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Evaluation of TLQP-21 in relation to oxidative stress biomarkers in obesity

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ABSTRACT

This study investigated serum TLQP-21, a VGF-derived peptide involved in energy balance, in human obesity and its relationship with oxidative stress. One hundred obese adults and 50 non-obese controls from Mosul, Northern Iraq, were compared. Serum TLQP-21 was measured by ELISA, alongside malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). Obese participants had significantly higher TLQP-21 ($p = 4.41 \times 10^{-33}$) and MDA ($p = 1.38 \times 10^{-37}$), and lower GSH ($p = 2.87 \times 10^{-42}$), SOD ($p = 5.10 \times 10^{-20}$), and CAT ($p = 1.13 \times 10^{-18}$) than controls; all differences remained significant after Bonferroni correction. TLQP-21 correlated positively with BMI and MDA and inversely with GSH, SOD, and CAT. In regression modelling, BMI, MDA, and GSH were associated with TLQP-21. The internally derived ROC area was 0.94. The authors conclude that serum TLQP-21 correlates with oxidative stress parameters in obesity, but the cross-sectional design and lack of external validation of the ROC cutoff preclude establishing causality or clinical diagnostic use at present.

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Introduction

Obesity is a major global public-health problem and is closely associated with type 2 diabetes, cardiovascular disease, and other metabolic dysfunctions. Obesity is influenced by a complex mix of genetic, environmental, behavioural, and endocrine determinants, and interpreting potential biomarkers of adiposity and metabolic stress requires clear differentiation between association, prediction, and clinical use [1, 2].

TLQP-21 is a VGF-derived neuropeptide, produced by neurons and neuroendocrine cells, and expressed in a variety of peripheral metabolic tissues. TLQP-21 signals through the complement C3a receptor 1 (C3aR1) and influences adrenergic lipolysis, energy expenditure, and metabolic activity in white and brown adipose tissue [3–6].

These observations provide a biological rationale for investigating TLQP-21 in obesity, particularly because adipose tissue metabolism and oxidative stress are closely interconnected. Increased adipose tissue metabolic activity, lipid mobilisation, mitochondrial dysfunction, and inflammation can contribute to reactive oxygen species production and oxidative imbalance [2, 7, 8]. In addition, signalling through the C3aR pathway may provide a mechanistic link between TLQP-21-related metabolic regulation and redox processes. However, despite evidence linking TLQP-21 with energy metabolism and obesity, the relationship between circulating TLQP-21 and oxidative stress biomarkers in human obesity remains insufficiently characterised, particularly in Middle Eastern populations. Therefore, investigating the association between TLQP-21 and oxidative stress markers in obese individuals from Mosul, Iraq, may provide population-specific evidence and help clarify whether circulating TLQP-21 is associated with the

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oxidative stress burden accompanying obesity [3,9,10].

Evidence on circulating TLQP-21 in human obesity remains limited. Although several preclinical studies have implicated TLQP-21 in adiposity, energy expenditure, and body weight control, they used experimental models, and findings cannot be translated to human studies by measuring circulating TLQP-21 levels [3,4,11].

Finally, while TLQP-21 has been implicated in experimental models of energy metabolism, including complement signalling, obesity is characterised by defects in mitochondrial function, inflammation, and an imbalance between oxidative and reductive processes. Here, we provide evidence of an association between circulating TLQP-21 and oxidative stress markers in humans.

Materials and methods

Study design

A cross-sectional analytical study was conducted at the departments of Mosul Teaching Hospital from January to June 2024. As no formal a priori sample-size calculation was performed, the study used a convenience sample. In total, 100 obese participants and 50 non-obese controls were recruited from eligible participants at the hospital during the study period. Consequently, no effect size, power, allocation ratio, minimum required sample size (using software), or provision for handling incomplete data was predetermined before participant recruitment.

Using the noncentral t distribution from SciPy (version 1.17.0) for a retrospective sensitivity analysis, we found that the available sample of 100 participants with obesity and 50 controls was sufficient to detect a minimum effect of Cohen's d = 0.49 with 80% power at a two-sided α = 0.05 using an independent-samples t-test, assuming equal variances, and a 2:1 allocation to the participants with obesity. Importantly, this is not a priori sample-size calculation but rather a characterisation of the available sample's sensitivity.

Inclusion criteria

Eligible study participants were adults aged 18 to 60 years of both sexes (self-reported). They had to fulfil a number of defined criteria. First, they were assigned to the non-obese control group or the obesity group based on their BMI and clinical assessment.

- Group 1 comprised 50 apparently healthy non-obese volunteers.
- Group 2 comprised 100 adults diagnosed with obesity. Recruited through the Obesity Surgery Centre at the Teaching Hospital of Mosul, Iraq, all participants with obesity were assessed for weight and height using conventional methods. A Medical Specialist confirmed the diagnosis of obesity in all cases with a BMI of ≥30 kg/m2, and detailed demographic and clinical data were collected using a structured questionnaire.

Participant exclusion criteria

The following conditions were used as exclusion criteria: pregnancy or lactation, diabetes mellitus type 1 or type 2, previously diagnosed cardiovascular disease or metabolic syndrome, active infection or inflammatory disease, liver or kidney failure, smoking, excessive alcohol consumption, use of corticosteroids, use of antioxidants, or other drugs that affect metabolism. Previous bariatric surgery was also an exclusion criterion. Blood pressure, measured on the day of the study, was provided as a clinical variable. However, this variable was not used to diagnose hypertension or to determine inclusion or exclusion in the study. The fact that one single measurement of blood pressure was higher than normal was not considered sufficient to establish a clinical diagnosis of CVD in participants without prior diagnosis of CVD. No additional blood pressure thresholds were used as exclusion criteria in retrospect.

Exclusion of metabolic syndrome was based on prior diagnosis information, not on a systematic assessment of all components of metabolic syndrome for all study participants. Therefore, undiagnosed metabolic syndrome could not be definitively excluded.

Study procedures

All participants underwent clinical assessment through medical history and a general physical examination. Participants' blood pressure and BMI were assessed using standard methods. The concentrations of TLQP-21 in participants' serum, as well as the concentrations of malondialdehyde (MDA) and reduced glutathione (GSH), and the activities of superoxide dismutase (SOD) and catalase (CAT), were measured subsequently.

Ethical approval

The study protocol was approved by the Research Ethics Committee of the College of Medicine,

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University of Mosul (approval No. UOM-COM-2024-001). Participants were recruited from patients attending Mosul Teaching Hospital in Mosul, Iraq, between January and June 2024. Written informed consent was obtained from all participants, and the study was conducted in accordance with appropriate ethical standards for research involving human participants.

Confidentiality and data protection

All participant information was kept confidential. Personal identifying information was kept safely by the researchers and was only accessed by members of the research team.

Blood collection and storage

Venous blood (10 mL) was collected into tubes without anticoagulant and allowed to clot. Serum was separated by centrifugation at 4000 rpm for 13 min. The available laboratory records did not document the interval or temperature between blood collection and centrifugation, the centrifugation temperature, or the duration and temperature of serum storage before analysis. Consequently, the stability of TLQP-21 immunoreactivity under the actual preanalytical conditions could not be independently assessed.

Serum TLQP-21 immunoreactivity was detected using a human TLQP-21 enzyme immunoassay (Phoenix Pharmaceuticals, Inc., USA, catalogue No. EK-003-90; lot number not recorded). According to the manufacturer's specifications, this assay had an analytical sensitivity of 0.15 ng/mL, a linear range of 0.15–2.7 ng/mL, an intra-assay variation of <10%, and an inter-assay variation of <15%. It demonstrated 100% reactivity with the human TLQP-21 peptide and 0% reactivity with the rat-derived TLQP-62 peptide and the human-derived AQEE-30 peptide among the tested peptides in the cross-reactivity panel. To detect serum MDA content, a competitive ELISA assay kit from Reed Biotech Ltd., China (RE10165) was used, with an analytical sensitivity of 9.15 ng/mL, a linear range of 31.25–2000 ng/mL, and intra- and inter-assay CVs of <10%. ELK Biotechnology, China, supplied a competitive-inhibition ELISA assay kit (ELK9096) to determine serum GSH concentration. SOD and CAT activities in serum samples were determined using commercial assay kits (quoted within individual methods) and assayed according to the manufacturer's protocols.

Information on lot numbers, dilution factors, the replicate measurement scheme, and laboratory quality control criteria for the assays was not recorded and therefore not reconstructed for this report. The MDA manufacturer stated that there was no significant cross-reactivity with related analogues; however, specific cross-reactivity information was not available for the GSH, SOD, and CAT assays, and this should be considered when interpreting results.

Statistical analysis

The main statistical analyses were conducted using IBM SPSS Statistics (Version 26.0; IBM Corp., Armonk, NY, USA). Tests were two-tailed, with a significance level of $\alpha = 0.05$. Normality of distributions for continuous data was assessed by the Shapiro-Wilk test and corresponding Q-Q plots. Variables that were normally distributed were expressed as mean (±SD) and analysed using corresponding parametric tests. Variables that were not normally distributed were expressed as median and corresponding interquartile range and analysed using the Mann-Whitney U test. Categorical variables were expressed as numbers of cases (in percentages) and analysed using chi-square tests or Fisher's exact tests where necessary (i.e., tests of expected cell sizes). All analyses were performed on available complete cases only, and no imputation of missing values was conducted.

For Table 1, continuous baseline variables were compared using independent-samples t-tests. For the categorical variables, a chi-square test was used. For Table 2, the mean of TLQP-21 was compared using an independent-samples t-test, and the distribution was compared using a Mann-Whitney U test. For the oxidative-stress markers in Table 3, independent-samples t-tests were used. For the Pearson correlations in Tables 4 and 5, the Pearson correlation coefficient was calculated. Tables 6A and 6B present the main multiple linear regression model and the sensitivity model, additionally adjusted for systolic and diastolic blood pressure, respectively. In these tables, to test multicollinearity, the variance inflation factors (VIF) and tolerance of the independent variables were calculated. Residual normality, homoscedasticity, autocorrelation and influential observations were checked using the Shapiro-Wilk test and corresponding Q-Q plot, Breusch-Pagan test, Durbin-Watson statistic, Cook's distance, studentized residuals and leverage values, respectively.

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For the sex-stratified analyses presented in Table 7, independent-samples tests compared means between groups, and interactions between obesity groups and sex were assessed using linear models. For the age-stratified analyses in Table 8A, a two-way linear model was used that included obesity status, age category, and their interaction. Pairwise comparisons of age categories in Table 8B were performed using Bonferroni-adjusted tests. Receiver operating characteristic (ROC) curves and related statistics were used for the analyses in Table 9, with cutoff values selected to maximise Youden's index. For the principal component analysis (PCA) in Tables 10A and 10B, correlation matrices were constructed from the standardised variables in each dataset, and principal components were extracted. For the exploratory machine-learning analysis presented in Table 11, a prespecified workflow of models was used, and performance was assessed using held-out testing as described in the Machine Learning Analysis section.

For all analyses presented in this manuscript, multiplicity was controlled not by applying a single global correction, but by controlling within specific sets of related comparisons. Bonferroni correction was applied to the TLQP-21 mean and median values in Table 2, the 4 oxidative stress parameters in Table 3, and the 3 within-study age pairwise comparisons in Table 8B for each study group. Both the unadjusted and the adjusted p-values are provided where appropriate. The analyses of correlation, regression, receiver operating characteristics, principal components analysis, and exploratory machine learning methods were treated as separate analytical objectives and were not subject to any manuscript-wide multiplicity correction; their results should be interpreted as exploratory, not confirmatory.

Results

Values are presented as mean ± standard deviation (SD) or n (%). Between-group comparisons used independent-samples t-tests for continuous variables and the chi-square test for categorical variables. All tests were two-sided. BMI, body mass index; BP, blood pressure; SD, standard deviation.

Table 1: Baseline Characteristics of Study Participants

Parameter	mean±SD Control Group (n=50)	Obese Group (n=100)	p-value
Demographics			
Age (years)	39.8 ± 9.2	42.3 ± 8.7	0.089
Gender (Male/Female)	22/28	45/55	0.823
Anthropometric Measurements			
Weight (kg)	65.2 ± 8.9	95.4 ± 12.8	**<0.001*** **
Height (cm)	169.2 ± 7.8	168.5 ± 8.3	0.598
BMI (kg/m^2)	22.8 ± 1.9	33.6 ± 3.2	**<0.001*** **
Waist circumference (cm)	78.3 ± 6.2	102.8 ± 9.4	**<0.001*** **
Hip circumference (cm)	92.4 ± 5.8	108.7 ± 8.9	**<0.001*** **
Waist-to-hip ratio	0.85 ± 0.04	0.95 ± 0.06	**<0.001*** **
Vital Signs			
Systolic BP (mmHg)	118.7 ± 9.8	128.4 ± 12.3	**<0.001*** **
Diastolic BP (mmHg)	76.2 ± 7.1	82.6 ± 8.9	**<0.001*** **

TLQP-21 levels

Obese subjects had higher serum TLQP-21 concentrations than controls (Table 2). Values are given as means ± SDs or medians (interquartile ranges). Mean differences were analysed using an independent-samples t-test, and median differences

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were analysed using the Mann–Whitney U test. Cohen's d was calculated using the pooled SD. Multiplicity-adjusted p-values were calculated by the Bonferroni procedure. All tests were two-sided. TLQP-21, VGF-derived 21-amino-acid peptide; SD, standard deviation; IQR, interquartile range; CI, confidence interval

Oxidative stress markers

Statistically significant differences in oxidative stress parameters between obese subjects and control subjects are presented in Table 3.

Table 2. Serum TLQP-21 concentrations in the study groups

Parameter	Control group (n=50)	Obese group (n=100)	Unadjusted p-value	Adjusted p-value[1]	Cohen's d (95% CI)
TLQP-21 (pg/mL), mean ± SD	298.7 ± 45.1	485.3 ± 78.2	4.41×10^{-33}	8.81×10^{-33}	2.70 (2.24–3.16)
TLQP-21 (pg/mL), median (IQR)	295.3 (268.9–325.4)	478.5 (432.8–531.2)	<0.001[2]	<0.001[2]	—

Table 3. Oxidative stress markers in the study groups

Parameter, mean ± SD	Control group (n=50)	Obese group (n=100)	Unadjusted p-value	Bonferroni-adjusted p-value	Cohen's d (95% CI)
Lipid peroxidation					
MDA (nmol/mL)	4.2 ± 0.9	8.9 ± 1.8	1.38×10^{-37}	5.51×10^{-37}	3.01 (2.53–3.49)
Antioxidant markers					
GSH (µmol/L)	398.4 ± 51.8	245.7 ± 42.3	2.87×10^{-42}	1.15×10^{-41}	−3.34 (−3.85 to −2.83)
SOD (U/mL)	18.9 ± 4.1	12.4 ± 3.2	5.10×10^{-20}	2.04×10^{-19}	−1.84 (−2.24 to −1.44)
CAT (U/mL)	24.7 ± 5.9	15.8 ± 4.6	1.13×10^{-18}	4.51×10^{-18}	−1.76 (−2.15 to −1.36)

For between-group comparisons, data were expressed as mean ± SD. Independent-samples t-tests were performed to test between-group differences, and effect size was quantified by calculating Cohen's d using the pooled SD and the corresponding 95% CI. Multiplicity-adjusted p-values were computed using the Bonferroni procedure for the 4 tests, and all tests were two-sided. MDA, malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase; CAT, catalase; SD, standard deviation; CI, confidence interval.

Compared with the control group, patients with obesity showed 111.9% higher MDA levels, whereas GSH concentrations, SOD activity, and CAT activity were decreased by 38.3%, 34.4%, and 36.0%, respectively. All differences remained significant after Bonferroni correction for the four comparisons.

Correlation analysis

TLQP-21 and oxidative Stress Markers

Strong correlations were observed between TLQP-21 and oxidative stress markers (Table 4).

Table 4: Correlation between TLQP-21 and oxidative stress markers

Parameter	Correlation Coefficient (r)	p-value	95% CI
Positive Correlations			
MDA	0.78	<0.001***	0.71-0.84
Negative Correlations			
GSH	-0.72	<0.001***	-0.79 to -0.64
SOD	-0.65	<0.001***	-0.73 to -0.55
CAT	-0.61	<0.001***	-0.70 to -0.50

*Pearson correlation coefficients. ***p<0.001,* TLQP-21, VGF-derived 21-amino-acid peptide; MDA, malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase; CAT, catalase; CI, confidence interval.

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TLQP-21 and anthropometric parameters

TLQP-21 showed significant correlations with anthropometric measurements (Table 5). Multiple linear regression analysis was performed to identify independent predictors of TLQP-21 levels (Table 6A).

Table 5: Correlation Between TLQP-21 and Anthropometric Parameters

Parameter	Correlation Coefficient (r)	p-value	95% CI
BMI	0.83	<0.001***	0.77-0.87
Waist circumference	0.79	<0.001***	0.72-0.85
Hip circumference	0.74	<0.001***	0.66-0.81
Waist-to-hip ratio	0.68	<0.001***	0.58-0.76

Pearson correlation coefficients are presented. *p < 0.05, **p < 0.01, ***p < 0.001. TLQP-21, VGF-derived 21-amino-acid peptide; BMI, body mass index; CI, confidence interval; Regression Analysis.

Table 6A. Multiple linear regression analysis of predictors of serum TLQP-21

Variable	B coefficient	Standard error	Standardized β	t-value	Exact p-value	95% CI for B	VIF	Tolerane
BMI (kg/m^2)	12.80	2.10	0.668	6.10	9.29×10^{-9}	8.65 to 16.95	3.42	0.292
MDA (nmol/mL)	18.40	3.20	0.446	5.75	5.14×10^{-8}	12.08 to 24.72	2.91	0.344
GSH (µmol/L)	−0.42	0.08	−0.320	−5.25	5.35×10^{-7}	−0.58 to −0.26	2.47	0.405
Age (years)	1.20	0.60	0.096	2.00	0.047	0.01 to 2.39	1.18	0.847
Sex, male[1]	−15.30	8.90	−0.068	−1.72	0.088	−32.89 to 2.29	1.09	0.917

[1] Female participants were used as the reference category. Model summary: $R^2 = 0.78$, adjusted $R^2 = 0.77$. BMI, body mass index; MDA, malondialdehyde; GSH, reduced glutathione; CI, confidence interval; VIF, variance inflation factor.

B is the unstandardised regression coefficient for that predictor. In contrast, standardised β represents the change in serum TLQP-21 levels in standard deviation units for a one-standard-deviation change in a predictor. Multicollinearity among the independent variables was evaluated using the variance inflation factor (VIF) and corresponding tolerance values for each independent variable. The VIF values for the present set of predictors ranged from 1.09 to 3.42, and the tolerance values ranged from 0.292 to 0.917. Because all VIF values are less than 5 and all tolerance values are greater than 0.20, no predictors show multicollinearity of concern. All tests were two-sided.

Regression diagnostics

The diagnostic checks did not reveal any serious violations of the model assumptions. Normality of the residuals was not rejected by the Shapiro-Wilk test (W = 0.989, p = 0.296) and the Q–Q plot looked fine. The Breusch-Pagan test also did not reveal heteroscedasticity ($\chi^2 = 6.12$, df = 5, p = 0.294). The Durbin-Watson statistic was 1.94. The maximum Cook's distance was 0.074, the maximum absolute studentized residual was 2.71, and the maximum leverage was 0.091.

Sensitivity analysis after adjustment for blood pressure

In the sensitivity model that additionally included

Table 6B. Sensitivity analysis of predictors of serum TLQP-21 after additional adjustment for systolic and diastolic blood pressure

Variable	Adjusted B	Standardized β	p-value
BMI	11.92	0.622	<0.001
MDA	17.61	0.427	<0.001
GSH	−0.39	−0.297	<0.001
Age	1.08	0.086	0.071
Sex, male	−14.21	−0.063	0.109
Systolic BP	0.48	0.061	0.281
Diastolic BP	0.37	0.028	0.594

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Sensitivity-model summary: $R^2 = 0.79$, adjusted $R^2 = 0.78$, $p < 0.001$. BMI, body mass index; MDA, malondialdehyde; GSH, reduced glutathione; BP, blood pressure; B, unstandardized regression coefficient; β, standardised regression coefficient.

After adjustment for systolic and diastolic blood pressure, the associations of BMI, MDA, and GSH with serum TLQP-21 remained in the same direction. After this adjustment, neither age (p = 0.071) nor sex (p = 0.109) was significantly associated with TLQP-21; neither systolic nor diastolic blood pressure was independently associated with TLQP-21. The main coefficients were similar in magnitude and sign.

To assess multicollinearity among BMI, MDA, GSH, age, and sex, Variance Inflation Factor (VIF) and tolerance values were calculated. The VIF values for these potential confounders ranged from 1.09 to 3.42, while their corresponding tolerance values ranged from 0.292 to 0.917. Since all VIF values were < 5 and all tolerance values were > 0.20, there was no serious multicollinearity among these potential confounders.

To check the assumptions of regression, we used the Shapiro–Wilk test and a Q–Q plot to assess residual normality. We also checked linearity by plotting the standardised residuals against the model's predicted values. Homoscedasticity was checked using the Breusch–Pagan test. Finally, we checked for influential observations by examining Cook's distance, studentized residuals, and each case's leverage. The Shapiro–Wilk test for residual normality gave a W-value of 0.989 and a corresponding p-value of 0.296. The Q–Q plot of the residuals showed no major departures from normality. The residual-versus-predicted plot showed no systematic curvature, which supports the assumption of linearity. The Breusch–Pagan test indicated no heteroscedasticity, with a chi-squared value of 6.12 on 5 and a p-value of 0.294. All cases had a Cook's distance of less than 0.1, with a maximum value of 0.074. The absolute values of the studentized residuals were less than or equal to 2.71, with a maximum value of 2.71. The maximum leverage value was 0.091, indicating no highly influential observations in the model.

Using the fitted regression model, 78% of the variation in serum TLQP-21 concentrations can be explained by this model. Checking for multicollinearity and performing residual diagnostics showed that, in addition to BMI, MDA and GSH are principal independent predictors of serum TLQP-21 concentrations. Age has a weak association with serum TLQP-21 concentration, whereas sex is not significantly associated.

Subgroup analysis

Gender-based analysis

The study found sex differences in serum TLQP-21 and MDA concentrations in both obese and control subjects and examined how these differences interacted with obesity in each sex (Table 7).

Table 7. Sex-stratified analysis of serum TLQP-21 and MDA concentrations

Parameter	Study group	Males, mean ± SD	Females, mean ± SD	Within-group sex comparison p-value	Obesity group × sex interaction p-value
TLQP-21 (pg/mL)	Obese[1]	468.2 ± 72.1	498.7 ± 81.4	0.050	0.723
	Control[2]	285.4 ± 38.9	308.9 ± 48.7	0.064	
MDA (nmol/mL)	Obese[1]	8.3 ± 1.6	9.4 ± 1.9	0.002	0.160
	Control[2]	3.9 ± 0.8	4.4 ± 0.9	0.043	

[1] Obese group: 45 males and 55 females.[2] Control group: 22 males and 28 females. TLQP-21, VGF-derived 21-amino-acid peptide; MDA, malondialdehyde; SD, standard deviation.

Although females had slightly higher serum TLQP-21 and MDA levels than males in both the obese and control groups, within-group sex differences in TLQP-21 were borderline significant only in the obese group (p = 0.050) and not significant in the control group (p = 0.064). In both study groups, however, females had higher MDA levels than males (obese females vs obese males, p = 0.002; control females vs control males, p = 0.043). The obesity-group, sex interactions, however, were not significant for either TLQP-21 (p for interaction = 0.723) or MDA (p for interaction = 0.160), indicating no evidence that the associations of obesity with TLQP-21 or MDA differed between males and females.

Age-based analysis

Participants were stratified into three age groups: 18-30 years (n=32), 31-45 years (n=68), and 46-60 years (n=50).

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Table 8A. Age-stratified analysis of serum TLQP-21 concentrations

Age group	Obese group, mean ± SD	Control group, mean ± SD	Between-group p-value	Obesity group × age interaction p-value
18–30 years	445.8 ± 65.3	278.2 ± 39.1	5.34×10^{-10}	0.572
31–45 years	492.1 ± 78.9	302.4 ± 46.8	9.70×10^{-19}	
46–60 years	518.7 ± 84.2	315.9 ± 48.2	3.56×10^{-14}	

Data are presented as mean ± SD. Between-group p-values were calculated to compare obese subjects with control subjects within each age category. The obesity-group × age interaction was analysed using a two-way linear model including the variables obesity group and age category, as well as their interaction. The p-value for the interaction term indicates whether the association between obesity group and serum TLQP-21 levels changes with age. All tests were two-sided. TLQP-21, VGF-derived 21-amino-acid peptide; SD, standard deviation.

Table 8B. Multiplicity-adjusted age-group comparisons within each study group

Study group	Age-group comparison	Mean difference, pg/mL	Unadjusted p-value	Bonferroni-adjusted p-value
Obese	31–45 vs 18–30 years	46.3	0.016	0.047
Obese	46–60 vs 18–30 years	72.9	<0.001	0.002
Obese	46–60 vs 31–45 years	26.6	0.158	0.473
Control	31–45 vs 18–30 years	24.2	0.127	0.382
Control	46–60 vs 18–30 years	37.7	0.035	0.104
Control	46–60 vs 31–45 years	13.5	0.390	1.000

Bonferroni-adjusted p-values were calculated separately for the three pairwise age comparisons within each study group.

Analyses were performed to assess serum TLQP-21 concentrations within 3 age categories for all participants. The models included a formal test of obesity-group × age interaction to assess whether the relationship between obesity status and serum TLQP-21 concentrations varied by age category.

Serum concentrations of the VGF-derived peptide TLQP-21 were increased in obese vs control subjects within all three age categories (all p<0.001). In the obese group, TLQP-21 concentrations were higher in 31–45-yr-old subjects than in 18–30-yr-old subjects after Bonferroni correction (adjusted p=0.047). Moreover, 46–60-yr-old obese subjects had higher concentrations of TLQP-21 than 18–30-yr-old obese subjects (adjusted p=0.002). In contrast, there were no significant differences between 31–45-yr-old and 46–60-yr-old obese subjects (adjusted p=0.473). In control subjects, none of the pairwise comparisons between the three age categories was statistically significant after multiplicity correction. There was no significant interaction between obesity group and age (p for interaction=0.572); thus, the magnitude of difference between obese and control subjects did not vary significantly with age in any category.

ROC analysis

A receiver operating characteristic (ROC) curve analysis was used to assess the ability of serum markers TLQP-21 and oxidative stress to classify obese individuals versus non-obese control subjects. The optimal cutoff values for each of the markers were determined by maximising Youden's Index (J = sensitivity + specificity − 1). Because these values were derived from the same samples used for assessment (i.e., internally derived), they should be regarded as provisional, exploratory values for diagnostic purposes and should not be used as clinically established thresholds.

AUC, area under the receiver operating characteristic curve; CI, confidence interval. Sensitivity confidence intervals were calculated using 100 participants with obesity, whereas specificity confidence intervals were calculated using 50 non-obese controls. The 95% confidence intervals for

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Table 9. Internally derived ROC analysis results

Parameter	AUC (95% CI)	p-value	Internally derived cutoff[1]	Classification direction	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Youden's index
TLQP-21	0.94 (0.90–0.98)	<0.001	365.2 pg/mL	≥365.2 pg/mL	89.0 (81.2–94.4)	92.0 (80.8–97.8)	0.81
MDA	0.96 (0.93–0.99)	<0.001	6.1 nmol/mL	≥6.1 nmol/mL	93.0 (86.1–97.1)	94.0 (83.5–98.7)	0.87
GSH	0.91 (0.86–0.96)	<0.001	320.5 µmol/L	≤320.5 µmol/L	87.0 (78.8–92.9)	88.0 (75.7–95.5)	0.75

[1] All cutoffs were selected internally by maximising Youden's index and were evaluated in the same cohort used for their derivation. They have not been validated in an independent population.

sensitivity and specificity were estimated using the exact Clopper–Pearson binomial method. The cutoffs are internally derived, unvalidated thresholds and should not be interpreted as established clinical diagnostic criteria.

TLQP-21 showed strong internal discrimination, with an AUC of 0.94 (95% CI: 0.90–0.98). The internally selected cutoff of 365.2 pg/mL yielded a sensitivity of 89.0% (95% CI: 81.2–94.4%) and specificity of 92.0% (95% CI: 80.8–97.8%). MDA demonstrated the highest observed AUC and Youden's index, whereas GSH showed comparatively lower discriminatory performance. Nevertheless, these performance estimates may be optimistic because the cutoffs were selected and evaluated using the same participants. Independent external validation is required before recommending any of these thresholds for clinical classification or diagnostic use.

Principal component analysis

To explore the relationship between serum levels of TLQP-21 and oxidative-stress markers and the set of anthropometric variables as a function of age, principal component analysis (PCA) was applied to the set of centred and standardised continuous variables. As the variables were measured in different units, the analysis was based on the correlation matrix. Component selection was based on criteria including eigenvalues greater than 1.0, the shape of the scree plot, and the amount of variance explained by the retained components. Loadings with an absolute value of at least 0.40 were considered salient.

Table 10A. Eigenvalues and variance explained by the principal components

Component	Eigenvalue	Variance explained (%)	Cumulative variance (%)	Retention decision
PC1	4.82	48.2	48.2	Retained
PC2	2.14	21.4	69.6	Retained
PC3	1.33	13.3	82.9	Retained
PC4	0.89	8.9	91.8	Not retained

Components were retained when their eigenvalues exceeded 1.0, and their retention was supported by inspection of the scree plot. PC, principal component.

Table 10B. Component-loading matrix for the retained principal components

Variable	PC1	PC2	PC3
TLQP-21	0.79	0.52	−0.12
MDA	0.79	−0.35	−0.36
GSH	−0.70	−0.33	−0.38
SOD	−0.69	−0.68	0.00
CAT	−0.67	−0.06	−0.51
BMI	0.75	−0.41	0.00
Waist circumference	0.77	−0.03	0.17
Hip circumference	0.72	−0.63	0.27
Waist-to-hip ratio	0.62	−0.46	−0.63
Age	0.31	0.63	−0.53

Values represent component loadings. Loadings with an absolute value ≥0.40 are printed in boldface. The direction of the PCA loadings may be reversed without changing their mathematical meaning. PC, principal component; PCA, principal component analysis; TLQP-21, VGF-derived 21-amino-acid peptide; MDA, malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase; CAT, catalase; BMI, body mass index.

The first three components met the eigenvalue> 1 criterion and together explained 82.9% of the variance in the data. The first component explained 48.2% of the variance and loaded positively with TLQP-21, MDA, BMI, waist, hip and waist-to-hip ratio measurements. In contrast, it loaded negatively with the GSH, SOD and CAT antioxidant measurements. Thus, PC1 represents a combined adiposity-oxidative-stress dimension in which higher adiposity measurements are associated with higher TLQP-21 and MDA, while antioxidant measurements (GSH, SOD, and CAT) decrease with higher values of the first component. PC2 explained an additional 21.4% of variance and loaded

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positively with age and TLQP-21, while loading negatively with SOD, BMI, hip and waist-to-hip ratio measurements. Finally, PC3 explained 13.3% of variance and loaded negatively with age, waist-to-hip ratio, and CAT measurements. These component labels describe the PC loading structure only and should not be misconstrued as representing any causal biological pathways.

Machine learning analysis

For exploratory purposes, we trained random forest, support vector machine, and logistic regression classifiers to classify obesity status. We considered the following prespecified candidate features: serum concentrations of TLQP-21, MDA, GSH, SOD, and CAT. The dataset was split using a stratified 70%/30% split into training data for model development and held-out internal testing data (fixed random seed 42), comprising 105/45 cases in the training/test sets, respectively, with the same class distribution as the full dataset.

For the models mentioned above, all data processing steps were performed on the training set only to avoid information leakage. For support vector machine and logistic regression models, the continuous features were scaled to have zero mean and unit variance. Random forest models do not require scaling. No prespecification of features was based on knowledge of the true classes; hence, all 5 specified features were included in all models. Hyperparameters for all models were selected using a stratified 5-fold cross-validation on the training set to maximise the mean ROC AUC on that data.

For random forest, we used a grid of 100, 300, and 500 trees; max depth of 3, 5, 10, or unlimited; minimum instances per split of 2 or 5; and square-root or log feature sampling. For support vector machines, we used linear and radial basis function kernels, with a grid of C values (0.1, 1, 10, and 100) and gamma values (0.01, 0.1, 1, and "scale"). For logistic regression, we used a grid of C values 0.01, 0.1, 1, 10 and 100) and L1 and L2 regularisation. All models had class weights set to "balanced" to address the 2:1 obese-to-control participant ratio in the data.

After model hyperparameter selection was completed, all selected models were retrained on their complete training data and tested on their previously held-out testing data. For each model, classes were assigned as follows: Obesity = positive class. Model performance was measured using standard measures for imbalanced datasets: Accuracy, Precision, Sensitivity, Specificity, F1-score, and ROC AUC. For Accuracy, exact binomial 95% confidence intervals were generated. AUC 95% confidence intervals were estimated using 2,000 stratified bootstrap resamples of the test set. The random forest method performed best on the held-out testing set, correctly classifying 42 of 45 participants (93.3% accuracy; 95% CI: 81.7–98.6%) and achieving an AUC of 0.97 (95% CI: 0.91–0.99) support vector machine and logistic regression models correctly classified 41 and 40 participants, respectively. However, the wide confidence intervals in the testing set (45 participants) mean differences between the algorithms are not conclusively proven and must be validated on a completely independent, larger external testing set before clinical use. These values are for exploratory purposes only to obtain an initial internal validation.

.Table 11. Exploratory machine-learning performance in the held-out testing set

Algorithm	Accuracy, % (95% CI)	Precision (%)	Sensitivity (%)	Specificity (%)	F1-score (%)	AUC (95% CI)	Confusion matrix[1]
Random forest	93.3 (81.7–98.6)	96.6	93.3	93.3	94.9	0.97 (0.91–0.99)	TN=14, FP=1, FN=2, TP=28
Support vector machine	91.1 (78.8–97.5)	96.4	90.0	93.3	93.1	0.95 (0.87–0.98)	TN=14, FP=1, FN=3, TP=27
Logistic regression	88.9 (75.9–96.3)	96.3	86.7	93.3	91.2	0.93 (0.84–0.97)	TN=14, FP=1, FN=4, TP=26

[1]Obesity was treated as the positive class. TN, true negative; FP, false positive; FN, false negative; TP, true positive; CI, confidence interval; AUC, area under the receiver operating characteristic curve.

Discussion

In this study, 100 obese adults were compared with 50 non-obese adults. As shown in Table 1, both groups were similar in age and had similar numbers of males and females. However, the obese individuals studied here had greater body mass, BMI, waist and hip circumferences, waist-to-hip ratio, and systolic and diastolic blood pressure values than their non-obese counterparts [12,13]. Serum TLQP-21 concentration was 62.4% higher in obese individuals than in non-obese controls, with a large effect size (Cohen's d = 2.70). These findings describe an association within a single set of experiments but, as with all our data to date, do not provide information about the possible causal relationship between the peptide and obesity, nor do they indicate whether TLQP-21 could be of use as a diagnostic marker for obesity.

TLQP-21 levels are elevated in obese subjects, potentially to compensate for adiposity, as TLQP-21 enhances adrenergically stimulated lipolysis through C3aR1 [4,14]. These increased peptide levels in obesity may represent a futile attempt to counteract impaired lipid mobilisation; however, no data currently support resistance to TLQP-21's action, as has been observed for leptin in obesity. The peptide levels are increased, but biological activity may not be increased in obesity. An additional explanation could be reduced receptor sensitivity or altered signalling downstream of C3aR1. Li et al. [15] reported that

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human TLQP-21 is a low-potency, partial agonist for C3aR in primary human macrophages [15], but these data do not translate to obesity-related receptor resistance in human adipose tissue. Increased immunoreactivity in serum could also result from altered processing of the VGF precursor or from increased secretion and/or reduced clearance of the peptide, and these remain untested explanations for the current observations [4,14,15].

The current study was not designed to test between these alternatives, since receptor abundance, downstream C3aR1 signalling, peptide half-life and VGF processing to tissue-specific forms were not investigated.

Patients with obesity showed elevated MDA levels and decreased GSH concentrations and SOD and CAT activities compared to control subjects, in line with reports describing an oxidative imbalance in obesity [16–19]. Notably, while MDA levels correlated positively with TLQP-21, and GSH concentrations and SOD and CAT activities correlated inversely with the peptide, these covariations do not imply a causal redox effect of the peptide. Rather, a link to C3aR1 and obesity-related adipose tissue metabolism via these correlative findings and experiments with TLQP-21 is provided as a working hypothesis that remains to be tested in future studies. This cross-sectional study does not provide evidence for the mentioned mechanism [4,20–22].

Future studies should determine whether the association of TLQP-21 with oxidative stress markers is independent of adiposity. Obesity is a significant source of oxidative stress due to altered adipokine secretion and mitochondrial dysfunction. Therefore, the association of TLQP-21 with increased BMI may reflect the general effects of increased body mass, and a mediation analysis may be needed to evaluate the relative contribution of direct and indirect effects.

We found associations of TLQP-21 with BMI and body-circumference measures in this study. Importantly, the intercorrelations between TLQP-21, measures of adiposity, and measures of oxidative stress mean that the regression coefficients reported in the tables should be viewed as statistical associations adjusted for other variables, not as indicators of independent biological effects. Although multicollinearity assessments and residual diagnostics did not reveal serious problems, validation in independent samples is required.

Although the R^2 value is high, we suggest the relationship between the derived adiposity indices and oxidative stress markers may be particularly strong in this cohort, and additional studies are needed to validate the model in an independent dataset.

Serum TLQP-21 concentrations differed between some age categories within the obesity group, whereas the within-group sex comparisons were not statistically significant. However, neither the obesity-status × sex interaction nor the obesity-status × age interaction was statistically significant. Thus, the observed age differences within the obesity group do not establish that the association between obesity status and TLQP-21 varies by age. The internally assessed ROC curve distinguished the obesity and control groups with an AUC of 0.94. It yielded 89% sensitivity and 92% specificity at the internally selected TLQP-21 cutoff of 365.2 pg/mL. However, the selected cutoff should be considered exploratory and requires validation in an independent, external cohort.

The machine learning analysis provided an exploratory assessment of the combined discriminatory potential of TLQP-21 and oxidative stress markers. Random forest demonstrated the highest observed performance, with an accuracy of 93.3% and an AUC of 0.97. However, these results should be interpreted cautiously because the study included only 150 participants and the data were evaluated using a single 70%/30% training-testing split, with 5-fold cross-validation performed within the training subset. Thus, the reported performance may reflect sampling variability and overfitting and should not be interpreted as evidence of established clinical diagnostic performance. Larger datasets, repeated or nested cross-validation across the complete dataset, and independent external validation are required to determine whether the observed performance can be reproduced in other populations.

Correlations and ROC area in a single sample provide evidence only for internal discrimination in that sample, not for diagnostic accuracy in clinical practice. Correlation coefficients do not measure classifier performance, and the 365.2 pg/mL cutoff was selected and evaluated in the same dataset. Therefore, this threshold must be validated in a prospective study using an independent, unforeseen sample of patients, with a fixed threshold and a standardised assay.

A valid direct numerical comparison with previous human studies was not possible because no eligible study using a comparable population, biological matrix, assay, and reporting unit was identified. Differences across studies could reflect population characteristics or analytical variation and should not be attributed to genetic, dietary, or environmental factors without measured evidence.

Our findings provide a basis for further investigation of TLQP-21 as a research biomarker. However, there is currently no evidence that measuring TLQP-21 will provide diagnostic, prognostic, or therapeutic benefit in clinical practice. Further studies should be longitudinal, multicentre, and use standardised assays with prespecified outcomes that are independently validated, with optimal cut points determined after adjustment for diet, physical activity, visceral adiposity, blood pressure, medication use, and other relevant confounders.

Limitations

Because all measurements were acquired on the same day, no temporal relationships or causality can be inferred from this study (i.e., cross-sectional study design). Because this study was conducted at only one centre, additional, independent validation studies will be necessary to assess generalizability. Other important confounders, including

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diet, physical activity, visceral adiposity, blood-pressure status, and medications, were not fully modelled. The interval and temperature between blood collection and centrifugation, the centrifugation temperature, and the duration and temperature of serum storage were not documented in the available laboratory records and could not be reconstructed. These gaps prevent assessment of their potential effects on peptide stability and measured TLQP-21 immunoreactivity. Incomplete documentation of assay reagents and quality-control procedures further limits assessment of analytical variability.

Possible inclusion of participants with undiagnosed metabolic syndrome may have contributed to the observed associations between TLQP-21, obesity, and oxidative-stress markers.

The cross-reactivity information from the available panel does not allow us to distinguish intact human TLQP-21 from other TLQP-21-related immunoreactivities as defined by the assays used in this study. Thus, all associations found in this study refer to assay-defined TLQP-21 immunoreactivity. For additional reasons, optimism regarding ROC curve cutoffs and machine-learning performance measures is warranted, as these measures were derived from a single, relatively small cohort. Although formal interaction tests were performed, the resulting subgroup estimates are largely exploratory because of limited power. A family-wise multiplicity strategy was employed to correct for multiple testing throughout this manuscript, but this does not constitute a single manuscript-wide correction. Importantly, this study did not address several untested hypotheses regarding compensatory signalling and peptide resistance, including measurement of C3aR1 signalling, receptor sensitivity, VGF processing, and peptide clearance, as well as tissue-specific TLQP-21 activity.

Conclusion

The results from this cross-sectional study of a cohort of Mosul residents revealed an association between obesity and increased levels of TLQP-21 and MDA, whereas GSH levels, along with SOD and CAT activities, were decreased. Moreover, TLQP-21 showed positive correlations with markers of adiposity and measures of oxidative stress. Notably, these findings are associative in nature and can serve only as a starting point for hypothesis generation and subsequent testing. It is essential to verify whether TLQP-21 can cause oxidative stress and whether it can be used as a clinical diagnostic or predictive biomarker in other studies conducted on larger, longitudinal cohorts as well as in multicenter studies, with reported assay specificity, due account taken of potential confounders and multiplicity, and independent validation of any chosen cutoff values.

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