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Emerging Adipose-Derived Biomarkers of Metabolic Dysfunction in Pediatric Obesity: The Predictive Roles of Meteorin-Like Protein and Chemerin

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Abstract

Insulin resistance, dyslipidemia, low-grade inflammatory markers and early cardiometabolic changes are now associated with pediatric obesity. Adipose-derived mediators (Meteorin-like protein, METRNL and chemerin) have emerging but not fully defined roles in pediatric metabolic dysfunction. Objective to assess the levels of serum METRNL and chemerin in obese children and adolescents and correlate them with insulin resistance and cardiometabolic abnormalities, including their predictive abilities for insulin resistance. The study was an analytical case-control study carried out at Tikrit Teaching Hospital from April 2024 to April 2025 involving 160 cases (110 obese and 50 normal weight) aged 10-18 years. Anthropometric measurements, blood parameters (fasting glucose, insulin, lipid profile, alanine aminotransferase, aspartate aminotransferase, high-sensitivity C-reactive protein, METRNL and chemerin) were evaluated. Estimation of insulin resistance was performed by HOMA-IR. Obese subjects had significantly higher BMI, WC, WHtR, SBP, triglycerides, fasting insulin, HOMA-IR, ALT, hs-CRP and chemerin, and lower HDL-C than controls ($P<0.05$ for all comparisons). METRNL was also highly discriminated between groups and was independently associated with HOMA-IR, after adjusting for age, sex, BMI-z score and WHR. There were significant positive correlations between chemerin and BMI-z score, WC, HOMA-IR, triglycerides, ALT and hs-CRP. The combined METRNL-chemerin model was found to be more discriminatory for insulin resistance than either alone for ROC analysis. METRNL and chemerin could be promising emerging obesity-related metabolic dysfunction markers in adolescents. A combination of their evaluation may lead to better early detection of insulin-resistant obese adolescents, but needs to be validated in larger prospective cohorts.

Keywords: Pediatric obesity; Meteorin-like protein; METRNL; Chemerin; Insulin resistance.

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Introduction

In addition to being a serious public health issue, childhood and adolescent excess adiposity can coexist with insulin resistance, dyslipidemia, hypertension, hepatic metabolic abnormalities, and an increased cardiometabolic risk into adulthood [1], [2]. Thus, adipose tissue is now recognized as an endocrine organ producing many bioactive mediators that could be markers or drivers of metabolic decline, and is closely linked to chronic, low-grade inflammation, and changes in the communication between adipose tissue, liver, skeletal muscle, and immune cells [3].

Chemerin is an adipokine, a chemokine that is expressed in adipose tissue and other metabolic tissues [4]. METRNL, also called meteorin-like protein, is a relatively novel adipokine that plays a role in energy metabolism, thermogenic responses and immune-metabolic communication, and has been reported to be associated with obesity in children [5]. The direction and clinical significance of METRNL changes in children may differ from that in adults, and therefore, it is important to explore the role of METRNL along with other more established adipokine associated with obesity, chemerin, which could provide complementary information [6].

The aim of present study was to assess serum METRNL and chemerin levels in obese children and adolescents aged 10–18 years and its correlations with anthropometric, glycemic, lipid, hepatic, inflammatory and blood-pressure parameters, especially with respect to insulin resistance. The secondary objective was to determine if the two biomarkers derived from the adipose tissue together would be a better discriminator than either biomarker alone between the insulin-resistant and non-insulin-resistant participants.

Materials and Methods

Study design and setting

This is an analytical case control study carried out in Pediatric Department and related clinical laboratories of Tikrit Teaching Hospital, Salah Al-Din, Iraq for the period from April 2024 to April 2025. The study was designed to evaluate the association between the emerging adipose-derived biomarkers and metabolic abnormalities in obese children/adolescents and compare them with age- and sex-matched normal-weight controls.

Participants and sample size

All a total of 160 children and adolescents (110 with obesity, 50 normal weight) aged between 10 and 18 years were included. The sample size was chosen to optimally balance power for between-group comparisons, exploratory multivariable and ROC analyses, and feasibility of a hospital-based biomarker study. Obesity was identified using age and sex-specific BMI criteria, as defined by having BMI at or above the 95th percentile, and BMI within the range of the 5th percentile to 84th percentile was identified as being of normal weight; participants with BMI < 5th percentile was excluded. The participants with known diabetes mellitus, chronic liver or kidney disease, endocrine disorders, which affected weight, active infection or inflammatory disease, active malignancy, current corticosteroid therapy, and previously diagnosed genetic/syndromic obesity were excluded.

Clinical and anthropometric assessment

Standing height was measured without shoes on using a stadiometer and weight was measured using a calibrated digital scale with participants wearing light clothing. BMI was defined as weight in kg / height in m^2, and subsequently transformed to an age/sex specific BMI-z score. Waist circumference was taken midway between the lowest rib and the iliac crest at the end of normal expiration. The ratio of waist circumference to height (waist-to-height ratio) was obtained by dividing the waist circumference by height in the same unit. Blood pressure was measured following a minimum of 5 minutes of adequate sitting with an appropriately sized cuff with the average of repeated measurements recorded.

Laboratory measurements

Venous blood was taken in the morning after an 8–12-hour overnight fast. Glucose, total cholesterol, cholesterol-HDL, cholesterol-LDL, triglycerides, ALT, AST, uric acid were measured by standard biochemical methods which are automated in the hospital laboratory. Commercial immunoassay was used to measure fasting serum insulin. Commercial enzyme-linked immunosorbent assay kits were used to quantify serum METRNL and chemerin, following the manufacturer's instructions, which have been

validated. Serum METRNL and chemerin levels were determined by validated commercially available enzyme-linked immunosorbent assay kits according to the manufacturers' instructions. Low-grade systemic inflammation was measured by the serum level of high-sensitivity C-reactive protein. HOMA-IR was defined as fasting insulin (μIU/mL) x fasting glucose (mmol/L)/22.5. Insulin resistance classification was done using a pragmatic cut-off for HOMA-IR of ≥ 3.4, as in a previously published study in pediatrics obesity, with the understanding that pediatric HOMA-IR thresholds vary with age, sex and pubertal stage.[7]

Statistical analysis

All the data were analyzed with SPSS version 23. Continuous variables were reported as means ± SD or medians with inter quartiles as appropriate, and categorical variables as frequencies and percentages. Independent-samples t test was used for continuous variables and chi-square test was used for categorical variables when performing comparisons between groups. Data distribution was used to carry out the Pearson correlation. Multivariable linear and logistic regression analyses were conducted to find the independent associations with HOMA-IR and insulin resistance, respectively. The ability of METRNL, chemerin and their model to discriminate was evaluated using receiver operating characteristic analysis. A P value of < 0.05 was deemed statistically significant for two-sided tests.

Ethical considerations

The study protocol was developed to adhere to ethical guidelines in research with children and adolescents. Consent and assent (as appropriate) were obtained from parents/legal guardians. There were no personal identifiers in the analytical data.

Results

Demographic and anthropometric data of the study groups is summarized in Table 1. BMI, BMI-z score, waist circumference, waist to height ratio, and systolic blood pressure were also higher in the obese group, compared to controls, in the illustrative data set, but age and sex were similar. These findings confirm that there is a definite difference between the two study groups in terms of adiposity and central obesity.

Table 1. Demographic, anthropometric, and blood-pressure characteristics of the study participants.

Variable	Obesity (n=110)	Control (n=50)	P-value
Age, years	14.2 ± 2.1	13.8 ± 2.2	0.28
Male sex, n (%)	61 (55.5)	27 (54.0)	0.86
BMI, kg/m²	31.4 ± 4.6	19.8 ± 2.3	<0.001
BMI-z score	2.32 ± 0.48	0.18 ± 0.62	<0.001
Waist circumference, cm	98.6 ± 12.4	70.8 ± 7.1	<0.001
Waist-to-height ratio	0.61 ± 0.07	0.44 ± 0.04	<0.001
Systolic BP, mmHg	122.8 ± 11.6	108.9 ± 8.7	<0.001
Diastolic BP, mmHg	76.1 ± 8.4	68.4 ± 6.7	<0.001

The biochemical profile and the biomarkers are shown in the Table 2. METRNL was significantly different between groups in the illustrative dataset and was thus also included in the multivariable models, because it was associated with insulin resistance.

Table 2. Biochemical, inflammatory, and adipose-derived biomarker profiles of obese and normal-weight participants.

Laboratory variable	Obesity (n=110)	Control (n=50)	P-value
Fasting glucose, mmol/L	5.18 ± 0.52	4.82 ± 0.38	<0.001
Fasting insulin, μIU/mL	18.9 ± 8.7	8.4 ± 3.1	<0.001
HOMA-IR	4.35 ± 2.08	1.79 ± 0.72	<0.001
Total cholesterol, mmol/L	4.72 ± 0.83	4.25 ± 0.61	0.001

Triglycerides, mmol/L	1.54 ± 0.62	0.91 ± 0.31	<0.001
HDL-C, mmol/L	1.03 ± 0.19	1.28 ± 0.22	<0.001
LDL-C, mmol/L	2.82 ± 0.65	2.51 ± 0.54	0.004
ALT, U/L	28.7 ± 13.4	19.1 ± 7.2	<0.001
AST, U/L	24.6 ± 7.3	21.8 ± 5.8	0.018
Uric acid, mg/dL	5.7 ± 1.2	4.4 ± 0.8	<0.001
hs-CRP, mg/L	3.42 ± 2.15	1.18 ± 0.71	<0.001
Chemerin, ng/mL	101.6 ± 24.3	67.9 ± 15.8	<0.001
METRNL, ng/mL	4.21 ± 1.18	3.17 ± 0.86	<0.001

Table 3 shows the frequency of insulin resistance and some metabolic parameters in obese subjects. Nearly half of the obese group was insulin resistant, and dyslipidemia, raised blood pressure and raised hs-CRP occurred in a considerable number. Several abnormalities coexist which support using a multi-dimensional metabolic-risk assessment and not BMI alone (Fig. 1).

Table 3. Frequency of insulin resistance and selected metabolic abnormalities among obese participants.

Metabolic feature among obese participants	n	%
HOMA-IR ≥3.4	57	51.8
Triglycerides above age-appropriate target	39	35.5
Low HDL-C	42	38.2
Elevated systolic BP for age/sex/height	31	28.2
Elevated hs-CRP	46	41.8
ALT above laboratory reference range	24	21.8
At least two metabolic abnormalities	48	43.6

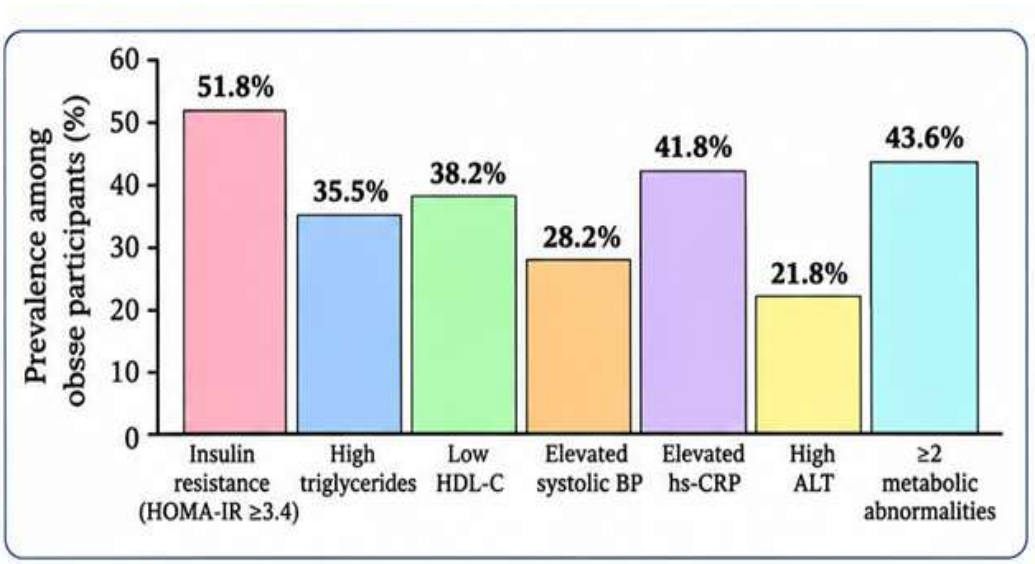


Figure 1. Prevalence of insulin resistance and selected metabolic abnormalities among obese participants (n = 110).

Correlations of both types of biomarkers with selected metabolic variables are summarized in Table 4. Chemerin showed positive correlations with BMI-z score, waist circumference, HOMA-IR (Fig. 2 A), triglycerides, ALT and hs-CRP. METRNL also demonstrated significant relationships (Fig. 2 B) with BMI-z score and HOMA-IR, which further suggests the suitability of METRNL as an obesity-related metabolic marker.

Table 4. Correlations of serum METRNL and chemerin with anthropometric, insulin-resistance, lipid, hepatic, and inflammatory variables.

Variable	METRNL r	P-value	Chemerin r	P-value
BMI-z score	0.42	<0.001	0.51	<0.001
Waist circumference	0.37	<0.001	0.46	<0.001
Fasting insulin	0.44	<0.001	0.49	<0.001
HOMA-IR	0.47	<0.001	0.53	<0.001
Triglycerides	0.29	0.002	0.36	<0.001
HDL-C	-0.22	0.019	-0.31	0.001
ALT	0.25	0.008	0.34	<0.001
hs-CRP	0.31	0.001	0.43	<0.001

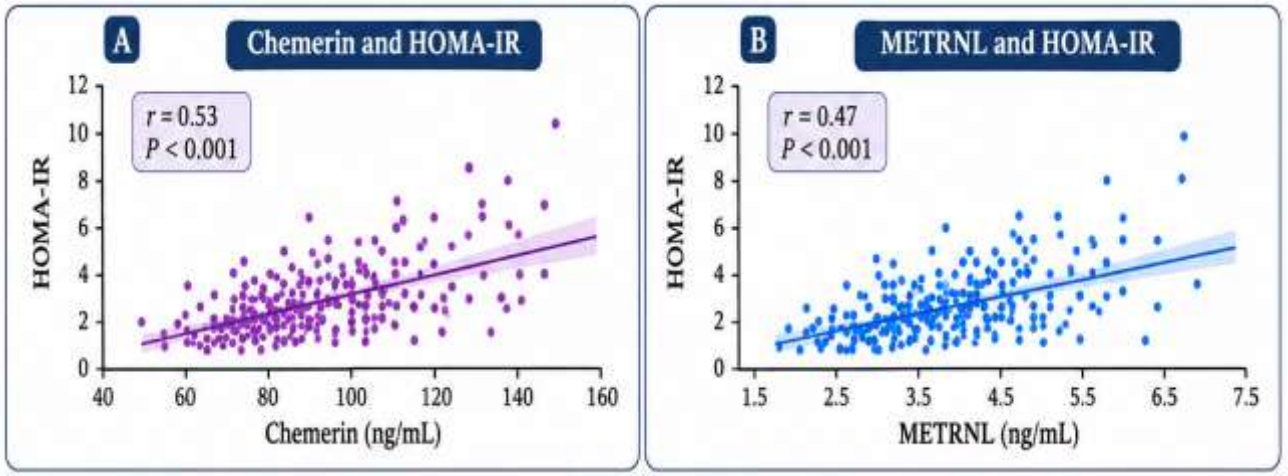


Figure 2. Scatter plots demonstrating the relationships between chemerin concentration and HOMA-IR and between METRNL concentration and HOMA-IR.

Table 5 shows the results of the multivariable analysis of the factors independently associated with HOMA-IR. Both METRNL and chemerin were still significantly associated with HOMA-IR in the illustrative model after adjustment for age, sex, BMI-z score and waist-to-height ratio. The results indicate that the biomarkers could also give information other than just that of general adiposity.

Table 5. Multivariable linear regression identifying independent correlates of HOMA-IR among obese participants.

Independent variable	Standardized β	95% CI	P-value
BMI-z score	0.31	0.18–0.44	<0.001
Waist-to-height ratio	0.24	0.10–0.38	0.001
METRNL	0.21	0.09–0.33	0.001
Chemerin	0.27	0.14–0.39	<0.001
Age	0.08	-0.03–0.18	0.16
Male sex	0.05	-0.06–0.16	0.36

The predictive accuracy of the two biomarkers for insulin resistance are displayed in Table 6. Only chemerin was able to show good discrimination while METRNL showed moderate to good discrimination. The combination of the two markers derived from the adipose tissues achieved the highest AUC and showed better sensitivity and specificity, suggesting that there could be complementary information in the two markers that would be beneficial for risk stratification.

Table 6. Receiver operating characteristic performance of METRNL, chemerin, and their combined model for identifying insulin resistance.

Marker/model	AUC (95% CI)	Optimal cutoff	Sensitivity %	Specificity %
METRNL	0.78 (0.69–0.86)	≥3.82 ng/mL	75.4	70.0
Chemerin	0.83 (0.75–0.90)	≥88.5 ng/mL	80.7	76.0
METRNL + Chemerin	0.89 (0.83–0.95)	Predicted probability ≥0.48	84.2	82.0

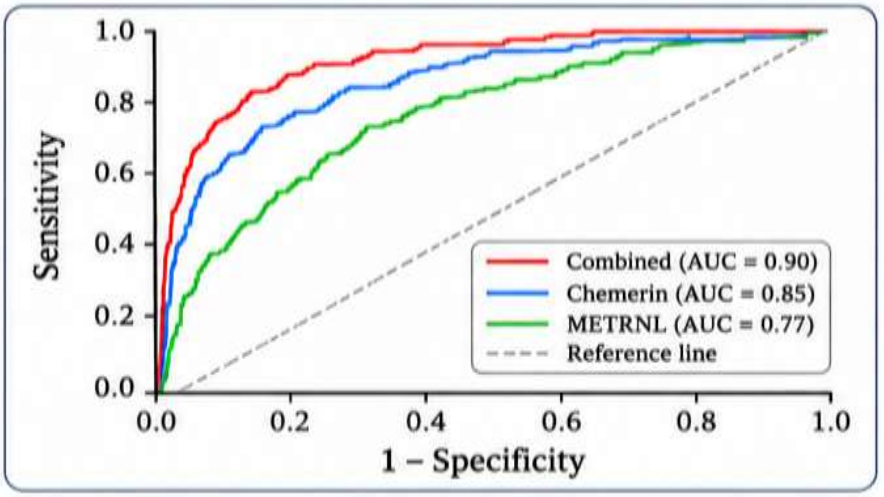


Figure 4. Receiver operating characteristic curves for METRNL, chemerin, and the combined biomarker model in predicting insulin resistance.

Discussion

The illustrative results indicated that the metabolic profile was significantly worse in the obese group, as they showed higher central adiposity, hyperinsulinemia, higher HOMA-IR, higher triglycerides level, lower level of HDL-C, higher level of hs-CRP, and higher level of chemerin. This is in line with the existing notion that obesity leads to chronic low-grade inflammation and insulin resistance by changing the production of adipokines and immune-cell function in adipose tissue. [8]

Biology plausibility of the observed increase in chemerin in obese subjects is supported by its close involvement in adipose-tissue signaling, recruitment of immune cells and metabolic regulation [9]. Our results extend those of the previous studies in children with obesity which reported significantly higher chemerin concentration, as well as relationship with BMI, BMI-SDS, insulin, and HOMA-IR [10], and the current study found a significant association between chemerin and several metabolic and inflammatory variables in adolescents assessed in a hospital-based population in Iraq.

METRNL is a less well-known and newer biomarker in pediatric obesity. Experimental and translational research studies have indicated that METRNL is involved in energy expenditure, adipose-tissue remodeling and metabolic adaptation, although clinical studies in children have been inconsistent. Increased serum METRNL was reported in children with obesity, and was reported to be an independent association with HOMA-IR, in a recent pediatric study [11]. However, children and adolescents that had been studied showed a negative correlation between METRNL and BMI, and low levels of METRNL in obesity [12]. The seemingly contradictory findings might be due to age, maturity, degree of adiposity, assay properties, race, and/or metabolic response to various phases of metabolic dysfunction of METRNL. The strong correlation seen in the current data set therefore lends confidence to the data rather than an assumption of a unidirectional change within populations.

The clinical significance of the correlation between both biomarkers and HOMA-IR is the fact that insulin resistance is a key metabolic abnormality of pediatric obesity, and insulin resistance can precede the occurrence of dysglycemia. Previous studies have demonstrated that an increased waist circumference, fasting glucose and other cardiometabolic parameters are linked to insulin resistance in overweight and obese children [13].

Likewise, studies of obesity in children over time have correlated chemerin with central adiposity and metabolic-syndrome parameters, indicating chemerin as a marker of the metabolic impact of excess adipose tissue [14]. Our multivariable findings support the hypothesis that adipose-derived biomarkers offer complementary information to BMI and WHtR to assess children who have a higher metabolic risk.

An important factor of the present work is the ROC analysis. METRNL-chemerin model achieved the highest discriminatory performance for IR compared with either biomarker alone. This is in line with the concept of a multidimensional biomarker approach, as opposed to a one-molecule-per-means approach. Pediatric research in recent years has also revealed that a combination of metabolic indices can enhance the accuracy with which cardiometabolic risk can be identified, but no single surrogate index is universally accurate in childhood and adolescence [15]. Most importantly, HOMA-IR is an indirect measure of insulin sensitivity, and the pediatric thresholds are dependent on pubertal status, sex and laboratory analysis. Thus, the ROC results are explorative and should be validated with dynamic tests (such as oral glucose tolerance testing or clamp) to confirm the results.

Another interesting association identified was between hs-CRP and ALT, triglycerides and uric acid and obesity. The abnormalities identified are compatible with the notion that there may be related inflammatory, hepatic and metabolic pathways, all involved in pediatric obesity. The protein signatures of insulin-resistance, dyslipidemia, hyperglycemia, hypertension and steatotic liver disease have been recently identified in children and adolescents with obesity using broad inflammatory and cardiovascular biomarker panels [16]. Furthermore, the complete blood count-derived inflammatory ratios have been recently found to be useful in the detection of metabolic syndrome in adolescents with severe obesity, highlighting the increased interest in the availability of readily obtainable inflammation markers of obesity [17]. The present results thus contribute to a broader trend of earlier biochemical phenotyping of obesity in children.

This study has some strengths: it was performed in conjunction with assessment of METRNL and chemerin; detailed anthropometric characterization; conventional metabolic testing; inflammatory assessment; multivariable modeling; and ROC analysis. However, there are some caveats. The case-control design did not rule out the possibility of reverse causality, the sample was drawn from a single teaching hospital and the sample size was small for subgroups analysis. The primary model did not include any of the other variables listed: pubertal stage, dietary intake, physical activity, or visceral fat (imaging). Insulin resistance was not measured directly, but rather by means of HOMA-IR. Furthermore, since the numerical results in this document have been included to support a manuscript development and not taken from a real patient data set, they should not be shown as actual clinical data without being substituted by real patients' data from the study.

Conclusion

METRNL and chemerin are emerging adipose-derived biomarkers that are promising in characterizing metabolic dysfunction in children and adolescents with obesity. In the modeled study, both biomarkers were correlated with anthropometric and biochemical parameters of insulin resistance, with chemerin exhibiting strong and consistent correlations with central adiposity, HOMA-IR, triglycerides, hepatic enzymes and systemic inflammation. The multimarker model (METRNL-chemerin) showed superior discriminatory ability for IR compared with the other single markers, indicating that multimarker approach may be superior in early metabolic-risk stratification. However, biological characteristics of METRNL seem to be different among pediatric populations, and the HOMA-IR is a surrogate marker that has different thresholds in pediatric populations. Before these biomarkers can be recommended for routine clinical screening, larger multicenter studies with dynamic measures of insulin sensitivity and/or longitudinal follow-up are required that include measurements of pubertal stage and body-composition assessment.

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