Effect of Visfatin on Insulin Resistance in Non-Obese Adolescents

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Abstract

Background: Evidence base indicate that insulin resistance (IR) is common among adolescents and related to Diabetes Mellitus (DM). The serum visfatin is adipocytokine derived from visceral fat that may represent a novel IR of metabolic syndrome include DM type II. Therefore, it is necessary to determine the role of serum visfatin and IR in non-obese adolescent. Also this role could help to illustrated more effective early detection for DM type II in non-obese adolescents.

Objective: The current study aimed to evaluate serum visfatin and IR in non-obese adolescents and determine its association.

Method: In cross-sectional study we recruited 155 normal weights between aged 13-18 years. Laboratory measurements were included triglyceride, fasting blood sugar, insulin and visfatin, also IR index calculated by homeostasis model assessment (HOMA). Anthropometric measurements were included height, weight, bicep and tricep skinfold thickness.

Results: Most of subjects were girl 114 (73.55 %). The mean of serum visfatin level was 57.72 ng/ml (range: 0.26-876.2 ng/ml) and HOMA level was 2.26 (range: 0.13-13.4). Non-obese adolescents were found IR. Serum visfatin was not statistical significant with IR (OR_{adj}= 3.23 (95%CI: 0.84–12.45), p= 0.098). All lipid profile (bicep, tricep skin fold thickness and triglyceride) were not affected to IR in non-obese adolescent.

Conclusions: Serum visfatin in non-obese adolescent is independent to IR. IR usually occurred with obese adolescent, but in this study also occurs with non-obese. The key point is lipid profile does not affect to IR status.

Keyword: *Visfatin, insulin resistance, non-obese, adolescent, homeostasis model assessment.*

Introduction

The increasing of insulin resistance (IR) is an important problem during adolescent. Also, adolescent is associated with decreased sensitivity to insulin.[1,2] Furthermore the IR appears to be associated with an increased risk factors of metabolic syndrome especially Diabetes Mellitus (DM) type II.[1,2] IR as well as insulin deficiency have been shown to be strong predictors in the future development of DM type II.[3-5] A clear definition of normal physiologic changes in IR that occur during puberty is necessary before an etiologic association between IR and metabolic syndrome can be considered in this age-group.[6-8] Hence research about IR in adolescent is paramount importance in preventing DM type II related mortality and morbidity in adults.[9,10]

Visfatin, is an adipocytokine that was highly expressed in visceral fat and was originally isolated as a secreted factor that synergizes with interleukin-7.[11] Visfatin is proposed as significant pro-inflammatory mediators, which also interfere with the regulation of insulin sensitivity.[12] Visfatin directly binds to and stimulates the insulin receptor, exerting insulin-

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mimetic affects in vitro and in vivo.[13] In addition, some research reported that visfatin is pro-inflammatory in the pathogenesis of beta-thalassemia major and its association with markers of endothelial function.[14] So, visfatin may be found in diseases not associated with obesity.

An initial study showed that IR and visfatin, as a significant positive association with total fat mass and body mass index (BMI), especially focus on obesity children and adolescent.[15,16] It was found that serum visfatin was markedly elevated in obesity (17), and obesity induces IR by fat tissue. [18] Furthermore, some recently research found that IR is high prevalence in South-Asian adolescents with normal BMI.[19] Since the hypothesis to describe the pathology of IR can find in normal weight.[20] In addition, newly identify cutoff points of HOMA established in adolescents for the diagnosis of IR, which use of the HOMA cutoff > 2.5 for both genders. [21]

Although, a study between visfatin and metabolic syndrome parameters, such as IR in obese adolescent has recently been undertaken. However the association between visfatin level and IR in normal weight adolescents have not been investigated. In this study, we aimed to evaluate serum visfatin and IR, and associations between serum visfatin and IR in normal weight adolescents.

Materials and Method

Design study and sample: The cross-sectional study in non-obese adolescents aged 13-18 years. The inclusion criteria included adolescent with normal weight as per International Obesity Taskforce (IOTF) criteria. [22] The exclusion criteria included subjects with diagnosed diabetes mellitus or taking metformin or any weight reducing drugs, subjects with any known systemic illness or endocrine or metabolic disorders, known to be associated with obesity, or subjects with symptoms to suggest hypothalamic obesity were excluded from the study. A total of 155 non-obese adolescent were recruited from 5 of 18 high schools in Mahasarakham province, Northeast Thailand. Informed consent was obtained from the adolescent and their parents before launching the study. The research protocol was approved by the ethical committee of Mahasarakham University.

Anthropometry: The weight of individual dressed in light clothing was measured using a carefully calibrated beam balance (Detecto@). Height measurement was taken by means of a vertical measuring rod. BMI in kilogram divided by height in square meter was calculated for each subject. Standard techniques were applied in measuring of triceps and biceps skin fold thickness.

Laboratory determination: Blood samples were collected about 10 mL from individual subject that was taken in the morning after an overnight fast. All of blood samples were immediately processed in divide into aliquots and stored at -80^{o}C until further determination. For triglycerides levels were determined using a commercially available test kit that obtained from Siemens Healthcare Diagnostic Inc. An enzymatic test was applied for measuring plasma glucose level by a test kit from Dade Behring Inc. Serum insulin was assessed by a commercially available radioimmunoassay test from Linco Research, Inc. The HOMA calculation was applied the formula fasting insulin (mU L^{-1}) x fasting glucose (mmol L^{-1}) divided by 22.5.[23, 24] A commercially available radioimmunoassay test was used to determine serum visfatin levels (LINCO Research, Inc, St., Charles, Missouri,USA). The cut- off point of serum visfatin for DM which was 9.55 ng/ml. [25]

Statistical analysis: The data were analyzed using Stata version 13.0.Continuous variables were expressed as minimum, maximum, standard deviation (SD) and median. Categorical variables were expressed as number and percentage. The associations of serum visfatin and IR, and the factors associated with IR were using multiple logistic regression analysis. A p-value < 0.05 was considered statistically significant. The classification of IR and non-IR group divided by HOMA cutoff > 2.5. [21]

Results

Demographic Characteristics: The 155 subjects non-obese adolescent were recruited in this study. The demographic, anthropometry and laboratory data showed that the ratio of boy and girl are 41/114. The serum levels of visfatin, insulin and fasting blood sugar were 57.72 (0.26-876.2) ng/mL, 19.05 (4.50: 143.9) mU/L and 87.57 (72-126) mg/mL, respectively. As, average value of HOMA was found 2.6 in non-obese adolescent. IR subject was 34.84 percentages and HOMA levels were showed higher than non-IR (1.71 *vs.* 3.18, P <0.05). The serum visfatin levels were found to be elevated in IR group (15.63 *vs.*38.62 ng/mL, P <0.05).

The effect between visfatin and other variables, with IR in non-obese adolescent: The variables effected with IR in non-obese adolescent included visfatin,

gender, bicep, tricep skinfold thickness and triglyceride (shown in Table 1). All of 155 subjects found that subject with IR was 34.84%. The effect between visfatin and IR from univariate analysis using simple logistic regression was not statistical significance (OR=3.44 (95%CI: 0.96–12.31), p=0.034).

The results of the multiple logistic regression analysis showed that after controlling for gender, bicep skinfold thickness, tricep skinfold thickness and triglyceride, merely the OR of visfatin (OR_{adj}= 3.23 (95%CI: 0.84–12.45), p = 0.098) was not significant. Furthermore the research found that tricep skinfold thickness (OR_{adj}= 1.05 (95%CI: 0.99–1.11), p=0.072) was likely to affect with IR. Therefore, serum visfatin is independent to IR in non-obese adoles-cent.

Discussions

In the present study, it has been reported that 1) serum visfatin is independent to IR in non-obese adolescent 2) all lipid profile are independent to IR in non-obese adolescent and 3) some adolescents with IR are non-obese.

These finding displayed that visfatin is independent with IR in non-obese adolescents. The previous knowledge explained that serum visfatin level which is activated in obesity, is correlated with BMI, and HDL-c in obese adolescents. [15] Visfatin is highly enriched in the visceral fat and bind to insulin receptor.[13] Although, some research reported high visfatin level was occurred with non-obese, it did not found in this study. However, visfatin was not marker role of metabolic syndrome development in normal weight adolescent that support by Oki *et al.* [26] found that serum visfatin is not correlated with IR and suggested that the serum visfatin are not associated with parameters of body composition or IR.[26] Other results we found that 34.84% of subjects was IR. So indicated that during puberty in children develop a transient state of IR. It is speculated that this physiologic, rather than pathologic, state of IR may allow for the accelerated growth that occurs during pubertal maturation.[16] And new research in 2016 is so interesting they found that low-birth-weight was correlated with insulin resistance at 12 months in non-obese infants. [27] Seem from some review revealed that high and low birth weights and followed by rapid postnatal growth were linked to increased risks of obesity, insulin resistance and high blood pressure in later life. [28] Thus, low-birth-weight may affect to IR status in non-obese adolescent.

Our finding that non-obese adolescent with IR and corresponding with Baba et al. [20] found that non-obese adolescents with impaired insulin sensitivity had higher systolic blood pressure and IR is associated with cardiovascular risk factors. However, IR in non-obese adolescent may utility for prevents them from developing real metabolic syndrome in the future.

Some limitations of this study need to be regarded, which we used a cross-sectional study for our design. Cross-sectional study provide information at a single point in time, cannot explain the cause and effect relationship of variables.

Table 1: Odds ratios (ORs) of having IR and their 95% confidence intervals for visfatin and each factor adjusted for all other factors

Variable	Number	% IR	Crude OR	Adjust OR	95%CI	p-value
Overall	155	34.84	NA**	NA**	NA**	NA**
Visfatin (ng/mL)						**0.098**
≤ 9.55	3	15.00	1	1		
>9.55	51	37.78	3.44	3.23	0.84-12.45	
Gender						**0.306**
Boy	41	36.59	1	1		
Girl	114	34.21	0.90	0.66	0.29-1.47	
Bicep skinfold thickness (mm)						**0.139**
≤ 19	81	25.93	1	1		
>19	74	44.59	2.30	1.74	0.83-3.66	
Tricep skinfold thickness (mm)	155	NA**	1.05	1.05	0.99-1.11	0.072
Triglyceride (mg/mL)	155	NA**	1.00	1.00	0.99-1.01	0.098

*p < 0.05, **Not applicable

Conclusions

This study shown that the visfatin in non-obese adolescent is independent to IR, and IR can found in non-obese adolescent. Further investigation is needed to determine tricep skinfold thickness level in non-obese adolescent for approach of clinicians toward prevention IR in future.

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Reference

1. Zaki ME, Amr KS, Abdel-Hamid M. Evaluating the association of APOA2 polymorphism with insulin resistance in adolescents. Meta gene. 2014; 2:366-73.
2. Yi KH, Hwang JS, Kim EY, Lee SH, Kim DH, Lim JS. Prevalence of insulin resistance and cardiometabolic risk in Korean children and adolescents: a population-based study. Diabetes research and clinical practice. 2014;103(1):106-13.
3. Li CL, Tsai ST, Chou P. Persistent impaired glucose tolerance, insulin resistance, and beta-cell dysfunction were independent predictors of type 2 diabetes. Journal of clinical epidemiology. 2005;58(7):728-32.
4. Thamer C, Haap M, Heller E, Joel L, Braun S, Tschritter O, et al. Beta cell function, insulin resistance and plasma adiponectin concentrations are predictors for the change of postprandial glucose in non-diabetic subjects at risk for type 2 diabetes. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2006;38(3):178-82.
5. Hanley AJ, Wagenknecht LE, Norris JM, Bryer-Ash M, Chen YI, Anderson AM, et al. Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: The Insulin Resistance Atherosclerosis Study (IRAS) Family study. Diabetologia. 2009;52(10):2079-86.
6. Kelsey MM, Zeitler PS. Insulin Resistance of Puberty. Current diabetes reports. 2016;16(7):64.
7. Morimoto S, Urakami T. Insulin Resistance during Puberty in Non-obese Japanese Children. Clinical pediatric endocrinology : case reports and clinical investigations : official journal of the Japanese Society for Pediatric Endocrinology. 2011; 20(1):1-6.
8. Pilia S, Casini MR, Foschini ML, Minerba L, Musiu MC, Marras V, et al. The effect of puberty on insulin resistance in obese children. Journal of endocrinological investigation. 2009;32(5):401-5.
9. Homaker LB, Kelly NR, Pickworth CK, Cassidy OL, Radin RM, Shank LM, et al. A Randomized Controlled Trial to Prevent Depression and Ameliorate Insulin Resistance in Adolescent Girls at Risk for Type 2 Diabetes. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine. 2016.
10. Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, et al. Insulin resistance in children: consensus, perspective, and future directions. The Journal of clinical endocrinology and metabolism. 2010;95(12):5189-98.
11. Samal B, Sun Y, Stearns G, Xie C, Suggs S, McNiece I. Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Molecular and cellular biology. 1994;14(2):1431-7.
12. Stofkova A. Resistin and visfatin: regulators of insulin sensitivity, inflammation and immunity. Endocrine regulations. 2010;44(1):25-36.
13. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307(5708):426-30.
14. Dehkordi EH, Nourbakhsh SM, Rostampour N, Boroujeni FA. Relationship between Serum Visfatin and Vascular Inflammation Markers Level in Beta Thalassemia Major Patients. International journal of preventive medicine. 2014;5(10):1269-73.
15. Jin H, Jiang B, Tang J, Lu W, Wang W, Zhou L, et al. Serum visfatin concentrations in obese adolescents and its correlation with age and high-density lipoprotein cholesterol. Diabetes research and clinical practice. 2008;79(3):412-8.

16. Lee JM. Insulin resistance in children and adolescents. Reviews in endocrine & metabolic disorders. 2006;7(3):141-7.
17. Haider DG, Schindler K, Schaller G, Prager G, Wolzt M, Ludvik B. Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. The Journal of clinical endocrinology and metabolism. 2006; 91(4):1578-81.
18. Lee SJ, Kim SH, Park KM, Lee JH, Park JW. Increased obesity resistance and insulin sensitivity in mice lacking the isocitrate dehydrogenase 2 gene. Free radical biology & medicine. 2016;99:179-88.
19. Khadgawat R, Thomas T, Gahlot M, Tandon N, Tangpricha V, Khandelwal D, et al. The Effect of Puberty on Interaction between Vitamin D Status and Insulin Resistance in Obese Asian-Indian Children. International journal of endocrinology. 2012;2012:173581.
20. Baba R, Koketsu M, Nagashima M, Tamakoshi A, Inasaka H. Role of insulin resistance in non-obese adolescents. Nagoya journal of medical science. 2010;72(3-4):161-6.
21. Andrade MI, Oliveira JS, Leal VS, Lima NM, Costa EC, Aquino NB, et al. [Identification of cutoff points for Homeostatic Model Assessment for Insulin Resistance index in adolescents: systematic review]. Revista paulista de pediatria: orgao oficial da Sociedade de Pediatria de Sao Paulo. 2016;34(2):234-42.
22. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. Bmj. 2000;320(7244):1240-3.
23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes care. 2004;27(6):1487-95.
24. Matthews DR, Hosker JP, 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(7):412-9.
25. Nakeeb S E-MH, Fatah W, Bayoumy E, Abd ElAziz R, Wakeil M. Serum Visfatin in Type II Diabetes Mellitus and Its Implication in Development of Diabetic Complications American Journal of Medicine and Medical Sciences 2014;4(6): 272-82.
26. Oki K, Yamane K, Kamei N, Nojima H, Kohno N. Circulating visfatin level is correlated with inflammation, but not with insulin resistance. Clinical endocrinology. 2007;67(5):796-800.
27. Giapros V, Vavva E, Siomou E, Kolios G, Tsabouri S, Cholevas V, et al. Low-birth-weight, but not catch-up growth, correlates with insulin resistance and resistin level in SGA infants at 12 months. The journal of maternal-fetal & neonatal medicine : The official journal of the European Association of Perinatal Medicine the Federation of Asia and Oceania Perinatal Societies the International Society of Perinatal Obstet. 2016:1-6.
28. Muhardi L, Abrahamse-Berkeveld M, Acton D, van der Beek EM. Differences in the anthropometry of Asian children and its role in metabolic health in later life: A narrative review. Obesity research & clinical practice. 2016;10 Suppl 1:S3-S16.