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Acanthosis nigricans and insulin resistance in obese children

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Abstract

Background Acanthosis nigricans (AN) is a skin condition characterized by darkening and thickening of skin. AN has been reported to be linked to insulin resistance (IR) - that associated with type 2 diabetes - in obese children in many country.

Objective To determine the relation between acanthosis nigricans and insulin resistance in obese children.

Methods We conducted a cross sectional study in Wenang district, Manado, from October 2009 until January 2010. We examined 54 obese children aged 10-14 yearsfor insulin resistance using Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR). We analyzed the results by t-test and phi coefficient correlation. The value of $P<0.05$ was significant in statistical analysis.

Results Acanthosis nigricans was positive in 33 children. Insulin resistance was found in 34 from 54 subjects, 28 of them has AN and 6 has no AN. Obese children with AN had higher HOMA-IR than children without AN. Presence of AN was associated with IR ($P<0.001$, $r_{\phi}=0.57$).

Conclusions There is a weak correlation between AN and IR in obese children. It is important to identify obese children with IR for early intervention and prevention of type 2 diabetes, but AN could not be a reliable marker of IR. **[Paediatr Indones. 2010;50:274-7]**.

Keywords: *acanthosis nigricans, insulin resistance, obese*

Acanthosis nigricans (AN) is a skin condition characterized by darkening and thickening of the skin caused by papillomatosis and hyperkeratosis.[1,2] Some studies reported the relation between AN and insulin resistance (IR) in obese children.[3-5] Insulin resistance is thought to be a major factor in the pathophysiology of type 2 diabetes in both adults and children.[6,7] Due to an increasing prevalence of obesity and type 2 diabetes prevalence in children, early identification is important so an appropriate intervention might be established. The aim of this study was to determine whether the presence of AN in obese children was related with IR. Our hypothesis was acanthosis nigricans in obese children related with insulin resistance.

Methods

We conducted a cross sectional study in Wenang district, Manado, from October 2009 until January

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2010. By doing random sampling of 44 elementary schools and 17 junior high schools, we took 20 elementary schools and 10 junior high schools. We estimated that 37 children were needed for this study. From all obese children in these schools, we took 60 subjects with consecutive sampling. The inclusion criteria were 10-14 years old obese children (BMI more than +3SD according to the 2007 WHO Growth Reference Charts) who had been in puberty state (Stage II or more based on Tanner staging). We excluded non-fasting subjects, low birth weight, Cushing syndrome and malignancy. We also excluded subjects used corticosteroid, antidiabetic drug and nicotinic acid therapy. We obtained informed consent from all parents and assent from all children after the nature of the procedures was explained and before testing commenced. We examined the subjects for acanthosis nigricans with inspection and palpation by an experienced dermatologist, then divided them into 2 groups, AN group and non-AN group. We tested all subjects for insulin resistance using Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR). The HOMA-IR was calculated as fasting insulin (μU/mL) multiplied by fasting glucose concentration (mmol/L) divided into 22,5. IR was defined as HOMA-IR $\geq$2.6.[8]

Comparison of HOMA-IR between AN and non-AN group were explored using student t-test. We analyzed the correlation between AN and IR using phi correlation coefficient. Statistical analysis was done using SPSS 17.0 version. The value of $P<0.05$ was considered significant in statistical analysis.

Results

From 60 obese children, we included 55 subjects. Five children had not puberty yet. One subject refused to do the blood test, so 54 subjects were enrolled. The characteristics of the subjects are given in **Table 1**. There were 33 children with positive AN. Acanthosis nigricans predominantly was seen on the posterior of neck. Just two of those children had AN at their axilla and one of them also had AN at the groin.

Table 1. Characteristics of study subjects with and without AN

Characteristic	AN	
	Negative n=21	Positive n=33
Age, mean (SD) yr	11.9 (1.0)	12.3 (1.1)
Male gender, n	17	20
Positive family history of DM, n	9	15

Mean of HOMA-IR in subjects with AN was 2.4 (SD 1.36) and was 5.0 (SD 3.20) in subjects without AN. Obese children with AN had higher HOMA-IR than children without AN ($t = 4.16$, $P<0.001$), with mean difference 2.6 (95% CI 1.4 to 3.9). The association between AN and IR were shown in **Table 2**. Insulin resistance was found in 34 from 54 subjects, 28 of them has AN and 6 has no AN. The x^2 test showed that the presence of AN was associated with IR with the weak correlation.

Table 2. Relation between acanthosis nigricans and insulin resistance

IR	AN		Total n=54	P	rϕ
	Negative n=21	Positive n=33			
Negative	15	5	20	P<0,001	0,57
Positive	6	28	34		

Discussion

In this study, we examined 54 obese children and found that 33 subjects had AN. The previous studies reported the lower prevalence of AN, 42% in 160 obese children in Turkey between the ages of 7 and 14 years and 41 subjects from 105 obese children 4-16 years old in Japan (39.0%).[4,9] The prevalence of AN in our study was higher than the previous study, because the subjects were older. The age of those children with AN was slightly older than those without AN in our study, but all subject had been in puberty state, so this might not affect the results.

Acanthosis nigricans in our subjects predominantly was seen on the posterior of neck. The

studies in many places found that AN in children most commonly found on the posterior neck and axilla. The other locations of AN are axilla, groin, antecubital and popliteal surfaces, umbilical area and even mucosal sufaces.[2,4,10] Insulin resistance due to obesity underlies the hyperinsulinemia in obesity-associated AN. Hyperinsulinemia results in binding of insulin to insulin-like growth factor receptors on keratinocytes and fibroblasts, with resultant hyperplasia, hyperkeratosis and papillomatosis of the skin.[11]

As for our study, we used Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR) to assessed IR. Several recent investigation have shown that HOMA-IR is both reliable and valid for use in pediatric populations.[12-14] We found that HOMA-IR in AN group is higher than non-AN group. This finding is similar to previous study.[4] Our results showed that AN indicates a weak correlation with the presence of IR in obese children. In some previous studies, AN was related with IR in obese children.[3-5] One study showed that there was no relation between AN and hyperinsulinemia in overweight children.[15] A previous study in population with all nutrition condition found that AN was more significantly associated with IR among obese than lean, normal or overweight subjects.[16]

The limitation of our study was the diagnosis of AN not done by skin biopsy, only by inspection and palpation. AN also was not graded among the subjects which would be more reliable information. Cohort studies are needed to assess the start time of AN and IR process in obese children.

In conclusion, there is a weak association between AN and IR in obese children. Considering that IR has central role in development of type 2 diabetes, it is important to identify IR in obese children for early intervention and prevention of type 2 diabetes, but AN could not be an important reliable marker of IR.

References

1. Morelli JG. Diseases of the epidermis. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson textbook of pediatrics. 18th ed. Philadelphia: WB Saunders, 2007;. p. 2708-14.
2. Kong AS, Williams RL, Smith M, Sussman AL, Skipper B, His AC, et al. Acanthosis nigricans and diabetes risk factors: prevalence in young person seen in Southwestern US primary care practises. Ann Fam Med. 2007;5:202-8.
3. Kobaissi HA, Weigensberg MJ, Ball GDC, Cruz ML, Shaibi GQ, Goran MI. Relation between acanthosis nigricans and insulin sensitivity in overweight hispanic children at risk for type 2 diabetes. Diabetes Care. 2004;27:1412-6.
4. Guran T, Turan S, Akcay T, Bereket A. Significance of acanthosis nigricans in childhood obesity. *J Paediatr Child Health.* 2008;44:338-41.
5. Yamazaki H, Ito S, Yoshida H. Acanthosis nigricans is a reliable cutaneous marker of insulin resistance in obese Japanese children. Pediatr Int. 2003;45:701-5.
6. Matthaei S, Stumvoll M, Kellerer M, Haring HU. Pathophysiology and pharmacological treatment of insulin resistance. Endocr Rev. 2000;21:585-618.
7. Varthakavi PK, Patel KL, Wadhwa SL, Shopkar U, Sengupta RA, Merchant PC, et al. A study of insulin resistance in subjects with acanthosis nigricans. J Assoc Physicians India. 2001;49:705-12.
8. Hettihewa LM, Palangasinghe S, Jayasinghe SS, Gunasekara SW, Weerarathna TP. Comparison of insulin resistance by indirect methods – HOMA, QUICKI and McAuley – with fasting insulin in patients with type 2 diabetes in Galle, Sri Lanka: a pilot study. OJHAS. 2006;5:1-8.
9. Katz AS, Goff DC, Feldma SR. Acanthosis nigricans in obese patients: presentation and implications for prevention of atherosclerotic vascular disease. Dermatol Online J. 2000;6:1-7.
10. Ikezaki A, Miura N, Kikuoka N, Hye SK, Matsuoka H, Ito K, et al. Clinical characteristics of obese Japanese children with acanthosis nigricans. Clin Pediatr Endocrinol. 2001;10:47-52.
11. Hardin DS. Screening for type 2 diabetes in children with acanthosis nigricans. Diabetes Educ. 2006;32:547-52.
12. Atabek ME, Pirgon O. Assessment of insulin sensitivity from measurements in fasting state and during an oral glucose tolerance test in obese children. J Pediatric Endocrinol Metab. 2007;20:187–95.
13. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatrics. 2004;144:47–55.
14. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics. 2005;115:e500–3.

15. Nguyen TT, Keil MF, Russell DL, *Pathomvanich A, Uwaifo GI, Sebring NG,* et al. Relation of acanthosis nigricans to hyperinsulinemia and insulin sensitivity in overweight African American and white children. J Pediatr. 2001;138:474–80.

16. Menon VU, Kumar KV, Gilchrist A, Sundaram KR, Jayakumar RV, Nair V, et al. Acanthosis nigricans and insulin levels in a south Indian population (ADEPS paper 2). Obesity Res Clin Practice. 2008;2:43-50.