Rate of Weight Gain and its Association with Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) among Obese Children attending Paediatric Endocrine Clinic, Hospital Universiti Sains Malaysia

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Abstract

Objective. We aimed to study the median time to gain weight from baseline and factors that were associated with rate of weight gain among obese children attending pediatric endocrine clinic Hospital USM.

Methodology. We recruited 70 participants with the mean age of 10.1 ± 2.94 years with exogenous or simple form of obesity from June 2019 until September 2020. We analyzed their demography (age, gender, ethnicity, family background), measured their anthropometry (weight, height, BMI) and monitored monthly weight increment and finally analyzed their HOMA-IR at baseline and after 6 months of follow up.

Results. The mean time to gain 5 kg from baseline was 16 weeks (95% CI): (15.2, 16.7). Multivariate analysis showed only HOMA-IR after 6 months was a significant predictor affecting time to gain 5 kg; Adjusted HR: (95% CI) 1.617 (1.232, 2.123), (p=0.001).

Conclusion. The time to gain 5 kg from baseline weight was increased 1.6 times in the presence of insulin resistance at 6 months follow up in patients with obesity. More intensive education and closed follow-up are recommended for children with obesity.

Key words: HOMA-IR, prognostic factor, obesity, insulin resistance

INTRODUCTION

Obesity in children and adolescents has become a massive health problem in many countries. Childhood obesity, especially in developed countries, has increased dramatically in the last 20 years.1 North America and the Eastern Mediterranean regions have higher prevalence of overweight and obesity (30-40%) than European (20-30%) while South-East Asia, Western Pacific, and African regions contributed about 10-20%.2

The worldwide prevalence of childhood overweight and obesity increased from 4.2% (95% CI: 3.2%, 5.2%) in 1990 to 6.7% (95% CI: 5.6%, 7.7%) in 2010.3 This trend was expected to reach 9.1% (95% CI: 7.3%, 10.6%) or 60 million in 2020. The prevalence of obesity was lower in Asia (4.9% in 2010) than in Africa (8.5% in 2010) but the numbers of affected children (18 million) was higher in Asia.3

The problem of childhood obesity is global and extends into the developing world. The prevalence of obesity in Thailand among 5-12 years old children increased from 12.2% to 15.6% within two years (WHO, 2003). The National Health and Morbidity survey (NHMS) by Institute of Public Health, 2015 reported that the prevalence of obesity among children aged 10-14 years in Malaysia was 14.4%.

Obesity is caused by an imbalance in energy input versus output, resulting in a positive energy balance. The International Obesity Task Force developed an international standard BMI for age, in which the 85th percentile and the 95th percentile for age roughly correspond to BMI of 25 kg/m² and 30 kg/m² respectively among those above 18 years old.4

Childhood obesity is associated with an increased risk for several metabolic complications, such as insulin resistance, glucose intolerance and type 2 diabetes mellitus (T2DM). In particular, insulin resistance is the most common metabolic alteration related to obesity, it represents an important link between obesity as well as cardiovascular complications.

Insulin Resistance is defined as a condition in which plasma insulin at normal concentration has an impaired ability to adequately promote peripheral glucose disposal, hepatic glucose suppression and inhibition of very low-density lipoprotein output.5 In IR, insulin production...
by the pancreatic β-cell is increased, causing hyper-insulinemia. Failure of the compensatory response leads to IGT and eventually T2DM.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is the most commonly used method in clinical practice and it is a way to measure insulin resistance in children.8 It is used to yield an estimate of insulin sensitivity and cell function from fasting plasma insulin and glucose concentration. The HOMA value was calculated as follows: fasting insulin (mU/L) x fasting glucose (nmol/L)/22.5 (using HOMA calculator version 2.2).6

According to a study by Chang-Rueda et al, among children and adolescents, HOMA-IR had a moderately significant correlation with an increase in BMI percentile for age \( r=0.198, p=0.037 \).7 The result showed that the combined prevalence of obesity and overweight was 66% with insulin \( p=0.010 \) and HOMA-IR \( p=0.015 \) values higher than those in the normal weight group. The HOMA-IR values correlated positively with age \( r=0.636 \), weight \( r=0.569 \), height \( r=0.578 \) and BMI percentile \( r=0.198 \).

A large prospective cohort study by Pepliesi et al., on the longitudinal association of lifestyle factor and weight status with insulin resistance (HOMA-IR) in preadolescent children was the first prospective study on IR in that population.8 The result of this study showed the strongest positive association of IR with BMI z-score \( OR=2.6 \) for unit change from the mean, 95% CI 2.1-3.1 and z score of waist circumference \( OR=2.2 \), for unit change from the mean, 95% CI 1.9-2.6, audio-visual media time \( OR=1.2 \) for an additional hour per day, 95% CI 1.0-1.4 in both models) and an inverse association determined physical activity \( OR=0.5 \) for 3 units compared to 1st quartile, 95% CI 0.3-0.9 in both models. A longitudinal reduction of HOMA-IR was accompanied with a parallel reduction of BMI.

This study supported the common hypothesis that excess body weight and obesity were the main determinants of IR. Their data also indicate that physical activity and a sedentary lifestyle was likewise associated with the development of IR, independent of weight status.

Insulin resistance syndrome is the most common comorbidity for obesity in many clinical trials, and the higher the weight or body mass index (BMI), the greater the risk to develop insulin resistance syndrome. As far as we know, there is no study looking for an association between rate of weight gain and insulin resistance syndrome in children. Therefore, the main purpose of this study is to investigate whether the rate of weight gain contributes to Insulin Resistence Syndrome or not.

**Research objectives**
To analyze the median time to gain 1 kg, 3 kg and 5 kg weight from the baseline and identify factors associated with the rate of weight gain.

**METHODOLOGY**

**Study design**
A prospective study with the recruitment period from June 2019 until September 2020. The participants were followed up every 3 month at the Endocrine clinic HUSM.

**Subjects and procedures**
We recruited 70 obese subjects according to inclusion and exclusion criteria. The inclusion criteria were all exogenous or primary obesity which was defined as BMI more than 95th centile according to age and gender, age less than 18 years old and waist circumference more than 90th percentile according to WHO waist circumference chart. The exclusion criteria were secondary forms of obesity such as monogenic disorder, syndromes, neurogenic, endocrine, drug induced and hypothalamic causes. Patient who failed to follow up and were not compliant with monthly weight measurement were excluded from this study.

Weight was measured while the subject dressed minimally, upright, without shoes using the same standing stadiometer and it was recorded to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm in a standing position, without shoes on a standard height board. Blood pressure was measured with the digital method using appropriate cuff and standard sphygmomanometer.

**Statistical analysis**
SPSS IBM version 26.0 was used to analyze the data. Numerical data were presented as mean (SD) or median
(IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). Median time to gain 1, 3 and 5 kg weight were analyzed with Kaplan-Meier survival analysis. Sample size was calculated with PS software (survival analysis), alpha=0.05, power=0.8 for primary objective and we used sample size G power software (survival analysis) with r=0.3, alpha=0.05 and power=0.8 for secondary objective. The calculated sample size was 80 patients for objective 1 and 84 for objective 2. The final sample size for objective 1 was 100 patients with 20% dropout and 105 patients with 20% dropout for objective 2. Predictive factors that influence the rate of weight gain were analyzed with Cox-Proportional Hazard regression test. All the demographic and clinical data were initially analyzed with simple Cox regression test. Variables with p<0.25 were further analyzed with multiple Cox regression. Forward LR and backward LR were used in the method. Two-way interaction and multicollinearity were checked for independent variables. We then checked the proportional hazard assumption and outliers with scatterplots and finally the fitness of the final model was checked with partial residuals.

Ethical approval
This study was approved by the Human Research Ethics Committee USM with its references USM/JEPeM/19020132.

RESULTS
Demographic characteristics of 70 patients in this study are summarized in Tables 1 and 2. There were 43 patient (61.4%) males and 27 patient (38.6%) females. Majority of the patients were Malay, 67 patients (95.7%); and 3 patients (4.3%) were Chinese. The mean age of the subjects was 10.1 ± 2.94 years. Thirty nine patients (55.7%) were between 10-18 years old and 31 patients (44.3%) were between 3-9 years old.

For the care-taker education background, the parents received primary education in 51.4%, secondary education level in 32.8% and tertiary education in 51.4%. In Malaysia, household income of less than USD 909 was defined as urban poverty or known as B40 group as categorized by Social Welfare Department of Malaysia and Ministry of Housing and Local Government. From this study, 46 patients (65.7%) were from the high income family group and 24 patients (34.3%) were from the low-income family group. Fifty patients (71.4%) had sedentary lifestyle group and 20 patients (28.6%) were non-sedentary. Sedentary lifestyle was defined as more than 2 hours of screen time per day and less than 60 minutes of moderate to vigorous physical activity per day according to WHO recommendation. In this study, only 22 patients (31.4%) met more than 60 minutes of moderate to vigorous physical activity per day but the others (68.6%) did not meet the recommendation.

Table 2 shows clinical and biochemical parameters of obese patients in this study. Thirty-two patients (45.7%) had BMI >30 kg/m² and 38 patient (54.3%) had BMI <30 kg/m². The BMI cutoff of 30 was used because it was more likely to be associated with obesity complications or co-morbidity.

Forty-seven patients (67.1%) had normal blood pressure during follow-up but 23 patients (32.9%) were diagnosed to have hypertension during this study period. Seven patients (10%) were pubertal and 63 patients (90%) were prepubertal.

From this study, 37 patients (52.8%) had normal MOGTT results while 33 patients (47%) had abnormal MOGTT results that comprised of 15 patients (21.4%) with impaired fasting glucose (IFG), 17 patients (24.2%) with impaired

| Table 1. Baseline characteristics of patients with obesity |
|----------------|----------------|
| Variable       | n (%)          |
| Gender         |                |
| Male           | 43 (61.4)      |
| Female         | 27 (38.6)      |
| Age (years)    |                |
| 1-9            | 31 (44.3)      |
| 10-18          | 39 (55.7)      |
| Race           |                |
| Malay          | 67 (95.7)      |
| Chinese        | 3 (4.3)        |
| Family income  |                |
| Low income     | 24 (34.3)      |
| High income    | 46 (65.7)      |
| Caretaker education |        |
| Primary        | 11 (15.7)      |
| Secondary      | 23 (32.8)      |
| Tertiary       | 36 (51.4)      |
| Sedentary lifestyle |    |
| Yes            | 50 (71.4)      |
| No             | 20 (28.6)      |
| Exercise       |                |
| None           | 7 (10)         |
| <15 min        | 13 (18)        |
| 15-30 min      | 11 (15.7)      |
| 30-60 min      | 17 (24.3)      |
| >60 min        | 22 (31.4)      |
| BMI <30        | 38 (54.3)      |
| >30            | 32 (45.7)      |
| BP             |                |
| Normal         | 47 (67.1)      |
| Hypertension   | 23 (32.9)      |
| Tanner staging |                |
| Prepubertal    | 63 (90)        |
| Pubertal       | 7 (10)         |
| Age Onset obesity (years)* | 5.99 ± 3.29 |
| Current Weight (kg)* | 63.89 ± 23.75 |
| Current Height (cm)* | 142.79 ± 15.83 |
| Waist circumference (cm)* | 91.96 ± 20.00 |
| Calories/day (kcal)* | 3503.62 ± 887.03 |
| HOMA Baseline* | 2.31 ± 0.96    |
| HOMA at 6 months* | 3.80 ± 1.65    |
| MOGTT Normal   | 37 (52.8)      |
| IFG            | 15 (21.4)      |
| IGT            | 17 (24.2)      |
| DM             | 1 (1.4)        |
| Dyslipidemia   |                |
| Yes            | 21 (30)        |
| No             | 49 (70)        |
| Transaminitis  |                |
| Yes            | 25 (35.7)      |
| No             | 45 (64.3)      |

*Mean±SD for numerical variables
n (%) for categorical variables

| Table 2. Baseline clinical and biochemical parameters of patients with obesity |
|----------------|----------------|
| Variable       | n (%)          |
| BMI <30        | 38 (54.3)      |
| >30            | 32 (45.7)      |
| BP             |                |
| Normal         | 47 (67.1)      |
| Hypertension   | 23 (32.9)      |
| Tanner staging |                |
| Prepubertal    | 63 (90)        |
| Pubertal       | 7 (10)         |
| Age Onset obesity (years)* | 5.99 ± 3.29 |
| Current Weight (kg)* | 63.89 ± 23.75 |
| Current Height (cm)* | 142.79 ± 15.83 |
| Waist circumference (cm)* | 91.96 ± 20.00 |
| Calories/day (kcal)* | 3503.62 ± 887.03 |
| HOMA Baseline* | 2.31 ± 0.96    |
| HOMA at 6 months* | 3.80 ± 1.65    |
glucose tolerance (IGT) and 1 patient (1.4%) with diabetes mellitus (DM). Twenty-one patients (30%) had dyslipidemia and 49 patients (70%) had normal fasting lipid profile. Twenty-five patients (35.7%) had transaminatis and 45 patients (64.3%) had normal ALT. The mean age of obesity onset was 5.59 ± 3.29 years with mean weight of 63.89 ± 23.75 kg, mean height of 142.79 ± 15.83 cm and mean WC of 91.96 ± 20.00 cm. The mean caloric intake was 3503.62 ± 887.03 kcal/day with mean HOMA at baseline of 2.31 ± 0.96; and the mean HOMA at 6 months was 3.80 ± 1.65.

From the Kaplan Meier analysis, the mean time to gain 1 kg was 7.9 weeks with (98% CI); (6.6, 9.2), mean time to gain 3 kg weight was 12 weeks (98% CI); (9.7, 14.2), and mean time to gain 5 kg from baseline was 16 weeks (98% CI); (15.2, 16.7).

Significant factors that were associated with 5 kg weight gain after univariate analysis were older age with patients 10-18 years, crude OR (95% CI); 0.551 (0.277, 1.091), non-Malay; 0.384 (0.117, 1.263), 10-18 years, crude OR (95% CI); 0.557 (0.277, 1.120), BMI >30 gain after univariate analysis were older age with patients 10-18 years, crude OR (95% CI); 0.557 (0.277, 1.120), BMI >30 gain after univariate analysis were older age with patients 10-18 years, crude OR (95% CI); 0.557 (0.277, 1.120), BMI >30

| Variables | Crude HR (95% CI) | p value |
|-----------|------------------|---------|
| Race      |                  |         |
| Malay     | 0.384 (0.117, 1.263) | 0.115   |
| Chinese   | 1.0              |         |
| Age (years) |                 |         |
| 1-9       | 0.557 (0.277, 1.120) | 0.101   |
| 10-18     | 1.0              |         |
| BMI <30   | 0.551 (0.278, 1.091) | 0.087   |
| >30       | 1.0              |         |
| Transaminits |               |         |
| Yes       | 1.59 (0.851, 2.975) | 0.146   |
| No        | 1.0              |         |
| Dyslipidemia |            |         |
| Yes       | 1.523 (0.813, 2.852) | 0.189   |
| No        | 1.0              |         |
| Total calories (kcal/day) | 1.000 (1.000, 1.001) | 0.140   |
| Current weight (kg)    | 1.010 (0.998, 1.023) | 0.099   |
| Current height (cm)    | 1.022 (1.000, 1.044) | 0.050   |
| Waist circumference (cm) | 1.014 (1.000, 1.028) | 0.056   |
| HOMA at baseline | 1.364 (0.984, 1.889) | 0.062   |
| HOMA after 6 months | 1.617 (1.232, 2.123) | 0.001   |

DISCUSSION

Previous research had identified numerous socio-demographic and factors associated with childhood obesity in Malaysia. A survey done by Ismail et al., had demonstrated increased prevalence of obesity with increasing age: 6.6% among 7-year-olds, which went up to 13.8% among 10-year-old group and a higher prevalence seen among males than females (12.5% compared to 5%).

Another study among children (6239 respondents) aged between 7 to 16 years in Kuala Lumpur by Kasmini et al., published in Asia Pacific Journal Clinical Nutrition, also showed that males were found to be more obese than females particularly in the pubertal age group (11 to 14 years old). Our study showed that the majority of obese children were male (61.4%) aged 10-18 years old (55.7%). This study had similar findings compared to others in which there were more obese males in the older age group.

Comparing our study with neighboring countries also showed similar findings. A study in Singapore showed that the overall prevalence rate of obesity was 3.51% with a significantly higher rate in boys (3.95%) than in girls (3.06%). There was a higher prevalence of obesity among 10-year-olds (4.29%) compared to 7-year-old students (2.75%) p=0.0001. This study suggested that the tendency to become obese increases with age and boys are more prone to obesity. In many Asian countries, boys are encouraged by their parents to take higher portions of energy dense food compared to girls and together with sedentary lifestyle practices resulted in positive energy balance and an increase in weight among boys.

A study of socioeconomic determinants of childhood obesity in Guangzhou, China (2016) also showed that the prevalence of obesity increased with increasing age (9.1% in 5-6 years compared with 22.0% in 11-12 years) and it was also higher in males (23.5%) compared with females (11.6%). The prevalence of obesity also increased with increasing quartile of household per-capita income and with higher maternal education.

Our study findings contradicted the findings of a study of socio demographic and life style determinants among preschool children in Babol, Northern Iran. This study showed no significant difference between genders and the odds ratio significantly decreased in tertiary parental education compared to primary parental education. However, our findings were similar with this study in terms of age distribution in which the higher prevalence of obesity was seen with increasing age. The odds of obesity was raised more than double among age 4-5 years compared with 2-3 years (OR=2.53, 95% CI:1.71-3.73).

Our study showed that majority of obese children were of Malay ethnicity (95.7%), with tertiary education background in the family (51.4%), with high income (65.7%) and with sedentary lifestyle (71.4%). Ismail and Tan et al., found ethnicity differences in their study with 16.8% of Malay being obese compared to approximately 11.0% of Chinese and Indian. However based on study by Kasmini et al, there was no significant difference between 3 major ethnic groups among obese children.

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There are no studies that compare ethnicity among pediatric patients in neighboring countries. The higher prevalence of obesity among Malay in our paper is primarily due to the greater proportion of Malay subjects that were recruited, reflecting the predominant Malay ethnicity in the state.

A cross-sectional study by Alagappan et al., among secondary school students (7247 respondents) in Batang Padang, Perak, Malaysia, showed that obesity was significantly (p < 0.05) associated with higher family education and low physical activity group. This study supported our finding that the higher prevalence of obesity was seen in those with good education background in the family and among those who were sedentary.

A study by Amuthaganesh et al., regarding physical activity and media environment as antecedent of childhood obesity in Malaysia support that excessive media viewing is consistently shown to be linked to increased BMI independent of physical activity. In comparison to our study, the prevalence of obesity was higher among sedentary lifestyle group which did not meet the WHO recommendation of physical activity for children; 71.4% were in sedentary lifestyle group with more than 2 hours of screen time and less than 60 minutes of moderate to vigorous physical activity per day. The physical activity level of the children in our study was low, only a small proportion (31.4%) reached the daily activity level recommended by WHO.

In contrast to the study in Iran, there was no significant association between higher prevalence of obesity with physical activity and sedentary lifestyle. Results showed spending ≥2 hours per day for TV watching and ≥1 hour for playing with computer games tends to increase the odds of overweight/obesity (OR = 1.31, P = 0.13 and OR = 1.46, P = 0.06 respectively) but it was not significant. However, the author did not explain the reason for the insignificant difference between physical activity and sedentary lifestyle.

The mean caloric intake per day among our participants was 3503.62 ± 887.03 kcal/day which was mainly high carbo diet based on 24-hour food recall. The high caloric consumption per day contributes to imbalance of energy input versus output, resulting in a positive energy balance. The sedentary lifestyle together with high caloric food consumption were factors that contribute to an increase in the rate of weight gain in this study.

High socio-economic status has also been associated with an increased prevalence of obesity among children in this study. A study in Peninsular Malaysia among 10-17 years obese children by Nurul et al., revealed that high socioeconomic status with household income of more than USD 708 was associated with a two fold increase in the odds ratio (OR 2.240, p = 0.049). This finding was consistent with our study in which 65.7% were in the high income group, defined as monthly household income of more than USD 913 as categorized by Social Welfare Department of Malaysia and Ministry of Housing and Local Government. The children that belong to higher income families had more access to various food resources and might have an increase in the food consumption while their parents were away.

In this study, we analyzed the time to gain weight from the baseline. As far as we know, there were no previous publications that reviewed time to gain weight from the baseline. Based on expert opinion, the usual increment of 5 kg weight from the baseline was 6 months on average. Guidelines also stated that weight reduction is between 0.5 kg-1.0 kg per month.

We found that the patients gained 5 kg within 16 weeks (98% CI): (15.2, 16.7). The rate was more rapid compared to what was recommended by the general consensus guidelines for obesity prevention.

A recent meta-analysis on impact of dietary and exercise intervention on weight change and metabolic outcomes in obese children by Ho et al., demonstrated that those children that were given intervention showed significant improvement in all anthropometric measurements as well as mean glucose and HbA1c. The early findings from 6 months of family-based intervention demonstrated decrease in BMI, fat mass, total cholesterol and insulin resistance. The main and first line management of obesity in children is diet and lifestyle intervention. However, most of the families find it hard to consistently maintain healthy diet and lifestyle; and with poor motivation, this would result in weight increment as proven by our study. We found that those with persistent weight gain among obese children were older patients 10-18 years; and had higher BMI, presence of transaminitis, dyslipidemia and abnormal MOGTT result.

Skeletal muscle mass affects locomotion and maintenance of posture. It is the most abundant insulin sensitive tissue that plays a crucial role in systemic glucose metabolism. Decreased muscle mass, known as sarcopenia, typical of the aging process, is a risk factor for insulin resistance and is associated with metabolic risk in children and adolescents. Furthermore, elevated body fat level may act in synergism with decreased skeletal muscle mass because adiposity is also closely linked to insulin resistance and thus, a low ratio of skeletal muscle to body fat (MFR) importantly predicts the development of metabolic syndrome.

Transaminitis was associated with increase of weight gain. A study by Wei et al., shown that 16% of obese children from a UK-based obesity clinic had raised alanine aminotransferase (ALT) and patient with transaminitis were more likely to fulfill the criteria for metabolic syndrome (p < 0.001) and had abnormal OGTT. In this prospective trial, there was a significant relationship between 12 months changes in BMI and corresponding change in ALT. Improvement in BMI over 1 year correlated with improvement in ALT levels.

Another study by Tock et al., showed that 11% of patients in the subgroup with raised ALT at the beginning of weight management program who have normalized their level after 12 months displayed a 9% reduction in BMI. Transaminitis in the form of raised ALT has been used as a surrogate marker for the diagnosis of nonalcoholic fatty liver disease (NAFLD). NAFLD is linked to adiposity, and is commonly associated with metabolic syndrome. The etiology of NAFLD in obese patients is multifactorial. Increased portal concentration of free fatty acid is found in patients with obesity and insulin resistance.
The increased level of free fatty acid causes damage to intracellular membrane and leads to the development of NAFLD.

Transaminitis in obese children has been associated with features of the metabolic syndrome such as obesity, hyperinsulinism and hyperlipidemia. In our study, obese patients who had elevated ALT showed significant increase of 5 kg weight from the baseline and some of these patients had dyslipidemia and abnormal MOGTT.

Although a relationship between insulin resistance and fat gain has been demonstrated, it is not clear whether insulin resistance is a promoting factor or simply a consequence of fat gain. A study by Odelye et al., regarding fasting hyperinsulinemia as a predictor of increased body weight gain and obesity among 5 to 9 years old Pima Indian children found that high fasting insulin level was associated with greater weight gain during 9 years of follow up.22

Moreover, similar results were reported from a number of Caucasian and African-American children, with a mean age of 8.1 ± 1.6 years and studied for over 3-6 years.23 These studies are consistent with the findings are also reported in other studies in which resistance favors fat gain during childhood and adolescent.

The findings are also reported in other studies in which there was a significant correlation of increase BMI with HOMA-IR; and a longitudinal reduction of BMI cause decline in HOMA-IR.7 These studies are consistent with our study in which there was a significant correlation between weight gain with HOMA-IR at 6 months follow up (r=0.737; p<0.001). The time to gain 5 kg from the baseline was 1.6 times increased in the presence of insulin resistance at 6 months follow up in patients with obesity.

Obesity is the excessive growth of adipose tissue depots arising from the chronic consumption of calories in excess of the energy need of the individuals. There is a specific link between visceral adipose tissue accumulation and insulin resistance that will explain why insulin resistance is higher in obese groups.

One possibility is that visceral fat is diabetogenic, because it secretes adipokines that impair the insulin sensitivity in tissue such as liver and muscle. The second reason is that the presence of visceral fat indicates the existence of ectopic lipid accumulation and lipotoxicity that cause insulin resistance in the liver and muscle. The third explanation is the excess lipid accumulation in visceral adipose tissue causes release of inflammatory cytokines that will impair insulin sensitivity. Another possibility is that the lipotoxicity in peripheral and visceral adipose tissue increases cytokine production that contributes to systemic insulin resistance.24

In this study, we found the significant association of weight gain and HOMA-IR after 6 months follow up among our study population. This favors the development of insulin resistance syndrome. Most of the patients that had high HOMA-IR index were also found to have clinical and biochemical findings compatible with metabolic syndrome. Without proper interventions, they are at risk of complications related to metabolic syndrome such as diabetes and cardiovascular complications.

Limitations of the study
We aimed to get a larger sample size, however we had difficulty in recruitment due to the COVID19 pandemic and movement restriction order (MCO) in our country. Our initial recruitment was 84 patients; however, the final sample size was only 70 patients because fourteen of them dropped out. The duration of follow up should be longer in order to ascertain whether the weight gain persists, however since this trial is only a short term of up to 6 months, we were unable to determine this.

CONCLUSION
In this prospective study, the mean time to gain 5 kg was 16 weeks. There were many factors associated with the time to gain 5 kg weight, however, only HOMA-IR after 6 months was a significant predictor affecting time to gain 5 kg with adjusted HR: (95% CI) 1.617(1.232, 2.123), (p<0.001) from multiple Cox Proportional Hazard regression. Intensive education and more frequent follow-up are recommended for children with obesity.

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