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RESEARCH ARTICLE

The Association between Plasma Soluble ICAM-1 and Adiponectin with Over Nutrition in Pediatric Patients with Dengue Infection

Ni Kadek Elmy Saniathi[1*], Soetjiningsih[2], Bambang Udji Djoko Rianto[3], Mohammad Juffrie[4]

1. *Faculty of Medicine and Health science Warmadewa University, Denpasar-Bali, Indonesia.*
2. *Pediatric Department Faculty of Medicine Udayana University/Sanglah General Hospital, Denpasar-Bali, Indonesia.*
3. *Ear, Nose, and Throat-Head and Neck Department Faculty of Medicine Gadjah Mada University/Sardjito General Hospital, Yogyakarta, Indonesia.*
4. *Pediatric Department Faculty of Medicine Gadjah Mada University/Sardjito General Hospital, Yogyakarta, Indonesia.*

***Corresponding Author:** *Ni Kadek Elmy Saniathi*

Abstract

Introduction: Dengue Hemorrhagic Fever (DHF) is one of the urgent health problems in tropical countries, including Indonesia. On the other hand, the prevalence of overweight is also increasing among children even in developing countries. Recent studies proved that adiponectin has significant influence toward immune system. Therefore, this study aimed to provide a preliminary data about the relationship between overweight and DHF with sICAM-1 as the biomarker. Method: An analytic observational study with nested case control study design was conducted using 78 subjects. The DHF status was established using 1997 WHO criteria while the sICAM-1 and Adiponectin were assessed using ELISA technique. All of the data were statistically analyzed. Result: The baseline characteristics of the subjects between the groups were considered homogenous. The Odds ratio of overweight toward the risk of dengue shock syndrome (DSS) was found to be quite high at 2.89 (95% CI: 0.81 – 12.25) while the adiponectin level was also significantly different between overweight and normal subjects in DHF group. However, no significant difference was found in sICAM-1 level between the groups. Conclusion: It can be concluded that sICAM-1 and adiponectin level was differ between patient with over-nutrition than normal counterparts with over-nutritional patients tended to have higher sICAM-1 and lower adiponectin level. But the difference was not statistically significant.

Keywords: *Dengue hemorrhagic fever, Overweight, sICAM-1, Dengue shock syndrome.*

Introduction

Dengue viral infection is one of the urgent health problems in tropical countries, including Indonesia. The disease usually fluctuates seasonally and increase incidence can be observed during rainy season. Dengue infection incidence is still considerably high with WHO estimated that about 50-100 million infections occur globally including 500,000 cases of dengue hemorrhagic fever (DHF) and approximately 20, 000 mortality [1]. It also estimated that there are 120 vulnerable countries with 4 billion people at risk, particularly, the Asia-Pacific [2].

In Indonesia, dengue infection tend to occurs cyclically between wet and dry season, peaking during wet season when high precipitation provide suitable environment and standing water for breeding mosquito [3]. Children are particularly vulnerable to Dengue infection with peak incidence often found in children aged 1-15 years old. However, the incidence in over 15-years old population has been increasing since 1980 [4].

According to the WHO report, Indonesia has the highest DHF report among South-East Asia countries with 94,564 reported incidences in 2001-2011 and mortality

ranged from 472-1,446 death per year [5]. Estimating exact incidence is still proved to be difficult because of under-reported dengue cases in Indonesia. However, it is estimated that the incidence is ranged between 2.2-168.5 cases/100,000 in 2013 [4]. The most dangerous form of dengue infection is dengue shock syndrome, where massive plasma leakage result in sharp decrease in blood pressure and often associated with high mortality rate [6].

However, plasma leakage is the hallmark of DHF and occurs even before the onset of DSS. Until now, predicting DSS is still posed a challenge for clinician while the combination of routine laboratory evaluations such as platelet count, hematocrit, urine protein, Glasgow Comma Scale and creatinine only yielded 60.5% sensitivity and 65% sensitivity [7, 8].

The plasma leakage in DHF is the result of uncontrolled inflammation induced by the virus and infected macrophage [9]. The cytokines that released during this process induced several changes in endothelial cells, in which increased expression of ICAM is one of them. According to Chuang et.al, macrophage inhibitory factor (MIF) is the cytokines responsible for increased ICAM-1 expression via induction of MAPK and PI-3K signaling pathway [10].

It also reported that ICAM-1 and MIF increased in relation with the degree of dengue infection [10]. However, there is no study evaluating direct relationship between ICAM-1 and over nutritional status in relation to DHF severity to date. On the other hand, the prevalence of overweight is also increasing among children even in developing countries [11].

Overweight and related adipose tissue stress is associated with decreased secretion of adiponectin, a peptide hormone with prolific molecular effects including insulin sensitizer, lipid metabolism, and anti-inflammation [12]. Due to its immunoregulatory properties, it is suspected that children with obese and overweight are in increased risk of more severe dengue infection [13]. Tan et.al reported that overweight dengue patients have longer hospitalization time than the non-overweight counterparts [14]. In pediatric population, Zulkipli et.al also mentioned that there is 38% increased risk of developing severe dengue infection in overweight children [15]. However, the reason behind this phenomenon is still poorly understood [1].Therefore, this study aimed to provide a preliminary data about the relationship between overweight and DHF. Here, the sICAM-1 is evaluated as potential biomarker due to its close connection with dengue-associated inflammation. The difference level of sICAM-1 in DSS and non-DSS patient was also evaluated to provide better evidence of clinical potential of sICAM-1.

Methods

An analytic observational study with nested case control study design was conducted in Pediatric Department of Sanglah General Hospital, Denpasar, Bali from January 2015 to October 2016. This study had approved by the ethic committee and Research and Development Department of Sanglah General Hospital.

The case group included pediatric patients with DHF which diagnosed according to 1997 World Health Organization (WHO) criteria was included in the case group. The dengue infection was determined by: 6 months to 12 years old children with established DHF diagnosis while those which were not allowed to participate by their parents and acquiring another infectious disease were excluded.

The control group consisted of all children with Dengue Fever in the same period with the case group and selected by consecutive sampling according to the inclusion and exclusion criteria. The minimum of 78 samples were required to maintain research validity and calculated according to Zα= 1.96, and Zß = 80%.sICAM-1 assessments were conducted in Molecular Biology Department of Eijkmann Institute by professional laboratory officers.

The technique used was ELISA using R & B system kit with all procedures were following the manufacturer instruction. The DHF status was established using 1997 WHO criteria in which the grade 3 and 4 were classified as Dengue Shock Syndrome (DSS) while grade 1 and 2 were considered as non-DSS group. The nutritional status was classified into over-nutrition and normal. The body weight and body length/height recorded was plotted to WHO curve (for children aged <2 years old) and CDC 2000 curve (for children aged >2 years old) so the ideal body

weight (IBW) can be calculated. The IBW then plotted using Water low so the percentage would be obtained. The over-nutrition status was established when the percentage > 110 % while IBW within 90-110% considered as normal nutritional status. Chi-square or its alternative was used to analyze categorical data while the numeric data were analyzed by using unpaired t-test or its alternative. The mean differences between the two study groups were also analyzed by t-test or its alternative. The risk estimate was also calculated and expressed as odds ratio.

Result

78 pediatric patients with dengue infection were participated in this study and divided into overweight and normal group, each consisted of 39 subjects. The baseline characteristics of each group were measured, and used to assess the comparability between the groups (Table 1). The groups were considered as homogeneous because no significant differences in the baseline characteristics between them.

Table 1: The baseline characteristic of the research subjects

Variable	Case Group (DHF; N: 39)	Control Group (DF; N: 39)	p-value
Age (years) Mean (±SD)	7,40 (±3.6)	7,21(±3.5)	0.993
Sex **Male** **Female**	 19 (47.5%) 21 (52.5%)	 25 (62.5%) 15 (37.5%)	0.261
Type of Infection **Primary** **Secondary**	 5 (12.5%) 35 (87.5%)	 10 (25%) 30 (75%)	0,152
Nutritional Status **Over nutrition** **Normal**	 18 (45%) 22 (55%)	 11(27.5%) 29 (72.5%)	0.081
Body Length/Body Height (centimeter)	122.01(±26.66)	118.04 (±24.74)	0.869
Body Weight (kilogram)	30.39 (±16.37)	26.52 (±15.22)	0.622

The overall risk of over nutrition and DSS, as the most severe complication of DHF, was assessed using chi-square test with Odds Ratio (OR). Overall, there were 9 cases of DSS in each over nutrition and normal group, representing 64.28% of the over nutrition subjects and 37.5% of the normal group. The effect size was relatively large at 26.78% with OR 2.89 (95%CI: 0.81 – 12.25). Despite being non-significant, the OR can be considered as clinically meaningful since the value is > 2.00 and approaching 3.00.

Table 2: The risk assessment of over-nutritional status as compared to normal subject

	case (DSS)	control (non-DSS)	N	OR	95%CI
Over nutrition	9	5	14	2.89	0.81 – 12.25
Normal	9	15	24		
N	18	20	38		

Table 3 depicts the association between nutritional status with sICAM-1 and adiponectin in subjects with DHF and DF. It appeared that the level of sICAM-1 was higher than in normal counterpart but not statistically significant. On the other hand, adiponectin level was significantly higher in normal group. On the contrary, neither sICAM-1 and adiponectin level were significantly different between the two groups.

Table 3: The association between nutritional status sICAM-1 and adiponectin in subjects with DHF and DF

Variable	DHF with overnutrition (N: 17)	Normal DHF (N: 22)	p-value	DF with overnutrition (N: 11)	Normal DF (N: 29)	p-value
sICAM-1 Level (ng/mL) Mean (±SD)	415.34 (±137.29)	354.42 (±87.49)	0.123	385.80 (±191.19)	359.71 (±146.88)	0.989
Serum adiponectin level (ng/mL) Mean (±SD)	7.65 (±5.10)	16.82 (±9.97)	0.018	17.15 (±7.42)	16.99 (±8.34)	0.983

Finally, the association between sICAM-1 and adiponectin level toward DSS was assessed. As depicted in Table 5, both variables have no association with DSS. However, the level of sICAM-1 and adiponectin in DSS group appears to be higher than in non-DSS group despite not statistically significant.

Tabel 4: Comparison between the level of sICAM-1 and serum adiponectin in over nutrition DSS vs. non-DSS groups

Variable	DSS with overnutrition (N: 9)	Non-DSS with overnutrition (N: 9)	p-value
sICAM-1 level (ng/mL)	367.25 (±105.86)	313.34 (±68.65)	0.253
Serum adiponectin level (ng/mL)	5.89 (±2.76)	8.50 (±2.73)	0.115

Discussion

The epidemiological transition experienced by many developing countries, which marked by increasing prevalence of chronic diseases while still having considerably high incidence of infectious disease, posed a hidden grave potential [3]. Both of the disease groups (degenerative and infectious) are based on inflammation. Thus, the co-occurrence of infectious and degenerative diseases at the same time in the same individual could aggravate the morbidity as well as mortality.

The overweight and obesity are two examples of underlying causes of degenerative diseases and they have become worldwide epidemic [11]. Obesity could induce an adipose tissue stress that changes the endocrine properties of adipose tissue [12].

Normally, adiponectin is the primary hormone secreted by adipose tissue and it could comprise a significant percentage of blood protein. However, in obesity patients, the adiponectin secretion decrease significantly which reduce its effect on glucose and lipid metabolism [12]. In addition, recent reports suggested that adiponectin could also harbor an immune-regulatory property which extends the scope of its physiologic effects [13].

The interaction between overweight and dengue infection severity was the main issue that this study tried to resolve. Dengue infection is still occurs in high rates in many developing countries that experienced demographic changes [1, 2, 3]. Dengue infection induces remarkable immune reactions that that could be influenced by the decreased level of adiponectin [6, 15]. Decrease immune-regulatory properties from adiponectin could result in more deregulated immune activation which potentially increased the risk of the most devastated consequences of dengue infection: dengue shock syndrome.sICAM-1 is inter-membrane protein commonly found in activated endothelial cells [16].

The most common inducer of its activation is inflammation in the nearby tissue environment. Increased expression of ICAM-1 can be induced after the exposure of TNFα, IL-1 β and IL-8 to endothelial cells [6, 16]. Co-incidentally, these are also the most common cytokines released in dengue infection and in larger scale than typical infections [6]. The adiponectin also proved to regulate the production of these cytokines and it can be predicted that lower level of adiponectin could resulted in much higher increased in these cytokines and markedly elevate the risk of DSS [13].

As reported in several researches, the overweight and obesity significantly affected the properties of dengue infection. Tan et.al reported that overweight dengue patients have longes hospitalization time than the non-overweight counterparts[14]. In pediatric population, Zulkipli et.al also mentioned that there is 38% increased risk of developing severe dengue infection in overweight children [15].

However, Trang et.al highlighted that the association between nutritional status and BMI is still unclear and further studies with larger number of sample are required [17].This study is considered as consistent with aforementioned reports that pointed out the effect of nutritional status toward the risk of more severe form of dengue infection. Despite being non-significant, it was clearly showed that the overweight increased the risk of DSS and the level of sICAM-1, one of the markers of plasma leakage, was higher in pediatric DHF patients with over nutrition. Furthermore, the serum adiponectin level was proved to be lower in patient with over

nutritional status which, considering its molecular mechanisms, potentially increased the risk of DSS. To date, this is the first study that evaluates the association and possible link between sICAM-1 with DHF severity. However, this study has some limitations. First, the number of samples was considerably low to justify generalization of the findings. Second, the study was conducted only in one center, which may not represent all races in Indonesia. Therefore, larger multicenter study is needed to confirm this finding and to generate more generalizable results.

Conclusion

It can be concluded that sICAM-1 and adiponectin level was differ between patient with over-nutrition than normal counterparts with over-nutritional patients tended to have higher sICAM-1 and lower adiponectin level. Despite non-statistically significant findings, the OR of the over nutrition toward the risk of DSS was proved to be clinically meaningful.

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