PREVALENCE OFABNORMAL GLUCOSE METABOLISM AMONG THAI OVERWEIGHT AND OBESE CHILDREN AND ADOLESCENTS

Pacharin Mungklarat, Anothai Juttuporn**, Wiphakorn Suphaphimon*, Warissara Sanor*, Chula Kooanantkul***, Nawaporn Numbenjapon*, Voraluck Phatarakijnirund**

***Division of Endocrinology, Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand**

****Division of Community Occupational and Family Medicine, Faculty of Medicine, Burapha University, Chon Buri, Thailand**

*****Kids Center, Vejthani Hospital, Bangkok, Thailand**

Abstract

Background: The prevalence of childhood obesity is increasingly worldwide. Abnormal glucose metabolism (AGM) including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes (T2DM) is a common endocrine complication among overweight and obese children and adolescents. Few studies of AGM are available in Thailand.

Objectives: The study aimed to establish the prevalence of AGM and identify associated complications among overweight and obese children and adolescents.

Methods: Data of overweight and obese children and adolescents, aged 6 to 18 years, undergoing oral glucose tolerance test (OGTT) at Phramongkutklao Hospital were reviewed retrospectively. Fasting blood sugar, Hemoglobin A1c (HbA1c), fasting insulin, triglyceride, high-density lipoprotein, low-density lipoprotein, aspartate transaminase and alanine aminotransferase were derived from fasting measurement. Homeostatic model assessment was calculated to represent the insulin resistance.

Result: A total of 204 children and adolescents (122 males) were included. Mean age was 12.1 ± 2.6 years and percent weight for height was 168.8 ±25.4%. The overall prevalence of AGM was 20.6%, 1% had T2DM, 0.5% had IFG, 36% had IGT and 1.5% had combined IFG/IGT. Among the AGM, IGT was the most frequent subtype representing 92.8% (39/42 cases) but only 2 cases of T2DM were diagnosed in our study. The AGM group had significantly higher FPG (p=0.034), HbA1c (p=0.006) and cholesterol levels (p=0.043) than those of the nonabnormal glucose metabolism (NGM) group.

Conclusion: Prevalences of AGM among overweight and obese children and adolescents were high. IGT was the most frequent subtype of AGM.

Keywords : Impaired glucose tolerance, Impaired fasting glucose, Type 2 diabetes, Insulin resistance

J Southeast Asian Med Res 2019; 3(2): 59-66.
http://www.jseamed.org

Correspondence to:
Phatarakijnirund V., Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, 315 Ratchawithi Road, Phayathai, Ratchathewi, Bangkok, Thailand, 10400
Email: phatara.voraluck@gmail.com, female_ying@hotmail.com

Introduction

The prevalence of obesity among children and adolescents is increasingly worldwide.[1] One recent study showed the prevalence of overweight and obesity among children and adolescents aged 5 to 19 years has risen dramatically from 4% in 1975 to over 18% in 2016.[2] Being obese is a major risk factor leading children to have many chronic diseases such as type 2 diabetes (T2DM), nonalcoholic fatty liver disease (NAFLD), coronary artery disease, stroke, obstructive sleep apnea, chronic kidney disease and psychiatric disorders.[3-5] Abnormal glucose metabolism (AGM) is a group of abnormal high blood glucose conditions including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and T2DM. This condition is the most common endocrine complication among overweight and obese children and adolescents. The mechanism of AGM results from increased proinflammatory cytokines production from excessive adiposity leading to impaired insulin signaling and insulin resistance (IR) secondary to pancreatic beta cell dysfunction.[5] At the initial stage of IR, the plasma glucose level will be higher than normal but lower than the diagnostic criteria of diabetes resulting in IFG and IGT, also called, "prediabetic phase".[6] When the IR progresses further, obese children will develop T2DM. Thus, identifying this critical phase in obese youth is important to prevent diabetes in the future.[7] To diagnose AGM, the American Diabetic Association (ADA) suggests that fasting plasma glucose (FPG), 2-h plasma glucose (PG) during a 75-g oral glucose tolerance test (OGTT) and A1C can be used to test for prediabetes or diabetes among children and adolescents who have specific risk factors [8,9] but related studies have shown that 2-h PG during a 75-g OGTT is superior to FPG in predicting AGM because the most frequent type of AGM is IGT.[10-13] Few studies of AGM are available in Thailand. The aims of our study were to determine the prevalence of AGM and identify associated complications among overweight and obese children and adolescents in our population.

Methods

Subjects

All overweight and obese children aged 6 to 18 years visiting the outpatient department (OPD) or admitted in Phramongkutklao Hospital and undergoing OGTT between January 2002 and December 2016 were included in our study and the details of medical history were reviewed. Subjects who had underlying diseases including syndromic obesity, endocrine disorders (growth hormone deficiency, hypothyroidism, Cushing syndrome), abnormal CNS (brain tumor, surgery), steroid use and incomplete data were excluded. All procedures were in accordance with the ethics standards of the Institutional Review Board, Royal Thai Army Medical Department.

Study design

The data of all subjects were retrospectively reviewed from medical records including weight, height, blood pressure and results of blood tests on the day of OGTT. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and BMI z-scores were calculated to compare values across different ages and sex.[14] Percent weight for height (PWH) was calculated by weight in kilograms divided by median age for height for children15 then multiplied by 100. Children with PWH from 120 to 140, >140 to 200 and >200% were classified as overweight, obese and morbidly obese, respectively.[14] Hypertension was classified according to age using systolic blood pressure or diastolic blood pressure. Elevated BP, stage 1 hypertension and stage 2 hypertension were classified as BP ≥90th to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower), ≥95th to <95th percentile +12 mmHg or 130/80 to 139/89 mm Hg (whichever is lower) and ≥95th percentile +12 mm Hg or ≥140/90 mm Hg (whichever is lower), respectively, in children aged 1 to <13 years. among children aged >13 years, elevated BP, stage 1 and stage 2 hypertension were classified as BP 120/<80 to 129/<80 mm Hg, 130/80 to 139/89 mm Hg and ≥140/90 mm Hg, respectively.[16] The standard OGTT was performed in the early morning after 12-hr overnight fasting using 1.75 gm/kg of glucose up to a maximum of 75 gm. Blood samples of plasma glucose and insulin were obtained at baseline and every 30 min for 120 min after an oral glucose load. Serum insulin, A1C, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), aspartate transaminase (AST) and alanine transaminase (ALT) were obtained once at baseline. Prediabetes was defined by two parameters, IFG and IGT. IFG was diagnosed when fasting glucose level was 100 to 126 mg/dL while IGT was diagnosed when 2-h PG during a 75-g OGTT was 140 to 200 mg/dL. T2DM was diagnosed when FPG was >126 mg/dL.[8] High TG, high LDL and low HDL were defined at the level of ≥150, ≥100 to 130 (depending on age group) and <40 mg/dL.[17,18] Dyslipidemia was diagnosed when one case of high TG, high LDL or low HDL was evidenced. NAFLD was diagnosed by the presence of persistently elevated levels of ALT more than 2 fold from the age and sex specific cutoff values.[14] IR was calculated by the homeostatic model assessment (HOMA score) for which a score >3 was considered IR.[19]

Statistical analysis

Continuous variables are shown as means and SD. Categorical variables are reported as number (percentage) of participants with the characteristics of interest. Between-group comparisons were performed by ANOVA for continuous variables. All statistical analyses were performed using the SPSS, Version 24.

Results

Between January 2002 and December 2016, OGTT was performed among 265 overweight or obese children and adolescents. Sixty-one were excluded because 7 had syndromic obesity, 12 had endocrine disorders, 8 had abnormal CNS, 5 had steroid use and 29 had incomplete data. Thus, a total of 204 subjects were included in our study and 122 (59.8%) were male. Mean age, BMI Z-score and PWH were 12.1 ± 2.6 years, 2.2 ± 0.3 and 168.8 ± 25.4%, respectively. Of them, 25 (12.2%) were classified as "overweight", 158 (77.5%) were "obese" and 21 (10.3%) were "morbidly obese". Health-related complications including hypertension, dyslipidemia and NAFLD were found in 41.2, 47.8 and 10.5% of cases, respectively. Sixty-one subjects (29.9%) had stage 1 hypertension and 23 (11.3%) had stage 2 hypertension. Baseline biochemical data of overweight and obese children and adolescents are shown in **Table 1**. A total of 114/200 patients (57%) had IR defined as HOMA-IR score >3.

Table 1. Biochemical studies of overweight and obese children and adolescents.

Characteristics	Mean ± SD
FPG (mg/dL)	80.2 ± 9.5
2-h PG during 75-g OGTT (mg/dL)	122.6 ± 26.2
A1C (%)	5.5 ± 0.4
Fasting insulin (μU/ml)	21.7 ± 15.3
HOMA-IR	4.3 ± 3.1
Triglycerides (mg/dL)	115.8 ± 74.4
Total cholesterol (mg/dL)	178.6 ± 33.5
LDL (mg/dL)	115.1 ± 31.4
HDL (mg/dL)	47.4 ± 11.1
AST (IU/l)	26.9 ± 20.2
ALT (IU/l)	34.6 ± 41.3

FPG; Fasting plasma glucose, LDL; low-density lipoprotein (LDL), HDL; high-density lipoprotein, AST; aspatate transaminase, ALT; alanine transaminase

The prevalence of AGM was 20.6% (42/204 cases). The prevalence of IFG, IGT, combined IFG/IGT and T2DM was 0.5, 17.6, 1.5 and 1%, respectively (**Fig. 1**). IGT was the most frequent subtype of AGM, representing 92.8% (39/42 cases) in the AGM group; 36 with IGT and 3 with combined IFG/IGT. IFG was found in 9.5% (4/42 cases), 1 had IFG alone and 3 had combined IFG/IGT. T2DM was diagnosed in 2 cases; 1 was diagnosed by FPG >126 mg/dL with IGT and 1 was diagnosed by 2-h PG during 75-g OGTT >200 mg/dL but normal FPG. One case was diagnosed with IFG without IGT.

Comparing between the NGM and AGM groups (Table 2), degrees of obesity defined by BMI Z-score and PWH did not significantly differ between groups. According to the possible influence of pubertal status on glucose metabolism, overweight/obese children and adolescents with AGM had older age compared with the NGM group (13.0 ± 2.5 vs. 11.8 ± 2.6, $p = 0.01$). Subjects in the AGM group also had significantly higher FPG (85.2 ± 15.4 vs. 79.8 ± 7.0, $p = 0.034$), A1C (5.7 ± 0.4 vs. 5.5 ± 0.4, $p = 0.006$) and cholesterol (188.1 ± 36.9 vs. 176.2 ± 32.2, $p = 0.043$) than the NGM group. Other biochemistries including TG, LDL, HDL, AST, ALT, fasting insulin and HOMA-IR did not significantly differ in both groups.

Table 2. Characteristics and biochemical studies between normal and abnormal glucose metabolism

Parameters	NGM (N = 162)	AGM (N = 42)	*p*-value
M/F	99/64	23/18	
	(61/39%)	(56/44%)	
Age (years)	11.8 ± 2.6	13.0 ± 2.5	0.01
BMI z-score	2.3 ± 0.3	2.2 ± 0.4	0.14
PWH (%)	169.2 ± 23.2	167.1 ± 33.2	0.72
Hypertension			
Stage 1	50 (30.7%)	11 (26.8%)	
Stage 2	19 (11.7%)	4 (9.8%)	
FPG (mg/dL)	79.8 ± 7.0	85.2 ± 15.4	0.03
A1C (%)	5.5 ± 0.4	5.7 ± 0.4	0.01
Fasting insulin (µU/mL)	21.2 ± 15.4	23.6 ± 15.3	0.37
HOMA-IR	4.0 ± 2.9	5.0 ± 3.5	0.07
Triglyceride (mg/dL)	108.7 ± 56.0	143.6 ± 113.3	0.06
Cholesterol (mg/dL)	176.2 ± 32.2	188.1 ± 36.9	0.04
LDL (mg/dL)	113.8 ± 29.1	120.4 ± 39.1	0.23
HDL (mg/dL)	48.0 ± 11.1	44.7 ± 10.9	0.09
AST (U/L)	25.9 ± 17.1	30.8 ± 29.2	0.16
ALT (U/L)	31.6 ± 34.7	46.2 ± 59.9	0.15

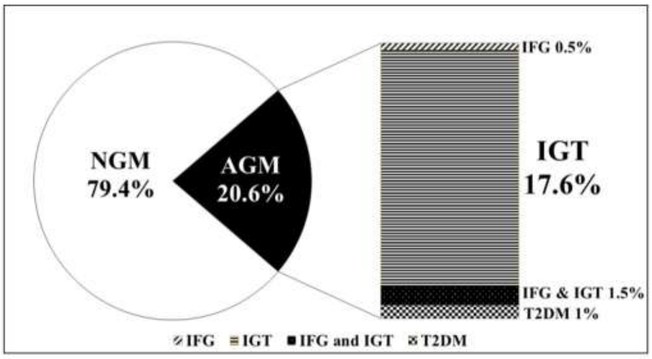

Figure 1. OGTT in 204 subjects and prevalence of abnormal glucose metabolism

Discussion

In our study, the overall prevalence of abnormal glucose metabolism (IFG, IGT, combined IFG/IGT and T2DM) among overweight and obese children and adolescents was 20.6%, comparable to related studies in Thailand [20] and Asian countries.[21-24] IGT is the most frequent subtype of AGM similar to reports from other studies worldwide [13, 20-26] (**Table 3**). The prevalence of IGT was 17.6%, similar to the related report in 2016 by Jaruratanasirikul S who showed the prevalence of IGT in southern Thailand was 15.3% [20] and also comparable with others countries in the Middle East and Asia such as Israel [21], Turkey [22], Bangladesh [23] and India [24] for which the prevalence of IGT ranged from 13 to 18% but lower than that in the United States (25%) [25] (**Table 3**). Interestingly, the IGT prevalence in our study was twice as high whereas the prevalence of IFG was significantly lower than that reported from European cohort studies such as in Italy [12, 27] and Sweden [28] (**Table 3**). The severity of obesity, average BMI and BMI *z*-score of the subjects included in those studies did not differ from our study, so this observation could be explained by differences in ethnicity but the exact reason remains unclear.

Table 3. Prevalence of abnormal glucose metabolism in overweight and obese children and adolescents

Authors	Year	N	Age (years)	Prevalence of AGM IFG (%)	IGT (%)	T2DM (%)	Combine IFG/IGT(%)
Sinha R [25]	2002	167	4-18	-	25	4	-
Shalitin S [21]	2005	192	5-22	-	13.5	0.5	-
Atabek ME [22]	2007	196	7-18	6.6	18	-	-
Cambuli VM [12]	2009	535	7-14	7.66	3.2	0.2	-
Maffeis C [26]	2010	536	4-17	-	6.9	0.1	-
Brufani C [13]	2010	510	3-18	0.8	10	0.4	1.2
Panamonta O [29]	2010	186	10-15	1.1	-	2.2	-
Mohsin F [23]	2012	161	6-18	-	16.9	2.1	-
Ek AE [28]	2015	134	11-17	35.8	6	0	14.2
Bonito PD [27]	2017	3088	7-15	3.3	3.8	0	0.3
Jaruratanasirikul S [20]	2016	177	9-14	-	15.3	2.3	-
Choudhary K [24]	2017	180	10-18	-	13.9	0.5	-
This study	**2019**	**204**	**6-18**	**0.5**	**17.6**	**1.0**	**1.5**

Silent T2DM was rarely diagnosed among asymptomatic overweight and obese children and adolescents. [12,13, 21, 23-29] In our study, T2DM was diagnosed in 1 case by 2-h PG during 75-g OGTT with normal FPG and another case by FPG criteria. All of our results emphasized that 2-h PG during 75-g OGTT is a sensitive method to detect AGM compared with FPG and FPG alone is not a good parameter to detect silent T2DM.[25]

Concerning obesity complications, excessive adipocyte in obesity leads to several metabolic and physiological effects. In our study, we found a high prevalence of dyslipidemia and the most prevalence involved high LDL level. Dyslipidemia was explained by increased hydrolysis of triglycerides from excessive fat tissue.[3,30,31] In the liver, liposomes in hepatocytes increase in size (steatosis) then form large vacuoles that are accompanied by a series of pathological stages including nonalcoholic fatty liver disease, steatohepatitis and cirrhosis.[3] In our study, 10.5% of our population had steatohepatitis due to elevated ALT level but we were unable to perform liver ultrasound to confirm this condition. We also found hypertension (stage 1 or 2) in 41.2% of subjects. This could be explained by chronic overactivity of the sympathetic nervous system in some patients with obesity by mechanical stress of fat tissue that caused renal compression and resulted in systemic hypertension.[3, 30, 31]

Between groups, AGM has significantly older age, higher FPG, A1C and cholesterol compared with NGM. Age is one of the most important factors associated with AGM, and a similar result was noted by Brufani et al., who showed the frequency of IGT appeared to increase gradually from Tanner stage I to III to IV (4.1 vs. 19.9% in Tanner stage I vs. III to IV).[13] This phenomenon was explained by the transient increase of IR observed throughout puberty[31,32] and this result was consistent with the recommendation from the ADA in which prediabetes or diabetes should be screened among asymptomatic overweight and obese children who are older than 10 years or have entered puberty.[8,9] FPG and A1C were significantly higher in the AGM group. For FPG, this finding was expected because subjects with IFG were classified in the AGM group and this finding was similar to many studies from European and the United States cohorts. [10, 21, 34, 35] Subjects in the AGM group had higher TG, TC, LDL and lower HDL level but only TC significantly differed between groups. Many studies have reported that TG was significantly associated with IGT [12, 21, 25, 36] but the study from Groot et al. showed TG, TC, LHL and HDL were unassociated with IGT.[34] Because controversy exists among studies, more sample size should be included to identify these factors. Our study limitation is that the data was derived from subjects attending an outpatient clinic or admission thus not fully representative of a population-based sample and small sample size.

In summary, we found the high prevalence of AGM in overweight and obese children and adolescents. Of them, IGT showed highest prevalence but only 2 T2DM cases were detected. Subjects with AGM had significantly older age, higher FPG, HbA1c and TC. Moreover, the prevalences of obesity complications such as dyslipidemia, nonalcoholic fatty liver disease and hypertension were high in our study. This could activate our awareness on metabolic syndrome among overweight and obese children in our population.

Acknowledgment

This work was financially supported by the Department of Pediatrics, Phramongkutklao Hospital.

References

1. WHO [homepage on the Internet]. Geneva: WHO; c2016 [updated 2018 Feb 16; cited 2019 Mar 12]. Available from: https://www.who.int/en/news- room/-fact-sheets/detail/obesity-and-overweight.
2. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017; 377: 13-27.
3. Heymsfield SB, Wadden TA. Mechanism, pathophysiology and management of obesity. N Engl J Med 2017; 376: 254-66.
4. Weiss R, Kaufman FR. Metabolic complications of childhood obesity. Diabetes Care 2008; 31: S310-6.
5. Lee YS. Consequences of childhood obesity. Ann Acad

Med Singapore 2009; 38: 75-81.

6. Weiss R, Taksali SE, Caprio S. Development of type 2 diabetes in children and adolescents. Current Diabetes Report 2006; 6: 182-7.
7. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: A high-risk state for diabetes development. Lancet 2012; 379: 2279-90.
8. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes 2019. Diabetes Care 2019; 42(Suppl. 1): S13-S28.
9. American Diabetes Association. Children and Adolescents: Standards of medical care in diabetes 2019. Diabetes Care 2019; 42(Suppl 1): S148-S164.
10. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in oral glucose status in obese youth. Diabetes Care 2005; 28: 902-9.
11. Anand SG, Mehta SD, Adams WG. Diabetes mellitus screening in pediatric primary care. Pediatrics 2006; 118: 1888-95.
12. Cambuli VM, Incani M, Pilia S, Congiu T, Cavallo MG, Cossu E, et, al. Oral glucose tolerance test in Italian overweight/obese children and adolescents results in a very high prevalence of impaired fasting glycaemia, but not of diabetes. Diabetes Metab Res Rev 2009; 25: 528-34.
13. Brufani C, Ciampalini P, Grossi A, Fiori R, Fintini D, Tozzi A, et, al. Glucose tolerance status in 510 children and adolescents attending an obesity clinic in central Italy. Pediatr Diabetes 2010; 11: 47-54.
14. Ruttanachuake S, Taweekul P, Aiumopas O, Suatvorawut O. Guideline for prevention and treatment in Thai obese children [Internet]. Thailand Pediatric Nutrition Association; 2014 [cited 2016 October 1]. Available from: http://www.thaipediatrics.org/Media/-media-20161208151655.pdf.
15. The reference values of weight and height in Thai population age 1 day-19 years old. Department of Health. Ministry of Public Health. Thailand 1999.
16. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et, al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017; 140: e20171904.
17. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011; 128 (suppl 5): S213–S256.
18. Bamba V. Update on screening, etiology, and treatment of dyslipidemia in children. J Clin Endocrinol Metab 2014; 99: 3093-102.
19. Matthews DR, Hosker JR, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9.
20. Jaruratanasirikul S, Thammaratchuchai S, Puwanant M, Mo-suwan L, Sriplung H. Progression from impaired glucose tolerance to type 2 diabetes in obese children and adolescents: a 3-6-year cohort study in southern Thailand. J Pediatr Endocrinol Metab 2016; 29: 1267-75.
21. Shalitin S, Abrahami M, Lilos P, Phillip M. Insulin resistance and impaired glucose tolerance in obese children and adolescents referred to a tertiary-care center in Israel. Int J Obes (Lond) 2005; 29:571-8.
22. Atabek ME, Pirgon O, Kurtoglu S. Assessment of abnormal glucose homeostasis and insulin resistance in Turkish obese children and adolescents. Diabetes Obes Metab 2007: 9: 304-10
23. Mohsin F, Mahbuba S, Begum T, Azad K, Nahar N. Prevalence of impaired glucose tolerance among children and adolescents with obesity. Mymensingh Med J 2012; 21: 684-90.
24. Choudhary K, Mathur P, Garg M, Gupta PP. Prevalence of impaired glucose tolerance test and diabetes in overweight, obese and apparently healthy school going adolescents. Int J Contemp Pediatr 2017; 4: 1081-7.
25. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Eng J Med 2002; 346: 802-10.
26. Maffeis C, Pinelli L, Brambilla P, Banzato C, Valzolgher L, Ulmi D, et, al. Fasting plasma glucose (FPG) and the risk of impaired glucose tolerance in obese

children and adolescents. Obesity (Silver Spring) 2010; 18: 1437-42.

27. Bonito PD, Pacifico L, Chiesa C, Valerio G, Del Giudice EM, Maffeis C. Impaired fasting glucose and impaired glucose tolerance in children and adolescents with overweight/ obesity. J Endocrinol Invest 2017; 40: 409-16.
28. Ek AE, Rossner SM, Hagman E, Marcus C. High prevalence of prediabetes in a Swedish cohort of severely obese children. Pediatric Diabetes 2015; 16: 117-28.
29. Panamonta O, Thamsiri N, Panamonta M. Prevalence of type II diabetes and metabolic syndrome among overweight school children in Khon Kaen, Thailand. J Med Assoc Thai 2010; 93: 56-60.
30. Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci 2013; 1281: 123-40.
31. Bussler S, Penke M, Flemming G, Elhassan YS, Kratzsch J, Sergeyev E. Novel insights in the metabolic syndrome in childhood and adolescence. Horm Res Peadiate 2017; 88: 188-93.

32 Ighbaliya A, Weiss R. Insulin Resistance, Prediabetes, Metabolic Syndrome: What Should Every Pediatrician Know?. J Clin Res Pediatr Endocrinol 2017; 9(Suppl 2): 49-57.

33. Moran A, Jacobs DR, Steinberger J, Hong CP, Prineas R, Luepker, et al. Insulin resistance during puberty. Results from clamp studies in 357 children. Diabetes 1999; 48: 2039-44.
34. Groot CJ, Grond JV, Delgado Y, Rings EH, Hannema SE, van den Akker EL. High predictability of impaired glucose tolerance by combining cardiometabolic screening parameters in obese children. J Pediatr Endocrinol Metab 2017; 30: 189-96.
35. Ehehalt S, Wiegand S, Körner A, Schweizer R, Liesenkötter KP, Partsch CJ, et, al. Low association between fasting and OGTT stimulated glucose levels with HbA1c in overweight children and adolescents. Pediatr Diabetes 2017; 18: 734-41.
36. Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Grüters A. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity--a problem that is no longer restricted to minority groups. Eur J Endocrinol 2004; 151: 199-206.