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Investigating the Role of *LRG1* in Hepatosteatosis and Insulin Resistance in Obese Children

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ABSTRACT

Objective: This study aimed to investigate the relationship between *leucine-rich alpha-2-glycoprotein 1* (*LRG1*), hepatosteatosis, and insulin resistance (IR) in obese children, and to evaluate the potential role of *LRG1* as a biomarker in these metabolic conditions.

Methods: A cohort of obese and non-obese children were enrolled. Obese subjects were further grouped by hepatosteatosis and IR status. Anthropometric measurements, biochemical parameters, and inflammatory markers including *LRG1*, adiponectin, and tumor necrosis factor-α (TNF-α) were evaluated. Associations between these markers and metabolic parameters were analyzed.

Results: The cohort consisted of 172 children, of whom 100 (58.1%) were obese and 72 were non-obese. Obese children had significantly higher body mass index (BMI), BMI standard deviation scores, waist and upper arm circumferences, triceps skinfold thickness, total and percentage body of fat (PBF), and elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) ($p<0.001$). Laboratory findings revealed elevated glucose, insulin, homeostatic model assessment of IR (HOMA-IR), alanine aminotransferase, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and lower high-density lipoprotein cholesterol (HDL-C) in the obese group ($p<0.05$). *LRG1* levels did not differ by obesity or hepatosteatosis status but were significantly lower in those with IR ($p=0.03$). *LRG1* was negatively correlated with waist circumference, DBP, insulin, HOMA-IR, TG, TC, and LDL-C, and positively with HDL-C ($p<0.05$). Adiponectin showed inverse correlations with waist circumference, SBP, insulin, HOMA-IR, TC, LDL-C, TG, and a positive correlation with HDL-C ($p<0.05$).

Conclusion: Findings suggest *LRG1* may not serve as a direct biomarker for hepatosteatosis in obese children but was negatively associated with IR and dyslipidemia. These results highlight a complex role for *LRG1* in obesity-related metabolic dysfunction and support further longitudinal and pathophysiological studies.

Keywords: LRG1, obesity, hepatosteatosis, insulin resistance, children, adipokines

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What is already known on this topic?

Leucine-rich alpha-2-glycoprotein 1 (*LRG1*) has emerged as an adipokine implicated in obesity-related metabolic dysfunction, particularly in adult populations. Adult studies have generally reported higher circulating *LRG1* levels in association with insulin resistance (IR), dyslipidemia, and cardiometabolic risk. The evidence regarding *LRG1* in pediatric obesity is limited, and its relationship with hepatosteatosis and IR in children remains unclear. Adiponectin is consistently linked to improved insulin sensitivity and a favorable metabolic profile, whereas tumor necrosis factor-α is a key proinflammatory cytokine associated with obesity-related low-grade inflammation. A combined assessment of adipokines/cytokines may provide a more comprehensive view of metabolic derangements in childhood obesity.

What this study adds?

This study is among the first to comprehensively evaluate *LRG1* in pediatric obesity with respect to hepatosteatosis and IR. The finding of lower *LRG1* levels in insulin-resistant children contrasts with adult data, suggesting distinct, age-specific pathophysiological mechanisms. The results imply that *LRG1* may act as more than an inflammatory marker and may be a complex metabolic regulator during growth and development.

Introduction

In the last decades, being overweight and obese have become recognized as major lifestyle-related health issues, ranking as the fifth leading cause of death globally according to recent statistics (1). Furthermore, research has indicated that low-grade chronic inflammation is a common symptom of these conditions and contributes significantly to the development of various physical issues and chronic illnesses, including cancer, diabetes, metabolic syndrome, cardiovascular diseases, and neurodegenerative disorders (1). Obesity is characterized by chronic systemic low-grade inflammation accompanied by deregulated circulating levels of adipokine and inflammatory markers (2).

Adipose tissue is recognized as a key endocrine organ that releases a variety of bioactive peptides, known as adipokines, many of which play a role in regulating overall energy balance and inflammation throughout the body (3). Several secretory molecules, including leptin, adiponectin, and retinol binding protein 4, have been identified in adipocytes (4,5,6). Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that plays a central role in obesity-related chronic low-grade inflammation and the development of insulin resistance (IR) (7). Disrupted expression, secretion, and function of these adipokines are linked to obesity, IR, and cardiovascular complications (3,7). However, the roles and identities of many other adipokines involved in obesity-related metabolic diseases are still largely unclear.

Adipokines have been found to exhibit both proinflammatory properties (e.g., leptin and resistin) and anti-inflammatory effects (e.g., omentin and adiponectin). However, it has been observed that adiponectin can be pro-inflammatory under certain conditions and in a tissue-dependent manner (8,9,10,11).

Leucine-rich alpha-2-glycoprotein 1 (*LRG1*), which was initially isolated from human plasma (12), is a member of a highly conserved protein family that contains the leucine-rich-repeat domains (13). In addition to regulating angiogenesis (13), variations in levels of *LRG1* have also been implicated in a number of diseases, including some cancers (13,14,15), arterial stiffness (16), heart failure (17), aging (18), and inflammatory disorders (19). However, the function and mechanisms of action of *LRG1* in metabolism remain unknown. *LRG1* has recently been recognized as anadipokine involved in metabolic regulation and inflammation. Experimental and clinical studies in adults have demonstrated that *LRG1* is secreted by adipose tissue and may contribute to obesity-related IR and hepatic lipid accumulation through mechanisms involving altered lipid metabolism and hepatocyte dysfunction. However, data regarding the role of *LRG1* in pediatric obesity are scarce, and its relationship with hepatosteatosis and IR during childhood remains poorly understood, which constituted the main rationale for the present study.

LRG1, either alone or in combination with other known factors, is considered a potential biomarker for inflammation and obesity. High levels of *LRG1* are positively correlated with obesity, while low plasma *LRG1* levels predict weight loss following surgery for obesity and metabolic diseases (20). Thus, elevated circulating and adipose tissue *LRG1* levels have been associated with increased body mass index (BMI), visceral adiposity, and waist circumference in obese individuals. Based on these findings and laboratory observations, it is hypothesized that *LRG1* contributes to increased fat storage by inhibiting the breakdown of fatty acids and promoting lipid production through the activation of sterol regulatory element-binding transcription factor 1. In addition, *LRG1* may facilitate hyperglycemia by reducing the expression of insulin receptor substrates (*IRS1* and *IRS2*) (21).

It has been suggested that *LRG1* may contribute to hepatosteatosis by enhancing *de novo* lipogenesis in the liver while inhibiting fatty acid oxidation (21). More specifically, it has been demonstrated that increased *LRG1* levels in the bloodstream, produced by adipocytes, can disrupt the function of hepatocytes, thereby playing a role in

the development of IR and hepatosteatosis (21). However, it should be noted that the majority of these findings have been derived from studies conducted in adult populations, and data regarding the role of *LRG1* in pediatric obesity and related metabolic complications remain limited.

In general, previous reports indicate that *LRG1* plays a role in the development of diabetes and obesity-related complications in adults. However, research on *LRG1* in the pediatric age group remains limited. This study aims to comprehensively elucidate the associations between *LRG1*, adiponectin, and TNF-α levels and a range of biochemical and clinical parameters in the pediatric and adolescent population, stratified by obesity status, presence of hepatosteatosis, and IR.

Methods

Study Design and Participants

This research was designed as a single-center, case-control study. Participants, aged between 6 and 18 years, were included. The obese group consisted of children diagnosed with obesity at the pediatric endocrinology outpatient clinic of our hospital. The control group consisted of healthy, non-obese volunteers of similar age and gender who visited the hospital for routine health checkups. Exclusion criteria for the obese group included chronic endocrine-related disease (e.g., Cushing's syndrome, hypothyroidism), obesity-related syndromes (e.g., Prader-Willi, Bardet-Biedl syndromes), other systemic diseases, or a history of medication use. The control group exclusion criteria were chronic systemic or endocrine diseases and obesity.

The clinical and laboratory features of the obese patients were compared to those of the control group. Obese individuals were categorized into two subgroups, hepatosteatosis (+) and hepatosteatosis (-), based on hepatobiliary ultrasound results and compared accordingly. In addition, obese individuals were classified into two further sub-groups, those with and without IR, and comparisons were made accordingly.

Ethical Considerations

Ethical approval was obtained from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee prior to the commencement of the study (protocol number: KAEK-340, date: 11.05.2022). The research was conducted in full compliance with the principles set forth in the Declaration of Helsinki and in accordance with ethical standards. Informed consent was obtained from the parents of all participants prior to their inclusion in the study.

Clinical Investigations and Anthropometric Measurements

Height was measured using a wall-mounted stadiometer, both while standing upright and during deep inspiration. BMI was calculated by dividing the weight in kilograms by the square of the height in metres (kg/m^2). Standard deviation scores (SDS) for height, weight, and BMI were determined using reference values for Turkish children (22).

Participants with a BMI above the 95th percentile for their age and sex, based on the reference values for Turkish children, were classified as obese and placed in the obese group. Those with a BMI between the 3rd and 85th percentiles were categorized into the non-obese group, excluding any overweight individuals. Waist circumference was measured with a tape measure at the level of the umbilicus, with the child standing upright and the abdomen exposed. Upper arm circumference was taken at the midpoint between the acromion and olecranon processes, with the elbow flexed at 90 degrees. All measurements were recorded in centimeters (cm) and analyzed. Triceps skinfold (TSF) thickness was measured with the arm hanging freely by the side of the body, using a caliper at the midpoint of the posterior surface of the upper arm. Waist-to-height ratio (WtHR) was calculated by dividing waist circumference by height, and participants were categorized as having central obesity when WtHR was ≥0.5. Bioelectrical impedance analysis, using the Tanita BC-418 device (Tanita, Tokyo, Japan), was employed to assess fat mass and the percentage of body fat (PBF). Blood pressure was measured following a validated protocol: systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded twice on the right arm after a 10-minute rest in a supine position, using a calibrated sphygmomanometer, and performed by one of the investigators. The average of the two readings was taken. Hypertension was defined as blood pressure values above the 95th percentile for height, age, and gender (23). Pubertal evaluation was conducted based on the Marshall and Tanner (24) classification.

Peripheral blood samples were obtained in the morning (between 8:00 and 9:00 a.m.) after a 10-hour fasting period. Fasting glucose levels were measured using the hexokinase method, while fasting insulin levels were assessed with the radioimmunoassay technique. IR was evaluated using the homeostatic model assessment of IR(HOMA-IR) formula: fasting insulin (μU/mL)×fasting glucose (mg/dL)/405. Participants with HOMA-IR values greater than 4 during the pubertal stage and greater than 2.5 in the prepubertal stage were classified as having IR (25).

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using a spectrophotometric method. Triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) levels were determined enzymatically with the DP Modular Systems (Roche Diagnostic Corp., Indianapolis, IN, USA). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula when plasma TG levels were <400 mg/dL.

The measurement methods and kit details for adipokines are as follows;

LRG1: Serum samples were analyzed using the Enzyme-Linked Immunosorbent Assay (ELISA) method with a Elabscience brand kit (Elabscience Bionovation Inc, Houston, TX, USA) (Kit catalog no: E-EL-H6067). Intra-assay coefficient of variation (CV) was <10%, and the inter-assay CV was also <10%. The kit sensitivity was 0.38 µg/mL, and measurement linearity ranged from 0.65-40 µg/mL. The kit was stored at 2-8 °C until use.

Adiponectin: Serum samples were analyzed using the ELISA method with an Elabscience kit (Kit catalog no: E-EL-H6122). Intra-assay CV was <10%, and inter-assay CV was <10%. The kit sensitivity was 0.1 µg/mL, and measurement linearity ranged from 0.16-10 µg/mL. The kit was stored at 2-8 °C until use.

TNF-α: Serum samples were analyzed using the ELISA method with an Elabscience kit (Kit catalog no: E-EL-H0109). Intra-assay CV was <10%, and inter-assay CV was <10%. The kit sensitivity was 4.69 pg/mL, and measurement linearity ranged from 7.81-500 pg/mL. The kit was stored at 2-8 °C until use.

The diagnosis and grading of hepatosteatosis were performed using ultrasonographic imaging according to standard criteria assessing liver echogenicity, vascular structure visibility, and diaphragm clarity (26), with all examinations conducted by the same qualified radiologist.

Statistical Analysis

Measures of association for categorical variables were analyzed with chi-square and Fisher exact test. Skewed distributions of continuous variables in groups were compared by Wilcoxon-Rank Sum test. Pearson's correlation analysis was conducted to evaluate the relationships between *LRG1*, adiponectin, TNF-α, and clinical as well as biochemical parameters. All analyses were performed using STATA software, version 17.0 Basic Edition (StataCorp LLC, 4905 Lakeway Drive, College Station, TX 77845, USA). A p-value of <0.05 was considered statistically significant.

Results

The clinical and laboratory characteristics of obese and non-obese subjects are summarized in Table 1. The age, gender, and pubertal status were similar in the two groups. The BMI, SDS, waist and upper arm circumferences, TSF thickness, total body fat mass, PBF, and systolic and DBPs were significantly greater in the obese group (p<0.001). When laboratory parameters were investigated, fasting glucose, insulin, HOMA-IR, ALT, TG, TC and LDL-C levels were significantly higher in obese patients while HDL-C was lower (p<0.05). When comparing obese and non-obese patients, *LRG1* and adiponectin levels were similar (p=0.58; p=0.08; respectively), whereas TNF-α levels were significantly higher in the obese group p<0.001. In the control group, only two participants (2.8%) had a WtHR ≥0.5, whereas in the obese group, only three participants (3%) had a WtHR <0.5. Due to the highly unbalanced distribution, further statistical comparisons based on WtHR categories were not performed.

Out of the 69 patients with hepatosteatosis, 46 (66.7 %) had grade 1, 18 (26.1 %) had grade 2, and 5 (7.2 %) had grade 3 hepatosteatosis. Comparisons of the clinical and laboratory characteristics of obese subjects with and without hepatosteatosis are shown in Table 2. In patients with and without hepatosteatosis, similar age, gender, and pubertal status were observed. The BMI, SDS, waist and upper arm circumferences, and total body fat mass were significantly greater in patients with hepatosteatosis (p<0.05). Insulin, HOMA-IR, and TG levels were significantly higher in those with hepatosteatosis while HDL-C was lower (p<0.05). No statistically significant differences were observed in *LRG1*, adiponectin, and TNF-α levels among those with or without hepatosteatosis.

In the total cohort, IR was present in 66 patients, whereas 106 patients had normal HOMA-IR values when pubertal status was taken into consideration. Comparison of the clinical and laboratory characteristics of subjects with and without IR are shown in Table 3. Although gender distribution and pubertal status were comparable between patients with and without IR, the mean age of patients exhibiting IR was significantly higher (p=0.0005). The BMI, SDS, waist and upper arm circumferences, TSF thickness, total body fat mass, PBF, and systolic and DBPs were significantly greater in the IR group (p<0.001). When laboratory parameters were analyzed, fasting glucose, insulin, HOMA-IR, ALT, TG, TC and LDL-C levels were significantly greater patients with IR, while HDL-C was lower (p<0.05) in IR group. *LRG1* and adiponectin levels were significantly lower, while TNF-α levels were significantly higher in patients with IR (p=0.03, p=0.008, and p=0.004, respectively).

Correlation analysis revealed several significant associations between serum biomarkers and clinical parameters in obese subjects (Table 4). Serum *LRG1* levels showed significant negative correlation with waist circumference (r=-0.220, p=0.028), DBP (r=-0.201, p=0.045), insulin (r=-0.288, p=0.004), HOMA-IR (r=-0.267, p=0.007), TG (r=-0.283, p=0.004), TC (r=-0.269, p=0.007), and LDL-C (r=-0.307, p=0.002). Conversely, LRG1 was positively correlated with HDL-C (r=0.332, p=0.0007).

Adiponectin levels were negatively correlated with waist circumference (r=-0.247, p=0.013), SBP (r=-0.208, p=0.038), insulin (r=-0.281, p=0.005), HOMA-IR (r=-0.264, p=0.008), TG (r=-0.260, p=0.009), TC (r=-0.208, p=0.038), and LDL-C (r=-0.240, p=0.016); while a positive correlation was observed with HDL-C (r=0.270, p=0.007).

Table 1. The clinical and laboratory characteristics of obese and non-obese subjects

	Obese subjects (n=100)	Non-obese subjects (n=72)	p value
Age (year)	12.1±3.2	11.3±2.7	0.08
Male (%)	55.2	44.8	0.57
Pubertal (%)	58.5	41.5	0.85
BMI (kg/m^2)	32.3±6.4	18±2.4	**<0.001**
BMI-SDS	2.9 (2.6-3.4)	-0.13 (-0.985-0.395)	**<0.001**
Waist circumference (cm)	93.8±13.6	61.9±7.2	**<0.001**
Upper arm circumference (cm)	32.5±4.8	21.8±3.1	**<0.001**
TSF thickness (mm)	22.1±7.3	7.2±3.9	**<0.001**
Fat mass (kg)	32.5±14.9	7.9±3.2	**<0.001**
PBF (%)	38.3 (35.7-42.7)	21.5 (17.25-23.8)	**<0.001**
SBP (mmHg)	120±12	100±11	**<0.001**
DBP (mmHg)	80±10	65±8	**<0.001**
Glucose (mg/dL)	88± 7	85±6	**0.008**
Insulin (uIU/mL)	26±16	8±4	**<0.001**
HOMA-IR	5.6±3.6	1.7±0.8	**<0.001**
ALT (U/L)	24±14	14±9	**<0.001**
AST (U/L)	22±8	22±6	0.74
TG (mg/dL)	110±55	67±25	**<0.001**
TC (mg/dL)	164±28	155±25	**0.04**
LDL-C (mg/dL)	100±24	87±20	**<0.001**
HDL-C (mg/dL)	48±11	60±14	**<0.001**
LRG1 (µg/mL)	84.9±53.9	94.6±63.1	0.58
TNF-α (pg/mL)	44.7±27.8	24.4±18.1	**<0.001**
Adiponectin (µg/mL)	14.4±9.2	17.2±11.2	0.08

Data are given as mean±SD, median (IQR 25-75 percentile) or n (%). Bold values indicate statistical significance (p<0.05).
BMI: body mass index, BMI-SDS: standard deviation score of body mass index, TSF: triceps skinfold, PBF: percentage of body fat, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR, homeostasis model assessment of insulin resistance, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, TNF- α: tumor necrosis factor-α, *LRG1: leucine-rich alpha-2-glycoprotein 1,* IQR: interquartile range

Table 2. Comparison of the clinical and laboratory characteristics of obese subjects with and without hepatosteatosis

	Hepatosteatosis (+) group (n=69)	Hepatosteatosis (-) group (n=31)	p value
Age (year)	12±0.4	11±0.5	0.28
Male (%)	33.3	29.1	0.67
Pubertal (%)	85.5	77	0.31
BMI (kg/m^2)	33.2±0.83	30.2±0.84	**0.03**
BMI-SDS	3.1 (2.7-3.5)	2.8 (2.5-3)	**0.01**
Waist circumference (cm)	97±2	87±2	**<0.01**
Upper arm circumference (cm)	33±0.6	31±0.8	**0.01**
TSF thickness (mm)	22.7±0.9	20.8±1.2	0.22
Fat mass (kg)	35±2	27±2	**0.01**
PBF (%)	39.3 (36.3-44.1)	37.5 (34.8-41)	0.09
SBP (mmHg)	119±1	116±2	0.09
DBP (mmHg)	77±1	76±2	0.79
Glucose (mg/dL)	88±1	88±1	0.98
Insulin (uIU/mL)	28.5±2	19.5±1.9	**0.007**
HOMA-IR	6.2±0.5	4.3±0.5	**0.01**
ALT (U/L)	26±2	20±2	0.06
AST (U/L)	22±1	22±2	0.99
TG (mg/dL)	118±7	91±6	**0.02**
TC (mg/dL)	163±3	164±5	0.89
LDL-C (mg/dL)	99±3	100±5	0.91
HDL-C (mg/dL)	47±1	52±2	**0.01**
LRG1 (µg/mL)	80.1±5.7	95.6±11.8	0.18
TNF-α (pg/mL)	43.9±2.9	46.5±6.4	0.67
Adiponectin (µg/mL)	13.6±0.9	16.1±1.9	0.21

Data are given as mean±SD, median (IQR 25-75 percentile) or n (%). Bold values indicate statistical significance (p<0.05).
BMI: body mass index, BMI-SDS: standard deviation score of body mass index, TSF: triceps skinfold, PBF: percentage of body fat, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, TNF- α: tumor necrosis factor-α, *LRG1: leucine-rich alpha-2-glycoprotein 1,* IQR: interquartile range

No statistically significant correlations were found between TNF-α and any of the measured clinical or laboratory parameters.

Discussion

This study comprehensively examined the metabolic effects of childhood obesity and the roles of biomarkers, including *LRG1*, adiponectin, and TNF-α in this context. Our findings demonstrated significant metabolic disturbances in obese children. Specifically, there were marked increases in BMI and waist circumference, as expected, together with elevated insulin, HOMA-IR, TG, and LDL-C in combination with significant decreases in HDL-C and adiponectin levels. These results align with previous studies reporting the central role of obesity in the development of metabolic syndrome and IR (21,27).

Further stratification revealed that children with hepatosteatosis and IR exhibited more pronounced metabolic abnormalities, confirming that hepatic steatosis and IR are critical determinants of the clinical progression of obesity. These findings highlight

Table 3. Comparison of the clinical and laboratory characteristics of obese subjects with and without insulin resistance

	IR (+) group (n=66)	IR (-) group (n=106)	p value
Age (year)	12.7±0.3	11.2±0.3	**0.0005**
Male (%)	41.4	58.6	0.563
Pubertal (%)	40.1	59.9	0.299
BMI (kg/m^2)	33.7±0.8	21.7±0.6	**<0.001**
BMI SDS	3 (2.7-3.5)	0.4 (-0.5-2.5)	**<0.001**
Waist circumference (cm)	98.2±1.5	69.4±1.4	**<0.001**
Upper arm circumference (cm)	33.7±0.5	24.5±0.5	**<0.001**
TSF thickness (mm)	23.6±0.9	11.1±0.7	**<0.001**
Fat mass (kg)	36.2±1.9	13.5±1	**<0.001**
PBF (%)	39.9 (36.3-45.6)	23.6 (19.6-34.1)	**<0.001**
SBP (mmHg)	119±1	105±1	**<0.001**
DBP (mmHg)	78±1	68±1	**<0.001**
Glucose (mg/dL)	89.1±0.8	84.7±0.6	**<0.001**
Insulin (uIU/mL)	32.8±1.8	9.3±0.4	**<0.001**
HOMA-IR	7.2±0.4	2±0.1	**<0.001**
ALT (U/L)	26.8±1.9	15±0.8	**<0.001**
AST (U/L)	22±1	21.7±0.6	0.802
TG (mg/dL)	116.3±7.1	76.5±3.5	**<0.001**
TC (mg/dL)	166.7±3.1	155.8±2.6	**0.008**
LDL-C (mg/dL)	101.7±2.7	89.9±2.2	**0.001**
HDL-C (mg/dL)	47.3±1.4	57±1.3	**<0.001**
LRG1 (µg/mL)	76.7±5.8	96.6±6.1	**0.03**
TNF-α (pg/mL)	45±3.5	30.7±2.2	**0.004**
Adiponectin (µg/mL)	12.9±1	17.2±1.1	**0.008**

Data are given as mean±SD, median (IQR 25–75 percentile) or n (%). Bold values indicate statistical significance (p<0.05).
BMI: body mass index, BMI-SDS: standard deviation score of body mass index, TSF: triceps skinfold, PBF: percentage of body fat, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, ALT: alanine aminotransferase, AST: Aspartate aminotransferase, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, TNF- α: tumor necrosis factor-α, *LRG1: leucine-rich alpha-2-glycoprotein 1,* IQR: interquartile range

Table 4. The relationship between LRG1, TNF-α, adiponectin and clinical and laboratory parameters in the obese subjects

	LRG1	TNF-α	Adiponectin
Age (years)	p=0.2537 r=-0.115	p=0.2194 r=0.124	p=0.0839 r=-0.174
BMI SDS	p=0.3459 r=-0.095	p=0.4617 r=0.074	p=0.2952 r=-0.106
Waist circumference (cm)	p=0.0281* r=-0.220	p=0.8257 r=-0.022	p=0.0131* r=-0.247
Upper arm circumference (cm)	p=0.2698 r=-0.111	p=0.3860 r=0.088	p=0.1508 r=0.145
TSF thickness (mm)	p=0.7227 r=-0.036	p=0.2756 r=0.110	p=0.1621 r=-0.141
Fat mass (kg)	p=0.2342 r=-0.120	p=0.4819 r=0.071	p=0.1225 r=-0.155
PBF (%)	p=0.8019 r=-0.025	p=0.8125 r=0.024	p=0.7756 r=-0.029
SBP (mmHg)	p=0.0614 r=-0.188	p=0.4335 r=0.079	p=0.0379* r=-0.208
DBP (mmHg)	p=0.0446* r=-0.201	p=0.9630 r=-0.005	p=0.0929 r=-0.169
Glucose (mg/dL)	p=0.9114 r=0.011	p=0.5052 r=0.067	p=0.8831 r=-0.015
Insulin (uIU/mL)	p=0.0037* r=-0.288	p=0.4568 r=0.075	p=0.0046* r=-0.281
HOMA-IR	p=0.0074* r=-0.267	p=0.4584 r=0.075	p=0.0080* r=-0.264
ALT (U/L)	p=0.1455 r=-0.147	p=0.2073 r=-0.127	p=0.4072 r=-0.084
AST (U/L)	p=0.7748 r=-0.029	p=0.1803 r=-0.135	p=0.9020 r=-0.012
TG (mg/dL)	p=0.0043* r=-0.283	p=0.7863 r=-0.027	p=0.0090* r=-0.260
TC (mg/dL)	p=0.0068* r=-0.269	p=0.7801 r=-0.028	p=0.0382* r=-0.208
LDL-C (mg/dL)	p=0.0019* r=-0.307	p=0.8452 r=-0.020	p=0.0161* r=-0.240
HDL-C (mg/dL)	p=0.0007* r=0.332	p=0.5220 r=0.065	p=0.0066* r=0.270

*Statistically significant correlation
BMI-SDS: standard deviation score of body mass index, TSF: triceps skinfold, PBF: percentage of body fat, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol

the importance of early intervention in childhood obesity to prevent metabolic complications (21).

Regarding *LRG1* protein levels, our results differ from several reports in the literature. While prior studies have suggested a positive correlation between *LRG1* and inflammation, positioning *LRG1* as a biomarker for cardiometabolic diseases (13,21,27), our study found significantly lower *LRG1* levels in insulin-resistant individuals, with negative correlations observed between *LRG1* and waist circumference, insulin, and HOMA-IR. This discrepancy may be attributed to physiological and metabolic differences unique to the pediatric and adolescent populations. In contrast to findings in adult studies, *LRG1* levels may serve as a negative marker during childhood and adolescence. Therefore, further studies are needed to investigate the longitudinal changes of *LRG1* levels and their relationship with metabolic parameters.

This apparent discrepancy might also reflect the pleiotropic and context-dependent functions of *LRG1*. In adults, *LRG1* has been associated with metabolic deterioration, including obesity-related hepatosteatosis and IR (21), whereas other findings suggest that *LRG1* may promote insulin sensitivity and suppress inflammation (27). In pediatric populations, particularly during puberty, a period characterized by hormonal fluctuations, rapid adipose tissue expansion, and transient IR, the expression and function of *LRG1* may be regulated differently. Moreover, the tissue-specific expression of *LRG1* and its interaction with transforming growth factor beta signaling could vary between developmental stages, potentially explaining contrasting findings in different age groups (13,21). These observations highlight the need for further age-stratified and mechanistic studies to delineate the precise role of *LRG1* in metabolic regulation during growth and maturation. On the other hand, the secretion of *LRG1* from different tissues such as adipose tissue, liver, and immune cells may complicate the biological interpretation of measured serum levels. Therefore, future studies should be supported by translational approaches evaluating tissue-specific expression of *LRG1*.

Methodological variations and biological heterogeneity also contribute to differences in findings. Variability in ELISA assay sensitivity and specificity, along with genetic and environmental factors, may account for the heterogeneity in *LRG1* levels. Although TNF-α levels were elevated in obese subjects, no significant correlation with *LRG1* was observed, suggesting that LRG1 might act through molecular mechanisms distinct from classical inflammatory markers. This indicates that *LRG1* may have functions beyond being an inflammatory biomarker in obesity and metabolic diseases.

Consistent with previous research, our findings concerning adiponectin showed decreased levels and negative correlations with obesity and IR markers. Given the role of adiponectin in enhancing insulin sensitivity and its anti-inflammatory and cardioprotective properties, the reduced adiponectin levels in obesity likely contribute to the development of metabolic risk (28,29). The lack of significant correlations between TNF-α and metabolic parameters reinforces the concept that inflammatory processes in obesity involve a complex interplay of multiple cytokines, and a single biomarker cannot fully capture the clinical picture. In pediatric patients, Ultrasonography (USG) is a useful non-invasive method for detecting hepatic lipid accumulation but USG is not capable of a definitive assessment of hepatic inflammation (30). In the present study, as in many previous pediatric reports, a substantial proportion of patients with hepatosteatosis were classified as grade 1, a stage in which inflammatory changes may not yet be fully established. Therefore, TNF-α levels may not differ significantly between groups, and other proinflammatory cytokines may likewise not exhibit the alterations commonly described in adult populations.

The lower circulating *LRG1* levels observed in obese children compared with adult populations may reflect age-related and developmental differences in adipokine regulation. During childhood and adolescence, metabolic and inflammatory pathways are dynamically regulated, and compensatory mechanisms may prevent the overt activation of pathways commonly observed in adults with long-standing obesity. Moreover, pubertal status, shorter disease duration, and differences in adipose tissue distribution may contribute to the distinct *LRG1* profile observed in pediatric patients. These findings suggest that the role of *LRG1* in obesity-related metabolic dysfunction may be both age dependent and evolve over time.

Study Limitations

This study has some limitations that should be considered. The case-control design limits the ability to infer causality, and the relatively small sample size, particularly in subgroup analyses, may affect the statistical power. In addition, as the study was conducted at a single center, the generalizability of the findings may be limited. Biomarker measurements were performed at a single time point, which may not fully capture temporal variations. Although efforts were made to control for confounding factors, the possibility of residual confounding cannot be completely ruled out. Furthermore, the difference in pubertal stage distribution between the obese and non-obese groups may have introduced potential bias, as pubertal status may influence metabolic parameters. The markedly unbalanced distribution of WtHR categories limited the feasibility of subgroup analyses based on central obesity. Although liver biopsy is considered the gold standard for the diagnosis of nonalcoholic fatty liver disease, its invasive nature limits its routine use in pediatric populations and therefore, ultrasonographic evaluation was used in the present study as this was ethically more acceptable, but should be considered a limitation.

Conclusion

The present study suggests that the role of *LRG1* in childhood obesity may differ from that in obese adults. This highlights the necessity for age-specific evaluations of *LRG1* as a clinical biomarker and will require longitudinal studies with larger cohorts. Furthermore, given the complex nature of obesity and metabolic syndrome, multi-parameter analyses including adiponectin, TNF-α, and a wider range of hormonal and adipokine biomarkers will be necessary for a more comprehensive understanding of the biological functions of *LRG1* at different ages and pubertal stages.

Ethics

Ethics Committee Approval: Approval was obtained from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee prior to the commencement of the study (protocol number: KAEK-340, date: 11.05.2022). The research was conducted in full compliance with the principles set forth in the Declaration of Helsinki and in accordance with ethical standards.

Informed Consent: Informed consent was obtained from the parents of all participants prior to their inclusion in the study.

Footnotes

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authorship Contributions

Surgical and Medical Practices: Berna Singin, Zeynep Donbaloğlu, Ebru Barsal Çetiner, Bilge Aydın Behram, Aynur Bedel, Mesut Parlak, Hale Ünver Tuhan, Concept: Berna Singin, Hale Ünver Tuhan, Design: Berna Singin, Hale Ünver Tuhan, Data Collection or Processing: Berna Singin, Zeynep Donbaloğlu, Ebru Barsal Çetiner, Bilge Aydın Behram, Aynur Bedel, Mesut Parlak, Hale Ünver Tuhan, Analysis or Interpretation: Berna Singin, Sebahat Özdem, İkbal Özen Küçükçetin, Hale Ünver Tuhan, Literature Search: Berna Singin, Mesut Parlak, Hale Ünver Tuhan, Writing: Berna Singin, Hale Ünver Tuhan.

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References

1. Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med. 2021;136:104754. Epub 2021 Aug 16.
2. Bulcão C, Ferreira SR, Giuffrida FM, Ribeiro-Filho FF. The new adipose tissue and adipocytokines. Curr Diabetes Rev. 2006;2:19-28.
3. Funcke JB, Scherer PE. Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication. J Lipid Res. 2019;60:1648-1684. Epub 2019 Jun 17.
4. Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Müller C, Carling D, Kahn BB. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature. 2002;415:339-43.
5. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med. 2002;8:731-7. Epub 2002 Jun 17.
6. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005;436:356-62.
7. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15:6184-223.
8. Askin L, Abus S, Tanriverdi O. Resistin and cardiovascular disease: a review of the current literature regarding clinical and pathological relationships. Curr Cardiol Rev. 2022;18:e290721195114.
9. Choi HM, Doss HM, Kim KS. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. Int J Mol Sci. 2020;21:1219.
10. Pérez-Pérez A, Sánchez-Jiménez F, Vilariño-García T, Sánchez-Margalet V. Role of leptin in inflammation and vice versa. Int J Mol Sci. 2020;21:5887.
11. Sena CM. Omentin: a key player in glucose homeostasis, atheroprotection, and anti-inflammatory potential for cardiovascular health in obesity and diabetes Biomedicines. 2024;12:284.
12. Haupt H, Baudner S. Isolation and characterization of an unknown, leucine-rich 3.1-S-alpha2-glycoprotein from human serum. Hoppe Seylers Z Physiol Chem. 1977;358:639-46.
13. Wang X, Abraham S, McKenzie JAG, Jeffs N, Swire M, Tripathi VB, Luhmann UFO, Lange CAK, Zhai Z, Arthur HM, Bainbridge J, Moss SE, Greenwood J. LRG1 promotes angiogenesis by modulating endothelial TGF-β signalling. Nature. 2013;499:306-11.
14. Wang CH, Li M, Liu LL, Zhou RY, Fu J, Zhang CZ, Yun JP. LRG1 expression indicates unfavorable clinical outcome in hepatocellular carcinoma. Oncotarget. 2015;6:42118-29. Epub 2015 Dec 8.
15. Zhong D, He G, Zhao S, Li J, Lang Y, Ye W, Li Y, Jiang C, Li X. LRG1 modulates invasion and migration of glioma cell lines through TGF-β signaling pathway. Acta Histochem. 2015;117:551-8. Epub 2015 Jun 3.
16. Pek SL, Tavintharan S, Wang X, Lim SC, Woon K, Yeoh LY, Ng X, Liu J, Sum CF. Elevation of a novel angiogenic factor, leucine-rich-α2-glycoprotein (LRG1), is associated with arterial stiffness, endothelial dysfunction, and peripheral arterial disease in patients with type 2 diabetes. J Clin Endocrinol Metab. 2015;100:1586-93. Epub 2015 Jan 30.
17. Watson CJ, Ledwidge MT, Phelan D, Collier P, Byrne JC, Dunn MJ, McDonald KM, Baugh JA. Proteomic analysis of coronary sinus serum reveals leucine-rich α2-glycoprotein as a novel biomarker of ventricular dysfunction and heart failure. Circ Heart Fail. 2011;4:188-97. Epub 2011 Jan 31.
18. Nakajima M, Miyajima M, Ogino I, Watanabe M, Hagiwara Y, Segawa T, Kobayashi K, Arai H. Brain localization of leucine-rich α2-glycoprotein and its role. Acta Neurochir Suppl. 2012;113:97-101.
19. Fujimoto M, Serada S, Suzuki K, Nishikawa A, Ogata A, Nanki T, Hattori K, Kohsaka H, Miyasaka N, Takeuchi T, Naka T. Leucine-rich α2-glycoprotein as a potential biomarker for joint inflammation during anti-interleukin-6 biologic therapy in rheumatoid arthritis. Arthritis Rheumatol. 2015;67:2056-60.
20. Pek SLT, Cheng AKS, Lin MX, Wong MS, Chan EZL, Moh AMC, Sum CF, Lim SC, Tavintharan S. Association of circulating proinflammatory marker, leucine-rich-α2-glycoprotein (LRG1), following metabolic/bariatric surgery. Diabetes Metab Res Rev. 2018;34:e3029.
21. He S, Ryu J, Liu J, Luo H, Lv Y, Langlais PR, Wen J, Dong F, Sun Z, Xia W, Lynch JL, Duggirala R, Nicholson BJ, Zang M, Shi Y, Zhang F, Liu F, Bai J, Dong LQ. LRG1 is an adipokine that mediates obesity-induced hepatosteatosis and insulin resistance. J Clin Invest. 2021;131:e148545.
22. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015;7:280-93.
23. Rosner B, Prineas RJ, Loggie JM, Daniels SR. Blood pressure nomograms for children and adolescents, by height, sex, and age, in the United States. J Pediatr. 1993;123:871-86.
24. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291-303. Epub 1969 Jun 1.

25. 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;28:412-9.

26. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002;123:745-50.

27. Choi CHJ, Barr W, Zaman S, Model C, Park A, Koenen M, Lin Z, Szwed SK, Marchildon F, Crane A, Carroll TS, Molina H, Cohen P. LRG1 is an adipokine that promotes insulin sensitivity and suppresses inflammation. eLife. 2022;11:e81559. Epub 2022 Nov 8.

28. Luo L, Liu M. Adiponectin: friend or foe in obesity and inflammation. Med Rev (2021). 2022;2:349-362.

29. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev. 2005;26:439-51.

30. Shannon A, Alkhouri N, Carter-Kent C, Monti L, Devito R, Lopez R, Feldstein AE, Nobili V. Ultrasonographic quantitative estimation of hepatic steatosis in children With NAFLD. J Pediatr Gastroenterol Nutr. 2011;53:190-5.