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Research Article

The Potential Role of LRG1 in Hepatosteatosis and Insulin Resistance in Obese Children

Singin B et al. LRG1 in Pediatric Obesity

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What is already known on this topic?
•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 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 TNF-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, indicating distinct, age-specific pathophysiological mechanisms.
•The results highlight that LRG1 may act not merely as an inflammatory marker but as a complex metabolic regulator during growth and development.

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 total of 172 children (100 obese, 72 non-obese) 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: Obese children had significantly higher body mass index (BMI), BMI Standard Deviation Scores (SDS), waist and upper arm circumferences, triceps skinfold (TSF) thickness, total and percentage of body fat (PBF), and elevated systolic (SBP) and diastolic blood pressure (DBP) ($p<0.001$). Laboratory findings revealed glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), alanine aminotransferase (ALT), 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 is 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

Introduction

In the last decades, being overweight and obesity are 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 now 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 (RBP4), have been identified in adipocytes (4–6). 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 act as pro-inflammatory under certain conditions and in a tissue-dependent manner (8–11).

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 (LRR) domains (13). In addition to regulating angiogenesis (13), LRG1 has also been implicated in a number of diseases such as cancer (13–15), 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 a novel adipokine 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 insulin resistance 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 insulin resistance 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).-Accordingly, 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. Additionally, 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.

Material and Methods

Study Design and Participants

This research was designed as a single-center, case-control study. A total of 172 participants, aged between 6 and 18 years, were included. The obese group consisted of 100 children diagnosed with obesity at the pediatric endocrinology outpatient clinic of our hospital. The control group consisted of 72 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. Moreover, obese individuals were classified into two groups, those with and without IR, and comparisons were made accordingly.

Clinical İnvestigations 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 by the square of the height (kg/m²). 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 from 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 Tanner classification (24).

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 Insulin Resistance (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). 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 ELISA (Enzyme-Linked Immunosorbent Assay) 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 <% 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 a Elabscience kit (Elabscience Bionovation Inc, Houston, TX, **USA**) (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 a a Elabscience kit (Elabscience Bionovation Inc, Houston, TX, **USA**) (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 (Copyright 1985-2021 StataCorp LLC). A p-value of <0.05 was considered statistically significant.

Results

The clinical and laboratory characteristics of obese and non-obese subjects were summarized in **Table 1**. The age, gender, and pubertal status were similar in the two groups. The BMI, BMI SDS, waist and upper arm circumferences, TSF thickness, total body fat mass, PBF, and systolic and diastolic blood pressures were significantly higher in the obese group ($p<0.001$). When laboratory parameters were revealed, 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, whereas TNF-α levels were significantly higher in the obese group ($p=0.58$; $p=0.08$; $p<0.001$). In the control group, only 2 participants (2.8%) had a WtHR ≥0.5, whereas in the obese group, only 3 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 were demonstrated in **Table 2**. In patients with and without hepatosteatosis, similar age, gender, and pubertal status were observed. The BMI, BMI SDS, waist and upper arm circumferences, and total body fat mass were significantly higher in patients with hepatosteatosis ($p<0.05$). ~~İnsulin~~ Insulin, HOMA-IR, and TG levels were significantly higher in obese patients while HDL-C was lower ($p<0.05$). No statistically significant differences were observed between the groups when comparing LRG1, adiponectin, and TNF-α levels.

IR was present in 66 patients, whereas 106 patients showed no signs of it. Comparison of the clinical and laboratory characteristics of obese subjects with and without IR were demonstrated 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, BMI SDS, waist and upper arm circumferences, TSF thickness, total body fat mass, PBF, and systolic and diastolic blood pressures were significantly higher in the obese group ($p<0.001$). When laboratory parameters were revealed, 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 obese and non-obese patients were compared, LRG1 and adiponectin levels were significantly lower, while TNF-α levels were significantly higher ($p=0.03$; $p=0.008$, $p=0.004$).

Correlation analysis revealed several significant associations between serum biomarkers and clinical parameters in obese subjects **(Table 4).** Serum LRG1 levels showed significant negative correlations with waist circumference ($r = -0.220$, $p = 0.0281$), diastolic blood pressure ($r = -0.201$, $p = 0.0446$), insulin ($r = -0.288$, $p = 0.0037$), HOMA-IR ($r = -0.267$, $p = 0.0074$), TG ($r = -0.283$, $p = 0.0043$), TC ($r = -0.269$, $p = 0.0068$), and LDL-C ($r = -0.307$, $p = 0.0019$). Conversely, LRG1 was positively correlated with HDL-C ($r = 0.332$, $p = 0.0007$). Adiponectin levels were negatively correlated with waist circumference ($r = -0.247$, $p = 0.0131$), systolic blood pressure ($r = -0.208$, $p = 0.0379$), insulin ($r = -0.281$, $p = 0.0046$), HOMA-IR ($r = -0.264$, $p = 0.0080$), TG ($r = -0.260$, $p = 0.0090$), TC ($r = -0.208$, $p = 0.0382$), and LDL-C ($r = -0.240$, $p = 0.0161$); while a positive correlation was observed with HDL-C ($r = -0.270$, $p = 0.0066$).

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 such as LRG1, adiponectin, and TNF-α in this context. Our findings demonstrate significant metabolic disturbances in obese children. Specifically, there were marked increases in BMI, waist circumference, insulin, HOMA-IR, TG, and LDL-C alongside significant decreases in HDL-C and adiponectin levels. These results align with previous studies emphasizing 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 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 is often associated with pro-inflammatory states and metabolic deterioration, yet some studies suggest it may play a compensatory or protective role under specific physiological conditions (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 TGF- β 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 are recommended to 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 a mere inflammatory biomarker in obesity and metabolic diseases.

Consistent with previous literature, our adiponectin findings showed decreased levels and negative correlations with obesity and IR markers. Given adiponectin's role in enhancing insulin ~~sensivity~~ 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 is a useful non-invasive method for detecting hepatic lipid accumulation; however, it does not allow for 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. Additionally, 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 age dependent and evolve over time.

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 statictical power. Additionally, 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. 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; therefore, ultrasonographic evaluation was used in the present study, which should be considered a limitation.

Conclusion

In conclusion, our study suggests that the role of LRG1 in childhood obesity may differ from that in adults. This underscores the necessity for age-specific evaluations of LRG1 as a clinical biomarker and highlights the importance of longitudinal studies with larger cohorts. Additionally, given the complex nature of obesity and metabolic syndrome, multi-parameter analyses including adiponectin, TNF-α, and other biomarkers are crucial for a more comprehensive understanding.

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Data Availability No datasets were generated or analysed during the current study.

Code Availability Not applicable.

Declarations

Ethics Approval

Approval was obtained from the Ethics Committee prior to the commencement of the study (protocol number: 70904504/324 dated May 30, 2022). Informed consent was obtained from the parents of all participants prior to their inclusion in the study. The research was conducted in full compliance with the principles set forth in the Declaration of Helsinki and in accordance with ethical standards.

Consent to Participate

Informed consent was obtained from all participants or their legal guardians before inclusion in the study.

Consent for Publication

All authors approved for the publication of this paper.

Competing Interests

The authors declare no competing interests.

Ethical and Legal Declarations

The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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

	Obese subjects (n=100)	Non-obese subjects (n=72)	P
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 mean ± SD, median (IQR 25–75 percentile) or n (%)

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.

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*
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 mean ± SD, median (IQR 25–75 percentile) or n (%)
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.

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*
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 mean ± SD, median (IQR 25–75 percentile) or n (%)
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.

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

	LRG1	TNF-α	Adiponectin
Age (year)	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.