

# The dynamic of Soluble Vascular Cellular Adhesion Molecule -1 (sVCAM-1) level in Overnutritious children with Dengue Infection



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Received: 2021-02-03  
Accepted: 2021-04-10  
Published: 2021-04-30

## ABSTRACT

**Introduction:** Dengue infection is still posed a significant medical challenge for pediatric population in developing countries. However, increased prevalence of overweight and obesity among children in those countries increased the possibility of the coexistence of these conditions. However, their interaction is still under investigated. Therefore, this study was aimed to study the dynamic of sVCAM-1 level as the known predictor of the severity of dengue infection with over nutritional status in children with dengue infection.

**Method:** An analytic observational nested case-control study was conducted in Paediatric Division Sanglah General Hospital, Bali. The children with DHF between 6 months old to 12 years old were included as the case group while control groups consisted of pediatric patients with just Dengue Fever (DF) with the same age range. The diagnosis of dengue was established using 1997 WHO criteria while nutritional status was assessed using WHO curve. The sVCAM-1 was evaluated using ELISA technique.

**Results:** The level of sVCAM-1 was significantly higher in patients with DHF than patients with DF only. The level was also fluctuated more in DHF patients. Likewise, the sVCAM-1 level was also significantly higher in DHF patients with overnutrition compared to normal DHF patients with a more fluctuated pattern over the course of 3 days (starting from day 4 to day 7). Finally, no significant finding was observed in sVCAM-1 level in DSS patients albeit the difference in concentration pattern.

**Conclusion:** Overnutrition is seems to be associated with higher concentration of sVCAM-1 and higher fluctuation of its concentration in children with DHF.

**Keywords:** Dengue, sVCAM-1, Overnutrition, Fluctuation.

**Cite This Article:** Saniathi, N.K.E., Juffrie, M., Rianto, B.U.D., Soetjningsih. 2021. The dynamic of *Soluble Vascular Cellular Adhesion Molecule -1* (sVCAM-1) level in Overnutritious children with Dengue Infection. *Bali Medical Journal* 10(1): 261-265  
DOI: 10.15562/bmj.v10i1.2304

## INTRODUCTION

Dengue hemorrhagic fever (DHF) affects 20/100.000 population in Indonesia annually and considered as one of important infectious diseases in South East Asia.<sup>1</sup> Children and adolescence are considered as vulnerable groups as these population comprised more than 50% of DHF patients.<sup>2</sup> Likewise, despite of the abundance of epidemiological study, only few studies had investigated in-depth about the DHF in children and the factors that affect its severity.<sup>2-4</sup>

Overnutrition is also an increasingly common findings in children, especially in Asiatic region.<sup>5,6</sup> The prevalence of overweight and obesity has been steadily increased in the last 20 years and they are

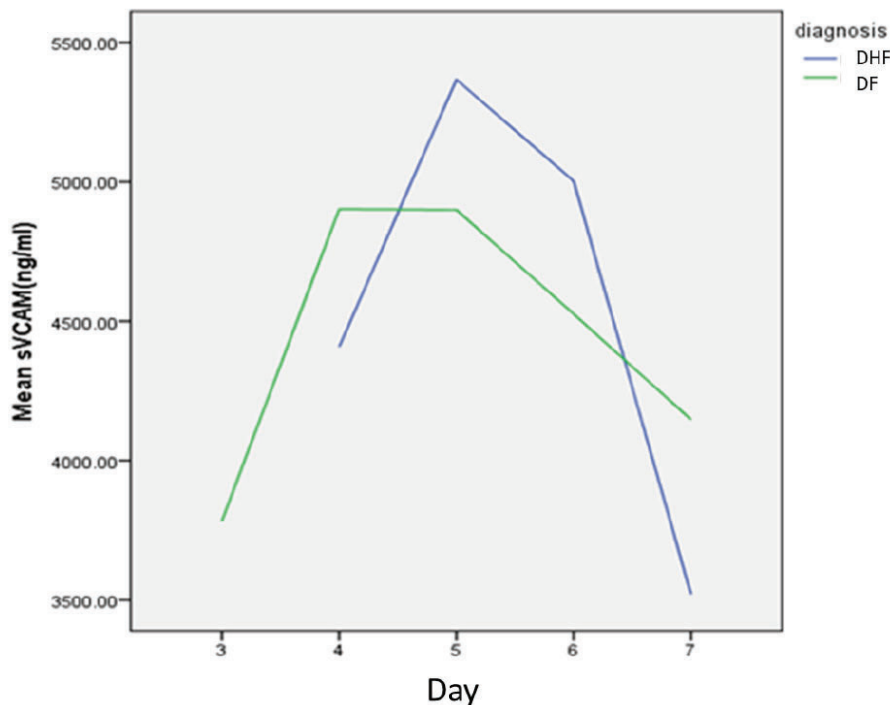
predicted to adversely affect the future health of the children, increasing their risk toward metabolic related diseases such as type 2 diabetes mellitus, hypertension, coronary heart disease, and dyslipidemia.<sup>6</sup> However, high prevalence of overnutrition also opened up a new possible interaction between this condition with infectious diseases commonly that occurred in tropical regions, but this possibility is rarely investigated.<sup>4</sup>

DHF and overnutrition share a similar pathogenic mechanism, albeit still unclear and need further rigorous investigation. Overnutrition causes chronic inflammation which is also the core mechanism in inducing the developments of chronic metabolic

diseases.<sup>7,8</sup> Similarly, DHF is also naturally induced inflammation which is mainly composed of Th1 immune response (anti-viral immune response).<sup>7,8</sup> However, superimposed inflammation if both conditions exist (overnutrition and DHF) is rarely investigated, but may have severe consequences.<sup>2-4</sup> Previous reports from our group showed that overweight was associated with increased risk of DSS. The level of sVCAM-1 was also higher in pediatric DSS patients with overnutrition compared to normal-DSS patients.<sup>9</sup> Increased level of VCAM-1 might indicate an active diapedesis of leukocytes and, possibly, more severe inflammation. Furthermore, adiponectin which is known as one of anti-inflammatory hormone, was

**Table 1.** The comparison of sVCAM-1 level between subjects with DHF and DF

Variable	Day of fever	N	DHF (n=40) Mean (SD)	n	DF (n=40) Mean (SD)	p
sVCAM-1 Level (ng/mL)	3	0	-	2	3783.39 (47.48)	0.039
	4	4	4407.77 (1209.35)	5	4901.92 (1315.08)	
	5	13	5366.89 (953.72)	11	4899.54 (1278.02)	
	6	21	5002.54 (970.11)	16	4525.52 (970.11)	
	7	2	3520.54 (419.21)	6	4147.32 (857.41)	

**Figure 1.** The trend of sVCAM-1 level in DHF and DF over the course of the infection

also significantly lower in DSS patients with overnutrition.<sup>10</sup>

Despite of the convincing evidences, the link between the two conditions is still elusive. However, considering its consequences, this interaction is need to be investigated further. Therefore, this study was aimed to evaluate the association between sVCAM-1 with the duration of fever in overnutritious pediatric patients with DHF.

## METHODS

An analytic observational nested case-control study was conducted in Paediatric Division Sanglah General Hospital, Bali, Indonesia from January 2015 to October 2016. This study was ethically approved by Research and Development Division of Sanglah General Hospital. The pediatric

patients with Dengue Haemorrhagic Fever as defined by World Health Organization (WHO) in 1997 which includes clinically diagnosed DHF and age between 6 months old to 12 years old were included in the case group. The control groups consisted of pediatric patients with just Dengue Fever (DF) with the same age range. Those which the parent disagreed to participate and having other infectious diseases were excluded from this study.

The DHF and DF were differentiated using 1997 WHO criteria. Dengue Shock Syndrome (DSS) is defined as DHF grade 3 and four while DF was defined as DHF grade 1 and 2. For nutritional status, the subjects would be classified into two categories namely normal nutritional status and overnutrition. To properly classify the subjects, the body weight

(BW) and body length (BL)/Body Height (BH) were measured and plotted as the WHO curve for children under two years of age and CDC for those who were older so the Ideal Body Weight (IBW) could be determined. The nutritional status then determined using Waterlow percentage which estimates the IBW according to the standard. Overnutrition was established if IBW > 110 % of standard and normal status if the IBW ranged between 90-110%. 3 ml of blood was collected from each subject and centrifuged at 2000 RCF to isolate the serum. The serums were stored at -80°C before sent to Eijkmann Laboratory in Jakarta for further analysis. The sVCAM-1 was measured using R & B system ELISA Kit according to manufacturer instruction. The categorical data were analyzed using Chi-square test or its alternative while numerical data were assessed using independent sample student t-test or its alternatives. Normality test was conducted prior further analysis for numerical data. Finally, odds ratio (OR) was calculated to estimate the extent of the risk of the case groups to control group. P-value < 0.05 was considered significant and all of the statistical analyses were conducted using SPSS version 17 for Windows.

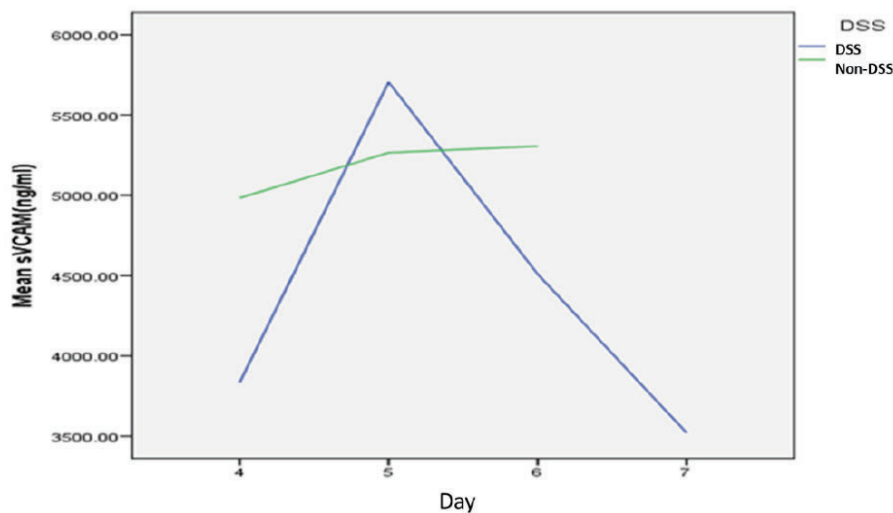
## RESULTS

40 children were eligible and enrolled as study subjects during the course of the study. The subjects were divided into control and case group depending on their nutritional status. Descriptive analysis showed that both groups had quite similar baseline characteristics and, thus, comparable for analysis.

Then the sVCAM-1 level in those who had DHF and DF was compared in fever day 3 to 7 (Table 1). As depicted, the level of sVCAM-1 was increasing from day 3 to 5 and declining afterwards. Also, the level of sVCAM-1 was higher in DHF

**Table 2.** The difference of sVCAM-1 level between DSS and non-DSS subjects between the day 4 and day 7 of fever.

Variable	Day of fever	DSS (n=15)		Non-DSS (n=25)		P
		n	Mean (SD)	n	Mean (SD)	
sVCAM-1 level (ng/mL)	4	2	3832.68 (1735.20)	2	4982.87 (231.82)	0.065
	5	3	5705.42 (867.88)	10	5265.34 (997.86)	
	6	8	4509.41 (805.52)	13	5306.01 (963.40)	
	7	2	3520.54 (419.21)	0	-	

**Figure 2.** The dynamic of sVCAM-1 level in DSS vs non-DSS subjects over the course of 4 days of fever (starting from day 4).

compared to DF in day 4-6 which was statistically significant. The trends of the dynamic of sVCAM-1 level in all subjects in both groups are presented in figure 1.

Then, the level of sVCAM-1 in DSS and non-DSS patients was analyzed according to the day of fever, starting from fever day 4. As depicted in the table 2 and figure 2, the level of sVCAM-1 was fluctuated more in patients with DSS compared to non-DSS, peaking at the 5<sup>th</sup> day. Comparatively, the sVCAM-1 level in non-DSS patients was more stable. However, the differences between the two groups were barely significant. Of note, there was no non-DSS patient recorded on the 7<sup>th</sup> day.

Finally, the level of sVCAM-1 was compared between DHF patients according to their nutritional status. As depicted in Table 3, the sVCAM-1 level was significantly higher in patients with overnutritions even from the 4<sup>th</sup> day and sharply dropped at the 7<sup>th</sup> day. Comparably, the sVCAM-1 level in control group was lower and had increasing trend until day 6. Unfortunately, no subject was recorded

on the 7<sup>th</sup> day which is hampering the comparison between the two groups. However, comparing the existing data between case and control groups shows that the difference in sVCAM-1 level between the two groups was statistically significant.

## DISCUSSION

Dengue infection is one of an urgent infectious problem in developing countries in tropical regions.<sup>11</sup> Despite of the advances in prevention, diagnosis, and treatment, this disease still contributes to a significant number of deaths annually, especially in pediatric population.<sup>1,11</sup> Furthermore, the behavior of this disease in special populations, such as obese and overweight children, is still largely unknown. However, previous studies conducted by our group had exposed important findings regarding the behavior of DHF in children with overnutrition.<sup>2-4,9,10</sup>

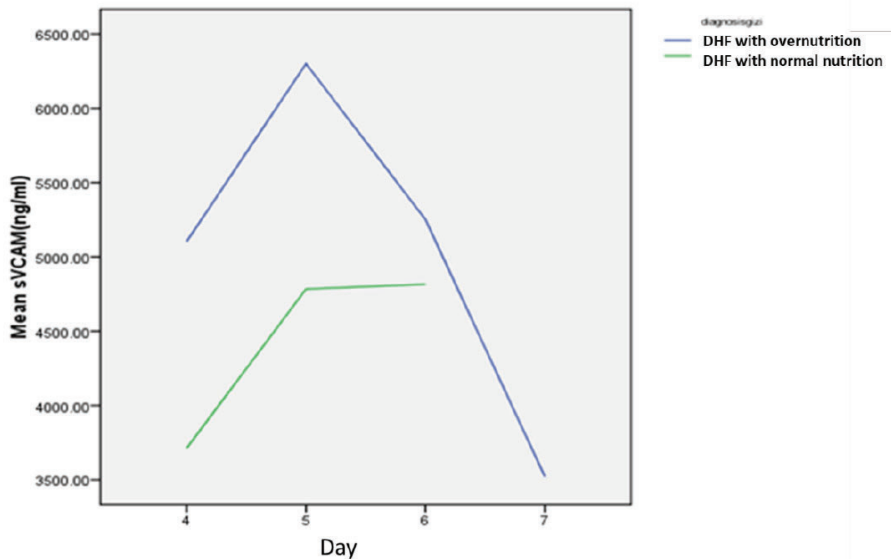
Evidences had shown that even in children, overweight and obesity results in impairment of immune response and the activation of chronic inflammation.<sup>12</sup> This phenomenon started from decreased production of adiponectin from adipose tissue, followed by increased synthesis of leptin, TNF- $\alpha$ , IL-6, and angiotensinogen.<sup>13</sup> Theoretically, this change should affect how the host responds to the infectious challenges, but there are only little evidences regarding this area and how it is affecting the clinical outcome of children with DHF.

This study was developed as a response from our previous findings. Previously we found that sVCAM-1 was significantly associated with over nutritional status in the children with DHF.<sup>9,10</sup> However, because of the acute nature of its expression and function, the dynamic of sVCAM-1 expression during the course of the disease is need to be investigated, in which there is currently no studies regarding this phenomenon. Therefore, our finding shed a light about the dynamic of sVCAM-1 level and, possibly, how the impaired immune response within children with overnutrition responded to dengue infection.

Our findings showed that the level of sVCAM-1 initially increased from day 3 to day 5 which is known as the critical period in the second phase of dengue infection. It was higher in patients with DHF than DF which might correlated with the more severe nature of DHF. Additionally, it also higher in children with DHF with overnutrition compared to their counterparts with normal nutritional status. However, the was no significant observable differences in DSS, albeit there was a sharp difference in sVCAM-1 trend between DSS with overnutrition and DSS with normal nutritional status. As far as we concern, this study is the first one that investigated sVCAM-1 in pediatric

**Table 3.** The comparison of sVCAM-1 level between DHF with overnutrition and the control group over the course of the disease

Variable	Day of Fever	n	DHF with overnutrition (n=18) Mean (SD)	n	DHF with normal nutritional status (n= 22) Mean (SD)	p
sVCAM-1 Level (ng/mL)	4	2	5103.2 (61.6)	2	3712.3 (1564.9)	0.035
	5	5	6299.9 (507.3)	8	4783.7 (633.8)	
	6	9	5251.4 (870.2)	12	4815.9 (1035.2)	
	7	2	3520.5 (419.2)	0	0 -	

**Figure 3.** The trend of sVCAM-1 level in children with DHF with overnutrition compared to DHF with normal nutrition

dengue infection with over nutrition.

The fluctuation of sVCAM-1 in all of our comparison models are still largely unexplainable. However, referring back to dengue virus pathophysiology, it may relate to the appearance of anti-dengue antibody that facilitate viral infection to macrophage which steadily increase the host's acute inflammation during the acute stage (day 1-4).<sup>14</sup> In the later stage, activation of Th2 immune response which boosts B cells proliferation and differentiation as well as antibody production suppress sVCAM-1 expression by lowering its inducer, IL-8.<sup>15</sup>

The inflammation theory also could explain the difference pattern of sVCAM-1 level in our subjects. Patients with overnutrition already have a chronic subclinical inflammation, in which they may have higher level of inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$  in their circulation.<sup>12</sup> Additionally, proinflammatory hormone such as leptin

and angiotensinogen are also produced in higher amount by the adipose tissue while the level of adiponectin decreased.<sup>8,12</sup> Thus, infectious agents such as dengue virus may induce a significantly higher level of inflammation in this population which may lead to severe outcome or longer hospital stay.<sup>3,4,6</sup> Our finding partially supports this argument because despite the non-significant result, the pattern of sVCAM-1 in patients with overnutrition was very dynamic compared to the control subjects.

However, our findings have several weaknesses in which the lack of association with additional clinical outcomes such as hospital stay, hemorrhage tendency, and overall general conditions is the most important ones. Furthermore, the samples were not collected serially which is less preferable in analyzing the trend of soluble factors. Analyzing the associated cytokines is also important to establish

the causality of the variables which was also not conducted in this study due to financial limitation. Future study should address these shortcomings in order to provide a more comprehensive insight about the relationship between nutritional status with DHF behavior.

## CONCLUSION

Overnutrition is associated with higher and more fluctuation trend of sVCAM-1 level. However, the findings still cannot fully explain the relevance of sVCAM-1 in clinical setting due to the absence of several clinical variables. Future studies should address these limitations in order to confirm the association between overnutrition with DHF behavior.

## CONFLICT OF INTEREST

All authors declared that there is no conflict of interest regarding the publication of this article.

## ETHIC APPROVAL

This study was ethically approved by Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada with ethical clearance number KE/FK/0026/EC/2016). A written informed consent was taken from all study subjects.

## AUTHOR CONTRIBUTION

All authors contributed equally in the research process and the writing of this article.

## FUNDING

This study was self-funded with no third-party contribution

## ACKNOWLEDGEMENT

The authors acknowledge and appreciate the contribution of the staffs of Pediatric Division Faculty of Medicine Udayana University/Sanglah General Hospital (dr. BNP Arhana Sp.A(K), DR. dr Dwilingga Sp.A(K), and dr Gustawan Sp.A(K), MSc) and ERIA Subdivision (DR. dr. Dyah Kanyawati, Sp.A(K), dr IB. Suparyatha Sp.A(K), and dr. Budi Hartawan Sp.A(K)), dr. Ketut Suarta Sp.A(K), the nurses from Jempiring Ward and Pediatric Intensive Care Unit of Sanglah General Hospital, medical record division, R. Tedjo Sasmono Ph.D.; Eijkman Institute for Molecular Biology, Jakarta; Prodia Laboratory, Denpasar; Biomolecular Laboratory of Faculty of Medicine and Health of Warmadewa University; Pediatrician Association of Bali; Mirah; Andhiko Suryo; Evans, Azel and Made Sutiasih.

## REFERENCES

- Utama IMS, Lukman N, Sukmawati DD, et al. Dengue viral infection in Indonesia: Epidemiology, diagnostic challenges, and mutations from an observational cohort study. *PLoS Negl Trop Dis.* 2019;13(10):e0007785. <https://doi.org/10.1371/journal.pntd.0007785>
- Zulkipli MS, Dahlui M, Jamil N, et al. The association between obesity and dengue severity among pediatric patients: A systematic review and meta-analysis. *PLoS Negl Trop Dis.* 2018;12(2):e0006263-e0006263. doi:10.1371/journal.pntd.0006263
- Trang NTH, Long NP, Hue TTM, et al. Association between nutritional status and dengue infection: a systematic review and meta-analysis. *BMC Infect Dis.* 2016;16:172. doi:10.1186/s12879-016-1498-y
- Pichainarong N, Mongkalagoon 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(2):283-288.
- Mazidi M, Banach M, Kengne AP, Group L and BPMC. Prevalence of childhood and adolescent overweight and obesity in Asian countries: a systematic review and meta-analysis. *Arch Med Sci.* 2018;14(6):1185-1203. doi:10.5114/aoms.2018.79001
- Mistry SK, Puthussery S. Risk factors of overweight and obesity in childhood and adolescence in South Asian countries: a systematic review of the evidence. *Public Health.* 2015;129(3):200-209. doi:10.1016/j.puhe.2014.12.004
- Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol.* 2017;13(11):633-643. doi:10.1038/nrendo.2017.90
- Ellulu MS, Patimah I, Khaza'i H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci.* 2017;13(4):851-863. doi:10.5114/aoms.2016.58928
- Saniathi NKE, Rianto BUD, Juffrie M., S. The Effect of Overnutrition Toward the Risk of Dengue Shock Syndrome in Pediatric Patient: In-Depth Investigation of sVCAM-1 and Adiponectin Level. *Bali Med Journal; Vol 7, No 1 (Available online 1 April 2018).* Published online 2018. <https://www.balimedicaljournal.org/index.php/bmj/article/view/912>
- Elmy Saniathi NK, Djoko Rianto BU, Juffrie M, Soetjningsih S. Dengue hemorrhagic fever: The role of Soluble E-Selektin, Soluble Intra Cellular Adhesion Molecule-1 (Sicam-1) and Soluble Vascular Cellular Adhesion Molecule -1 (Svcam-1) in overweight children. *Bali Med Journal; Vol 8, No 1 (Available online 1 April 2019).* Published online 2018. <https://www.balimedicaljournal.org/index.php/bmj/article/view/1289>
- Harapan H, Michie A, Mudatsir M, Sasmono RT, Imrie A. Epidemiology of dengue hemorrhagic fever in Indonesia: analysis of five decades data from the National Disease Surveillance. *BMC Res Notes.* 2019;12(1):350. doi:10.1186/s13104-019-4379-9
- de Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc.* 2012;71(2):332-338. doi:10.1017/S0029665112000092
- Ruiz LD, Zuelch ML, Dimitratos SM, Scherr RE. Adolescent Obesity: Diet Quality, Psychosocial Health, and Cardiometabolic Risk Factors. *Nutrients.* 2019;12(1):43. doi:10.3390/nu12010043
- Bhatt P, Sabeena SP, Varma M, Arunkumar G. Current Understanding of the Pathogenesis of Dengue Virus Infection. *Curr Microbiol.* 2021;78(1):17-32. doi:10.1007/s00284-020-02284-w
- Martina BEE, Koraka P, Osterhaus ADME. Dengue Virus Pathogenesis: an Integrated View. *Clin Microbiol Rev.* 2009;22(4):564 LP - 581. doi:10.1128/CMR.00035-09



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