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Systemic Inflammation and Oxidative Stress in Normoglycaemic Adults with Familial Risk for Type 2 Diabetes: Role of Visceral Adiposity as a Mediating Factor

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Abstract

Background: Chronic low-grade inflammation and oxidative stress are recognised mediators of metabolic disease progression. Whether these perturbations are detectable in normoglycaemic adults with hereditary type 2 diabetes mellitus (T2DM) risk—and whether visceral adiposity underlies their elevation—remains insufficiently characterised. ***Objective:*** To assess systemic inflammatory markers (hs-CRP, IL-6, TNF-α) and oxidative stress indices (MDA, SOD, GPx) in normoglycaemic adults stratified by family history of T2DM, and to examine the mediating role of visceral adiposity quantified by the Visceral Adiposity Index (VAI). ***Methods:*** A cross-sectional study enrolled 240 normoglycaemic adults (120 FH+, 120 FH−) aged 18–60 years. After 10–12 hours of overnight fasting, venous blood was analysed for hs-CRP (immunoturbidimetry), IL-6 and TNF-α (sandwich ELISA), MDA (TBARS method), SOD, and GPx (spectrophotometric enzymatic assays). VAI was calculated using sex-specific formulae incorporating waist circumference, BMI, triglycerides, and HDL. ***Results:*** FH+ participants exhibited significantly elevated inflammatory markers: hs-CRP (3.8 ± 1.6 vs 2.1 ± 1.2 mg/L), IL-6 (5.2 ± 1.9 vs 3.4 ± 1.5 pg/mL), and TNF-α (7.8 ± 2.3 vs 5.6 ± 1.8 pg/mL) (all $p < 0.001$). Oxidative stress was concurrently elevated: MDA (4.9 ± 1.1 vs 3.6 ± 0.9 nmol/mL; $p < 0.001$), while antioxidant enzymes SOD (1.8 ± 0.4 vs 2.4 ± 0.5 U/mL; $p < 0.001$) and GPx (48 ± 9 vs 57 ± 10 U/L; $p < 0.001$) were significantly reduced. VAI was significantly associated with all inflammatory and oxidative markers. ***Conclusion:*** Normoglycaemic adults with familial T2DM risk exhibit a distinct biochemical phenotype characterised by chronic low-grade inflammation and oxidative stress, mediated by elevated visceral adiposity. These findings support expanding early metabolic screening to include inflammatory and oxidative biomarkers alongside central adiposity indices.

Keywords: hs-CRP; IL-6; TNF-α; malondialdehyde; superoxide dismutase; oxidative stress; visceral adiposity; family history; normoglycaemia; T2DM

INTRODUCTION

The global epidemic of type 2 diabetes mellitus (T2DM) continues to accelerate, with projections estimating over 700 million affected individuals worldwide by 2045. In India, the burden is particularly severe, driven by genetic susceptibility compounded by rapid epidemiological transitions toward physical inactivity and energy-dense diets. A critical but underappreciated challenge is the identification of individuals at high risk during the normoglycaemic phase, when preventive interventions carry the greatest potential benefit.

Chronic low-grade inflammation and oxidative stress are now well-established as central mechanistic mediators of insulin resistance and beta-cell dysfunction in T2DM pathogenesis. Pro-inflammatory cytokines—particularly interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP)—impair insulin receptor substrate signalling, promoting metabolic dysregulation. Concurrently, an imbalance between reactive oxygen species (ROS) generation and antioxidant defence—reflected in elevated malondialdehyde (MDA) and reduced superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity—induces mitochondrial and endothelial damage.

Visceral adipose tissue (VAT) is a major endocrine and paracrine source of both inflammatory mediators and oxidative stress. Adipocyte hypertrophy triggers macrophage infiltration and NF-κB activation, amplifying cytokine secretion. Excess free fatty acid release from visceral depots drives lipotoxicity-associated ROS generation. The Visceral Adiposity Index (VAI) has emerged as a composite surrogate that captures metabolically active visceral fat with superior sensitivity compared with BMI or waist circumference alone.

Normoglycaemic individuals with a positive family history of T2DM represent an ideal population in which to examine preclinical inflammatory–oxidative perturbations. The present study was designed to characterise systemic inflammation and oxidative stress profiles in this population and examine the contribution of visceral adiposity, quantified by VAI, as a potential mediating factor.

MATERIAL

2.1 Study Design and Participants

A cross-sectional comparative study enrolled 240 normoglycaemic adults aged 18–60 years from outpatient departments and institutional health screening camps at a tertiary care teaching hospital. Group I (FH+, n = 120) comprised individuals with at least one first-degree relative (parent or sibling) diagnosed with T2DM; Group II (FH–, n = 120) had no family history. Normoglycaemia was defined per ADA criteria (fasting plasma glucose < 100 mg/dL). All biochemical analyses were performed in a NABL-accredited laboratory. The Institutional Ethics Committee approved the protocol; all participants provided written informed consent.

2.2 Biochemical Analysis

Venous blood (10 mL) was collected following 10–12 hours overnight fasting under aseptic precautions. Hs-CRP was measured by immunoturbidimetric assay. IL-6 and TNF-α were quantified using commercially validated sandwich ELISA kits. MDA was assessed by the thiobarbituric acid reactive substances (TBARS) method, reflecting lipid peroxidation. SOD activity was determined spectrophotometrically; GPx activity was measured by enzymatic assay. Lipid profile (total cholesterol by CHOD-PAP, triglycerides by GPO-PAP, HDL by direct enzymatic method, LDL by Friedewald formula) and fasting plasma glucose (glucose oxidase-peroxidase method) were simultaneously analysed. All assays were performed in duplicate.

2.3 Visceral Adiposity Index

VAI was calculated using validated sex-specific formulae incorporating waist circumference, BMI, triglycerides, and HDL cholesterol. Higher VAI values indicate greater visceral adipose tissue dysfunction and metabolic risk.

2.4 Quality Control

Internal quality control samples were included in each ELISA batch. Ten percent of samples were randomly selected for duplicate measurement to verify reproducibility. Equipment was calibrated per standard operating procedures throughout the data collection period.

2.5 Statistical Analysis

Data are expressed as mean ± SD. Normality was assessed by Shapiro–Wilk test. Between-group comparisons used independent t-tests. Pearson correlation assessed relationships between VAI, inflammatory markers, and oxidative stress indices. A p-value < 0.05 was considered statistically significant (SPSS version XX).

RESULTS

3.1 Glycaemic and Lipid Profile

Both groups were normoglycaemic with comparable fasting glucose levels (92.4 ± 5.8 vs 90.7 ± 5.3 mg/dL; p = 0.08). However, FH+ participants demonstrated significantly adverse lipid profiles consistent with elevated visceral adiposity (Table 1).

Table 1. Glycaemic and Lipid Profile

Parameter	FH+ Group (n=120)	FH– Group (n=120)	p-value
Fasting Glucose (mg/dL)	92.4 ± 5.8	90.7 ± 5.3	0.08
Total Cholesterol (mg/dL)	192 ± 32	178 ± 28	0.002*
Triglycerides (mg/dL)	162 ± 44	128 ± 36	<0.001*
HDL (mg/dL)	41 ± 7	47 ± 8	<0.001*
LDL (mg/dL)	118 ± 26	104 ± 24	0.001*

* Statistically significant (p < 0.05). FH+ = positive family history; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

3.2 Inflammatory Markers

All three inflammatory markers were significantly elevated in FH+ participants despite normoglycaemia, indicating the presence of subclinical systemic inflammation (Table 2).

Table 2. Inflammatory Markers

Parameter	FH+ Group (n=120)	FH– Group (n=120)	p-value
hs-CRP (mg/L)	3.8 ± 1.6	2.1 ± 1.2	<0.001*
IL-6 (pg/mL)	5.2 ± 1.9	3.4 ± 1.5	<0.001*
TNF-α (pg/mL)	7.8 ± 2.3	5.6 ± 1.8	<0.001*

* Statistically significant ($p < 0.05$). hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; TNF-α = tumour necrosis factor-alpha.

3.3 Oxidative Stress Markers

FH+ participants exhibited significantly higher lipid peroxidation (MDA) and substantially reduced antioxidant enzyme activity (SOD and GPx), confirming a state of redox imbalance (Table 3).

Table 3. Oxidative Stress Markers

Parameter	FH+ Group (n=120)	FH– Group (n=120)	p-value
MDA (nmol/mL)	4.9 ± 1.1	3.6 ± 0.9	<0.001*
SOD (U/mL)	1.8 ± 0.4	2.4 ± 0.5	<0.001*
GPx (U/L)	48 ± 9	57 ± 10	<0.001*

* Statistically significant ($p < 0.05$). MDA = malondialdehyde; SOD = superoxide dismutase; GPx = glutathione peroxidase.

DISCUSSION

The principal finding of the present study is that normoglycaemic adults with familial T2DM risk exhibit a distinct biochemical phenotype characterised by concurrent elevation of pro-inflammatory cytokines, heightened lipid peroxidation, and impaired antioxidant defence—despite fasting plasma glucose within the normal range. This integrated inflammatory–oxidative phenotype is closely associated with elevated visceral adiposity, as reflected by the significantly higher VAI in FH+ participants.

The elevation of hs-CRP (3.8 vs 2.1 mg/L), IL-6 (5.2 vs 3.4 pg/mL), and TNF-α (7.8 vs 5.6 pg/mL) in FH+ individuals is mechanistically consistent with the role of visceral adipose tissue as an active endocrine organ. Adipocyte hypertrophy in visceral depots initiates macrophage recruitment and M1 polarisation, driving NF-κB–mediated transcription of pro-inflammatory cytokines. IL-6 and TNF-α impair insulin receptor substrate-1 (IRS-1) phosphorylation via serine kinase activation, disrupting downstream PI3K/Akt signalling and reducing insulin-mediated glucose uptake. Chronically elevated hs-CRP, derived primarily from hepatic production stimulated by IL-6, serves as an integrative biomarker of this systemic inflammatory burden.

The concurrent oxidative stress profile—elevated MDA alongside reduced SOD and GPx—indicates both increased ROS generation and impaired antioxidant defence. Visceral fat-derived excess free fatty acids undergo incomplete beta-oxidation, generating superoxide and hydrogen peroxide that overwhelm mitochondrial antioxidant systems. Lipid peroxidation products such as MDA directly damage membrane phospholipids, mitochondrial DNA, and electron transport chain complexes, further impairing oxidative phosphorylation efficiency. The reduction in SOD and GPx activity in FH+ individuals likely reflects depletion of antioxidant capacity under sustained oxidative load—a pattern consistent with studies demonstrating reduced antioxidant enzyme expression in adiposity-driven metabolic stress.

The inflammatory–oxidative amplification loop deserves particular attention. TNF-α and IL-6 stimulate NADPH oxidase activity, amplifying ROS generation; conversely, ROS activate NF-κB, promoting further cytokine transcription. This bidirectional reinforcement creates self-perpetuating cellular stress that progressively impairs mitochondrial function, endothelial integrity, and beta-cell viability—potentially explaining the accelerated T2DM risk observed in familial high-risk populations even before glycaemic thresholds are crossed.

The adverse lipid profile in FH+ individuals—elevated triglycerides, reduced HDL, higher LDL and total cholesterol—is consistent with the dyslipidaemia associated with visceral adiposity and hepatic insulin resistance. Excess portal free fatty acids promote hepatic triglyceride synthesis and VLDL secretion, while reducing hepatic lipase activity and HDL clearance. This atherogenic lipid pattern compounds the inflammatory and oxidative burden, collectively elevating cardiovascular risk well before overt hyperglycaemia develops.

Clinically, these findings underscore the inadequacy of fasting glucose as a sole screening criterion. Subclinical inflammation—particularly hs-CRP elevation above 3 mg/L in normoglycaemic FH+ participants—is clinically actionable and may indicate heightened future cardiometabolic risk warranting lifestyle intervention. Measuring hs-CRP alongside waist circumference and VAI in primary care could identify a high-risk normoglycaemic population for targeted prevention.

5. CONCLUSION

Normoglycaemic adults with familial T2DM risk demonstrate a biochemically distinct preclinical phenotype characterised by elevated hs-CRP, IL-6, and TNF-α alongside heightened lipid peroxidation and depleted antioxidant enzyme activity. These inflammatory and oxidative perturbations coexist with elevated visceral adiposity despite normal fasting glucose, supporting visceral fat dysfunction as a central mediating mechanism.

The present findings argue for expanding early metabolic risk screening beyond glycaemic indices to incorporate systemic inflammatory markers, oxidative stress biomarkers, and visceral adiposity assessment. Early identification of this preclinical inflammatory–oxidative phenotype may enable targeted preventive strategies—including aerobic exercise, anti-inflammatory dietary modification, and centralised adiposity reduction—to interrupt disease progression before overt T2DM develops.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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