



# Subtle inflammation: a possible mechanism of future cardiovascular risk in obese children

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**Purpose:** The risk of cardiovascular disease (CVD) has been shown to be associated with systemic inflammation in obese adults with metabolic syndrome (MetS). The aims of this study were to evaluate the prevalence of MetS and its relation to inflammatory markers in obese Thai children.

**Methods:** A cross-sectional study was conducted. Children with history of endogenous obesity, chronic diseases, drug ingestion, and any acute illness within 2 weeks prior to enrollment were excluded. Their fasting blood glucose (FBG) levels, oral glucose tolerance tests, insulin, lipid profiles, and selected inflammatory markers, including interleukin-6, tumor necrosis factor-alpha, and high-sensitivity C-reactive protein (hs-CRP) levels, were tested.

**Results:** In this study, 58 obese Thai children (female, 20; male, 38) with a mean body mass index zscore of  $5.1 \pm 2.2$  were enrolled. The prevalence of MetS and prediabetes was 31% and 17.2%, respectively. None of the children had diabetes. FBG levels, 2-hour glucose levels, and lipid profiles were not statistically different between those with and without MetS. However, obese children with MetS had higher insulin levels and homeostasis model assessment of insulin resistance values. Elevated hs-CRP levels were found in 69% of the cases, although it was not statistically different between the 2 groups.

**Conclusion:** We described a substantial prevalence of MetS in Thai obese children. Regardless of MetS status, two-thirds of the obese children had elevated hs-CRP level, indicating subtle ongoing inflammatory process. This chronic inflammation feasibly predisposes them to CVD in the future, even in children without MetS.

**Key words:** Metabolic syndrome, Inflammatory markers, Childhood obesity

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## Introduction

The prevalence of childhood obesity has drastically increased and become an important global health issue<sup>1</sup>. If left unconcerned, these children will develop metabolic syndrome (MetS), consisting of central obesity, insulin resistance, dyslipidemia, and hypertension<sup>2</sup>. This condition has been well recognized and is associated with the low-grade chronic inflammatory process (metainflammation) which is orchestrated by metabolic cells in response to excess nutrients and energy<sup>3</sup>. Various proinflammatory cytokines and chemokines, such as interleukin-6 (IL-6), tumor necrosis factor (TNF), and monocyte chemo-attractant protein-1, are released in excess fat tissue. They are secreted locally and systemically by visceral adipocytes and induce migration of macrophages into the adipose tissue, which perpetually lead to cytokine release. Not only producing local effects, metainflammation also results in systemic inflammation which plays role in the development of insulin resistance. These inflammatory molecules, including C-reactive protein (CRP), also cause macrophage differentiation, low-density lipoprotein cholesterol (LDL-C) oxidation, and lipid-laden foam formation in the

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intima of arteries leading to atherosclerotic plaque formation<sup>4</sup>. This risk is particularly higher when obesity continues from childhood into adulthood, and is found to be markedly increased in the obese patients with MetS<sup>5</sup>.

Although CRP, regulated by various inflammatory cytokines, principally IL-6 and TNF- $\alpha$ , has been routinely used as an inflammatory marker to determine systemic inflammation, the high-sensitive CRP (hs-CRP) is more sensitive for subtle inflammation<sup>4,6,7</sup>. There are relationships between the elevation of hs-CRP and body mass index (BMI) in obese children and adolescents<sup>8</sup>. A previous study reported that hs-CRP (>3 mg/L) was associated with an increased 10-year risk of coronary heart disease, regardless of the presence or absence of cardiovascular risk factors<sup>9</sup>. Subjects being in the highest quartile of hs-CRP would experience the adjusted relative risk of 2.3 to 4.8 times for cardiovascular diseases (CVDs) compared with those in the lowest quartile<sup>4</sup>. Subsequent studies showed that hs-CRP levels were higher in adolescents with MetS than in those without MetS<sup>10,11</sup>. Moreover, elevation of hsCRP was reported to be associated with carotid artery media thickness in adolescents indicating early atherosclerotic plaque formation<sup>11,12</sup>. We hypothesized that obesity is associated with systemic inflammation and this association is stronger in those having MetS. This study aims to determine the prevalence of MetS and the association between inflammatory markers and MetS in obese Thai children.

## Materials and methods

This was a cross-sectional study, enrolling children and adolescents who were 6–8 years old with BMI greater than the 95th percentile by age and sex according to an international cutoff for BMI. They were diagnosed as exogenous obesity. Children with history of endogenous obesity (Prader-Willi syndrome, Cushing syndrome), chronic diseases (primary hyperlipidemia, asthma, diabetes mellitus, hypertension), drug ingestion and acute illnesses within 2 weeks were excluded.

Fasting blood glucose, insulin, lipid profiles, hs-CRP, IL-6, and TNF- $\alpha$  were obtained. Oral glucose tolerance tests (OGTTs) was carried out using glucose 1.75 g/kg, max 75 g, in which the blood glucose and insulin were repeatedly taken at 2 hours. The hs-CRP was measured by the electrochemiluminescent method, whereas IL-6 and TNF- $\alpha$  were measured by the enzyme-linked immunosorbent assay. The index of insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated.

Participants were subsequently categorized into 2 groups based on MetS status, using the modification of the definition of the MetS proposed by the International Diabetic Federation (IDF)<sup>13</sup>. Patients with MetS had to meet obesity diagnostic criteria and possessed at least two more of the following criteria, including triglyceride $\geq$ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C)<40 mg/dL,

systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg, and fasting blood glucose $\geq$ 100 mg/dL. Prediabetic patients were considered when they had impaired fasting glucose (100–125 mg/dL) or impaired glucose tolerance (IGT) (140–199 mg/dL) at 2-hour during OGTT, whereas diabetes mellitus will be diagnosed if either the fasting blood glucose $\geq$ 126 mg/dL or 2-hour blood glucose $\geq$ 200 mg/dL during an OGTT<sup>14</sup>. A diagnosis of hyperlipidemia was defined as follows: triglyceride>150, total cholesterol>200, and LDL-C>130 mg/dL. HDL-C was considered low if its level was below 40 mg/dL<sup>13</sup>. Finally, insulin resistance was diagnosed if the fasting insulin $\geq$ 15  $\mu$ U/mL or 2-hour insulin during OGTT $\geq$ 75  $\mu$ U/mL<sup>15</sup> or HOMA-IR>3.16 was observed<sup>16</sup>. There was no cutoff value or normal range available for IL-6 and TNF- $\alpha$  reported. However, hs-CRP>3 mg/L was considered to be clinically elevated<sup>9</sup>.

This project was approved by the Ethics Committee of Chiang Mai University hospital (approval number: PED-11-08-22A-13) and fully supported by the Faculty of Medicine Endowment Fund of the Faculty of Medicine of Chiang Mai University, Chiang Mai, Thailand. Written informed consents were obtained from the parents or guardians for all participants.

For comparison between groups, the Mann-Whitney *U* test was used for continuous variables, whereas chi-square and Fisher exact test were applied for categorical variables. Statistical analysis was performed using SPSS ver. 17 (SPSS Inc., Chicago, IL, USA). A *P* value of <0.05 was considered statistically significant.

## Results

### 1. Patient characteristics

Fifty-eight obese children and adolescents, 38 males (65.5%) and 20 females (34.5%), with a mean age and BMI z score of 11.6 $\pm$ 2.9 years old and 5.1 $\pm$ 2.2, respectively, were enrolled. Twenty participants (34.4%) were in the prepubertal stage. Table 1 summarizes the characteristics of the study participants.

### 2. Glucose, insulin resistance, and lipid profiles

The mean of the fasting blood glucose and 2-hour glucose during OGTT were 85.0 $\pm$ 7.9 and 117.0 $\pm$ 18.6 mg/dL, respectively. Regarding diabetic status, 17.2% of participants were defined as prediabetes (impaired fasting blood glucose, 1.7%; IGT, 15.5%). No subject met the criteria diagnosis of diabetes. The mean of the fasting insulin was 21.8 $\pm$ 13.3  $\mu$ U/mL and the mean of the 2-hour insulin during OGTT was 150.7 $\pm$ 113.4  $\mu$ U/mL. An elevated fasting insulin, 2-hour insulin during OGTT, and HOMA-IR were identified in 62.1%, 75.9%, and 60.3%, respectively. Dyslipidemia, including hypertriglyceridemia, hypercholesterolemia, high LDL-C, and low HDL-C, were identified in 24% to 45% of the cases (Table 1).

**Table 1.** Clinical and biochemical characteristics of 58 obese children

Characteristic	Value
Male sex	38 (65.5)
Age (yr)	11.6±2.9
Weight (kg)	72.9±23.1
Height (cm)	149.9±15.0
BMI z score	5.1±2.2
Waist circumference (cm)	97.5±14.6
Prepubertal stage	
Female:male	3 (5.1):17 (29.3)
Family history of diabetes mellitus	25 (43.1)
Family history of hypertension	28 (48.3)
Family history of dyslipidemia	16 (27.6)
Glucose homeostasis	
Fasting blood glucose (mg/dL)	85.0±7.9
Impaired fasting glucose	1 (1.7)
Diabetes	0 (0)
2-Hour glucose during OGTT (mg/dL)	117.0±18.6
Impaired glucose tolerance	9 (15.5)
Diabetes	0 (0)
Insulin	
Fasting insulin (μU/mL)	21.8±13.3
>15 μU/mL	36 (62.1)
2-Hour insulin during OGTT (μU/mL)	150.7±113.4
>75 μU/mL	44 (75.9)
Index for insulin resistance	
HOMA-IR	4.6±2.8
>3.16	35 (60.3)
Lipid profiles	
Triglyceride (mg/dL)	117.2±65.4
Hypertriglyceridemia	14 (24.1)
HDL-cholesterol (mg/dL)	41.4±8.1
Low HDL	26 (44.8)
Cholesterol (mg/dL)	183.0±42.4
Hypercholesterolemia	17 (29.3)
LDL-cholesterol (mg/dL)	121.4±39.5
High LDL-cholesterol	18 (31.0)
Inflammatory markers	
hs-CRP (mg/L)	6.37±6.68
>3 mg/L	40 (69.0)
IL-6 (pg/mL)	39.1±77.5
TNF-α (pg/mL) (n=53)	12.1±38.6

Values are presented as number (%) or mean±standard deviation. BMI, body mass index; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

### 3. Metabolic syndrome and inflammatory markers

The prevalence of MetS was 31%. The average value of hs-CRP was 6.37±6.68 mg/L, in which 69% of the participants showed elevated hs-CRP level. The mean of IL-6 and TNF-α were 39.1±77.5 pg/mL and 12.1±38.6 pg/mL, respectively.

### 4. Clinical and biochemical data in children with and without MetS

Obese children with the MetS were older (13.8 years vs. 11.2 years,  $P=0.009$ ) than those without MetS, but comparable BMI z score ( $P=0.850$ ). The fasting insulin (median [interquartile range], 25.9 [19.5–35.6] μU/mL vs. 17.8 [11.2–24.4] μU/mL,  $P=0.005$ ), 2-hour insulin during an OGTT (171.1 [90.3–293.8] μU/mL vs. 109.8 [57.4–154.9] μU/mL,  $P=0.026$ ), and HOMA-IR (4.9 [3.9–7.2] vs. 3.4 [2.4–5],  $P=0.020$ ) were also significantly higher in obese children with MetS. However, the fasting blood glucose, 2-hour glucose during an OGTT, and lipid profiles were not statistically different between the groups. Regarding inflammatory markers, hs-CRP, IL-6, and TNF-α were also not statistically different between 2 groups. However, the overall percentage of elevated hs-CRP were exceptionally high, even in obese children without MetS (Table 2)

## Discussion

This study demonstrated a high prevalence of metabolic syndrome and elevated hs-CRP among obese Thai children. As the elevation of hs-CRP level is suggestive of subtle inflammatory process, our finding may help increase awareness of CVD risk even in obese children without MetS.

Defining MetS in children is rather difficult, particularly in children due to pubertal effects and the low prevalence of CVD<sup>2</sup>. As a result, there have currently been no definite consensus guidelines providing specific diagnostic criteria for pediatric MetS<sup>17</sup>. However, there have been several inconsistent criteria, proposed by several authorities and organizations including the IDF, National Cholesterol Education Program Adult Treatment Panel III<sup>17,18</sup>. Yet, the use of waist circumference was not included in the pediatric criteria at the present time due to insufficient information and lack of specific guidance for clinical application, according to an expert committee of the American Medical Association and the Centers for Disease Control and Prevention Task Force on Assessment, Prevention, and Treatment of Childhood Obesity<sup>19</sup>. Additionally, reference values of waist circumference for Thai children has not been available. Therefore, we decided to exclude this parameter and employ the assessment on the MetS status with the modified MetS criteria proposed by IDF, in which the prevalence of MetS in our study was 31%. It was comparable to other reports and ranged from 16.9%–38.5%<sup>20–22</sup>.

Although there is a concept of the healthy obesity which has been believed not associated with the CVD risk, the diagnostic

**Table 2.** Clinical and biochemical data of 58 obese children stratified by metabolic syndrome status

Characteristic	Nonmetabolic syndrome (n=40)	Metabolic syndrome (n=18)	P value
Male sex	26 (65)	12 (66.6)	0.902
Age (yr)	11.2 (8.5–13.7)	13.8 (11.8–14.9)	0.009
Weight (kg)	64.8 (47.6–82.6)	80.6 (75.4–108)	0.001
Height (cm)	149.0 (131.5–158.1)	160.5 (153.5–163)	0.000
BMI z score	3.1 (3.3–5.9)	3.3 (4–8.2)	0.850
Waist circumference (cm)	95 (86.6–99)	106 (98–109)	0.001
Prepubertal stage	18 (45)	2 (11.1)	0.016
Glucose homeostasis			
Fasting blood sugar (mg/dL)	87.5 (82–90.2)	81.0 (78.0–91)	0.070
Impaired fasting glucose	0 (0)	1 (5.5)	0.133
Diabetes	0 (0)	0 (0)	1.000
2-Hour Glucose During OGTT (mg/dL)	111.5 (102.8–126.2)	114 (105–121)	0.853
Impaired glucose tolerance	8 (20)	1 (5.5)	0.160
Diabetes	0 (0)	0 (0)	1.000
Insulin			
Fasting insulin ( $\mu$ U/mL)	17.8 (11.2–24.4)	25.9 (19.5–35.6)	0.005
Fasting insulin >15 $\mu$ U/mL	20 (50.0)	16 (88.8)	0.005
2-Hour insulin during OGTT ( $\mu$ U/mL)	109.8 (57.4–154.9)	171.1 (90.3–293.8)	0.026
>75 $\mu$ U/mL	28 (70)	16 (88.8)	0.120
Index for insulin resistance			
HOMA-IR	3.4 (2.4–5)	4.9 (3.9–7.2)	0.020
>3.16	20 (50)	15 (83.3)	0.016
Lipid profiles			
Cholesterol (mg/dL)	178 (150.3–200.5)	172.0 (157–223)	0.528
Hypercholesterolemia	11 (27.5)	6 (33.3)	0.652
LDL-cholesterol (mg/dL)	119 (89.3–132.8)	105 (93–158)	0.451
Elevated LDL-cholesterol	11 (27.5)	7 (38.8)	0.386
Inflammatory markers			
IL-6 (pg/mL)	7 (2–48.1)	5.4 (2.3–13.6)	0.102
TNF- $\alpha$ (pg/mL)	4.62 (1.7–11.9)(n=38)	4.68 (1.9–7.6)(n=15)	0.538
hs-CRP (mg/L)	3.7 (2.3–7.8)	3.7 (1–7.8)	0.267
>3 mg/L	28 (70)	12 (66.6)	0.800

Values are presented as number (%) or median (interquartile range).

BMI, body mass index; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor-alpha; hs-CRP, high-sensitivity C-reactive protein.

criteria of MetS have not included inflammatory markers as well as features of nonalcoholic fatty liver disease<sup>23,24</sup>. The presence of subclinical inflammations could play a key role in distinguishing metabolically healthy from metabolically nonhealthy individuals<sup>24</sup>. Although there were no statistically significant differences between participants with and without MetS, we demonstrated the incredibly high prevalence of cases with elevated hs-CRP level, indicating the presence of low grade inflammatory process which possibly predispose to CVD in both obese children and adolescents. This finding challenges the concept of the healthy obesity and could feasibly lead to the inclusion of inflammatory markers in the criteria diagnosis of

MetS.

Our results were in alignment with previous studies, demonstrating that obese children had elevated inflammatory markers, for instance hs-CRP<sup>8,25–32</sup>, TNF- $\alpha$ <sup>26,27,29,33</sup>, and IL-6<sup>26,28,34</sup>. Compared to the study done by El-shorbagy and Ghoname<sup>25</sup> demonstrating a prevalence of hs-CRP>3 mg/L of 35%, our study showed as much as twice higher prevalence. Unfortunately, we could not identify MetS as a potential risk for increasing the selected inflammatory cytokines even though there was a report to that effect<sup>35</sup>. This may reflect racial difference and severity obesity influence on metainflammation among different populations.

There were several limitations in our study. Firstly, our study did not have a matched control nonobese group due to the ethical reason. Secondly, our study had a small sample size with heterogeneous age and pubertal status, which could affect the insulin resistance and MetS status. Lastly, this study was a cross-sectional study while MetS and atherosclerosis are chronic processes. Therefore, the long-term follow up study of these children is needed.

In summary, we described a high prevalence of elevated inflammatory markers in obese children. Nonetheless, there was no statistical difference of hs-CRP level in obese children with or without MetS. This piece of information affirms existing knowledge regarding the presence of subtle chronic inflammatory process in obese children. If left unrecognized, it could be one of predisposing factors of CVD in their future life, so early weight intervention should be emphasized. Further studies are still needed to firmly endorse these clinical implications and whether an increase in inflammatory markers should be integrated as a parameter in the criteria diagnosis of MetS.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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