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Original Article

The association between adiponectin level and non alcoholic fatty liver disease (NAFLD) in obese adolescents

Maria Mexitalia[1], Suci Romadhona[1,2]

[1]Bagian / KSM Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Diponegoro / RSUP Dr. Kariadi Semarang
[2]Direktorat Mutu Akreditasi Rumah Sakit Kementerian Kesehatan Republik Indonesia Jakarta

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Afiliasi Penulis:
Bagian / KSM Ilmu Kesehatan Anak
Fakultas Kedokteran Universitas Diponegoro/
RSUP Dr. Kariadi Semarang

Korespondensi Penulis:
Maria Mexitalia
Jl. Dr. Sutomo No. 16, Semarang,
Jawa Tengah 50244, Indonesia

E-mail:
dr.mexitalia@gmail.com

Abstract

Background : Non alcoholic fatty liver disease (NAFLD) has been associated with cytokines and inflammatory mediators. Adiponectin has insulin sensitizing effects and has correlation with severity of NAFLD disease. However, the study about the relationship between adiponectin level and NAFLD is lacking. The objective of the study was to determine the association between adiponectin level and NAFLD in obese adolescents through the role of insulin resistance.
Methods : This was a cross-sectional study, that was done in August 2007. The inclusion criteria were obese adolescents aged 11–14 years, and normal weight adolescent as control group. Adiponectin was assessed by using ELISA, insulin resistance was obtained by Homeostasis Model Assessment Insulin Resistance (HOMA-IR). NAFLD was confirmed by abdominal ultrasound, which represented by fatty liver imaging. The comparison of adiponectin level and HOMA-IR among 3 groups were analyzed by Kruskal Wallis test, meanwhile the correlation between adiponectin level and some variables were analyzed by Spearman correlation.
Results : There were 73 subjects, consisted of 37 obese and 36 non obese. Among obese subjects, 54.1% got NAFLD. All of our obese subjects were insulin resistance, the HOMA-IR level of obese non NAFLD was 6.1 and obese with NAFLD was 6.8. The adiponectin levels in normal children was (5.1g / ml), obese non NAFLD (4.1g / ml) and obese with NAFLD (4.0g / ml) (p <0.001). There were no association between adiponectin level and other variables.
Conclusions : There were significant differences of adiponectin levels and insulin resistance measured by HOMA-IR between normal and obese subjects, but no significant differences between the obese groups with or without NAFLD.

Keywords : NAFLD, adiponectin, HOMA-IR, obesity, adolescent

INTRODUCTION

Obesity has emerged as a global epidemic in children with a spectrum of psychosocial and medical consequenses manifesting a lifespan. The serious health problem of obese children includes metabolic syndrome, insulin resistance and non alcoholic fatty liver disease (NAFLD).[1,2] Our previous study in Semarang Indonesia showed that the prevalence of metabolic syndrome among obese children was 31.6%.[3]

The amount of NAFLD increases with increasing cases of obesity, and the prevalence is around one–third of the obese children.[4] NAFLD characterized by the accumulation of fat in the liver without a history of alcoholism or known liver pathology.[1,5] There was increasing evidence that NAFLD often represents a component of the metabolic syndrome characterized by obesity, hyperinsulinemia, insulin resistance, diabetes, hypertriglyceridemia, and hypertension.[2,6,7] It was reported that 53% ofobese children have NAFLD.[8,9] NAFLD was confirmed by abdominal ultrasonography which was represented by bright liver / fatty liver imaging. Abdominal ultrasonography has 94% sensitivity and 84% specificity to detect NAFLD that described increase echogenicty as a bright liver.[10,11]

Adiponectin also known as Acrp30 is a 30k Dalton protein that is almost exclusively secreted from white adipose tissue. It is a potent modulator of glucose and lipid metabolism and an indicator of metabolic disorders. The gene expression and plasma levels of this hormone corelated with the insulin sensistive state. Dysregulation in the synthesis and/or secretion from the adipose tissue may play a role in the pathogenesis of insulin resistance in obesity. Adiponectin level was lower in the obese children and had associated with insulin resistance, which was obtained by homeostasis model assessment (HOMA–IR) equation.[12–14] Low adiponectin level was an indicator of NAFLD in adults, but it seems do not correlate with the degree of hepatic steatosis in children.[15]

Therefore the purpose of the study was to determine the association between adiponectin level and NAFLD in obese adolescent and the correlation between adiponectin with insulin resistance measured by HOMA–IR.

METHODS

The design was a cross–sectional study. The inclusion criteria were obese adolescents aged 11–14 years grade VIII from private high school in Semarang, and non obese adolescents for control. The study was conducted at August 2007. Anthropometric measurements, weight (to the nearest 100 g) and fat percentage were measured by Biolectrical impedance analysis (BIA) Tanita BC 545 and height (to the nearest 0.1 cm) were measured by *microtoise*. All obese adolescents had a body mass index (BMI) above 95th percentile CDC 2000 chart, where as non obese adolescents had a BMI between the 50th and 75th percentiles CDC 2000 growth chart. Venous blood sample was taken after 8 hours of fasting for measuring insulin, fasting blood glucose and adiponectin. Adiponectin level (g/ml) was assessed by using ELISA ELX 800 Universal Microplate Reader. Fasting blood glucose level (mg/dl) and insulin level (IU/L) was assessed using Spectrofotometer COBAS MIRA. Homeostasis model assessment (HOMA–IR) (mg/dl) was calculated from fasting glucose level multiplied by fasting insulin level divided by 22.5. Insulin resistance was considered if HOMA–IR > 3.16 mg/dl.[16] Abdominal ultrasound only conducted for obese subjects, and was assessed by one radiologist medical doctor in Dr. Kariadi Hospital. The same ultrasound printout was reassessed by the same radiologist 2 month after ultrasound examination (Kappa 0.8).

The comparison of adiponectin level and HOMA–IR among 3 groups were assessed by Kruskal Wallis test, meanwhile the correlation between adiponectin level and some variables including HOMA–IR was analyzed by Spearman correlation. P value were considered significant if $p < 0.05$ with 95% confidence interval. Data analysis were done using *Statistics Program for Social Science* v.15.0. (SPSS Inc, USA). Informed consents were signed by subject's parents, and the study had been approved by the Faculty of Medicine Diponegoro University/Dr. Kariadi Hospital Ethic Committee (IRB) with number 45/EC/FK/RSDK/2007.

RESULTS

There were 73 subjects, consisted of 37 obese and 36 non obese adolescents as control. Among obese subjects, 26 (70.3%) boys and 11 (29.%) girls; and 20 (54.1%) got NAFLD and 17 (45.9%) without NAFLD. Table 1 showed the characteristic of the obese and non obese (normal) subjects and table 2 showed the correlation between adiponectin and some variables.

Based on the HOMA–IR >3.16 was insulin resistance, our data showed that all obese subjects was insulin resistance.

DISCUSSION

Our study revealed that 54.1% of obese children had NAFLD. This was lower compared to New Delhi, where the prevalence of NAFLD among adolescent obese is 62.5%.[17] Zou in China found that the prevalence of NAFLD was 55.75% of children with obesity, while Aksoy in Turkey revealed that 21.6% patients with NAFLD had already got non alcoholic steatohepatitis (NASH).[5,18] NAFLD often occurs in obese children. The risk of NAFLD was risen with increasing of waist circumference, elevated total cholesterol, triglycerides,

TABLE 1
The comparison among normal, obese non NAFLD, and NAFLD subjects on various variables

Variables	Normal	Obese Non NAFLD	Obese NAFLD	*p*
n	36	17	19	
BMI (kg/m^2)	18.4 ± 1.13	27.97 ± 2.23	29.9 ± 2.79	0.025§ *
		p < 0.001 ¶ *		
Fasting Insulin (IU/L)	13.9 ± 9.60	26.9 ± 17.90	27.4 ± 19.84	0.949§
		p < 0.001 ¶ *	31,0	31,0
Fasting glucose (mg/dl)	91.2 ± 7.97	90.9 ± 10.17	98.8 ± 10.03	0.023§ *
		0.014 ¶ *		
HOMA-IR	3.1 ± 2.25	6.1 ± 4.22	6.8 ± 5.05	0.716§
		< 0.001 ¶ *		
Adiponectin (µg/ml)	5.1 ± 1.63	4.1 ± 0.96	4.0 ± 0.98	0.739§
		0.029 ¶ *		

§ Mann–Whitney (the difference between obese non NAFLD and obese NAFLD subjects)
¶ Kruskal Wallis (the difference among normal, obese non NAFLD and obese NAFLD subjects)
*significant *p* < 0.05

TABLE 2
Correlation between adiponectin level and some variables

Variables	Adiponectin level (µg/ml)	
	r	*p*
Fasting blood glucose level (mg/dl)	-0.56	0.634
Insulin level (IU/L)	-2.02	0.083
HOMA-IR (mg/dl)	-2.02	0.082

*Spearman correlation test n=75

blood glucose, fasting insulin and the HOMA–IR index. According to Propokowiz's study, the best independent predictive factor for diagnosing NAFLD in obese children was fasting insulin.[4] Whereas Keskin *et al*. showed that the cut off value of HOMA–IR for diagnosing insulin resistance was 3.16.[16]

Insulin resistance is a key mechanism in the pathogenesis of fatty liver disease. It causes fat accumulation in hepatocytes through two main mechanisms namely lipolysis and hyperinsulinemia. Insulin resistance is a pathophysiological abnormality that underlies the development of significant disease in the clinic, including the deterioration of insulin potential in regulation of energy metabolism, control of transmembrane ion transport for protein synthesis, control of gene transcripts, and cell proliferation. Practically insulin resistance is used to explain the deterioration of insulin potential both endogenous and exogenous to increase the uptake and use of glucose by the body's cells. While the main role of insulin itself in hepatocytes is to control liver glucose production by suppressing glycogenesis. Various component, especially those released by adipocytes have the potential to cause insulin resistance. These include proinflammatory cytokines such as Interleukin–6 (IL–6), Tumor Necrosis Factor–TN (TNF–α), angiotensinogen, leptin, resistin, and adiponectin. Adiponectin is a polypeptide that is useful as an antidiabetic, antiaterogenic, anti–inflammatory which is closely related to systemic insulin sensitivity. Adiponectin increases the oxidation of fatty acids in muscles, increases the action of insulin in the liver and decreases lipid accumulation in macrophages.[7,19,20]

Our study revealed that insulin fasting level was 27.4 IU/L in the NAFLD obese group, not significantly different from the non NAFLD obese group, 26.9 IU/L, but these results were significantly different from the control group with normal nutritional status i.e 13.9 IU/L. One study found that the best independent predictive risk factor for diagnosing NAFLD in obese children was fasting insulin >18.9 IU/L.[4] However we did not try to find a predictive risk factor for NAFLD but in both our subject groups with obesity, the fasting insulin greater than 18.9 IU/L were obtained.

All of our obese subjects were insulin resistance, with the HOMA–IR level of obese non NAFLD was 6.1 and obese with NAFLD was 6.8. There was no difference of HOMA–IR level between obese NAFLD and obese

without NAFLD. Our results are almost the same as Kim's study in South Korea where the HOMA–IR of obese adolescents with NAFLD was 6.5 but the obese adolescents without NAFLD was 4.2 that is lower than our results.[2] Kim also found that HOMA–IR (p=0.030) was a significant indicator of NAFLD. The HOMA–IR of overweight adolescents with NAFLD in New Delhi was 4.2 and overweight without NAFLD 3.0, it was lower than our subjects.[17]

Adiponectin level was lower in subjects with obesity and NAFLD or without NAFLD than to normal subjects. Our study found a significant differences between adiponectin levels in normal children (5.1µg/ml) and obese without NAFLD (4.1µg/ml) and obese with NAFLD (4.0µg/ml), but not significant between groups with or without NAFLD. One study in China which compared three obese children groups, namely the group without fatty liver, the group with fatty liver and the group with fatty liver and liver dysfunction, found that the serum adiponectin in the group without fatty liver was significantly higher (4.24µg/ml) compared to subjects with fatty liver (3.37µg/ml) and subjects with fatty liver and liver dysfunction (3.12µg/ml), but did not differ significantly between the fatty liver groups with or without liver dysfunction.[18]

In conclusion, we found significant differences of adiponectin levels and insulin resistance measured by HOMA–IR between normal and obese subjects, but no significant differences between the obese groups with or without NAFLD. Likewise, there is no relationship between adiponectin levels and insulin resistance. In suggestion, we need to do a further study regarding the correlation between adiponectin levels and NAFLD in obese adolescents by using liver biopsy.

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