-α levels in the acute phase of DHF and DSS patients, found that elevated levels did not differ between sexes (P=0.2) or nutritional status (P = 0.3).[21] Thus, further studies are needed to clearly define an association between obesity and DSS.

Plasma leakage with hematocrit increase > 25% was associated with DSS (OR=2.506; 95% CI 1.122 to 5.593) in this study. Similarly, Chuansumrit *et al*. reported that predictors for DSS were hematocrit increase > 25%, platelet count <40,000/μL, activated partial thromboplastin time (APTT) > 44 seconds, prothrombin time (PTT) > 14 seconds, and thrombin time (TT) > 16 seconds.[7] Tantracheewathorn *et al*. reported that DHF patients with bleeding and hemoconcentration > 22% showed earlier signs of shock (adjusted OR = 15.5; 95% CI 4.4 to 54.6).[9]

Several studies have shown an association between hematocrit level and DSS, although they used different cut-off values than our study. A retrospective study in Jakarta found that hematocrit level > 41.5% in DSS and DHF were found in 68% and 32% of patients, respectively (OR=1.7; 95% CI 1.1 to 2.6).[22] Malavige *et al*. reported hematocrit value > 45% in dengue fever and DHF was 11% and 58% of patients, respectively (P <0.001).[18] Kan *et al*. concluded that the hematocrit level of > 46% was associated with shock in DHF.[23]

Change in hematocrit value is a marker of plasma leakage and the bleeding process. As such, it may be used as a simple monitoring tool. However, hematocrit level cannot be used as an indicator of shock in DHF, since it is influenced by bleeding and fluid administration.[24] Bleeding may cause decreased hematocrit, while dehydration and plasma leakage may lead to increased hematocrit, tissue perfusion disturbances, and subsequently, shock.

Sarwanto reported that adequate fluid management at the beginning of the disease may reduce the risk of death in patients with DHF.[1] Tantracheewathorn *et al*. also mentioned that prompt and proper fluid management may stabilize the intravascular fluid and maintain stable hemodynamics, preventing the progression to shock.[9] However, we found that inadequate fluid management was not a risk factor for severity of DHF (OR=8.10; 95% CI 0.98 to 66.70).

Low platelet count may cause bleeding in DHF, accelerating the occurrence of shock. We found that the platelet count <20,000/μL did not relate to DHF severity (OR=0.93; 95% CI 0.43 to 2.02). In contrast, Dewi *et al*. found that patients with DSS often had platelet count <20,000/μL compared to that of non-DSS patients (OR=4.4; 95% CI 1.9 to 9.8).[22] Also, Kan *et al*. reported that platelet count <50,000/μL was associated with the occurrence of DSS.[23] Sutaryo found that most shock cases had platelet count <100,000/μL.[8] Our different results were probably due to inadequate data recording on bleeding. Of 342 subjects, only 1 had the bleeding volume recorded. Hence, our analysis of the relationship between severity of bleeding and DHF severity was not valid.

Type of infection was not a risk factor for DSS in this study (OR=1.33; 95% CI 0.36 to 4.96). However, it is believed that antibodies produced during dengue infection consist of IgG which inhibit virus replication in monocytes, namely, enhancing antibodies and neutralizing antibodies. Non-neutralizing antibodies produced during primary infection may result in the formation of immune complexes in secondary infection, stimulating viral replication. Therefore,

secondary infection by different serotypes tends to develop into more severe DHF manifestations (DSS).[5]

A limitation of this study was incomplete data collection, a consequence of a retrospective study using medical records. Missing data included lack of routine procedure examination, serologics for dengue infection diagnoses, and incomplete records on fluid management from prior hospitalizations. These problems may have led to bias and affected the results of this study. Another limitation of our study was the lack of IL-6, IL-8, and TNF-α measurements, as risk factors for severe DHF (DSS).

In conclusion, this study reveals that obesity is not a risk factor for DSS, while plasma leakage with hematocrit increase > 25% is associated with DSS.

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References

1. Sarwanto. Kematian karena DBD pada anak dan faktor penentunya. Surabaya: Pustlitbang Pelayanan dan Teknologi Kesehatan; 2007.
2. Halstead SB. Dengue haemorrhagic fever-a public health problem and a field for research. Bull World Health Organ. 1980;58:1-21.
3. World Health Organization (WHO). Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd ed. Geneva; 1997.
4. Suroso T, Umar AI. Epidemiologi dan Penanggulangan Penyakit Demam Berdarah Dengue (DBD) di Indonesia saat ini. In: Hadinegoro SR, Satari HI, editors. In: Naskah lengkap pelatihan bagi pelatih dokter spesialis anak & dokter spesialis penyakit dalam dalam tatalaksana kasus DBD. Jakarta: Fakultas Kedokteran UI; 2000. p. 14-31.
5. Soedarmo SSP, Garna H, Hadinegoro SRS, Satari HI. Buku ajar infeksi & pediatri tropis: infeksi virus dengue. 2nd ed. 2008. p. 155-60.
6. Kalayanarooj S, Nimmannitya S. Is dengue severity related to nutritional status? Southeast Asian J Trop Med Public Health. 2005;36:378-84.
7. Chuansumrit A, Puripokal C, Butthep P, Wongtiraporn W, Sasanakul W, Tangnararatchakit K, *et al*. Laboratory predictors of dengue shock syndrome during the febrile stage. Southeast Asian J Trop Med Public Health. 2010;41:326-32.
8. Sutaryo. Dengue. Yogyakarta: Medika Fakultas Kedokteran UGM; 2004.
9. Tantracheewathorn T, Tantracheewathorn S. Risk factors of dengue shock syndrome in children. J Med Assoc Thai. 2007;90:272-7.
10. Juffrie M, Meer GM, Haasnoot K, Sutaryo, Veerman AJ, Thijs LG. Inflammatory mediators in dengue virus infection in children: interleukin-6 and its relation to C-reactive protein and secretory phospholipase A2. Am J Trop Med Hyg. 2001; 65:70-5.
11. Bosch I, Xhaja K, Estevez L, Raines G, Melichar H, Warke RV, *et al*. Increased production of interleukin-8 in primary human monocytes and in human epithelial and endothelial cell lines after dengue virus challenge. J Virol. 2002;76:5588-97.
12. Novrianti H. Respon imun dan derajat kesakitan demam berdarah dengue dan dengue shock syndrome. Cermin Dunia Kedokteran. 2002;134:47-50.
13. Calabro P, Chang DW, Willerson JT, Yeh ET. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. J Am Coll Cardiol. 2005;46:1112-3.
14. Madiyono B, Moeslichan SM, Sastroasmoro S, Budiman I, Purwanto SH. Perkiraan besar sampel. In: Sastroasmoro S, Ismael S, editors. Dasar-dasar metodologi penelitian klinis. Jakarta: Sagung Seto; 2002. p. 259-87.
15. World Health Organization (WHO) and United Nations of Children's Funds (UNICEF). WHO child growth standards and the identification of severe acute malnutrition in infants and children. Geneva: WHO; 2006.
16. Anto S, Sebodo T, Sutaryo, Suminta, Ismangoen. Nutritional status of dengue haemorrhagic fever in children. Paediatr Indones.1983;23:15-24.
17. Thysakorn U, Nimmannitya S. Nutritional status of children with dengue haemorrhagic fever. Clin Infect Dis.1993;16:295-7.
18. Malavige GN, Ranatunga PK, Velathanthiri VG, Fernando S, Karunatilaka DH, Aaskov J, *et al*. Patterns of disease in Sri Lankan dengue patients. Arch Dis Child. 2006;91:396-400.
19. Chuansumrit A, Phimolthares V, Tardtong P, Tapaneya-Olarn C, Tapaneya-Olarn W, Kowsathit P, *et al*. Transfusion

requirements in patients with dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health. 2000;31:10-4.
20. Pichainarong N, Mongkalangoon N, Kalayanarooj S, Chaveepojnkamjorn W. Relationship between body size and severity of dengue hemorrhagic fever among children aged 0-14 years. Southeast Asian J Trop Med Public Health. 2006;37:283-8.
21. Hung NT, Lan NT, Lei H, Lin Y, Lien LB, Huang K, *et al.* Association between sex, nutritional status, severity of dengue hemorrhagic fever, and immune status in infants with dengue hemorrhagic fever. Am J Trop Med Hyg. 2005;72:370–4.
22. Dewi R, Tumbelaka AR, Syarif DR. Clinical features of dengue hemorrhagic fever and risk factors of shock event. Paediatr Indones. 2006;46:144-8.
23. Kan EF, Rampengan TH. Factors associated with shock in children with dengue hemorrhagic fever. Paediatr Indones. 2004;44:171-5.
24. Gatot D, Perubahan Hematologi pada infeksi Dengue. In: Hadinegoro SRH, Satari HI, editors. Naskah lengkap pelatihan bagi pelatih dokter spesialis anak dan dokter spesialis penyakit dalam dalam tatalaksana kasus DBD. Jakarta: Fakultas Kedokteran UI; 2000. p. 45.