บทฟื้นฟูวิชาการ • Review Article

ภาวะอ้วนเกินและภาวะดื้อต่ออินซูลินในวัยรุ่น

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Obesity and Insulin Resistance in Adolescents

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ภาวะอ้วนเกินในวัยรุ่นนับเป็นปัญหาสุขภาพที่มีความสำคัญเพิ่มขึ้นอย่างมากในประเทศแถบเอเชียรวมทั้งประเทศไทย ภาวะอ้วนเกินไปมีความสัมพันธ์กับภาวะผิดปกติทางเมแทบอลิกต่างๆ และภาวะแทรกซ้อนของระบบหัวใจและหลอดเลือด ภาวะดื้อต่ออินซูลินนับเป็นองค์ประกอบที่สำคัญของกลุ่มความผิดปกติทางเมแทบอลิก และความชุกของภาวะดื้อต่ออินซูลินนี้พบได้มากในกลุ่มประชากรไทยที่มีอายุน้อย และนับวันจะเพิ่มจำนวนมากขึ้นโดยเฉพาะในเด็กก่อนวัยรุ่นและเด็กวัยรุ่น ปัจจัยต่างๆ มากมายที่มีผลเกี่ยวข้องกับพยาธิสรีรวิทยาของภาวะอ้วนเกินและสัมพันธ์กับภาวะดื้อต่ออินซูลิน ปัจจุบันมีการพัฒนาวิธีการตรวจที่แม่นยำและน่าเชื่อถือที่สามารถนำมาใช้ประเมินความรุนแรงของภาวะดื้อต่ออินซูลิน ประเมินปัจจัยเสี่ยงอื่นๆ ที่เกี่ยวข้อง และประเมินผลการปรับเปลี่ยนวิถีการดำเนินชีวิตและการใช้ยารักษา สำหรับบทฟื้นฟูวิชาการนี้จะเน้นประเด็นภาวะดื้อต่ออินซูลินในวัยรุ่นที่อ้วนเกินและภาวะแทรกซ้อนที่เกี่ยวข้อง การพัฒนาโปรแกรมการป้องกันภาวะดื้อต่ออินซูลินในเด็กวัยรุ่นที่มีน้ำหนักมากเกินและเกิดภาวะอ้วนเกิน ได้แก่ อาหารลดความอ้วน การออกกำลังกาย และ/หรือการใช้ยาในการรักษาพบว่ามีความสำคัญในการเพิ่มประสิทธิภาพการทำงานของหลอดเลือดและลดภาวะแทรกซ้อนต่างๆ ที่เกี่ยวข้อง

Adolescent obesity has increasingly become a major health problem in many Asian countries, including Thailand. Obesity is associated with many metabolic disorders and cardiovascular complications. Insulin resistance is a key component of the metabolic syndrome, and its prevalence in Thai pediatric population is increasing, particularly among obese children and adolescents. Several factors are implicated in the pathophysiology of obesity-related insulin resistance. Currently, valid and reliable methods are essential to assess the presence and the extent of insulin resistance, the associated risk factors and the effect of pharmacological and lifestyle interventions. This review focuses on obesity-related insulin resistance in obese adolescents and its associated complications. The development of preventive programs involving dietic food, exercise and/or early medical treatment in children and adolescents with overt overweight and obesity appears to be essential to improve vascular function and reduce associated complications.

Key words: Adolescent, cytokines, insulin resistance, metabolic syndrome, obesity

ศรีนครินทร์เวชสาร 2552; 24(4): 344-50 • Srinagarind Med J 2009; 24(4): 344-50

The prevalence of adolescent obesity

The global increase in obesity in children and adolescents heightens the risk of insulin resistance and type 2 diabetes[1]. Obesity is the most common cause of insulin resistance in children[2], and it is also associated with dyslipidemia, type 2 diabetes, and long-term cardiovascular complications[3,4]. Of importance, insulin resistance is the most common metabolic alteration related to obesity, and it represents an

important link between obesity and other metabolic as well as cardiovascular complications.[5] Childhood obesity frequently tracks into adulthood[6], thus representing a major contributor to the adult obesity epidemic and to the increased cardiovascular morbidity and mortality in adult life. The prevalence of childhood and adolescent obesities has been increasing worldwide in the past decade. A longitudinal study in Thailand in 2005 showed that the prevalence of overweight in boys and girls at grade 7 were 13.6% and 9.9%, and at grade 12 were 14.0% and 10.5%, respectively. In addition, the prevalence of obesity in boys and girls at grade 7 were 26.8% and 13.5%, and at grade 12 were 15% and 10.8%, respectively[7]. Another study in 2008 found the prevalence of obesity among students grade 7-12 in Phutthamonthon districts, Nakhon Pathom province was 8.7%[8]. Recently, a similar trend of overweight and obesity studied by our group in secondary schools located in a municipal area of Khon Kaen province shows the prevalence of overweight based on body mass index (BMI) for age in boys and girls at grade 7-12 were 9.85% and 10.44%, and for obesity were 5.18% and 4.92%, respectively[9]. All of these data are alarming and underline how obesity is a real threat for the health of Thai children and adolescents.

Obesity in relation to insulin resistance

The insulin resistance (metabolic) syndrome (IRS), also known as syndrome X, is characterized by a clustering of factors associated with cardiovascular risk, including obesity, impaired glucose metabolism, hypertension, and dyslipidemia.[10] Specifically, it is characterized by a decrease in the ability of insulin to stimulate the use of glucose by muscles and adipose tissue and to suppress hepatic glucose production and output.[11] Furthermore, it accounts for a resistance to insulin action on protein and lipid metabolism and on vascular endothelial function and genes expression.[12] In obesity, it has been established that there is a decrease in insulin receptor binding and a decrease in the phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1) in muscle.[13] There is also a dramatic decrease in insulin-stimulated IRS-1-associated phosphatidylinositol 3 kinase (PI 3-kinase) activity and glucose uptake[13,14].

Obesity and adipose tissue

Obesity is the major risk factor for the development of insulin resistance in children and adolescents. Approximately, 55% of the variance in insulin sensitivity in children can be explained by total adiposity, after adjusting for other confounders, such as age, gender, ethnicity and pubertal stage[2]. It is demonstrated that obese children have hyperinsulinemia and insulin resistance with 40% lower insulin-stimulated glucose metabolism than non-obese children[15]. A recent study performed in American adolescents found that insulin resistance was detected in approximately 50% obese subjects[16], suggesting adiposity was the most important factor affecting insulin sensitivity. Adipose tissue plays a key role in the pathogenesis of insulin resistance through several released metabolites, hormones and adipocytokines that can affect different steps in insulin action[17]. Adipocytes produce non-esterified fatty acids, which inhibit carbohydrate metabolism via substrate competition and impaired intracellular insulin signaling[18,17]. Adiponectin, one of the most common cytokines produced by adipose tissue, is an important insulin-sensitizer and associated with anti-atherogenetic property[19]. As obesity is generally associated with an increased release of metabolites by adipose tissue and the level of adiponectin is inversely related to adiposity[17], therefore, reduced level of the adipocytokine has been implicated in the pathogenesis of insulin resistance and metabolic syndrome.

The body fat distribution

Alteration of fat distribution between subcutaneous and visceral has been associated with insulin resistance[20]. Visceral fat has a better correlation with insulin sensitivity than subcutaneous or total body fat.[21] This could be due to a higher lipolytic activity of visceral when compared with subcutaneous fat, and therefore to a greater amount of free fatty acids and glycerol carried directly to the liver[11]. Previous studies conducted in pediatric population have shown that the amount of visceral fat in girls was directly correlated with basal- and glucose-stimulated insulin levels and inversely correlated - with insulin sensitivity and the rate of glucose uptake[21]. In contrary, no correlation was found between abdominal subcutaneous fat and these metabolic indices[21]. A deposit of fat in the liver or muscle can also be responsible

for insulin resistance in obese subjects, since accumulation of fat in these sites impairs insulin signaling, with a reduced glucose uptake in the muscle and a decreased insulin-mediated suppression of hepatic glucose production[5].

Intramyocellular lipid (IMCL) deposit is another factor related to decreased insulin sensitivity[22,23]. The levels of visceral fat and IMCL in obese insulin sensitive children and adolescents are lower than obese insulin resistant children[24]. Moreover, a higher IMCL has been reported in obese children with impaired glucose tolerance (IGT) when compared with normal glucose tolerance[25], suggesting a pathogenesis role of IMCL in development of insulin gluose resistance and IGT. Fatty liver is also another aspect which is associated with insulin resistance, independently of adiposity[26]. Recently, it has been suggested that deposits of fat around blood vessels can produce several cytokines and these contribute to development of insulin resistance, through a so-called "vasocrine" effect[27].

Complications of the insulin resistance in obese adolescents

Insulin resistance in obese children and adolescents is strongly related to the development of metabolic syndrome[28], including hypertension[29,30], dyslipidemia[31], IGT[32], and hepatic steatosis[33]. In addition, insulin resistance is associated with endothelial dysfunction, systemic inflammation, early atherosclerosis and disordered fibrinolysis, non-alcoholic fatty liver disease and polycystic ovary syndrome (PCOS)[34]. The presence of these alterations in prepubertal children is particularly worrying, as insulin resistance and related complications might be further aggravated by the influence of puberty, due to the physiological decrease in insulin sensitivity associated with normal pubertal development. The degree of insulin resistance and the risk for complications may be differ among obese children with a similar BMI, for example, a greater risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease[35]. In obese children and adolescents, insulin resistance is the best predictor for the development of IGT[32] and T2DM.[36]

It has also been known that insulin resistance in childhood can track in adult life.[37] A recent study has demonstrated that insulin resistance at the age of 13 years predicts insulin resistance at age 19, independently of BMI, and is also associated with cardiovascular risk in adulthood.[37] The presence of obesity, mainly visceral obesity and reduced insulin sensitivity are the main mechanisms implicated in the development of the syndrome. Hence, a direct correlation between the degree of obesity and insulin resistance and the prevalence of the metabolic syndrome has been reported in obese youths[28].

It is well-known that insulin resistance is a major contributor of high blood pressure in children independently of BMI.[29,38] A potential mechanism involved in insulin resistance induced high blood pressure is an insulin-mediated effect on the sympathetic nervous system and on renal sodium reabsorption.[39,40]

Insulin resistance is also associated with an abnormal lipid profile in obese children characterized by hypercholesterolemia, low HDL-cholesterol and hypertriglyceridemia, which increase the risk of developing early atherosclerosis. [41] Moreover, like in adults, there is an association between insulin resistance and hepatic accumulation of fat in obese children[33], resulting in a reduced effect of insulin action on adipose tissue, thereby increased lipolysis and increased flux of free fatty acids to the liver[42]. This effect, together with an increased hepatic lipogenesis are responsible for the accumulation of triglycerides in the hepatocytes and the development of steatosis[42]. Increased levels of liver enzymes, particularly alanine aminotransferase (ALT) enhance the worsening of insulin sensitivity[43]. Based on the association of steatosis and increased ALT with insulin resistance and impaired glucose tolerance (IGT), steatosis is the hepatic manifestation of the metabolic syndrome.

Increased levels of inflammatory markers, such as C-reactive protein and IL-6, have been suggested as additional components of the metabolic syndrome in obese children[44]. Moreover, increased levels of plasminogen activator inhibitor-1 and fibrinogen have also been associated with insulin resistance, and they might contribute to the enhanced coagulability and the risk of cardiovascular diseases related to obesity and insulin resistance[24].

Recently, insulin resistance has been suggested to be involved with the development of polycystic ovary syndrome (PCOS), an ovulatory dysfunction associated with hyperandrogenism.[45] A screening of adolescents with PCOS demonstrated that 30% had IGT and 4% already had

diabetes,[46] indicating an increased risk of T2DM in obese girls with PCOS.

Insulin resistance has also been suggested to be a potential risk factor for the development of respiratory problems, such as asthma, especially in severe obese children and adolescents. It is found that obese children with asthma have a higher degree of insulin resistance than obese children without this respiratory problem, and a possible mediator of this relationship might be the state of inflammation associated with insulin resistance[47].

Prevention and treatment of obesity and insulin resistance

Prevention of obesity and insulin resistance is needed to be implemented as early as possible, such as during pregnancy and the perinatal period. It is important to strongly recommend breast feeding and offer guidance for appropriated food choice, caloric intake and exercise for children.[48] The aim of prevention must put towards maintaining normal BMI. A rapid weight gain during the first years of life must be avoided as it leads to an early adiposity rebound, which is a well-known risk factor for future persistence of obesity.[49] When obesity is already developed, a programme of secondary prevention is required, in order to reverse or at least to avoid progression of obesity. Control of body weight is also particularly important during adolescence, which is a delicate period and associated with physiological insulin resistance and hyperinsulinemia. Therefore, the presence of obesity in this period represents an additional stress for the body, with an increased risk for complications.[50] Preventive strategies need to be further intensified in the presence of other risk factors, such as a family history of obesity, The type 2 diabetes mellitus or cardiovascular disease, or the presence of risk factors for insulin resistance, such as ethnicity.[51] The preventive strategies of obesity in children and adolescents are often of limited success and require major efforts. However, previous studies have shown that the successful interventions to prevent obesity are at least associated with improved dietary habits and physical activity.[52]

A balanced diet and increased physical activity have major effects on prevention and treatment of obesity and insulin resistance in children and adolescents. Decreases in body weight have been associated with the improvement of insulin sensitivity.[53] A recent study has demonstrated that an 8-week exercise training programme in obese children increased insulin sensitivity and was associated with an improvement of cardiorespiratory fitness but was independent of measurable changes in body composition.[54] There is not a wide experience with the use of medications for weight control or insulin sensitizers in children and adolescents. Metformin has been shown to improve insulin sensitivity and BMI in non-diabetic obese adolescents with fasting hyperinsulinemia and a family history of T2DM.[55] In addition, a similar efficacy of metformin on insulin sensitivity and BMI has been found in obese normoglycemic adolescents.[56] Sibutramine seems to have a good efficacy in reducing body weight in children, however, its effect on increased blood pressure and heart rate limits its wide use in the paediatric population.[57] Orlistat is another weight loss drug used in children, although several side effects, such as gastrointestinal disturbances, multiple vitamin deficiencies have been associated with its use.[58] Thiazolidinediones have also been shown to have a good efficacy in improving insulin sensitivity,[59] however, their use in children has not been yet approved. Therefore, further controlled trials are required in order to have a better assessment of the safety and efficacy of drugs used for treatment of obesity and insulin resistance in children and adolescents, and for clarification which subjects really needs pharmacological interventions.

Conclusions

Insulin resistance is a central feature of the metabolic syndromes and represents a serious and common complication of obesity during childhood and adolescence. An early diagnosis and appropriated prevention and treatment are important in order to reduce associated risk of metabolic and cardiovascular complications, thereby, improve health of our children and strengthen our societies in the future.

Acknowledgements

Phouvang Sengmeuang received financial support for studying towords a PhD program in Medical Physiology from the Khon Kaen University Scholarship for Human Resource Development of Neighboring Countries and the Faculty of Medicine, Khon Kaen University.

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