Leptin-to-adiponectin ratio in obese adolescents with nonalcoholic fatty liver disease

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The leptin-to-adiponectin (L/A) ratio has been used to show insulin resistance (IR) in recent years. The aim of this study was to investigate the L/A ratio in obese adolescents and compare this ratio in patients with and without nonalcoholic fatty liver disease (NAFLD) and also with healthy controls. The second aim was to search the possible correlations between the L/A ratio with the markers of IR and inflammation.

A total of 47 obese (mean age: 13.1±2.1 years) and 19 healthy children (mean age: 13.8±0.3 years) were included in the study. The presence of fatty liver was identified by ultrasonography. Cases were divided into three groups as NAFLD (+) and NAFLD (-) obese patients and controls. Liver biochemistries, insulin and serum lipids, C-reactive protein, tumor necrosis factor-alpha (TNF-alpha), interleukin-6, adiponectin, and leptin were determined. The L/A ratio was calculated. IR was estimated according to the homeostasis model assessment of insulin resistance (HOMA-IR).

The L/A ratio was significantly higher in NAFLD (+) patients than in the other two groups, and in NAFLD (-) patients than the healthy peers. Moreover, L/A ratio correlated more strongly with weight for height (r: 0.528, p<0.0001), alanine aminotransferase (ALT) (r: 0.499, p<0.0001), triglyceride (r: 0.591, p<0.0001), and HOMA-IR (r: 0.574, p<0.0001) than did either leptin and adiponectin alone.

This study shows that the L/A ratio is a noninvasive predictor of NAFLD in obese children and correlates with weight for height, ALT, triglyceride, and HOMA-IR better than each single adipokine.

Key words: children, leptin-to-adiponectin ratio, nonalcoholic fatty liver disease, obesity.

Nonalcoholic fatty liver disease (NAFLD) is the accumulation of fat in the liver in the absence of alcohol consumption. In children, it is commonly related with obesity and insulin resistance (IR), and with the increasing prevalence of obesity in childhood, it is a growing problem in the world.

Adipose tissue is not only a passive site of lipid storage, it is also an endocrine organ producing several proteins (adipokines like adiponectin and leptin) and cytokine mediators (interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]) with many biological activities[1]. Development and complications of obesity consist of complex mechanisms including numerous adipokines, hormones and cytokines[1]. Adipokines, when imbalanced, together orchestrate a proinflammatory and insulin-resistant state that further contributes toward the pathogenesis of NAFLD and its progression to nonalcoholic steatohepatitis (NASH)[2]. Increased TNF-α and IL-6, but decreased adiponectin and IL-10 levels, are associated with increased inflammation and complications of obesity. Adiponectin sensitizes the liver and muscles to the action of insulin[3]. Serum adiponectin concentrations have been shown to be decreased in patients with IR, type 2 diabetes, NAFLD, and visceral obesity[4,5]. It

has also been shown to have anti-inflammatory and anti-arteriosclerotic functions. Leptin has important functions in the control of satiety and appetite, thus being a key regulator of body weight. Serum leptin concentrations have been shown to be increased in patients with obesity, IR and NAFLD[6].

The leptin-to-adiponectin (L/A) ratio and adiponectin-to-leptin ratio (A/L) have been used to show IR in many adult studies in recent years. Moreover, both ratios (L/A and A/L) have been investigated separately as a potential atherogenic index in obese or type 2 diabetic patients. On the other hand, there is limited data in the literature investigating the L/A ratio for predicting NAFLD in obese patients. The first aim of the present study was to investigate the L/A ratio in obese adolescents and compare this ratio in patients with and without NAFLD and also with healthy controls. The second aim of this study was to investigate the possible correlations between the L/A ratio and the markers of IR (homeostasis model of insulin resistance [HOMA-IR]) and inflammation (C-reactive protein [CRP], TNF-α and IL-6) in these groups.

Material and Methods

Patients

Patients aged 11-18 years who were diagnosed as obesity were enrolled in the study. Physical examinations and anthropometric measurements of all patients were performed. The body mass index (BMI) of all children was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Obesity was defined as a BMI exceeding the 95th percentile[7]. In addition, weight for height was calculated for each child.

A total of 47 obese patients (25 male, mean age: 13.1±2.1 years) were included in the study. Patients who had diabetes mellitus, Cushing syndrome, hypothyroidism, growth hormone deficiency, acute or chronic liver disease and hypertension, and who used corticosteroids were not included. All patients were asymptomatic. The study population was divided into two groups: patients with NAFLD (Group 1) and patients without NAFLD (Group 2). Diagnosis of NAFLD was made by the pediatric gastroenterologist (NA) based on increased echogenicity via ultrasonography compatible with fatty infiltration of the liver with or without elevated alanine aminotransferase (ALT) levels. NAFLD grading by ultrasonography was done according to previous literature[8,9].

Nineteen age- and sex-matched healthy children constituted the control group (11 male, mean age: 13.8±0.3 years, Group 3). BMI and weight for height of children in the control group were in normal ranges.

Samples

Blood collection was performed by venipuncture in the forearm on the morning after a 12-hour overnight fast. Blood samples for routine biochemical analysis, IL-6, TNF-α, and adipokines were obtained in tubes without anticoagulant. Samples were centrifuged at 3000 *g* in 4°C for 10-15 minutes. Sera were frozen in -80°C until further analysis.

Parameters

The levels of fasting serum glucose, ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) were measured. ALT and AST normal limits were 5-45 U/L[10]. Specific investigations were done to eliminate infectious, metabolic, and immunological liver pathologies in patients with elevated ALT levels.

The estimate of IR was calculated by HOMA-IR (fasting insulin [μU/ml] × fasting glucose [mmol/ml]/22.5), as described by Matthews et al.[11]. A cut-off HOMA level of > 4.0 in adolescents was used to identify an insulin-resistance status[12].

Sandwich enzyme-linked immunosorbent assay (ELISA) method was used for detection of serum leptin, adiponectin, IL-6, and TNF-α levels. The ELISAs were performed according to the instructions of the manufacturer, and the intra- and interassay coefficients of variation were <10%. The molar ratio of L/A was calculated by dividing leptin (in ng/ml) by

adiponectin (in μg/ml)[6]. All assays were conducted twice on the same occasion and the average value obtained, and they were conducted within the same laboratory under the same conditions.

Statistical Analysis

Data were evaluated using the Statistical Package for the Social Sciences (SPSS) 15.0 program for Windows and by analyzing descriptive statistics (means ± standard errors of mean), comparing the means of quantitative data for dual groups using the Mann-Whitney U test. Intercorrelations between parameters were computed through the Spearman correlation analysis. Correlation coefficient indicated low correlation at 0.10–0.29, medium correlation at 0.30–0.49, and high correlation at ≥0.50. All *p* values are two-tailed, and group differences or correlations with $p<0.05$ were considered to be statistically significant. Area under the receiver operating characteristic curve (AUROC) was used to illustrate the diagnostic ability of the L/A ratio and HOMA-IR index in distinguishing between obese patients with and without NAFLD.

Ethical Considerations

The study protocol was designed in compliance with the Declaration of Helsinki. Informed consent was obtained from both the children and their parents on enrollment in the study. The study was approved by the Ethical Committee of Dokuz Eylül University Medical Faculty.

Results

There were 20 obese patients with NAFLD. ALT, GGT and TG levels were significantly higher in Group 1 than in the other two groups and in Group 2 than Group 3 (Table I). Fasting blood glucose was similar in all groups (88.3±1.8, 86.5±1.4 and 90.7±1.6 mg/dl, respectively, p: 0.194), whereas insulin level and HOMA-IR were significantly higher in Group 1 than in the other two groups (Table I).

Leptin, CRP, IL-6, and TNF-α levels were significantly higher, whereas adiponectin levels were lower, in both obese groups compared to the control group (Table I). On the other hand, the mean L/A ratio showed a significant difference between patients with NAFLD,

Table I. Comparison of Liver Functions, Lipids, Pro-Inflammatory Cytokines, Inflammatory Markers, and Adipokine Levels between Patients with NAFLD (Group 1), without NAFLD (Group 2), and Healthy Controls (Group 3)

	Group 1 (n: 20)	Group 2 (n: 27)	Group 3 (n: 19)	Group comparisons (p value)
Insulin (μU/ml)	16.7±1.9	9.6±1.0	7.2±0.6	1-2 (0.006), 1-3 (0.001), 2-3 (0.13)
HOMA-IR	3.7±0.4	2.1±0.2	1.5±0.2	1-2 (0.003), 1-3 (0.001), 2-3 (0.16)
ALT (U/L)	37.6±6.0	20.5±2.2	11.0±0.8	1-2 (0.005), 1-3 (0.001), 2-3 (0.001)
GGT (U/L)	22.4±2.1	16.4±1.3	12.1±0.6	1-2 (0.02), 1-3 (0.002), 2-3 (0.04)
TG (mg/dl)	155.9±13.2	107.6±8.4	64.8±3.8	1-2 (0.002), 1-3 (0.001), 2-3 (0.001)
HDL-cholesterol (mg/dl)	41.6±2.3	50.1±2.4	47.7±2.6	1-2 (0.02), 1-3 (0.06), 2-3 (0.65)
LDL-cholesterol (mg/dl)	95.3±5.9	107.6±4.1	85.1±6.6	1-2 (0.11), 1-3 (0.25), 2-3 (0.004)
IL-6 (pg/ml)	4.5±0.5	4.3±0.5	2.7±0.6	1-2 (0.77), 1-3 (0.01), 2-3 (0.04)
TNF-α (pg/ml)	4.4±0.8	4.7±0.9	1.6±0.7	1-2 (0.97), 1-3 (0.006), 2-3 (0.002)
CRP (mg/L)	2.4±0.3	3.5±0.5	0.9±0.4	1-2 (0.28), 1-3 (0.001), 2-3 (0.001)
Leptin (ng/ml)	42.3±4.8	40.8±3.0	8.3±2.6	1-2 (0.90), 1-3 (0.001), 2-3 (0.001)
Adiponectin (μg/ml)	4.1±0.7	5.7±0.6	8.8±1.1	1-2 (0.08), 1-3 (0.001), 2-3 (0.01)
L/A ratio	14.7±3.2	8.2±0.9	1.6±0.7	1-2 (0.04), 1-3 (0.001), 2-3 (0.001)

Values are given as mean ± SEM.
ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. GGT: Gamma-glutamyl transpeptidase. HDL: High-density lipoprotein. HOMA-IR: Homeostasis model assessment of insulin resistance. IL: Interleukin. LDL: Low-density lipoprotein. TG: Triglyceride. TNF: Tumor necrosis factor-α.

Table II. Comparison of Alanine Aminotransferase Levels, Pro-Inflammatory Cytokines, Inflammatory Markers, and Adipokine Levels between Obese Patients with IR (IR+), without IR (IR-) and Controls

	IR+ (n:12)	IR - (n:33)	Controls (n:19)	Group comparisons (p value)
ALT (U/L)	38.9±8.9	23.9±2.7	11.0±0.8	IR+ vs IR- (0.04), IR+ vs C (0.001), IR- vs C (0.001)
IL-6 (pg/ml)	5.5±0.8	4.1±0.4	2.7±0.6	IR+ vs IR- (0.09), IR+ vs C (0.008), IR- vs C (0.036)
TNF-α (pg/ml)	4.3±1.6	4.3±0.6	1.6±0.7	IR+ vs IR- (0.51), IR+ vs C (0.03), 2-3 (0.002)
CRP (mg/L)	2.2±0.6	3.3±0.4	0.9±0.4	IR+ vs IR- (0.08), IR+ vs C (0.01), IR- vs C (0.001)
Leptin (ng/ml)	47.5±6.1	39.6±2.9	8.3±2.6	IR+ vs IR- (0.36), IR+ vs C (0.001), IR- vs C (0.001)
Adiponectin (μg/ml)	3.7±0.6	5.4±0.6	8.8±1.1	IR+ vs IR- (0.17), IR+ vs C (0.001), IR- vs C (0.005)
L/A ratio	18.0±4.8	8.4±0.8	1.6±0.7	IR+ vs IR- (0.01), IR+ vs C (0.001), IR- vs C (0.001)

Values are given as mean ± SEM.
A: Adiponectin. ALT: Alanine aminotransferase. CRP: C-reactive protein. IL: Interleukin. IR: Insulin resistance. L: Leptin. TNF: Tumor necrosis factor.

patients without NAFLD and controls (p: 0.0001). The L/A ratio was significantly higher in Group 1 than in the other two groups, and in Group 2 compared to Group 3 in the post-hoc test (Table I).

There were 12 obese patients with IR (9 of them also had NAFLD). None of the children in the control group had IR. HOMA-IR level was significantly higher in patients with IR (5.1±0.3) than patients without IR (1.9±0.1, p: 0.001) and controls (1.5±0.2, p: 0.001). On the other hand, there was no difference between patients without IR and controls regarding HOMA-IR levels (p: 0.14). IL-6, TNF-α, CRP, and leptin levels were significantly lower, whereas adiponectin level was significantly higher, in control patients than in both the IR- positive and -negative obese groups (Table II). On the other hand, mean ALT levels and L/A ratio were significantly higher in patients with IR than in the other two groups and in those without IR compared to the control group (Table II).

The L/A ratio powerfully correlated positively with leptin (r: 0.753, p<0.0001) and inversely with adiponectin (r: -0.735, p<0.0001). The L/A ratio also correlated more strongly with weight for height (r: 0.528, p<0.0001), ALT (r: 0.499, p<0.0001), TG (r: 0.591, p<0.0001), and with HOMA-IR (r: 0.574, p<0.0001) than did leptin and adiponectin alone (Table III).

The AUROC curve of HOMA-IR for distinguishing fatty liver disease between the patients was 0.843 (p: 0.000). For a cutoff value at 2.07, sensitivity was 0.79, specificity 0.71, positive predictive value 0.54, and negative

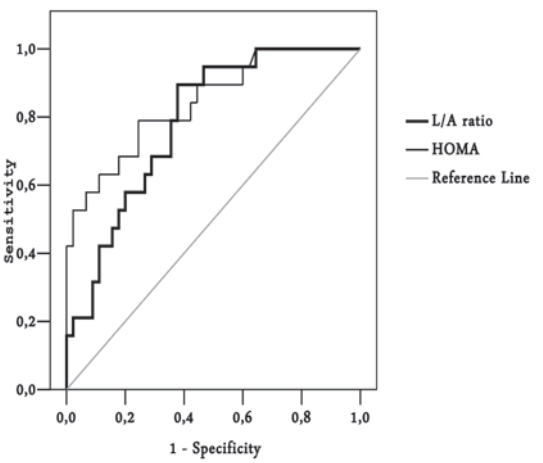

Fig. 1. Receiver operator characteristic curve of the HOMA-IR and L/A ratio for the diagnosis of fatty liver (AUROC was 0.843 for HOMA-IR and 0.788 for L/A ratio).

Table III. Spearman Correlation Coefficients between W/H, CRP, ALT, HOMA-IR, Cytokines, and Adipokines among All Subjects

	W/H	ALT	TG	HDL-C	LDL-C	TNF-a	IL-6	CRP	Leptin	Adip	L/A
ALT	.447**										
TG	.360**	.607**									
HDL-C	-.061	-.192	-.335**								
LDL-C	.051	.150	.173	.135							
TNF-α	.231	.170	.150	.020	.191						
IL-6	.228	.053	.099	-.323*	.045	.268*					
CRP	.400**	.379**	.348**	.022	.328*	.400**	.199				
Leptin	.491**	.274*	.360**	-.148	.145	.213	.303*	.438**			
Adiponectin	-.338**	-.492**	-.492**	.382**	-.012	.044	-.141	-.092	-.380**		
L/A	.528**	.499**	.591**	-.283*	.034	.187	.205	.327*	.753**	-.735**	
HOMA-IR	.319*	.365**	.492**	-.406**	-.018	.068	.353**	.022	.433**	-.401**	.574**

*Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level
A: Adiponectin. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CRP: C-reactive protein. GGT: Gamma-glutamyl transpeptidase. HDL: High-density lipoprotein. HOMA-IR: Homeostasis model assessment of insulin resistance. IL: Interleukin. L: Leptin. LDL: Low-density lipoprotein. TG: Triglyceride. TNF: Tumor necrosis factor-α. W/H: Weight for height.

predictive value 0.86. The AUROC curve of the L/A ratio for distinguishing fatty liver disease between the patients was 0.788 (p: 0.000). For a cutoff value at 5.33, sensitivity was 0.90, specificity 0.55, positive predictive value 0.45, and negative predictive value 0.86 (Fig. 1).

Discussion

This study demonstrated that the L/A ratio of obese adolescents with and without fatty liver disease was significantly higher than in the control peers. Moreover, the L/A ratio was also higher in the NAFLD (+) group than in the NAFLD (-) patients, whereas there was no difference in leptin and adiponectin levels between the two groups. This is the first study investigating the L/A ratio in obese children with and without fatty liver disease.

An opposite role for adiponectin and leptin in obesity and IR has been largely reported in previous studies[1]. Here, we found higher leptin and lower adiponectin levels in both of the obese groups than the control group. Apart from leptin and adiponectin, the L/A ratios were higher in both obese groups than in the control group, and the L/A ratio positively correlated with weight for height in our patients. This correlation was stronger than with leptin or adiponectin alone. Similar to our results, recent pediatric age group studies detected a higher L/A ratio in the overweight/obese group than in lean children, which correlated positively with BMI or abdominal fat mass[6,13-15].

In this study, the L/A ratio was found positively correlated with HOMA-IR levels. Moreover, L/A ratios were significantly higher in patients with IR than in patients without IR, whereas leptin and adiponectin levels of the two groups were similar. Similarly, L/A ratios of obese children with and without IR were higher than in controls. Both the L/A and A/L ratios have been investigated separately as a potential atherogenic index, suggesting that the index is a better biomarker for atherosclerotic risk in obese or type 2 diabetic patients than either leptin or adiponectin alone. Results of studies in the pediatric age group, which investigated the relationship between the L/A ratio and IR, are inconclusive. Maahs et al.[16] found higher adiponectin and A/L ratio in children with type 1 diabetes than in children with type 2. In this study, the A/L ratio remained significantly higher after adjustment for BMI-z score and waist circumference[16]. In another study, the A/L ratio was found correlated with calculated HOMA-adiponectin level in predicting IR in children with metabolic syndrome[17]. On the

other hand, Murdolo et al.[18] found that both leptin levels and leptin-to-high molecular weight adiponectin ratio were correlated with adiposity in prepubertal children, whereas in multivariate models, leptin represented a strong and independent determinant of HOMA-IR other than the leptin-to-high molecular weight adiponectin ratio. Finally Eriksson[14] and Koebnick[19] found in their studies that the L/A ratio was not a better predictor of insulin sensitivity in children than the additive effects of leptin and adiponectin levels. More studies investigating the relationship between L/A ratio and IR status in children are needed.

In our study, the L/A ratio was positively correlated with serum TG and CRP levels, whereas they were inversely correlated with high-density lipoprotein (HDL)-cholesterol levels. The L/A ratio has been suggested as an proinflammatory and atherosclerotic index in addition to predicting IR in patients with and without diabetes[20,21]. In an adult study, it was found that the L/A ratio was a powerful independent predictor of carotid intima media thickness (IMT) in healthy subjects and correlated with BMI, waist circumference, HOMA-IR, and TG better than each single adipokine[21]. In a pediatric study, Masquio et al.[22] found that the A/L ratio was increased in obese adolescents with weight loss, and changes in the A/L ratio were independent predictors of carotid IMT alterations. On the other hand, in recent adult studies, no correlation was found between carotid IMT and leptin or L/A ratio, whereas an inverse correlation was detected with adiponectin levels[23,24]. We did not perform carotid IMT in our study. On the other hand, in our previous study, we found increased carotid IMT in obese adolescents with NAFLD compared to the control group[25]. Moreover, a positive correlation was found between severity of NAFLD and the carotid IMT[25]. Therefore, it can be concluded that the presence of NAFLD in obese adolescents may predict increased carotid IMT, which is an early indicator of atherosclerosis. Further studies are needed to clarify the relationship between NAFLD, L/A ratio and atherosclerosis.

In our study, the L/A ratio was positively correlated with ALT levels, and the L/A ratio was significantly higher in obese adolescents with NAFLD than in the obese group without liver steatosis. Different animal models and *in vitro* studies have suggested that leptin and adiponectin are probably the most important players in NAFLD pathogenesis[26-29]. It has been shown that leptin could be a contributor in fibrogenesis[27], while adiponectin was reported to have an antifibrogenic and protective effect in the liver[28,29]. There are only two adult studies investigating the L/A ratio in obese patients with NAFLD[29,30]. In the first study, which consisted of severely obese patients, Argentou et al.[30] found that the L/A ratio was positively correlated with the NAFLD stage at liver biopsy. In the second study, Lemoine et al.[31] found that the A/L ratio was lower in biopsy-proven NASH patients than in simple steatosis, and that the combination of HOMA with A/L ratio was predictive of NASH. We did not perform liver biopsy in our study, and diagnosed the fatty liver by ultrasonography and liver chemistry. Thus, we could not discriminate the patients with NAFLD regarding liver fibrosis or inflammation status. Leptin and adiponectin levels were not different in the two obese groups in our study; on the other hand, the L/A ratio was higher in the NAFLD group. Because leptin and adiponectin generally exhibit opposite variations, we determined the L/A ratio in order to sensitize the adipokine changes, similar to other studies[31]. We used the AUROC analysis to describe the diagnostic ability of the HOMA-IR index and L/A ratio in distinguishing between obese patients with and without NAFLD. Both the HOMA index and L/A ratio showed a good predictive value (AUROC was 0.843 for HOMA-IR and 0.788 for L/A ratio) for the diagnosis of NAFLD in our obese patients.

In conclusion, we have shown here that the L/A ratio is a noninvasive predictor of NAFLD in obese children and correlates with weight for height, ALT, TG, and HOMA-IR better than each single adipokine. Further studies are warranted to clarify whether modification of the L/A ratio after lifestyle changes could result in beneficial effects in terms of NAFLD.

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