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PEROXIREDOXIN AND ARACHIDONATE 15-LIPOXYGENASE AS DETERMINANTS OF LIPID PEROXIDATION IN OBESE YOUNG MEN

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ABSTRACT

Obesity is characterized by chronic inflammation and oxidative stress that is associated with lipid peroxidation. We investigated the relationships among peroxiredoxin (an antioxidant enzyme), arachidonate 15-lipoxygenase (15-LOX; a pro-oxidant enzyme), and F2-isoprostanes (a marker of lipid peroxidation) in young obese males. This case-control study compared 135 obese males (body mass index [BMI]≥30 kg/m2) with 135 age-matched lean controls (BMI 18.5-24.9 kg/m^2). Peroxiredoxin activity was measured fluorometrically; 15-LOX and F2-isoprostane concentrations were measured using the Enzyme-Linked Immunosorbent Assay (ELISA). Anthropometric and clinical parameters (glucose, hemoglobin A1c [HbA1c], and high-sensitivity C-reactive protein [hs-CRP]) were assessed. Receiver operating characteristic (ROC) analysis determined optimal diagnostic cut-offs. Obese participants showed significantly reduced peroxiredoxin activity (31±3.7 *vs.* 55±7.2 U/L), elevated 15-LOX (96.95±11.5 *vs.* 55.22±6.7 pg/mL), and increased F2-isoprostanes (53.7±5.7 *vs.* 17.35±2.2 pg/mL; all $p<0.001$). ROC analysis demonstrated excellent diagnostic performance: F2-isoprostane (area under the curve [AUC]=0.988; sensitivity=94.8%; specificity=91.1%), 15-LOX (AUC=0.986, sensitivity=97.0%, specificity=87.4%), and peroxiredoxin (AUC=0.958, sensitivity=100%, specificity=71.1%). Obesity induces a redox imbalance characterized by impaired antioxidant defense, enhanced enzymatic lipid oxidation, and pronounced lipid peroxidation. The high discriminative capacity of these biomarkers (AUC>0.95) reflects their sensitivity to the profound oxidative metabolic differences that distinguish obese from lean individuals.

Introduction

Obesity (body mass index [BMI]≥30 kg/m^2) has reached epidemic proportions globally and is a major public health burden.[1] Beyond its established associations with metabolic syndrome, type 2 diabetes, and cardiovascular disease, obesity is fundamentally characterized by chronic low-grade inflammation and sustained oxidative stress.[2] Visceral adipose tissue acts as an active endocrine organ, secreting pro-inflammatory cytokines, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1, that, together with adipocyte hypertrophy, tissue hypoxia, and infiltrating M1 macrophages, create a permissive environment for excessive reactive oxygen species (ROS) generation.[3] The oxidative burden in obesity arises from enhanced mitochondrial electron-transport chain activity, increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, uncoupled nitric oxide synthase, and diminished antioxidant defenses.[4,5] This redox imbalance damages lipid-rich structures, including cellular membranes and lipoproteins.[5] Lipid peroxidation, the oxidative degradation of polyunsaturated fatty acids (PUFAs), proceeds through initiation, propagation, and termination phases, generating reactive aldehydes, lipid hydroperoxides, and isoprostanes.[6,7] F2-isoprostanes, formed by non-enzymatic free-radical peroxidation of arachidonic acid esterified in membrane phospholipids, are chemically stable, formed *in vivo*, and regarded as the gold standard for assessing oxidative lipid damage.[8,9]

Peroxiredoxins (Prxs) are cysteine-dependent peroxidases that scavenge

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hydrogen peroxide and organic hydroperoxides. Six isoforms (Prx1-6) are categorized by subcellular localization; mitochondrial Prx3 and Prx5 are particularly relevant to obesity, as Prx5-deficient mice show heightened susceptibility to high-fat diet-induced obesity, and peroxiredoxin regulates adipogenesis.[10-12]

Arachidonate 15-lipoxygenase (15-LOX) represents a distinct enzymatic route of lipid oxidation. It catalyzes oxygenation of arachidonic acid to 15-hydroperoxyeicosatetraenoic acid (15-HpETE), which can yield pro-inflammatory or pro-resolving lipid mediators.[13,14] Excessive 15-LOX activity can oxidize membrane phospholipids and low-density lipoprotein (LDL), contributing to atherogenesis, and has recently been identified as a critical regulator of ferroptosis, iron-mediated cell death driven by lipid peroxidation.[15,16] Its dual role makes 15-LOX a compelling target in obesity research.

The primary goal of this study is to thoroughly investigate the interrelationships among antioxidant enzyme activity (specifically peroxiredoxin), pro-oxidant enzymatic pathway activity (notably arachidonate 15-LOX), and the burden of lipid peroxidation, as measured by isoprostane levels, in young obese males. To achieve this, the research will quantify peroxiredoxin activity in serum from young obese males compared to age-matched lean controls. It will also measure arachidonate 15-LOX activity in the same biological samples and determine plasma F2-isoprostane concentrations, which serve as the gold standard biomarker for lipid peroxidation. Additionally, correlation analyses will clarify the relationships among these three parameters. The study will assess whether peroxiredoxin activity inversely correlates with isoprostane levels, indicating a protective antioxidant role, and whether 15-LOX activity positively correlates with isoprostane levels, suggesting its contribution to oxidative lipid damage. Finally, the research aims to explore potential interactions between the activities of these antioxidant and pro-oxidant biomarkers.

Materials and Methods

Study design and population

This case-control study was conducted between September 2024 and March 2025 at the Biochemistry Laboratory, College of Science, University of Babylon, Iraq. Two groups of 135 participants each were enrolled: obese males (cases) and normal-weight males (controls).

Inclusion and exclusion criteria

Cases: males aged 18-35 years, BMI≥30 kg/m^2, weight-stable (±2 kg) for ≥3 months. Controls: age-matched males (±2 years), BMI 18.5-24.9 kg/m^2, no first-degree relatives with obesity. Both groups excluded: type 2 diabetes (fasting glucose ≥126 mg/dL or hemoglobin A1c [HbA1c]≥6.5%), cardiovascular or chronic kidney disease, active inflammatory conditions, malignancy within 5 years, current smoking or cessation within 6 months, alcohol >2 units/day, and use of antioxidant supplements, anti-inflammatory, or lipid-lowering medications within 3 months.

Anthropometric and clinical measurements

Height (stadiometer, ±0.1 cm), weight (calibrated digital scale, ±0.1 kg), BMI, waist circumference (narrowest point between ribs and iliac crest), and waist-to-hip ratio were recorded. Fasting blood glucose, HbA1c, and high-sensitivity C-reactive protein (hs-CRP) were measured by standard clinical laboratory methods.

Biochemical assays

Blood was collected after an overnight fast (10-12 h). For isoprostane measurement, ethylenediaminetetraacetic acid tubes were supplemented immediately with butylated hydroxytoluene (50 µM; Sigma-Aldrich, St. Louis, MO, USA) to prevent *ex vivo* peroxidation; plasma was isolated by centrifugation (2000×g, 15 min, 4°C) and stored at −80°C. Peroxiredoxin activity was quantified fluorometrically using monobromobimane as a fluorophore and tert-butyl hydroperoxide as the substrate, thereby avoiding catalase interference.[17] F2-isoprostane and 15-LOX concentrations were measured with commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits (Elabscience, Wuhan, China).

Statistical analysis

Data are expressed as mean ± standard deviation. Between-group differences were assessed using an unpaired Student's *t*-test after Shapiro-Wilk normality testing (GraphPad Prism v8; GraphPad Software, San Diego, CA, USA). Receiver operating characteristic (ROC) curves were constructed to derive the area under the curve (AUC) with 95% confidence intervals (CIs) and optimal sensitivity/specificity thresholds, and $p<0.05$ was considered significant.

Results

Anthropometric, metabolic, inflammatory, and oxidative stress parameters are compared in Table 1 (all between-group differences $p<0.001$).

Obese participants had markedly higher BMI (33.5±2.8 *vs.* 21.7±1.7 kg/m^2) and waist circumference (103±8 *vs.* 75±4 cm), confirming central adiposity. Fasting glucose was elevated in the obese group (106±12 *vs.* 88±6 mg/dL), and HbA1c approached the pre-diabetic range (6.1±0.7 *vs.* 5.2±0.4%), suggesting chronic hyperglycemia. The fivefold elevation in hs-CRP (5.8±1.8

Table 1. Comparison of anthropometric and biochemical parameters between obese and normal-weight participants.

Parameter	Normal weight (n=135)	Obese (n=135)	Trend	Physiological implication
BMI (kg/m^2)	21.7±1.7	33.5±2.8*	↑	Confirms obesity classification
Waist circumference (cm)	75±4	103±8*	↑	Indicator of central adiposity and metabolic risk
Glucose (mg/dL)	88±6	106±12	↑	Impaired glucose metabolism; insulin resistance
HbA1c (%)	5.2±0.4	6.1±0.7	↑	Chronic hyperglycemia; elevated diabetes risk
hs-CRP (mg/L)	1.2±0.5	5.8±1.8*	↑	Systemic low-grade inflammation
Peroxiredoxin activity (U/L)	55±7.2	31±3.7*	↓	Impaired H_2O_2 detoxification; weakened antioxidant defense
Arachidonate 15-LOX (pg/mL)	55.22±6.7	96.95±11.5*	↑	Promotes lipid peroxidation and pro-inflammatory mediator synthesis
F2-isoprostane (pg/mL)	17.35±2.2	53.7±5.7*	↑	Gold-standard marker of *in vivo* lipid peroxidation

*$p<0.001$ *vs.* normal-weight group. BMI, body mass index; HbA1c, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; LOX, lipoxygenase.

Table 2. ROC-derived diagnostic parameters for the three biomarkers.

Biomarker	Cut-off	Sn (%)	Sp (%)	AUC	95% CI	p-value
Arachidonate 15-LOX	>66.50 pg/mL	97.04	87.41	0.9858	0.9766-0.9949	<0.001
F2-isoprostane	>32.01 pg/mL	94.81	91.11	0.9883	0.9788-0.9978	<0.001
Peroxiredoxin	<49.50 U/L	100.0	71.11	0.9577	0.9337-0.9816	<0.001

Sn, sensitivity; Sp, specificity; AUC, area under the ROC curve; CI, confidence interval; LOX, lipoxygenase.

vs. 1.2±0.5 mg/L) confirmed systemic low-grade inflammation. Peroxiredoxin activity was approximately 44% lower in obese participants (31±3.7 *vs.* 55±7.2 U/L), reflecting substantially impaired antioxidant defense. Conversely, 15-LOX was 76% higher (96.95±11.5 *vs.* 55.22±6.7 pg/mL), and F2-isoprostane levels were more than threefold elevated (53.7±5.7 *vs.* 17.35±2.2 pg/mL), indicating pronounced *in vivo* lipid peroxidation. ROC analysis (Table 2, Figure 1) showed that all three biomarkers achieved AUC>0.95. F2-isoprostane exhibited the highest overall accuracy (AUC=0.9883; 95% CI: 0.9788-0.9978; cut-off >32.01 pg/mL), with sensitivity 94.8% and specificity 91.1%. Arachidonate 15-LOX demonstrated near-equivalent performance (AUC=0.9858; 95% CI:

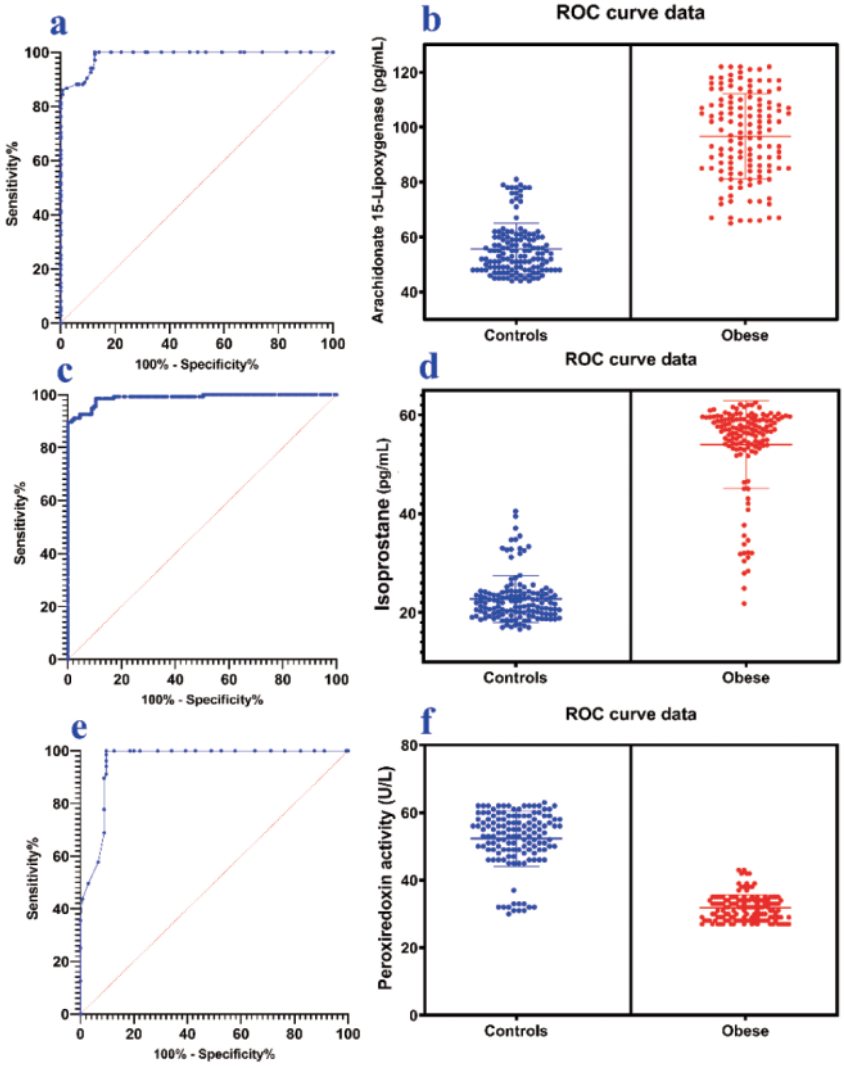

Figure 1. ROC analysis and biomarker distributions. ROC curves for (**a**) arachidonate 15-LOX, (**c**) F2-isoprostane, and (**e**) peroxiredoxin distinguishing obese from healthy control participants. Corresponding biomarker distributions at ROC-optimized thresholds for (**b**) arachidonate 15-LOX, (**d**) F2-isoprostane, and (**f**) peroxiredoxin.

Table 3. Multivariate linear regression, effect of obesity status on each biomarker and metabolic parameter. Each model tests whether obesity status (group: 0 = healthy control; 1 = obese) remains independently associated with the outcome after adjusting for all other measured variables as covariates.

Outcome variable	Univariate β	Univariate p	Univariate R^2	Adjusted β	95% CI	Adjusted p	Adj. R^2
hs-CRP (mg/L)	4.413	<0.001	0.900	3.686	2.922-4.450	<0.001	0.903
Peroxiredoxin activity (U/L)	−20.496	<0.001	0.722	−21.224	−28.595-−13.853	<0.001	0.718
Arachidonate 15-LOX (pg/mL)	41.030	<0.001	0.720	54.045	39.870-68.221	<0.001	0.719
F2-Isoprostane (pg/mL)	31.271	<0.001	0.831	26.525	18.525-34.525	<0.001	0.830
BMI (kg/m²)	11.983	<0.001	0.876	9.908	7.482-12.334	<0.001	0.880
Fasting glucose (mg/dL)	18.030	<0.001	0.475	6.559	−4.943-18.061	0.263 (ns)	0.478

β, unstandardized regression coefficient; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; LOX, lipoxygenase; BMI, body mass index.

0.9766-0.9949; cut-off >66.50 ng/mL), with sensitivity 97.0% and specificity 87.4%. Peroxiredoxin achieved perfect sensitivity (100%) at a cut-off <49.50 ng/mL (AUC=0.9577; 95% CI: 0.9337-0.9816), though with lower specificity (71.1%), positioning it as an optimal screening marker. All p<0.001.

To assess the independence of the observed between-group differences, multivariate linear regression was performed for each outcome variable, with obesity status as the primary predictor and all other measured variables as covariates. In five of the six models, the association between group status and the outcome variable remained highly significant after full adjustment (all p<0.001), as shown in Table 3. Specifically, obesity was independently associated with elevated hs-CRP (adjusted β=3.686; 95% CI: 2.922-4.450), reduced peroxiredoxin activity (β=−21.224; 95% CI: −28.595 to −13.853), elevated arachidonate 15-LOX (β=54.045; 95% CI: 39.870-68.221), elevated F2-Isoprostane (β=26.525; 95% CI: 18.525-34.525), and elevated BMI (β=9.908; 95% CI: 7.482-12.334). Fasting glucose, however, did not reach statistical significance in the fully adjusted model (β=6.559, 95% CI: −4.943 to 18.061; p=0.263), suggesting that its between-group difference is substantially mediated through shared variance with BMI and hs-CRP rather than representing an independent group effect. The minimal attenuation of the group effect for the other five outcomes, combined with high adjusted R^2 values (0.718-0.903), confirms that these associations are not confounded by inter-variable relationships and reflect the independent contribution of obesity to the observed inflammatory and oxidative stress profile.

Spearman rank correlation analysis of the combined cohort (n=270) revealed strong and statistically significant associations among all variables (Table 4; all p<0.001). Peroxiredoxin activity was inversely correlated with F2-isoprostane concentration (r=−0.696), consistent with its antioxidant role, whereby reduced peroxiredoxin activity permits greater accumulation of lipid peroxidation products. 15-LOX concentration was positively correlated with F2-isoprostane levels (r=0.704), supporting the contribution of enzymatic lipid oxidation *via* the LOX pathway to the overall burden of *in vivo* lipid peroxidation. Peroxiredoxin and 15-LOX were inversely correlated with each other (r=−0.658), reflecting their opposing roles in oxidative lipid metabolism. With respect to metabolic parameters, peroxiredoxin activity showed significant inverse correlations with BMI (r=−0.671), fasting glucose (r=−0.564), and hs-CRP (r=−0.679), while 15-LOX showed significant positive correlations with the same parameters (r=0.705, 0.615, and 0.703, respectively). F2-isoprostane was similarly positively correlated with BMI (r=0.742), hs-CRP (r=0.734), and fasting glucose (r=0.590). Importantly, within-group analyses demonstrated that the majority of these correlations were absent or weak in each subgroup (healthy control: all key pairs non-significant; obese: all key pairs non-significant), indicating that the observed associations in the combined cohort are driven by systematic between-group differences rather than continuous, linear within-group relationships.

Discussion

The present study contributes significantly to the extant body of research in multiple essential respects. Although the association between obesity and oxidative stress is well recognized, this investigation is the first to quantify a cytosolic antioxidant enzyme (peroxiredoxin), a pro-oxidant LOX (15-LOX), and a benchmark marker of lipid peroxidation (isoprostane) concurrently in the same well-characterized cohort of young obese males. This approach extends beyond merely observing increases in individual markers. It elucidates how a diminished antioxidant defense mechanism, in conjunction with heightened lipid oxidation, contributes to oxidative damage of lipids. Furthermore, investigating young males aged 18 to 35 enhances our understanding of the underlying mechanisms by detecting early indicators of redox imbalance before the emergence of age-related health concerns. Collectively, these considerations offer a more precise mechanical and chronological perspective, distinguishing this study from previous research that concentrated solely on individual markers or older, more complex populations.

The ROC analysis herein does not diagnose obesity, which is defined by a BMI≥30 kg/m^2. Instead, the high discriminative capacity of its biomarkers (AUC>0.95) underscores their sensitivity to metabolic differences between obese and lean individuals. The ROC thresholds signify increased oxidative stress rather than an obesity diagnosis. Clinically, these cut-offs can help stratify metabolic risk by identifying obese individuals with a high oxidative load, who are at an increased risk of cardiovascular, metabolic, or inflammatory issues. However, external validation is still needed before they can be adopted in clinical practice.

The fivefold difference in hs-CRP levels underscores that obesity is linked to chronic low-grade inflammation, which has come to be characterized as meta-inflammation. Adipose tissue, especially visceral fat, acts as an active endocrine organ, producing pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1. These cytokines induce the liver to synthesize acute-phase proteins, such as CRP, thereby increasing blood hs-CRP levels. The chronic increase in hs-CRP observed in the case of obese subjects has proven to be significant because, on its own, it predicts an increased risk of cardiovascular disease and has been associated with the development of atherosclerosis, insulin resistance, and endothelial dysfunction.[18]

Peroxiredoxins are a group of thiol-dependent peroxidases that play a vital role in protecting cells against oxidative stress by catalyzing the reduction of hydrogen peroxide and organic hydroperoxides. The significant impairment of peroxiredoxin activity in obesity indicates a weakened antioxidant defense system and increased cell susceptibility to oxidative stress. The impairment may occur through several mechanisms, including inactivation of the enzyme *via* hyperoxidation of catalytic cysteine residues in response to chronic excessive oxidative stress, reduced enzyme expression, or reduced substrate availability.[19] The reduced activity of peroxiredoxin enzymes in obese patients likely explains the increased accumulation of reactive oxygen species and consequent oxidative damage to cellular macromolecules.

The elevated 15-LOX concentrations observed in the obese group suggest several potential biochemical implications warranting further investigation. First, increased 15-LOX expression is associated with an accumulation of oxidized lipid products, which may facilitate oxidative chain reactions and subsequent cellular membrane damage.[20] Furthermore, 15-LOX-derived metabolites have been implicated in activating inflammatory signaling, potentially establishing a deleterious oxidative-inflammatory cycle.[21] Recent studies also identify 15-LOX as a key regulator of ferroptosis, an iron-dependent form of programmed cell death characterized by lipid peroxidation.[22-24] In this context, the higher levels of 15-LOX observed here may contribute to chronic inflammation and ferroptotic tissue injury; however, longitudinal data are required to confirm whether these markers directly predict clinical outcomes. However, it is important to note that the biological role of 15-LOX is inherently complex and not exclusively pro-oxidant.[25] Under physiological conditions and during the active resolution of inflammation, 15-LOX products, such as lipoxin A4 and 15-oxo-ETE, exert anti-inflammatory and pro-resolving effects.[26] These mediators function by limiting neutrophil recruitment, promoting macrophage efferocytosis of apoptotic cells, and modulating mast cell degranulation.[27,28]

Table 4. Spearman rank correlation matrix between oxidative stress biomarkers and metabolic parameters in the combined study cohort (n=270).

Variable	PRX (U/L)	15-LOX (pg/mL)	F2-IsoP (ng/L)	hs-CRP (mg/L)	BMI (kg/m^2)	Glucose (mg/dL)
PRX (U/L)	1.000	−0.658*	−0.696*	−0.679*	−0.671*	−0.564*
15-LOX (pg/mL)	−0.658*	1.000	0.704†	0.703†	0.705†	0.615*
F2-IsoP (ng/L)	−0.696*	0.704†	1.000	0.734†	0.742†	0.590*
hs-CRP (mg/L)	−0.679*	0.703†	0.734†	1.000	0.780†	0.633*
BMI (kg/m^2)	−0.671*	0.705†	0.742†	0.780†	1.000	0.624*
Glucose (mg/dL)	−0.564*	0.615*	0.590*	0.633*	0.624*	1.000

Values are Spearman's r. All off-diagonal correlations p<0.001. r≥0.70 (strong); 0.60≤r< 0.70 (moderate-strong); r<0.60 (moderate); †r≥ 0.70; *p<0.001; PRX, peroxiredoxin; LOX, lipoxygenase; IsoP, isoprostanes; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index.

Consequently, 15-LOX is best described as a context-dependent modulator of inflammation resolution.[29,30] In the chronic low-grade inflammation associated with obesity, characterized by M1 macrophage polarization and sustained pro-inflammatory signaling (*e.g.*, TNF-α, IL-6), the enzymatic balance may shift toward pro-oxidant outputs such as 15-HpETE.[31,32] Thus, the elevated 15-LOX concentrations found in this study likely reflect a dysregulated or "frustrated" resolution response in the obese state rather than the simple upregulation of a uniformly harmful enzyme.[32] These exploratory findings suggest a potential metabolic pathway for future therapeutic targeting, though they do not yet establish actionable diagnostic thresholds.

Isoprostanes are prostaglandin-like molecules produced by non-enzymatic, free radical-mediated peroxidation of arachidonic acid in cellular membranes.[33] Isoprostanes are regarded as "gold-standard" indices of oxidative stress and lipid peroxidation *in vivo* owing to their cyclooxygenase-independent synthesis and stable chemical nature.[9] The greater-than-threefold increase in isoprostane levels in obese individuals reflects a pronounced oxidative insult to lipid membranes in this condition. Isoprostanes also exhibit biological activity, including vasoconstriction and platelet aggregation, which may contribute to the cardiovascular manifestations of obesity.[34] In addition, elevated isoprostane levels indicate ongoing ferroptotic events, a key biochemical hallmark of which is lipid peroxidation.[35]

A range of findings presented in Table 1 can be integrated into an overarching pathophysiological mechanism explaining oxidative stress and metabolic dysfunction in the context of obesity. Excess adiposity, particularly visceral adiposity, creates an environment with elevated cytokine and hs-CRP levels due to chronic inflammation.[2] Metabolic impairment due to insulin resistance and hyperglycemia, together with a high cytokine and hs-CRP environment, results in an overproduction of ROS through a range of mechanisms, including mitochondrial dysfunction, activation of NADPH oxidase, and enhanced lipid peroxidation.[36] Overproduction of ROS overwhelms the defense mechanism, leading to ROS accumulation due to low peroxiredoxin activity and oxidative injury. Concurrently, there is increased 15-LOX activity, which promotes enzymatic lipid peroxidation and produces lipid mediators that enhance inflammation and induce ferroptotic cell death.[22-24] Indeed, decreased antioxidant defenses, combined with increased pro-oxidant enzyme activity, pose a significant oxidative insult, as evidenced by very high isoprostane levels. Moreover, lipid peroxidation not only degrades cellular membranes but also generates reactive lipids that can modify proteins and DNA.[37]

Metabolically, this oxidative-inflammative environment is associated with disturbed glucose regulation, a known feature of obesity. Oxidative stress and the inflammatory state are known to directly contribute to the intracellular insulin signaling cascade, contributing to the development of peripheral insulin resistance.[35] Additionally, oxidative injury to β-cells in the pancreas may contribute to inhibition of insulin secretion, thereby accelerating progression to diabetes mellitus in an insulin-resistant state.[36]

While the observed changes in peroxiredoxin activity and oxidative stress markers provide preliminary insights into the metabolic landscape of obesity, these findings remain exploratory. The significant reduction in antioxidant capacity and the concomitant rise in oxidative stress markers suggest potential pathways warranting further investigation as possible therapeutic targets. Specifically, while antioxidants or oxidative stress-reducing interventions have been proposed as supportive measures, their clinical efficacy requires validation through large-scale, longitudinal studies. Furthermore, although lifestyle modifications, such as exercise and dietary changes, have shown promise in modulating these biochemical parameters,[38] translating the pharmacological targets identified here, including 15-LOX or ferroptosis inhibitors, into actionable clinical strategies remains a subject for future investigation.[22] These results serve as a foundational hypothesis for subsequent research into the management of obesity-related comorbidities rather than established clinical guidelines.

From a research perspective, the close relationships among obesity, oxidative stress, and metabolic disturbances provide a compelling case for mechanistic studies to elucidate their interrelationships. Longitudinal analyses of changes in peroxiredoxin activities, 15-LOX levels, and isoprostane concentrations following weight-reducing interventions are highly desirable to clarify the reversibility of oxidative damage induced by obesity. Furthermore, investigation of the pathogenic contribution of ferroptosis in an obese setting is a promising new realm of research with potential for uncovering novel therapeutic options.

Study strengths and limitations

This study uses robust methods, including 270 participants and a comprehensive assessment of oxidative stress biomarkers (antioxidant defense, enzymatic oxidation, lipid peroxidation), with gold-standard F2-isoprostanes. Careful sample collection reduces variability. The high discriminative capacity of these biomarkers (AUC>0.95) reflects their sensitivity to the profound oxidative metabolic differences that distinguish obese from lean individuals.

Studying young obese males captures early disease changes. Combining anthropometric, metabolic, and inflammatory data provides a comprehensive profile. However, the exclusive enrolment of young adult males (18-35 years) from a single center in Babylon, Iraq, constitutes a notable limitation that must be highlighted. Sex-related differences in adipose tissue distribution, hormonal milieu (*e.g.*, estrogen and its antioxidant properties), and LOX expression patterns mean that the observed peroxiredoxin and 15-LOX profiles may not be directly applicable to females, in whom obesity-associated oxidative stress may be differentially regulated. Similarly, age-related changes in antioxidant enzyme capacity and lipid mediator production preclude extrapolation to older or pediatric populations. Geographic and dietary homogeneity within this cohort, for example, adherence to a Middle Eastern dietary pattern rich in omega-6 fatty acids, the primary substrate for 15-LOX, may also influence baseline biomarker concentrations, limiting broader applicability. Future multicenter studies enrolling both sexes, diverse age groups, and ethnically varied populations, with dietary assessment and physical activity monitoring, are essential to determine the generalizability of these findings.

Conclusions

Obesity causes a redox imbalance characterized by low antioxidant levels, high pro-oxidant enzyme activity, and lipid peroxidation. Suppressed peroxiredoxin, increased 15-LOX, and isoprostanes suggest oxidative stress may contribute to metabolic and inflammatory issues. Changes in glucose and inflammation highlight the need to address metabolic, inflammatory, and oxidative interactions holistically in obesity.

Contributions: Mahmoud Hussein Hadwan, Ban Mahmood Shaker Al-Joda, Asad M. Hadwan: conceptualization, validation, methodology, data curation, investigation, writing – original draft, writing – review & editing; Ruaa Altaee, Abdulrazaq S. Alsalman: conceptualization, validation, methodology, writing – review & editing. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors have no conflict of interest to declare.

Ethics approval and consent to participate: the study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the College of Science Ethics Committee, University of Babylon, Iraq (Ref. No. 217A; 15 September 2024). All participants provided written informed consent.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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