METABOLIC CONSEQUENCES OF CHILDHOOD OBESITY

Suttipong Wacharasindhu

Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Lifestyle changes are among the many factors influencing the growing epidemic of childhood obesity worldwide, as this age group spends more time on computers, inactive, and have more access to 'fast food'. Based on International Obesity Task Force (IOTF) criteria, the prevalence of overweight and obesity in school-age children has increased in all regions of the world, from 2000 to 2010 (Fig 1) (Wang and Lobsein, 2006).

A number of human biological substances secreted from adipose tissue play an important role in weight control, such as interleukin-6 (IL-6), which causes hyperglycemia and insulin resistance; tumor necrosis factor alpha (TNF-alpha), which influences fatty acid oxidation and insulin resistance; and plasminogen activator inhibitor-1 (PAI-1), which is associated with cardiovascular diseases (Blake and Ridker, 2002). Two known peptides, leptin and adiponectin, are associated with adiposity. Adiponectin is a peptide that enhances insulin sensitivity and has a negative correlation with adiposity (Haluzik *et al,* 2004).

Complications of childhood obesity (Weiss and Kaufman, 2008; Lee, 2009)

The complications of childhood obesity may be classified into non-metabolic and metabolic complications.

Non-metabolic complications. Non-metabolic complications can occur in a number of systems. From the respiratory viewpoint, snoring and sleep apnea occur, culminating as the Pickwickian syndrome. The bones are also affected, presenting as Blount disease, slipped capital femoral epiphysis, and degenerative arthritis. Other systems can also emerge as complications, including dyslipidemia and hypertension in the cardiovascular system, depression and poor self-esteem for psychological disorders, and pseudotumor cerebri and stroke under neurological diseases.

Metabolic complications. When children become obese, both their hormonal pattern and metabolism malfunction. Insulin resistance and impaired glucose tolerance are more likely, leading eventually to type II diabetes. These children also have subnormal growth hormone (GH) secretion during GH provocative test. In addition, their sex hormone and puberty are affected, where polycystic ovarian syndrome can ensue. Acanthosis nigricans as seen in obese children may be regarded as a sign of insulin resistance. Insulin resistance leads to the so-called "metabolic syndrome." Several factors give rise to insulin resistance, such as some genetic or ethnic groups, small-for-gestational age infants, degree of obesity, lipid partitioning and physiological changes during puberty.

Obesity, impaired glucose tolerance and diabetes mellitus

When an obese child becomes insulin resistant as a result of the combination of genetics, puberty, and the environment, there will be no clinical evidence. Only a laboratory investigation, the glucose tolerance test, will detect the abnormality. At this stage the compensatory mechanism is in place where sufficient pancreatic beta cell function copes, leading to more insulin secretion in the face of the on-going, increased insulin resistant status. If the situation continues; however, eventually the system will no longer be able to compensate and clinical diabetes emerges.

A multiethnic cohort study (Sinha *et al*, 2002) of 50 obese children, aged 4-10 years, and 112 adolescents, aged 11-18 years, aimed to determine the prevalence of impaired glucose tolerance, reached three main conclusions. First, the impaired glucose tolerance (GT) has a high prevalence among severe obese children and adolescents. Second, impaired GT is associated with insulin resistance with preserved beta-cell function. Third, overt type 2 diabetes mellitus is linked to beta-cell failure.

An important point with insulin resistance is that it can lead to metabolic syndrome (MS) in children. MS in children, who are aged 10-16 years, may be defined according to 2007 International Diabetic Federation (IDF) (IDF*,* 2005) as obesity; demonstrated by an abdominal waist circumference of over 90th percentile plus two of the following features: hypertriglyceridemia (triglycerides >150 mg/dl); low HDL (<40 mg/dl); hypertension (systolic >130 mmHg or diastolic <85 mmHg); or glucose intolerance (fasting plasma glucose >100 mg/dl or known diabetes mellitus Type 2). To date, a definition for younger children cannot be agreed upon.

A study published in 2004 (Weiss *et al,* 2004) regarding childhood metabolic syndrome indicates that the overall prevalence of MS was 38.7% in moderately obese subjects, with 49.7% in those severely obese. None is found, however, in the no overweight and non-obese groups. Similarly, the Princeton Lipid Research Clinics Follow-up Study (Morrison *et al,* 2007) found that childhood MS predicts with significant certainty adult cardiovascular diseases (CVD) development 25 years on. Among patients with pediatric MS, 19.4% went on to have CVD, as compared to 1.5% for those without MS as children. Through multivariate logistic analyses, pediatric MS was a significant predictor of CVD (OR: 14.7; p=0.0001). Lipid partitioning also has a role in insulin sensitivity. Differences in insulin sensitivity (IR) depend on the different patterns of lipid partitioning. Severe IR is demonstrated in individuals with increased deposition of lipid in visceral and intramyocellular compartments (Weiss *et al,* 2003).

A cross sectional study (Promsaree and Wacharasindhu, 2011) of 30 obese children, aged 6-15 years at King Chulalongkorn Memorial Hospital found more incidence of obesity in male than female (70:30%). Most of the children were between the ages of 10-16 years, the adolescent period. Over 80% of the cohort was in the moderate to severe obesity groups. Metabolic complications were compared with studies in Malaysia (Wee *et al,* 2011) and Singapore (Lee *et al,* 2006) (Table 1).

Table 1
Comparison of metabolic complications of a study at King Chulalongkorn Memorial Hospital, Thailand study with Studies in Malaysia and Singapore.

	Chula/Bangkok Age 6-15 yr	Malaysia[a] Age 9-12 yr	Sinapore[b] Age 11.1±3 yr
	%	%	%
Hypertension	35	6.3	17.9
Acanthosis nigricans	90		
Hypercholesterolemia	25		
Hypertriglyceridemia (>150 mg/dl)	27.5	12.5	36.8
Low HDL cholestrol (<40 mg/dl)	28.2	19.7	16.4
Impaired FBS (>100 mg/dl)	5	5.8	
Type 2 DM	2.5		4.5
IGT	20		12.9
Microalbuminuria	7.5		
Metabolic syndrome (IDF criteria)		5.3	

[a]Wee *et al*, 2011; [b]Lee *et al*, 2006.

It is therefore recommended to screen for type 2 DM those children who are obese (American Diabetes Association, 2000). This should be performed in children with overweight (BMI ≥85th percentile for age and gender, weight for height ≥85th percentile, or weight ≥120 percentile of ideal for height).

In addition, any two of the following risk factors: 1) Family history of Type 2 diabetes in first- or second-degree relatives; 2) Race and ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander); or 3) Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS).

The screening should be performed at 10 years of age or at the onset of puberty, if puberty occurs at a younger age. Fasting plasma glucose test is preferred every 2 years.

Obesity is known to affect the kidneys in a number of ways. It increases renal blood flow and glomerular filtration rate, which causes renal hypertrophy and proteinuria (Wahha and Mak, 2007). Microalbuminuria occurs in up to ten percent of obese children (Burgert *et al,* 2006). A renal biopsy shows focal segmental glomerulosclerosis and mesangial proliferation. Hypertension was found as a risk factor of microalbuminuria from a study at King Chulalongkorn Memorial Hospital (Promsaree and Wacharasindhu, 2011).

Obesity during childhood may lead to early signs of puberty (thelarche) in girls and pubertal delay in boys. Early breast development may in part reflect increased peripheral aromatization of adrenal androgens in an expanded adipose tissue. Two main activating mechanisms may explain early puberty in obese children. 1) the “central pubertal activation” is due to the

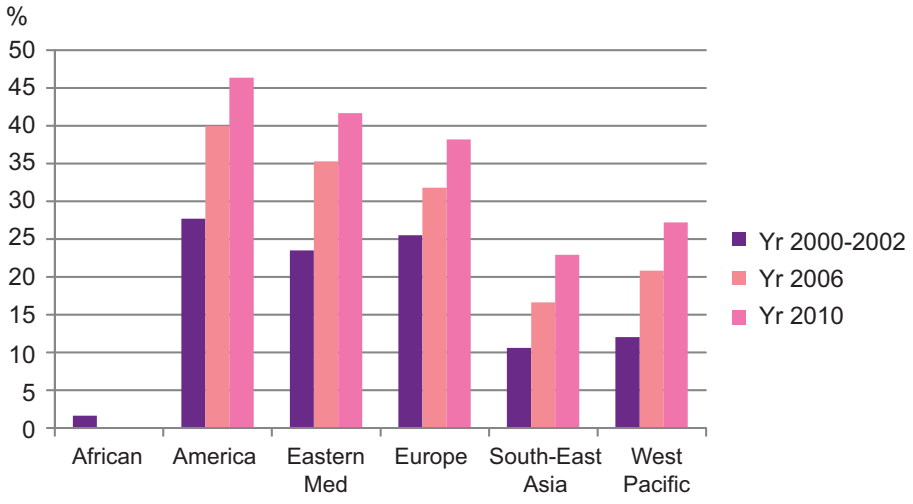

Fig 1–Trend of overweight and obesity in school-age children based on IOTF criteria.

leptin secreted from adipose tissue which has an effect on the premature activation of GnRH pulse generator; and 2) the "peripheral pubertal activation," conversely, is due to increased aromatization by the adipose tissue which converts the adrenal androgens to estrogens (Solorzano and McCartney, 2010; De Leonibus *et al,* 2012).

An epidemiological study (Must *et al,* 1992) was conducted on the association of obesity and Type 2 diabetes mellitus, and the increased risk of developing cancer and increased mortality from various cancers. Nutrition and obesity raise insulin growth factor IGF-I levels, and also promote cancer growth and mortality. The risk of colon cancer is 9.1 fold in elderly men who had been obese as adolescents. In obese women, the prevalence of endometrial cancer, cervical cancer, and renal cancer are increased.

Currently, obesity in children and adolescents is one of the main health problems worldwide, including in ASEAN countries. As pediatricians, we should urge the families and all related in the society to be aware of metabolic and non-metabolic complications that may occur in adult life. National policies should set up guidelines to control this emerging heath care enemy.

REFERENCES

American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000; 23: 381-9.

Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. *J Intern Med* 2002; 252: 283-94.

Burgert TS, Dziura J, Yeckel C, *et al*. Microalbuminuria in pediatric obesity: prevalence and relation to other cardiovascular risk factors. *Int J Obes* 2006; 30: 273-80.

De Leonibus C, MarcovecchioML, Chiarelli F. Update on statural growth and pubertal development in obese children. *Pediatr Rep* 2012; 4: 119-23.

Haluzik M, Parizkova J, Haluzik M. Adipo-

nectin and its role in the obesity-induced insulin resistance and related complications. *Physiol Res* 2004; 53: 123-9.

International Diabetes Federation (IDF). The IDF consensus worldwide definition of the metabolic syndrome. Brussels: IDF, 2005. [Cited 2014 May 7]. Available from: URL: http://www.idf.org/webdata/docs/IDF-Metasyndrome-definition.pdf

Lee YS. Consequences of childhood obesity. *Ann Acad Med Singapore* 2009; 38: 75-81.

Lee YS, Kek BLK, Poh LKS, Vaithinatham R, Saw SM, Loke KY. Characterisation of metabolic consequences in severly obese children. In: Paediatric endocrinology: looking into the future. Proceeding of the 4th Biennial Scientific Meeting. Asia Pacific Paediatric Endocrine Society, 2006 Nov 1-4, Bangkok, Thailand. Bangkok: Asia Pacific Paediatric Endocrine Society; 2006: 92.

Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular diseases 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics* 2007; 120: 340-5.

Must A, Jacques PF, Dallal GE, *et al*. Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1992-1935. *N Engl J Med* 1992; 327: 1350-5.

Promsaree S, Wacharasindhu S. Association between microalbuminuria and cardiovascular risk factors in obese children. Bangkok: Thai Medical Council, 2011. 67 pp. Thesis.

Sinha R, Fisch G, Teague B, *et al*. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002; 346: 802-10.

Solorzano CMB, McCartney CR. Obesity and the pubertal transition in girls and boys. *Reproduction* 2010; 140: 399-410.

Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediar Obesity* 2006; 1: 11-25.

Wahha IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanism links to chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 550-62.

Wee BS, Poh BK, Bulgiba A, *et al*. Risk of metabolic syndrome among children living in metropolitan Kuala Lumpur: a case control study. *BMC Public Health* 2011; 333.

Weiss R, Dufour S, Taksali SE, *et al*. Prediabetes in obese youth: a syndrome of impaired glucose tolerance , severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet* 2003; 362: 951-7.

Weiss R, Dziura J, Burgert TS, *et al*. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004; 350: 2362-74.

Weiss R, Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. *Diabetes Care* 2008; 31(suppl) : 310-6.