

RELATIONSHIP BETWEEN LEPTIN-ADIPONECTIN RATIO AND INSULIN RESISTANCE IN OBESE SUBJECTS

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ABSTRACT

Objective: Leptin and adiponectin are important hormones secreted from adipocytes that are involved in the regulation of energy homeostasis and might contribute to the link between obesity and insulin resistance. The aim of this study was to determine the relationships among various adipokine measures (leptin, adiponectin, and the ratio of leptin to adiponectin (L/A)), insulin resistance, and obesity.

Material and Method: The study included 110 obese and 90 non-obese subjects. Fasting glucose, insulin, HDL cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-C), leptin, adiponectin and anthropometric parameters were measured. Each subject's homeostasis model assessment of insulin resistance (HOMA-IR) index and leptin to adiponectin ratio (L/A) were calculated.

Results: The L/A ratio was significantly correlated with HOMA-IR in both obese ($r=0.25$, $p<0.01$) and non-obese ($r=0.68$, $p<0.01$) subjects. In obese subjects, leptin and the L/A ratio were significantly correlated with body mass index (BMI) ($p<0.01$) and waist ($p<0.01$) and hip ($p<0.01$) circumferences and adiponectin was significantly correlated with HOMA-IR ($r=-0.68$, $p<0.01$). Best cut off value of L/A for BMI was found to be 0.78, sensitivity was 93.6% and specificity was 81.1% according to receiver operating characteristic (ROC) analysis.

Conclusion: The results suggest that the L/A ratio might be a more sensitive and reliable indicator of insulin resistance in obese subjects than adiponectin or leptin concentrations.

Keywords: Obesity, leptin, adiponectin, insulin resistance
Nobel Med 2015; 11(3): 10-16

OBEZ BİREYLERDE LEPTİN - ADİPONEKTİN ORANI VE İNSÜLİN DİRENCİ ARASINDAKİ İLİŞKİ

ÖZET

Amaç: Leptin ve adiponektin, adipositler tarafından sentez edilen ve enerji dengesinin düzenlenmesinde yer alan önemli hormonlardır. Bu hormonlar obezite ile insülin direnci arasındaki patolojik mekanizmaya da katkıda bulunabilmektedirler. Bu çalışmanın amacı leptin, adiponektin ve leptin-adiponektin oranının (L/A) insülin direnci ile obezite arasındaki ilişkiyi değerlendirmekteki etkilerini karşılaştırmaktır.

Materyal ve Metot: Çalışma 110 obez ve 90 obez olmayan birey içermektedir. Çalışma kapsamında açlık kan şekeri, HDL-kolesterol (HDL-K), trigliserit (TG), total kolesterol (TK), LDL-kolesterol (LDL-K), leptin, adiponektin ve antropometrik parametrelerin ölçümü yapılmıştır. Homeostatik model değerlendirme indeksi

(HOMA-IR) ve leptin-adiponektin oranı (L/A) hesaplanmıştır.

Bulgular: L/A oranı hem obez ($r=0,25$, $p<0,01$) hem de obez olmayan ($r=0,68$, $p<0,01$) grupta HOMA-IR ile istatistiksel olarak anlamlı bir korelasyon göstermiştir. Obez bireylerde leptin ve L/A oranı ile vücut kitle indeksi (VKİ) ($p<0,01$), bel ($p<0,01$) ve kalça ($p<0,01$) çevreleri arasında anlamlı korelasyon belirlenmiştir. Adiponektin obez grupta HOMA-IR ile istatistiksel olarak anlamlı bir korelasyon göstermiştir ($r=-0,68$, $p<0,01$). İşlem karakteristik (ROC) analizi ile VKİ'ye göre L/A için en iyi kesim noktası 0,78, sensitivite 93,6, spesifite 81,1'dir.

Sonuç: Sonuçlar obez kişilerde insülin direnci değerlendirmesinde L/A oranının tek başına leptin veya adiponektine göre daha duyarlı ve güvenilir olabileceğini göstermektedir.

Anahtar kelimeler: Obezite, leptin, adiponektin, insülin direnci
Nobel Med 2015; 11(3): 10-16

INTRODUCTION

Obesity currently qualifies as a worldwide health epidemic. It is defined by accumulation of adipocytes throughout the body and is also associated with a variety of metabolic diseases. Obesity is closely linked with insulin resistance and is a major risk factor for development of type 2 diabetes mellitus.¹

Adipose tissue, in addition to its function as the major storage depot for triglycerides, is an active endocrine organ secreting adipokines that influence insulin sensitivity and whole-body energy homeostasis.² These adipokines include leptin and adiponectin, which are secreted into the serum. Leptin levels increase with obesity, whereas adiponectin levels decrease.³ These parameters are thought to link obesity, insulin resistance, and related disorders.^{4,5}

Leptin primarily acts in the hypothalamus and plays a key role in the regulation of food intake, body weight, energy expenditure, and neuroendocrine function. Leptin has direct peripheral effects on several tissues, including the pancreas. Basal leptin and insulin concentrations correlate with each other; insulin and glucose appear to increase leptin secretion. In turn, leptin has been demonstrated to increase peripheral insulin sensitivity, decrease insulin secretion, increase skeletal muscle uptake and utilisation of glucose, and decrease hepatic glucose production.⁶

Adiponectin levels, unlike those of other adipokines, which increase with excess body fat mass, are lower in obese and diabetic than normal subjects.⁷ Adiponectin is thought to play an important role modulating glucose and lipid metabolism in insulin-sensitive tissues in both humans and animals.⁸

The leptin to adiponectin (L/A) ratio may be a more accurate marker of insulin resistance than the more widely used index, the homeostasis model assessment of insulin resistance (HOMA-IR), in subjects with or without hyperglycemia.⁹ HOMA-IR is widely used to evaluate insulin resistance in large epidemiologic studies, although it is not an accurate indicator of insulin resistance in individuals with impaired glucose tolerance or elderly patients with poorly controlled diabetes.

The aim of this study was to compare levels of leptin and adiponectin, as well as the L/A ratio, in non-obese and obese subjects and determine their relationships with anthropometric and metabolic parameters, including HOMA-IR.

MATERIAL AND METHOD

This prospective study included two groups of patients who visited the outpatient clinic of the Endocrinology

Department in Famagusta Government Hospital. One group was composed of 110 obese patients having a mean age of 40.38 ± 8.71 years and BMI 35.75 ± 6.88 kg/m². The second group was composed of 90 non-obese subjects with mean age 38.76 ± 9.46 years and mean BMI 22.68 ± 1.75 kg/m². None of the participants had hypertension or liver, kidney, thyroid, cardiovascular, or any active inflammatory diseases, were taking any medications that might affect lipid or glucose metabolism, or had participated in any dietary or exercise programs. All subjects provided written informed consent before enrollment and the study was approved by the Near East University Research Ethics Committee (2011/3-15).

All measurements were performed in the morning following overnight fast. Anthropometric measurements including weight (kg), height (m), hip circumference (cm), and waist circumference (cm) were measured barefoot and lightly clothed. Hip circumference was measured by placing a tape measure around the patient's hips at the level of the prominences over the greater trochanters of both femurs. Waist circumference was taken midway between the lowest rib (laterally) and the iliac crest landmark by flexible tape. BMI was calculated as body weight (kg) divided by the square of height (m²) and obesity was defined as BMI ≥ 30 kg/m².¹⁰

Blood samples were obtained after overnight fast. Serum glucose, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured using a fully automated clinical chemistry analyser (Abbott Architect C8000). Fasting insulin concentrations were measured using an electrochemiluminescence kit (ref. 12017547) (Elecsys, Lenexa, KS, USA). Insulin resistance index was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR), as the product of fasting insulin (μ U/mL) and fasting glucose (mmol/L) divided by 22.5.¹¹

Plasma leptin and adiponectin levels (ng/mL) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (DRG Intl., Inc., USA for leptin and Biovendor Laboratory, Inc., Brno, Czech Republic for adiponectin) according to the manufacturers' protocols. Leptin to adiponectin ratio was calculated by dividing the leptin level by the adiponectin level.

Continuous variables were expressed as means \pm standard deviation (SD). Differences in baseline characteristics between groups were analysed by Student's t-test for continuous variables. Correlation analysis was performed using Pearson tests. A p value of less than 0.05 was considered to indicate statistical

Table 1. Baseline anthropometric and metabolic characteristics			
Parameter	Non-obese subjects	Obese subjects	p
	(n=90)	(n=110)	
Age	38.76 ± 9.46	40.38 ± 8.71	0.20
BMI (kg/m ²)	22.68 ± 1.75	35.75 ± 6.88	<0.001
Waist circumference (cm)	85.57 ± 7.52	112.25 ± 12.83	<0.001
Hip circumference (cm)	99.40 ± 5.99	120.89 ± 12.33	<0.001
Fasting glucose (mg/dL)	89.73 ± 7.46	103.35 ± 23.45	<0.001
Total cholesterol (mg/dL)	203.62 ± 34.28	234.00 ± 37.32	<0.001
LDL cholesterol (mg/dL)	123.86 ± 28.18	144.55 ± 32.41	<0.001
HDL cholesterol (mg/dL)	55.29 ± 9.36	47.84 ± 10.23	<0.001
Triglycerides (mg/dL)	105.41 ± 40.18	166.97 ± 83.39	<0.001
Leptin (ng/ml)	8.27 ± 4.08	24.47 ± 13.90	<0.001
Adiponectin (µg/ml)	17.24 ± 8.74	8.99 ± 3.94	<0.001
HOMA-IR	1.90 ± 0.66	4.58 ± 3.95	<0.001
L/A ratio	0.51 ± 0.17	3.12 ± 1.52	<0.001

Data are expressed as means ± SD and were compared by t-test.
BMI: Body mass index, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein, **HOMA-IR:** homeostasis model assessment of insulin resistance, **L/A:** leptin to adiponectin ratio.

Table 2. Correlation coefficients between leptin, adiponectin and L/A ratio with other variables in non-obese subject						
Variable	Leptin		Adiponectin		L/A ratio	
	r	p	r	p	r	p
BMI (kg/m ²)	0.33	0.001	-0.11	0.3	0.15	0.16
Waist circumference (cm)	0.11	0.3	-0.09	0.39	0.09	0.39
Hip circumference (cm)	0.31	0.003	-0.06	0.57	0.15	0.16
Fasting glucose (mg/dL)	0.12	0.26	-0.05	0.64	0.34	0.001
Total cholesterol (mg/dL)	0.20	0.06	-0.18	0.09	0.01	0.92
LDL cholesterol (mg/dL)	0.16	0.13	-0.12	0.26	0.05	0.64
HDL cholesterol (mg/dL)	-0.13	0.22	0.02	0.85	-0.09	0.39
Triglycerides (mg/dL)	0.21	0.06	-0.19	0.07	0.04	0.70
HOMA-IR	0.3	0.004	-0.10	0.35	0.68	<0.001

BMI: Body mass index, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein, **HOMA-IR:** homeostasis model assessment of insulin resistance, **L/A:** leptin to adiponectin ratio.

significance. Receiver operating characteristic (ROC) curves were plotted. All statistical analyses were performed using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Descriptive statistics of anthropometric and metabolic characteristics of the study population are presented in Table 1. Obese and non-obese subjects did not differ in age, while L/A ratio, plasma glucose, total cholesterol, triglycerides, LDL cholesterol and leptin levels were significantly higher and mean HDL cholesterol levels were significantly lower in obese than non-obese subjects. Non-obese subjects had significantly higher

adiponectin levels and lower HOMA-IR compared to obese subjects.

Correlation coefficients between L/A ratio and plasma leptin and adiponectin levels with other biochemical parameters in non-obese subjects are presented in Table 2. Leptin levels correlated positively with BMI ($r=0.33$, $p=0.01$), hip circumference ($r=0.31$, $p=0.003$), and HOMA-IR ($r=0.3$, $p=0.004$), while adiponectin levels did not significantly correlate with any other parameter. L/A ratio was significantly correlated with plasma glucose levels ($r=0.34$, $p=0.01$) and HOMA-IR ($r=0.38$, $p<0.001$).

Table 3 shows correlation coefficients between L/A ratio and plasma leptin and adiponectin levels with other biochemical parameters in obese subjects. Leptin levels were significantly correlated with BMI ($r=0.6$, $p<0.001$), HDL cholesterol ($r=-0.3$, $p=0.001$) and waist ($r=0.44$, $p<0.001$) and hip ($r=0.69$, $p<0.001$) circumferences. On the other hand, adiponectin levels were significantly correlated with HOMA-IR ($r=-0.28$, $p=0.003$). L/A was significantly correlated with all of these variables, with the exception of HDL cholesterol.

In this study, L/A was the best predictor of BMI in both obese and non-obese subjects. The cutoff value of L/A based on ROC curve for BMI was 0.78 with sensitivity 93.6% and a specificity of 81.1% (1). Best cutoff value of leptin for BMI was found to be 13, sensitivity was 82.7% and specificity was 86.7% according to receiver operating characteristic (ROC) analysis (Figure 2). For BMI best cutoff value of adiponectin level was found to be 13.46, sensitivity was 83.6% and specificity was 65.6% (Figure 3).

DISCUSSION

Obesity is a chronic disease defined as excessive growth of adipose tissue. Adipose tissue secretes adipokines, such as adiponectin and leptin, whose profile changes in response to the amount and condition of adipose tissue and profoundly influence insulin sensitivity and glucose metabolism.¹² These adipokines have also been suggested to provide a molecular link between obesity and insulin resistance. In the present study, we observed that the L/A ratio was significantly correlated with HOMA-IR in both obese and non-obese subjects. Additionally, adiponectin levels were correlated with HOMA-IR in obese subjects. Leptin was positively correlated with BMI and hip circumference in all subjects, with HOMA-IR in non-obese subjects and with waist circumference and HDL-cholesterol levels in obese subjects.

Leptin levels correlate positively with body mass index; body fat mass is the most important factor determining leptin concentration.¹³ The positive correlation of leptin levels with BMI has been corroborated widely.¹⁴⁻²⁰ In accordance, we also found a significant correlation between BMI and leptin concentration in both obese and non-obese subjects.

Leptin has direct effects on food intake and body weight regulation, and although a direct impact of leptin on insulin sensitivity is controversial, it may be independently involved in insulin secretion and action.^{6,12} After food intake, insulin stimulates leptin biosynthesis and secretion from adipose tissue. Leptin in turn stimulates peripheral insulin sensitivity and modulates pancreatic beta cell function. This bidirectional feedback loop between adipose tissue and pancreatic islets is called the "adipoinular axis". Several studies have shown that leptin signaling is attenuated in obesity; the resulting leptin resistance would explain the failure of high leptin levels to control food intake and energy expenditure. In our study, although we observed a significant correlation between leptin and HOMA-IR in non-obese subjects, the correlation did not appear in obese subjects, which would be consistent with pancreatic leptin resistance in obesity.²¹ Although the mechanism and process of leptin resistance remain unclear, we conclude that obese subjects are leptin-resistant, as leptin-independent insulin secretion would explain the weak correlation between these hormone concentrations.

Adiponectin is the most abundant adipokine secreted by adipose tissue and is a key regulator of insulin sensitivity. Low levels of adiponectin in humans have been related to several diseases, such as type-2 diabetes and insulin resistance.²² A number of studies have reported on the inverse associations of adiponectin concentrations with insulin resistance has been widely examined in different studies.^{23,26} Accordingly, our study showed that adiponectin level was negatively correlated with HOMA-IR in obese subjects. These results suggested that adiponectin could be a marker of the obesity-linked insulin resistance.

Leptin and adiponectin are secreted by adipocytes and have both paracrine and endocrine effects on a variety of tissues. Increased leptin levels and decreased adiponectin levels are cross-sectionally associated with high insulin resistance in obesity.²⁴ A simple index of insulin sensitivity based on fasting glucose and insulin levels, such as HOMA-IR, is easily obtained and may be a useful tool for large epidemiologic studies, although the fact that it measures only fasting blood glucose and fasting blood insulin means that it does not accurately

Table 3. Correlation coefficients between leptin, adiponectin and L/A ratio with other variables in obese subjects

Variable	Leptin		Adiponectin		L/A ratio	
	r	p	r	p	r	p
BMI (kg/m ²)	0.6	<0.001	-0.04	0.67	0.4	<0.001
Waist circumference (cm)	0.44	<0.001	-0.13	0.17	0.31	<0.001
Hip circumference (cm)	0.69	<0.001	-0.09	0.35	0.37	<0.001
Fasting glucose (mg/dL)	0.02	0.83	-0.02	0.83	0.04	0.68
Total cholesterol (mg/dL)	0.01	0.92	-0.11	0.25	0.05	0.60
LDL cholesterol (mg/dL)	0.01	0.92	-0.01	0.92	0.001	0.99
HDL cholesterol (mg/dL)	-0.3	0.001	0.03	0.75	-0.13	0.17
Triglycerides (mg/dL)	0.12	0.21	-0.14	0.14	0.03	0.75
HOMA-IR	0.18	0.06	-0.28	0.003	0.25	0.008

BMI: Body mass index, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein,
HOMA-IR: homeostasis model assessment of insulin resistance, **L/A:** leptin to adiponectin ratio.

measure insulin resistance in hyperglycemic subjects.²⁵ On the other hand, the L/A ratio is not easily affected by fasting blood glucose and may be a more accurate indicator of insulin resistance regardless of glycemic status. The ratio of leptin to adiponectin (L/A) would thus likely better correlate with insulin resistance than leptin or adiponectin levels themselves.²⁶ Oda et al. showed the L/A ratio in diabetic patients to be a marker of insulin resistance and also a useful indicator of which drug would be most effective for treating diabetes mellitus.²⁷ Likewise, Inoue et al. reported that the L/A ratio might be a more accurate marker of insulin resistance than HOMA-IR not only in patients with type 2 diabetes but also in subjects without hyperglycemia.⁹ Furthermore, Yoon et al. demonstrated that the L/A ratio provides significant adjunctive information on the risk of metabolic syndrome beyond HOMA-IR.²⁸ Our findings are in accordance with the abovementioned studies. As leptin and adiponectin are counter-regulated, they may exert opposing effects on insulin sensitivity, suggesting that the L/A ratio could be a marker for insulin resistance in obesity, as neither adipokine is affected by blood glucose.

Although leptin has been reported to affect glucose homeostasis mainly through actions on the hypothalamus, it has also been shown to have peripheral effects, interacting with insulin actions in skeletal muscle, the liver, and adipose tissue.^{29,30} Furthermore, besides these peripheral tissues, the pancreatic β -cell is a key target of leptin. Circulating glucose and insulin appear to stimulate leptin secretion.³¹ Indeed, animal models with defects in leptin or leptin receptors such as ob/ob and bd/bd mice develop insulin resistance, hyperinsulinemia, and impaired glucose homeostasis.³² Leptin administration to ob/ob mice reduces plasma glucose levels and hyperinsulinemia.³³ On the other hand, adiponectin also affects pancreatic β -cell function

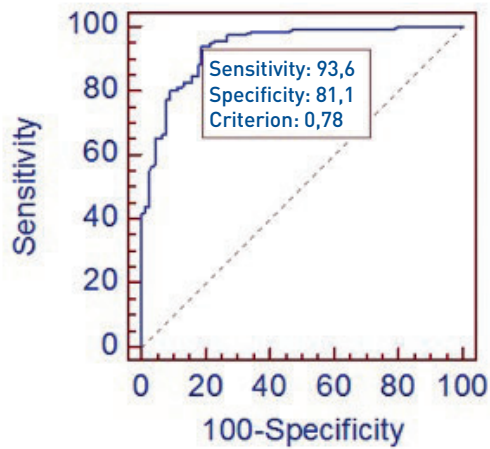


Figure 1. ROC curves for leptin to adiponectin ratio (L/A) as a predictors of BMI. The area under the curve (AUC) is 0.93.

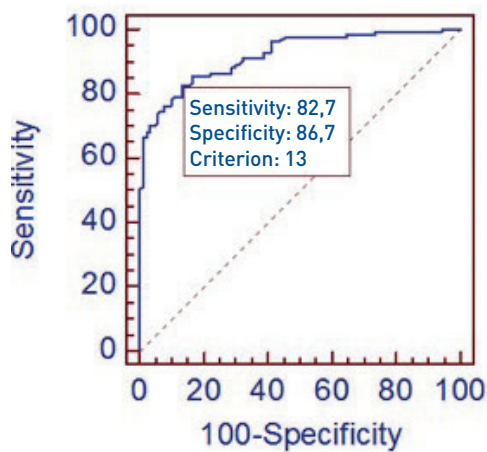


Figure 2. ROC curves for leptin as a predictors of BMI. The area under the curve (AUC) is 0.81.

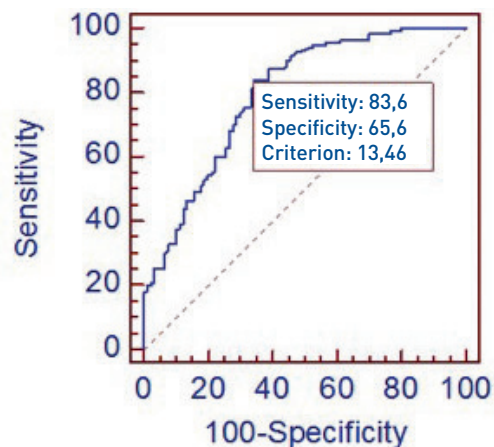


Figure 3. ROC curves for adiponectin as a predictors of BMI. The area under the curve (AUC) is 0.79.

and glucose metabolism, inducing glucose uptake and suppresses gluconeogenesis in muscle and liver. Yamauchi et al. reported that low levels of adiponectin were strongly implicated in the development of insulin

resistance in mouse models of both obesity and lipodystrophy, and insulin resistance improved upon administration of adiponectin.³⁴ Accordingly, our study showed that glucose levels are positively correlated with the L/A ratio in non-obese subjects.

Leptin activates AMPK (AMP-activated protein kinase) which, in turn, inactivates acetyl-CoA carboxylase (ACC), an enzyme involved in the initial phase of triacylglycerol and fatty acid synthesis. Moreover, leptin also enhances the intracellular expression of peroxisome-proliferator-activated receptor- γ 2 co-activator 1 α (PGC-1 α), thus increasing mitochondrial fatty acid (FA) oxidation. Most obese individuals have high leptin levels and abnormal lipoprotein levels. In cases of leptin resistance, such as in obesity, AMPK fails to inhibit ACC, leading to increased synthesis of TAGs and FAs and simultaneous blocking of FA oxidation. Therefore, increased plasma TAG is almost always associated with reduced HDL cholesterol levels in obese subjects.³⁵ In our study, leptin was negatively correlated with HDL cholesterol in obese subjects, in agreement with findings by Zhuo et al. and Esteghamati et al., who reported the same correlation in both female and male subjects with metabolic syndrome.^{19,36} In light of these data, our results suggest that leptin resistance is also associated with lipoprotein metabolism.

Body mass index (BMI) is the most widely used obesity indicator, but waist and hip circumference have been suggested as better diagnostic markers of obesity because they estimate the amount of visceral and subcutaneous adipose tissue, which contribute most to metabolic changes.³⁷ Waist circumference reflects primarily total abdominal fat, both visceral and subcutaneous, while hip circumference gives an estimate of gluteal subcutaneous fat. Leptin and adiponectin are expressed at higher levels in subcutaneous than visceral fat, and blood leptin and adiponectin levels have been reported to be associated with subcutaneous fat distribution.³⁸ We observed a significant correlation of leptin with hip circumference in both obese and non-obese subjects, and with waist circumference in obese subjects. Yadav et al. and De Courten et al. also found a positive correlation between leptin and waist and hip circumferences.^{18,39} Rather than leptin and adiponectin concentrations themselves, the L/A ratio has been proposed as a better marker for obesity.^{26,40} Zhuo et al. and Yoon et al. showed a significant correlation between the L/A ratio and waist circumference; our data support this association.^{19,27} We demonstrated a significant correlations between the L/A ratio and waist and hip circumference in obese subjects. Thus, the L/A ratio seems to be a better indicator of insulin resistance, as the two adipokines are oppositely associated with metabolic disease.

CONCLUSION

In conclusion, our investigation of the relationship between L/A ratio and HOMA-IR suggests that the L/A ratio could be an important surrogate marker of obesity and insulin resistance. Further detailed studies based

on greater populations are needed to confirm these findings and improve our understanding of metabolic changes in obesity.

* The authors declare that there are no conflicts of interest.



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✓	DELIVERING DATE: 08 / 10 / 2014 • ACCEPTED DATE: 26 / 12 / 2014

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