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Research Article
Effect of Vitamin C Supplementation on Inflammation Marker in Obese Children: A Quasi-experimental Study

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Abstract

Background and Objective: The prevalence of obesity among school-aged children has increased. Obesity is commonly associated with an increased risk of cardiovascular disease as it increases secretion of inflammatory markers. Vitamin C has been shown to reduce inflammation. The current study examined the effect of vitamin C supplementation on high sensitivity-C reactive protein (hsCRP) and soluble intercellular adhesion molecules-1 (sICAM-1) levels in school-aged, Indonesian children. **Materials and Methods:** Twenty eight obese children aged 6-12 years old participated in our quasi-experimental study conducted in 2013. Subjects were classified into two groups: Intervention (300 mg day^{-1} vitamin C for 6 weeks) and control (50 mg day^{-1} vitamin C for 6 weeks). The hsCRP and sICAM-1 levels were measured in both groups before and after each individual supplementation. **Results:** The Mean±Standard Deviation baseline hsCRP level at baseline in the intervention and control groups was 1.77±1.24 and 3.84±4.00 mg L^{-1}, respectively ($p>0.05$). After 6 weeks, the mean hsCRP level in the intervention and control groups was 3.00±4.73 and 2.94±4.00 mg L^{-1}, respectively ($p>0.05$). There were no significant differences in hsCRP level within each group before and after treatment. **Conclusion:** The HsCRP levels in obese children included in the present study were higher than accepted normal values (<1.04 mg L^{-1}). Supplementation with vitamin C (300 mg day^{-1} total) for 6 weeks did not effectively reduce hsCRP levels among obese school-aged children. Further study is needed to determine a safe and effective dosage regimen of vitamin C for obese children at greater risk for cardiovascular complications.

Key words: High sensitivity-C reactive protein, obesity, vitamin C, school-aged children, inflammatory markers

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The prevalence of obesity among children in Indonesia is increasing[1]. A 2013 national survey reported that 8.8% of school-aged children were obese[2]. Obese children have a high risk of hypertension, diabetes mellitus type 2, metabolic and mental disorders[3-5]. The risk of cardiovascular problems among obese children is associated with the occurrence of inflammation and endothelial dysfunction[6]. Inflammation influences metabolic control, which negatively affects insulin sensitivity and glucose transport[7]. Thus, someone who is obese with increased levels of inflammatory markers may have physiological adaptations that negatively affect metabolic and cardiovascular health[8].

Previous studies among adult populations have shown an association between increased inflammatory marker levels and cardiovascular disorders[9]. For example, increased levels of Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6) and C Reactive Protein (CRP) have been shown to induce cardiovascular disease in both men and women and are also indicators of type 2 diabetes and metabolic disease[10]. Waist circumference and Body Mass Index (BMI) are also found to be strongly associated with elevated levels of TNF-α, IL-6 and CRP in both adults and children[11]. Increases in markers of inflammation are highest in obese children compared to children of normal weight[11,12].

Supplementation with antioxidants is a potential approach to reducing the risk of cardiovascular problems caused by inflammation. Vitamin C is an antioxidant that can stabilize free radicals and inhibit the chain reaction of free radical formation which can cause oxidative stress[13]. Previous studies among adults populations have shown that certain antioxidants can decrease inflammatory marker levels and improve endothelial function[14,15]. However, study on the effect of vitamin C supplementation on inflammation in obese children is limited. The current study aims to identify the levels of the inflammatory marker high sensitivity-CRP (hsCRP) as well as to determine the effect of vitamin C supplementation on the levels of high sensitivity-C reactive protein (hsCRP). The concentration of soluble intercellular adhesion molecules-1 (sICAM-1) was also measured to examine endothelial dysfunction among obese children.

MATERIALS AND METHODS

Study design and participants: The current study had a pre and post-test quasi-experimental design. Participants included obese children aged 6-12 years old from Makassar, Indonesia, with Body Mass Index (BMI) for age z-scores >2 Standard Deviation (SD) according to World Health Organization (WHO) growth standards[16]. Sixty obese children were identified after a preliminary screening of five elementary schools; 30 were eligible and willing to participate. Children on a medication/treatment program and/or suffering from chronic disease during the study period were excluded. Participants were randomly divided into two groups: Intervention (n = 15) and control (n = 15). However, two participants in the intervention group were eventually excluded because they did not follow the study protocol completely. Therefore, the intervention group included 13 children.

Study protocol: Ethical approval was obtained from the institutional ethical committee at Hasanuddin University (Makassar, Indonesia) prior to study onset. A written consent to permit the children to participate in the study was obtained from the parents. Participant body weight was measured by using a digital scale (Seca) and their standing height was measured by using Microtoise (Seca). The BMI for age z-scores were calculated using WHO AnthroPlus version 1.0.3 software[17]. All anthropometric measurements were performed by the investigator and a well-trained nutritionist.

The intervention group was given 100 mg of vitamin C tablet three times a day (300 mg day^{-1} total) for 6 weeks[18], while control participants were given a lower dose of vitamin C tablet (50 mg day^{-1} in one dose) for 6 weeks[19]. Measurement of hsCRP and sICAM-1 levels in each group was conducted before and after supplementation. Blood sample collection and laboratory analyses were performed by Prodia Clinical Laboratory, Makassar.

Data analysis: An independent t-test was used to compare anthropometric parameters as well as hsCRP and sICAM-1 levels, between intervention and control groups. Anthropometric parameters, hsCRP and sICAM-1 levels within each group were compared using a paired t-test. A $p<0.05$ was considered statistically significant.

RESULTS

The current study included a total of 28 obese children (16 males and 12 females) aged 6-12 years old (Mean±Standard Deviation, 10.2±0.8 years), which were divided into two groups: Intervention (n = 13) and control (n = 15) groups. The mean systolic blood pressure for all

participants at baseline was 111.3 mmHg, while mean hsCRP and sICAM-1 levels were 2.88 mg L^{-1} and 275.30 ng mL^{-1}, respectively (Table 1). Although mean hsCRP and sICAM-1 levels in the control group were slightly higher and lower, respectively, than in the intervention. No significant differences between these groups were found at baseline (Table 1). Intergroup differences after supplementation are shown in Table 2; neither hsCRP or sICAM-1 levels were significantly different between the groups ($p = 0.96$ and 0.06, respectively). The intervention group showed significant increases in body weight and body fat percentage before and after supplementation (Table 3). However, hsCRP levels were not significantly changed (after 3.002 mg L^{-1} and baseline 1.766 mg L^{-1}) as well as sICAM-1 levels (after 300.15 mg L^{-1} and baseline 295.79 mg L^{-1}). The control group showed no significant difference in hsCRP or sICAM-1 levels before and after supplementation (Table 4).

Table 1: Demographic, anthropometric and clinical variables at baseline

Variables	Intervention group (n = 13) Mean±SD	Control group (n = 15) Mean±SD	Total (n = 28)
***Gender**			
Male	7 (25.0%)	6 (21.4%)	9 (32.1%)
Female	6 (21.4%)	16 (57.1%)	12 (42.9%)
Age (years old)	10.20±0.90	10.20±0.80	10.20±0.8 (9-12)
Body weight (kg)	50.30±11.6	49.30±8.00	49.80±9.6 (33.7-77.8)
BMI (kg m^{-2})	25.60±3.60	24.90±2.20	25.20±2.9 (19.9-34.1)
BMI for age z-score (BAZ)	2.66±0.47	2.50±0.25	2.57±0.37 (2.0-3.4)
Body fat (%)	35.60±2.00	35.50±2.20	35.60±2.0 (32-40)
Systolic blood pressure (mmHg)	111.60±11.3	110.00±7.10	111.30±9.1 (90-130)
Diastolic blood pressure (mmHg)	75.70±4.90	74 .00±5.00	74.80±4.9 (70-80)
hs-CRP level (mg L^{-1})	1.77±1.24	3.84±4.00	2.88±3.18 (0.15-12.48)
sICAM-1 level (ng mL^{-1})	300.15±90.58	253.76±89.96	275.30±85.92 (107.2-26.54)

*Frequency is used, n (%). No significant differences were found between the intervention and control groups by independent t-test

Table 2: Comparison of anthropometric and clinical parameters between intervention and control group after 6 weeks supplementation

Variables	Intervention group (n = 13) Mean±SD	Control group (n = 15) Mean±SD	*p-value
Body weight (kg)	51.28±11.5	50.73±8.40	0.88
BMI (kg m^{-2})	25.40±3.50	25.10±2.30	0.78
BMI for age z-score (BAZ)	2.54±0.45	2.47±0.32	0.64
Body fat (%)	36.00±1.80	35.40±2.20	0.45
Systolic blood pressure (mmHg)	102.30±5.90	106.00±7.30	0.16
Diastolic blood pressure (mmHg)	73.00±7.50	74.60±6.30	0.55
hs-CRP level (mg L^{-1})	3.00±4.73	2.94±4.00	0.96
sICAM-1 level (ng mL^{-1})	295.79±90.58	234.44±1.67	0.06

*Probability using independent t-test

Table 3: Change in anthropometric and clinical parameters within the intervention group before and after supplementation

Variables	Before supplementation (n = 13) Mean±SD	After supplementation (n = 13) Mean±SD	*p-value
Body weight (kg)	50.37±11.61	51.28±11.5	0.042
BMI (kg m^{-2})	25.61±3.64	25.43±3.54	0.451
BMI for age z-score (BAZ)	2.66±0.47	2.54±0.45	0.077
Body fat (%)	35.60±2.00	36.00±1.80	0.040
Systolic blood pressure (mmHg)	111.60±11.3	102.30±5.90	0.012
Diastolic blood pressure (mmHg)	75.70±4.90	73.07±7.50	0.357
hs-CRP level (mg L^{-1})	1.766±1.25	3.002±4.73	0.322
sICAM-1 level (ng mL^{-1})	300.15±76.94	295.79±90.58	0.740

*Probability using paired t-test

Table 4: Change in anthropometric and clinical parameters in control group before and after supplementation

Variables	Before supplementation (n = 15) Mean±SD	After supplementation (n = 15) Mean±SD	*p-value
Body weight (kg)	49.38±8.06	50.73±8.46	0.028
BMI (kg m^{-2})	24.93±0.56	25.11±2.31	0.547
BMI for age z-score (BAZ)	2.50±0.25	2.47±0.32	0.603
Body fat (%)	35.50±2.20	35.40±2.20	0.546
Systolic blood pressure (mmHg)	111.00±7.10	106.00±7.30	0.140
Diastolic blood pressure (mmHg)	74.00±5.00	74.60±6.30	0.719
hs-CRP level (mg L^{-1})	3.841±4.00	2.938±1.67	0.257
sICAM-1 level (ng mL^{-1})	253.76±89.96	234.44±73.76	0.052

*Probability using paired t-test

DISCUSSION

The present study found the mean systolic blood pressure of obese school-aged children to be high, similar to previous reports[20,21]. The mean hsCRP levels in obese children included in the present study were also found to be higher than the normal (accepted) value (<1.04 mg L^{-1}) for children aged 4-18 years old[22]. Previous studies have shown that increased hsCRP levels in adult patients with cardiovascular disease versus healthy subjects can predict acute coronary events[23,24]. Although, serum hsCRP levels are an indicator of coronary heart disease risk particularly in obese children, it is unclear whether heightened levels are predictive of cardiovascular disease as the child ages.

Interestingly, baseline sICAM-1 levels were in the normal range (206.8-486.8 ng mL^{-1}) for all participants regardless of group[25]. In contrast, a previous study of adolescent populations showed that mean sICAM-1 levels among obese teens to be higher than those of non-obese teens[26]. Although, the present study found sICAM-1 levels in obese, school-aged children to be in the normal range, it is possible their levels will increase as they transition into adolescence or older.

The present study showed that vitamin C supplementation was not effective in modifying hsCRP levels in obese children. Conversely, several previous studies reported that vitamin C supplementation reduced heightened hsCRP levels in obese and non-obese adults[27,28]. This disparity is most likely due to differences in age, dosage and/or duration of treatment as adults were given higher doses of vitamin C in each of these studies for longer periods of time. For example, Block *et al.*[27] administered 1000 mg day^{-1} for 2 months, while Ellulu *et al.*[28] used 500 mg twice a day (1000 mg day^{-1} total) for 8 weeks. Meanwhile, this study used a total of 300 mg day^{-1} for only 6 weeks. We chose to use this lower dosage to decrease the risk of adverse effects caused by longer treatment and higher dosages of vitamin C in children[29].

The effect of supplementation with high doses of vitamin C in children is not well documented. Although one study reported that supplementation with 500 mg of vitamin C twice daily for 8 weeks in older children (14-18 years old) showed a positive outcome and decreased sICAM-1 levels[26], the safety and efficacy of this dosage in younger children remains unclear. Moreover, one previous study of vitamin C intake among adults showed that $\geq$1000 mg daily is associated with a higher risk of kidney stones[30], administration and dose in children should be carefully implemented. Therefore, further study to determine the safety and efficacy of higher doses able to decrease hsCRP levels among obese children is needed.

The current study has several limitations. First, this study is lack of random assignment and no non-obese control group and the number of subjects included in each group is relatively small. Second, we did not take into account the total daily intake of vitamin C from other sources for each participant. Nonetheless, the current study provides initial evidence that low doses of vitamin C for shorter time periods are less effective at decreasing hsCRP levels in obese children aged 6-12 years old.

CONCLUSION AND FUTURE RECOMMENDATIONS

The present study found that sICAM-1 levels in obese, school-aged children are in the normal (accepted) range, while hsCRP levels were found to be high. Supplementation with 100 mg of vitamin C thrice daily did not effectively reduce hsCRP levels in obese children aged 6-12 years old. Therefore, further study with higher doses of vitamin C and/or long administration periods is recommended. Future studies should consider the total intake of vitamin C, involve a larger sample size and apply a randomized control study.

SIGNIFICANCE STATEMENTS

Obesity is associated with a higher risk of cardiovascular disease by increasing inflammation and inflammatory markers, such as hsCRP. Vitamin C is an antioxidant that has been shown to reduce the risk of cardiovascular issues by reducing inflammation in adults. However, little is known about the effect of vitamin C supplementation on the levels of inflammation in obese, school-aged children. Thus, determining the occurrence of inflammation and identifying an appropriate treatment to reduce the inflammation marker among obese children are emerging requirement of all stakeholders to set an appropriate policy.

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