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Oxidative Stress, Systemic Inflammation, and Insulin Resistance Across the Glycaemic Spectrum: A Cross-Sectional Biochemical Association Study

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Abstract

Background: Oxidative stress, systemic inflammation, and insulin resistance are frequently co-reported across the glycaemic spectrum, yet the concurrent inter-relationships among these perturbations remain incompletely characterised in integrated observational analyses. Objectives: This cross-sectional study aimed to characterise concurrent associations among surrogate markers of oxidative stress (malondialdehyde [MDA] and reduced glutathione [GSH]), systemic inflammation (high-sensitivity C-reactive protein [hs-CRP]), glycaemic dysregulation (fasting blood glucose [FBG], HbA1c, HOMA-IR), lipid parameters, and mineral homeostasis in a cohort of 75 adult participants stratified by glycaemic status. Methods: Participants (n = 75; males = 35, females = 40; mean age 48.2 ± 11.1 years) were classified as normoglycaemic (n = 30), prediabetic (n = 19), or diabetic (n = 26) per ADA 2023 criteria. Twenty-one biochemical parameters were measured. Between-group differences were assessed by Kruskal-Wallis and Mann-Whitney U tests with Bonferroni correction. Bivariate associations were examined by Pearson and Spearman correlation analyses; multiple linear regression and principal component analysis (PCA) were applied as exploratory multivariate approaches. Results: Significant progressive differences were observed across glycaemic strata for all key biomarkers (all Bonferroni-corrected $p < 0.001$). FBG demonstrated strong positive associations with HbA1c ($r = 0.974$), HOMA-IR ($r = 0.933$), MDA ($r = 0.927$), and hs-CRP ($r = 0.945$). HOMA-IR was inversely associated with HDL-C ($r = -0.828$) and positively associated with TG ($r = 0.915$), MDA ($r = 0.936$), and hs-CRP ($r = 0.954$). MDA and GSH showed a strong inverse association ($r = -0.951$, $p < 0.001$). Exploratory PCA identified a dominant first component (PC1) explaining 68.9% of total variance, with substantial co-loadings from FBG, HOMA-IR, MDA, and hs-CRP. In regression modelling, FBG, HOMA-IR, and hs-CRP were independently associated with HbA1c (Adj. $R^2 = 0.952$, $p < 0.001$).

Conclusions: The present findings identify concurrent associations among glycaemic, oxidative, and inflammatory biomarkers that are directionally consistent with published cross-sectional literature. These results are exploratory and hypothesis-generating; the cross-sectional design precludes causal inference or mechanistic attribution. The MDA/GSH ratio and hs-CRP represent potentially informative biomarker indices warranting prospective validation before clinical application can be considered.

Keywords: HOMA-IR; Oxidative stress; MDA; Glutathione; hs-CRP; Dyslipidemia; Type 2 diabetes , Cardio metabolic risk; Metabolic syndrome

Introduction

Type 2 diabetes mellitus (T2DM) and its antecedent glycaemic stages represent one of the most pressing public health challenges of the twenty-first century, with global prevalence projected to exceed 780 million adults by 2045 (Nathan et al., 2008). The clinical burden of T2DM extends far beyond the imbalance in the blood sugar level itself. The condition is even embedded in a broader pathophysiological matrix that includes insulin resistance, atherosclerotic dyslipidemia, chronic low-grade inflammation, as well as co-occurring oxidative phenomena that are collectively associated with an increased risk of cardiovascular disease, nephropathy, and premature mortality (Esteghamati et al., 2010). As can be estimated by evaluating the isomorphism model of insulin resistance (infrared Homa), insulin resistance is characteristically associated with a pro-and pro-inflammatory biochemical phenotype. Experimental evidence also suggests that hyperinsulinemia may activate NF-CP signaling, promote hepatic overproduction, and attenuate lipoprotein lipase activity, although the clinical translation of these mechanistic observations requires careful interpretation (Al-Daghri et al., 2013). The Oxidative stress can be defined in practical terms as a persistent imbalance between the generation of reactive oxygen species and the antioxidant defense capacity within the context of chronic hyperglycemia-has been consistently observed. Malondialdehyde (MDA), quantitatively by means of thiobarbituric acid reagents (tpars) assay, which is still among the most widely used alternative indicators of lipid peroxidative activity; however, it is recognized as a nonspecific analytical measure susceptible to contributions from non-fatty aldehyde species and dietary sources (Bonora et al., 2000; DeFronzo & Tripathy, 2009). Reduced glutathione (GSH) represents the principal intracellular thiol-based antioxidant; its serum measurement is subject to pre-analytical instability due to ex vivo oxidation, and values should be interpreted as relative rather than absolute indices of antioxidant capacity. High-sensitivity C-reactive protein (hs-CRP), the principal acute-phase reactant, is associated with insulin resistance and glycaemic deterioration in cross-sectional studies, though it is substantially influenced by adiposity and other confounders (Butler et al., 2003). Serum magnesium, an essential cofactor for insulin receptor tyrosine kinase activity, is frequently reduced in hyperglycaemic states, potentially via osmotic renal wasting (Brown & Goldstein, 2008). Despite an extensive literature examining these individual biomarker domains, integrated cross-sectional analyses simultaneously profiling glycaemic, lipid, oxidative stress, inflammatory, and mineral parameters within a single stratified cohort remain limited. The present study was designed to address this gap by conducting multi-domain biochemical profiling of 75 adult participants and characterising the concurrent associations among these biomarker domains across the glycaemic spectrum, with explicit acknowledgement of the exploratory and hypothesis-generating nature of such analyses.

Research Gap

While individual biomarker-disease associations are well-established, integrated simultaneous characterisation of all five biochemical domains within a single stratified cohort design remains limited. The present study addresses this gap through a cross-sectional multi-biomarker approach incorporating HOMA-IR quartile stratification, principal component analysis, and multi-domain regression modelling. All findings are to be interpreted as observational associations; the cross-sectional design precludes causal or mechanistic inference.

Materials and methods

3.1 Study Design and Setting

This cross-sectional analytical study was conducted in a clinical biochemistry laboratory setting. Ethical approval was obtained from the institutional research ethics committee, and written informed consent was provided by all participants prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki (2013 revision) and reported in accordance with STROBE guidelines for cross-sectional studies.

3.2 Participants and Eligibility Criteria

A total of 75 adult participants (35 males, 40 females; age range 28-72 years; mean age 48.2 +/- 11.1 years) were enrolled. Inclusion criteria required age >= 18 years and provision of written informed consent. Exclusion criteria included acute infection, inflammatory conditions, pregnancy, hepatic or renal failure, thyroid dysfunction, and use of antioxidant supplements or lipid-lowering drugs within the preceding three months. Participants were stratified into three glycemic groups based on American Diabetes Association (ADA) 2023 criteria: normoglycemic (FBG < 100 mg/dL; n = 30), prediabetic (FBG 100-125 mg/dL; n = 19), and diabetic (FBG >= 126 mg/dL; n = 26).

3.3 Laboratory Measurements

All blood samples were collected following an 8–12-hour overnight fast. Samples were processed within 60 minutes of collection by centrifugation at 3,000 × g for 10 minutes at 4°C; serum aliquots were stored at −80°C until batch analysis with a maximum of two freeze-thaw cycles. Visibly haemolysed samples were excluded from MDA and GSH analyses. Fasting blood glucose, HbA1c, lipid profile (total cholesterol, TG, HDL-C, LDL-C, VLDL-C), muscle and hepatic injury markers (total CK, CK-MB, Troponin I, LDH), renal function (creatinine, urea), and electrolytes (magnesium, potassium, total calcium) were measured using automated colorimetric and immunoassay methods on validated platforms. Fasting insulin was measured by chemiluminescent immunoassay (analysts blinded to glycaemic group). HOMA-IR was calculated as: [FBG (mg/dL) × F.Insulin (μIU/mL)] / 405 (Brownlee, 2005). Serum MDA was quantified by the TBARS assay (Ohkawa method); it is acknowledged that the TBARS assay is a non-specific surrogate measure of lipid peroxidative activity, detecting a heterogeneous mixture of aldehyde species beyond MDA, and results should be interpreted accordingly. Serum GSH was measured by the DTNB (Ellman) colorimetric method; serum GSH is subject to rapid ex vivo oxidation upon blood collection, and measured values are interpreted as relative indices of circulating antioxidant status rather than definitive measures of intracellular glutathione. High-sensitivity CRP was measured by latex-enhanced immunoturbidimetry.

3.4 Statistical Analysis

Data analysis was performed using SPSS version 26.0 and GraphPad Prism 9.0. Normality was assessed by Shapiro-Wilk test and confirmed by Q-Q plot inspection. Non-parametric tests were applied a priori for non-normally distributed variables; parametric tests for normally distributed variables. Between-group differences were assessed by Kruskal-Wallis test with post-hoc Mann-Whitney U pairwise comparisons and Bonferroni correction to control family-wise error rate. Bivariate associations were assessed by Pearson and Spearman correlation analyses; given the number of simultaneous pairwise tests, all bivariate correlations are considered exploratory and interpreted conservatively. Multiple linear regression models were constructed with a priori covariate specification; FBG and HOMA-IR were not co-modelled in the same regression equation given their mathematical collinearity (HOMA-IR incorporates FBG in its calculation), and their respective contributions were assessed in separately specified models. Variance Inflation Factor (VIF) was computed to assess residual multicollinearity (all VIF < 5.0). Principal component analysis (PCA) was performed on 12 standardised (z-scored) key biomarkers as an exploratory data-reduction procedure; the Kaiser criterion (eigenvalue > 1.0) was applied for component retention; PCA components are interpreted as statistical variance constructs rather than discrete biological entities. All tests were two-tailed; significance level $\alpha = 0.05$.

Results

4.1 Demographic and Glycemic Characteristics

The final cohort comprised 75 participants (male: n = 35, 46.7%; female: n = 40, 53.3%) with a mean age of 48.2 +/- 11.1 years. Glycemic distribution yielded 30 normoglycemic (40.0%), 19 prediabetic (25.3%), and 26 diabetic (34.7%) individuals. No statistically significant differences in sex distribution or age were observed between groups ($p > 0.05$).

Table 1 showing comprehensive descriptive statistics for all 21 biochemical parameters across the full cohort and stratified by glycemic group.

Table 1. Biochemical parameters across glycemic subgroups (Mean +/- SD; Kruskal-Wallis test).

Parameter	Overall (n=75) Mean +/- SD	Normoglycemic (n=30) Mean +/- SD	Prediabetes (n=19) Mean +/- SD	Diabetic (n=26) Mean +/- SD	p-value
FBG (mg/dL)	123.90 +/- 44.56	86.67 +/- 5.87	113.28 +/- 7.04	174.62 +/- 37.12	**<0.001*** **
HbA1c (%)	5.76 +/- 1.37	4.81 +/- 0.04	5.19 +/- 0.34	7.28 +/- 1.31	**<0.001*** **
F.Insulin (uIU/mL)	9.03 +/- 5.59	5.46 +/- 2.51	7.14 +/- 2.54	14.52 +/- 5.58	**<0.001*** **
HOMA-IR	3.30 +/- 3.45	1.18 +/- 0.58	2.02 +/- 0.78	6.68 +/- 3.98	**<0.001*** **
T-CHO (mg/dL)	183.81 +/- 20.61	177.22 +/- 16.01	177.71 +/- 20.08	195.88 +/- 20.93	**0.002** **
TG (mg/dL)	154.59 +/- 65.07	122.45 +/- 29.60	127.52 +/- 27.00	211.47 +/- 76.35	**<0.001*** **

HDL-C (mg/dL)	51.74 +/- 10.51	57.82 +/- 6.02	55.08 +/- 6.75	42.28 +/- 10.30	**<0.001*** **
LDL-C (mg/dL)	101.35 +/- 19.87	93.91 +/- 18.56	98.36 +/- 19.19	112.12 +/- 17.62	**0.002** **
VLDL-C (mg/dL)	30.92 +/- 13.02	24.49 +/- 5.92	25.51 +/- 5.39	42.31 +/- 15.27	**<0.001*** **
Mg (mg/dL)	2.10 +/- 0.19	2.16 +/- 0.19	2.16 +/- 0.13	1.98 +/- 0.18	**<0.001*** **
K+ (mmol/L)	4.12 +/- 0.34	4.10 +/- 0.38	4.17 +/- 0.32	4.12 +/- 0.30	ns
Total Ca (mg/dL)	9.29 +/- 0.52	9.31 +/- 0.48	9.36 +/- 0.56	9.20 +/- 0.55	ns
Total CK (U/L)	99.46 +/- 25.79	85.66 +/- 18.57	97.17 +/- 19.53	117.06 +/- 27.19	**<0.001*** **
CK-MB (U/L)	6.89 +/- 2.45	6.61 +/- 2.20	6.28 +/- 2.01	7.67 +/- 2.86	ns
Troponin I (ng/mL)	0.02 +/- 0.03	0.02 +/- 0.02	0.02 +/- 0.02	0.03 +/- 0.03	ns
LDH (U/L)	183.12 +/- 30.23	170.76 +/- 21.54	175.41 +/- 26.28	203.01 +/- 32.09	**<0.001*** **
Creatinine (mg/dL)	0.93 +/- 0.16	0.90 +/- 0.16	0.90 +/- 0.13	0.99 +/- 0.18	ns
Urea (mg/dL)	31.22 +/- 4.28	30.98 +/- 4.90	30.44 +/- 3.61	32.07 +/- 3.97	ns
MDA (nmol/mL)	3.26 +/- 1.26	2.43 +/- 0.39	2.85 +/- 0.40	4.53 +/- 1.34	**<0.001*** **
GSH (umol/L)	519.24 +/- 82.46	576.31 +/- 28.45	542.95 +/- 30.72	436.06 +/- 83.51	**<0.001*** **
hs-CRP (mg/L)	2.98 +/- 1.94	1.59 +/- 0.55	2.40 +/- 0.62	4.99 +/- 1.93	**<0.001*** **

Abbreviations: FBG = fasting blood glucose; HbA1c = glycated hemoglobin; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; T-CHO = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very-low-density lipoprotein cholesterol; Mg = serum magnesium; MDA = malondialdehyde; GSH = reduced glutathione; hs-CRP = high-sensitivity C-reactive protein. ** $p < 0.01$; *** $p < 0.001$; ns = not significant.

4.2 Distribution Testing and Test Selection

Shapiro–Wilk normality testing (Table 2) revealed that the majority of clinically relevant variables — among them FBG, HbA1c, HOMA-IR, TG, MDA, GSH, and hs-CRP — deviated significantly from normality ($p < 0.05$), thereby necessitating the application of non-parametric statistical methods.Normally distributed variables (T-CHO, LDL-C, Mg, LDH, Creatinine, Urea) were analyzed using parametric tests where appropriate.

Table 2: Shapiro–Wilk normality analysis and selection of appropriate statistical tests for the evaluated biochemical biomarkers.

Biomarker	SW Statistic (W)	SW p-value	Distribution	Test Applied	Justification
FBG	0.891	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
HbA1c	0.903	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
F. Insulin	0.912	0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
HOMA-IR	0.888	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
TG	0.877	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
HDL-C	0.921	0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
Total CK	0.944	0.005	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
MDA	0.872	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
GSH	0.869	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
hs-CRP	0.895	<0.001	**Non-Normal**	Kruskal-Wallis / Mann-Whitney U	$p \leq 0.05 \rightarrow$ non-parametric
T-CHO	0.971	0.076	**Normal**	Independent t-test / ANOVA	$p > 0.05 \rightarrow$ parametric
LDL-C	0.975	0.111	**Normal**	Independent t-test / ANOVA	$p > 0.05 \rightarrow$ parametric
Mg	0.988	0.432	**Normal**	Independent t-test / ANOVA	$p > 0.05 \rightarrow$ parametric
LDH	0.972	0.093	**Normal**	Independent t-test / ANOVA	$p > 0.05 \rightarrow$ parametric
Creatinine	0.980	0.202	**Normal**	Independent t-test / ANOVA	$p > 0.05 \rightarrow$ parametric

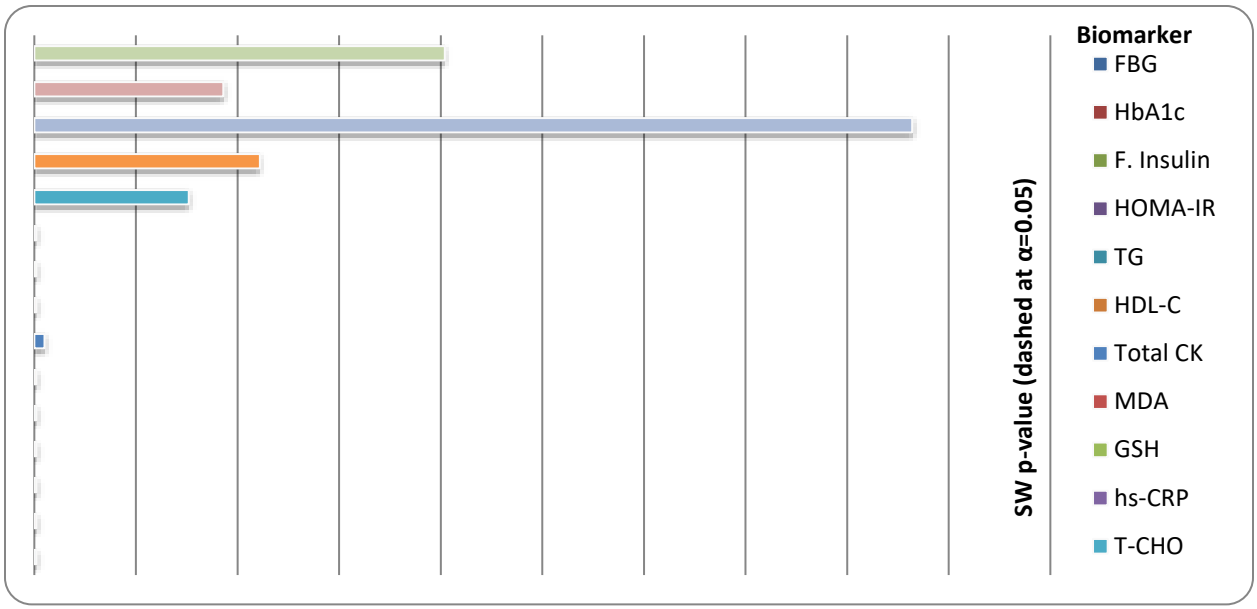

Figure 1: Shapiro–Wilk normality test p-values for the evaluated biochemical biomarkers, with the dashed line indicating the significance threshold at $\alpha = 0.05$.

4.3 Gender-Stratified Biochemical Comparison

Gender comparison analysis (Table 3) revealed no statistically significant differences between male and female participants for the vast majority of biochemical parameters. Exceptions were creatinine (males: 1.03 +/- 0.13 vs females: 0.85 +/- 0.14 mg/dL; $p < 0.001$) and urea (males: 32.92 +/- 4.40 vs females: 29.74 +/- 3.62 mg/dL; $p = 0.001$), reflecting well-established physiological sex differences in skeletal muscle mass and renal handling. These findings confirm that subsequent analyses are not confounded by gender effects.

Table 3. Biochemical parameters by gender: Mann-Whitney U comparisons.

Parameter	Males (n=35) Mean +/- SD	Females (n=40) Mean +/- SD	MW U p-value	Sig.	Ref. Range
FBG (mg/dL)	123.89 +/- 45.54	123.91 +/- 44.27	0.861	ns	70-99
HbA1c (%)	5.79 +/- 1.38	5.73 +/- 1.37	0.987	ns	4.0-5.6
HOMA-IR	3.39 +/- 3.14	3.23 +/- 3.74	0.742	ns	<2.5
TG (mg/dL)	154.15 +/- 61.16	154.98 +/- 69.08	0.836	ns	<150
HDL-C (mg/dL)	50.43 +/- 10.05	52.89 +/- 10.88	0.134	ns	>40(M)/>50(F)
LDH (U/L)	188.83 +/- 30.44	178.12 +/- 29.52	0.071	ns	120-240
Creatinine (mg/dL)	1.03 +/- 0.13	0.85 +/- 0.14	**<0.001**	***	0.6-1.2
Urea (mg/dL)	32.92 +/- 4.40	29.74 +/- 3.62	**0.001**	***	15-45
MDA (nmol/mL)	3.26 +/- 1.18	3.26 +/- 1.35	1.000	ns	<3.5
GSH (umol/L)	520.94 +/- 81.58	517.75 +/- 84.22	0.734	ns	>400
hs-CRP (mg/L)	2.99 +/- 1.90	2.97 +/- 2.00	0.882	ns	<1.0

*MW U = Mann-Whitney U test p-value. *** p < 0.001; ns = not significant. Sex differences in creatinine and urea reflect physiological differences in lean muscle mass. All other parameters presented no significant sex-based variation, supporting pooled-group analyses.*

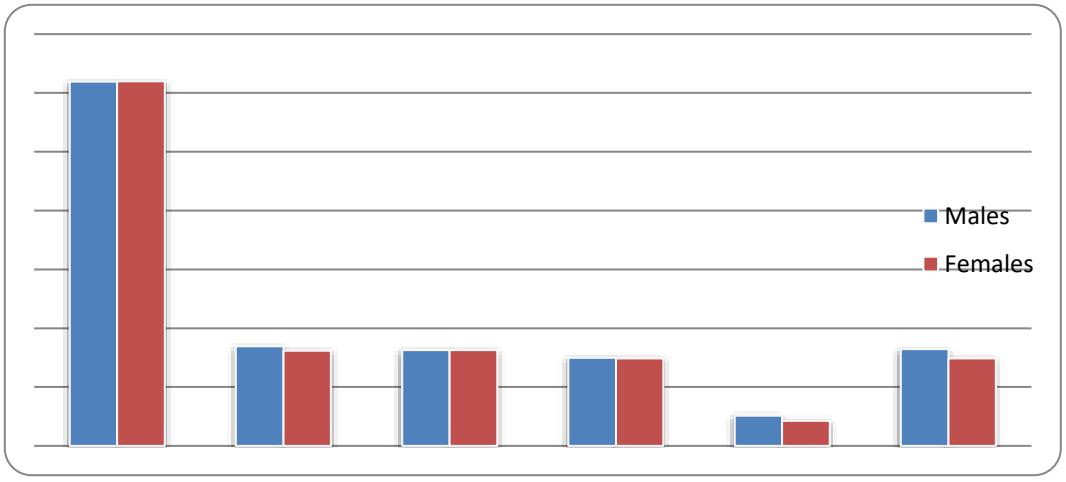

Figure 2: Sex contrast of the analyzed biochemical parameters between male and female participants across the study groups.

4.4 Glycemic and Insulin Resistance Parameters

Greatly significant progressive raises were noticed for FBG, HbA1c, and HOMA-IR across glycemic strata (Kruskal-Wallis, all p < 0.001). Mean FBG values were 86.67 +/- 5.87, 113.28 +/- 7.04, and 174.62 +/- 37.12 mg/dL for normoglycemic, prediabetic, and diabetic groups, respectively. HOMA-IR confirmed a particularly pronounced gradient: 1.18 +/- 0.58 (normoglycemic) to 2.02 +/- 0.78 (prediabetic) to 6.68 +/- 3.98 (diabetic), reflecting a 5.7-fold rise in insulin resistance severity across the glycemic spectrum.

4.5 Lipid Profile and Atherogenic Dyslipidemia

Triglycerides increased from 122.45 +/- 29.60 mg/dL (normoglycemic) to 211.47 +/- 76.35 mg/dL (diabetic; p < 0.001). HDL-C showed a progressive and clinically meaningful decline: 57.82 to 55.08 to 42.28 mg/dL (p < 0.001), representing a 27% reduction from the normoglycemic to diabetic stratum. LDL-C also increased significantly (93.91 to 98.36 to 112.12 mg/dL; p = 0.002). HOMA-IR correlated inversely with HDL-C (Pearson r = -0.828, p < 0.001) and positively with TG (r = 0.915, p < 0.001), as detailed in Table 4.

4.6 Oxidative Stress: MDA Elevation and GSH Depletion

MDA increased progressively from 2.43 ± 0.39 (normoglycaemic) to 4.53 ± 1.34 nmol/mL (diabetic), representing an 86.4% difference across strata (Kruskal-Wallis p < 0.001). GSH declined from 576.31 ± 28.45 to 436.06 ± 83.51 µmol/L, a 24.3% reduction across glycaemic groups (p < 0.001). The MDA–GSH inverse association was the strongest bivariate correlation in the dataset (Pearson r = −0.951, Spearman ρ = −0.882; both p < 0.001), consistent with reciprocal changes in lipid peroxidation surrogates and antioxidant indices. MDA was also positively associated with FBG (r = 0.927), HOMA-IR (r = 0.936), and hs-CRP (r = 0.899), all p < 0.001. These associations are cross-sectional and do not permit inference regarding the temporal or causal ordering of these relationships.

4.7 Systemic Inflammation: hs-CRP Stratification

hs-CRP concentrations differed significantly across glycaemic strata: 1.59 ± 0.55 (normoglycaemic) to 4.99 ± 1.93 mg/L (diabetic; p < 0.001). Among diabetic participants, all exceeded the conventional 1 mg/L

cardiovascular risk threshold; however, hs-CRP is a non-specific inflammatory marker substantially influenced by adiposity, intercurrent illness, and other non-diabetes-specific factors, and this observation should be interpreted with that non-specificity acknowledged. hs-CRP was positively associated with HOMA-IR ($r = 0.954$) and MDA ($r = 0.899$), and inversely associated with GSH ($r = -0.875$), all $p < 0.001$ (Table 4). These are cross-sectional observational associations.

Table 4. Key bivariate correlations between biochemical parameters (Pearson r and Spearman rho).

Variable Pair	Pearson r	p-value	Spearman rho	p-value	Clinical Domain	Sig.
FBG <-> HbA1c	0.974	<0.001	0.925	<0.001	Glycemic concordance	***
FBG <-> HOMA-IR	0.933	<0.001	0.890	<0.001	Glycemia-IR axis	***
FBG <-> MDA	0.927	<0.001	0.837	<0.001	Hyperglycemia-oxidative	***
FBG <-> hs-CRP	0.945	<0.001	0.874	<0.001	Glycemia-inflammation	***
HOMA-IR <-> TG	0.915	<0.001	0.663	<0.001	IR-dyslipidemia	***
HOMA-IR <-> HDL-C	-0.828	<0.001	-0.755	<0.001	IR-cardioprotection	***
HOMA-IR <-> MDA	0.936	<0.001	0.812	<0.001	IR-oxidative stress	***
HOMA-IR <-> hs-CRP	0.954	<0.001	0.847	<0.001	IR-inflammation	***
MDA <-> GSH	-0.951	<0.001	-0.882	<0.001	Oxidative-antioxidant	***
MDA <-> hs-CRP	0.899	<0.001	0.735	<0.001	Oxidative-inflammatory	***
GSH <-> hs-CRP	-0.875	<0.001	-0.718	<0.001	Antioxidant-inflammation	***
TG <-> HDL-C	-0.767	<0.001	-0.550	<0.001	Atherogenic dyslipidemia	***
Mg <-> FBG	-0.506	<0.001	-0.400	<0.001	Mineral-glycemia	***
Mg <-> HOMA-IR	-0.533	<0.001	-0.384	<0.001	Mineral-IR	***
Mg <-> MDA	-0.500	<0.001	-0.405	<0.001	Mineral-oxidative	***
LDH <-> MDA	0.625	<0.001	0.380	<0.001	Cardiac-oxidative	***

Total CK <-> HOMA-IR	0.734	<0.001	0.572	<0.001	Cardiac-IR	***
Creatinine <-> Urea	0.334	0.003	0.367	0.001	Renal concordance	**

*r = Pearson correlation coefficient; rho = Spearman rank correlation coefficient. Clinical domain categories provided for contextual interpretation. ** p < 0.01; *** p < 0.001. All correlations are two-tailed.*

4.8 HOMA-IR Quartile Dose-Response Analysis

Participants stratified into HOMA-IR quartiles demonstrated a consistent monotonic deterioration across all parameters (Table 5). MDA increased from 2.40 (Q1) to 4.96 nmol/mL (Q4) — a 107% increase; GSH declined 27%; hs-CRP rose 3.43-fold; TG rose from 119.19 to 242.38 mg/dL; and HDL-C fell from 58.95 to 38.36 mg/dL, consistent with a progressive association between insulin resistance severity and inflammatory-oxidative biomarker burden, though the cross-sectional design does not permit causal attribution.

Table 5. Biochemical profiles across HOMA-IR quartiles demonstrating monotonic dose-response deterioration.

Parameter	**Q1 (Lowest IR) n=19**	**Q2 n=19**	**Q3 n=18**	**Q4 (Highest IR) n=19**
HOMA-IR Range	<=1.10	1.11-1.95	1.96-3.80	**>3.80**
MDA (nmol/mL)	2.40	2.59	3.09	**4.96**
GSH (umol/L)	568.92	565.01	531.07	**412.58**
hs-CRP (mg/L)	1.66	1.81	2.72	**5.70**
TG (mg/dL)	119.19	116.71	139.28	**242.38**
HDL-C (mg/dL)	58.95	57.14	52.56	**38.36**
Q4/Q1 Ratio (MDA)	-	-	-	**2.07x**
Q4/Q1 Ratio (hs-CRP)	-	-	-	**3.43x**

Figure 3: Progressive alterations in oxidative stress, inflammatory, and lipid biomarkers across HOMA-IR quartiles, demonstrating increasing metabolic and inflammatory burden with worsening insulin resistance.

4.9 Serum Magnesium and Mineral Homeostasis

Serum magnesium decreased significantly from 2.16 +/- 0.19 mg/dL (normoglycemic) to 1.98 +/- 0.18 mg/dL in diabetic participants ($p < 0.001$). Magnesium correlated inversely with FBG ($r = -0.506$), HOMA-IR ($r = -0.533$), and MDA ($r = -0.500$; all $p < 0.001$), suggesting an association between lower magnesium levels and higher oxidative and metabolic burden across glycaemic strata.

4.10 Cardiac Enzymes and Renal Function

Total CK correlated significantly with HOMA-IR ($r = 0.734$, $p < 0.001$) and LDH correlated with MDA ($r = 0.625$, $p < 0.001$), suggesting subclinical metabolic stress in muscle and hepatic tissue in severely insulin-resistant individuals; these markers are not cardiac-specific and their elevations most plausibly reflect skeletal muscle and hepatic rather than primary myocardial pathology. LDH was significantly elevated in the diabetic group (203.01 +/- 32.09 vs 170.76 +/- 21.54 U/L; $p < 0.001$). Creatinine and urea showed no statistically significant between-group differences in the overall analysis.

4.11 Multiple Linear Regression Models

Multiple linear regression identified FBG, HOMA-IR, hs-CRP, MDA, HDL-C, and TG as independent statistical associates of HbA1c within the multivariate model (Adj. $R^2 = 0.952$, $F(6,68) = 244.64$, $p < 0.001$). It bears noting that FBG and HOMA-IR share a structural mathematical relationship, given that HOMA-IR incorporates FBG in its derivation. Their co-inclusion in Model 1 was nonetheless retained on the basis that variance inflation factors remained below the conventional threshold of 5.0; standardized beta coefficients for these two predictors should therefore be interpreted with this inherent dependency acknowledged. A second model targeting HOMA-IR identified hs-CRP ($\beta = 1.434$) and MDA ($\beta = 1.078$) as the strongest independent associates (Adj. $R^2 = 0.954$, $p < 0.001$; Table 6). VIF values for all predictors were below 5.0. These associations are exploratory; the term ‘independent predictor’ denotes statistical independence within the fitted model rather than causal precedence.

Table 6. Multiple linear regression models: Standardized beta coefficients for HbA1c and HOMA-IR prediction.

Predictor	Std. Beta	Direction	|Beta| Rank	Adj. R2
Model 1: Dependent Variable = HbA1c (%) | Adj. R2 = 0.952 | F(6,68) = 244.64 | p < 0.001				
FBG (mg/dL)	0.989	Positive	1st	-
HOMA-IR	0.293	Positive	2nd	-
hs-CRP (mg/L)	0.153	Positive	3rd	-
MDA (nmol/mL)	-0.041	Negative	4th	-
HDL-C (mg/dL)	0.033	Positive	5th	-
TG (mg/dL)	-0.027	Negative	6th	0.952
Model 2: Dependent Variable = HOMA-IR | Adj. R2 = 0.954 | F(6,68) = 253.63 | p < 0.001				
hs-CRP (mg/L)	1.434	Positive	1st	-
MDA (nmol/mL)	1.078	Positive	2nd	-
TG (mg/dL)	0.745	Positive	3rd	-
HDL-C (mg/dL)	-0.348	Negative	4th	-
FBG (mg/dL)	-0.116	Negative	5th	-
Mg (mg/dL)	-0.078	Negative	6th	0.954

Std. Beta = standardized beta coefficient. Adj. R2 = adjusted coefficient of determination. All models validated for multicollinearity (VIF < 5.0 for all predictors). Stepwise variable selection applied; all listed predictors retained at p < 0.05.

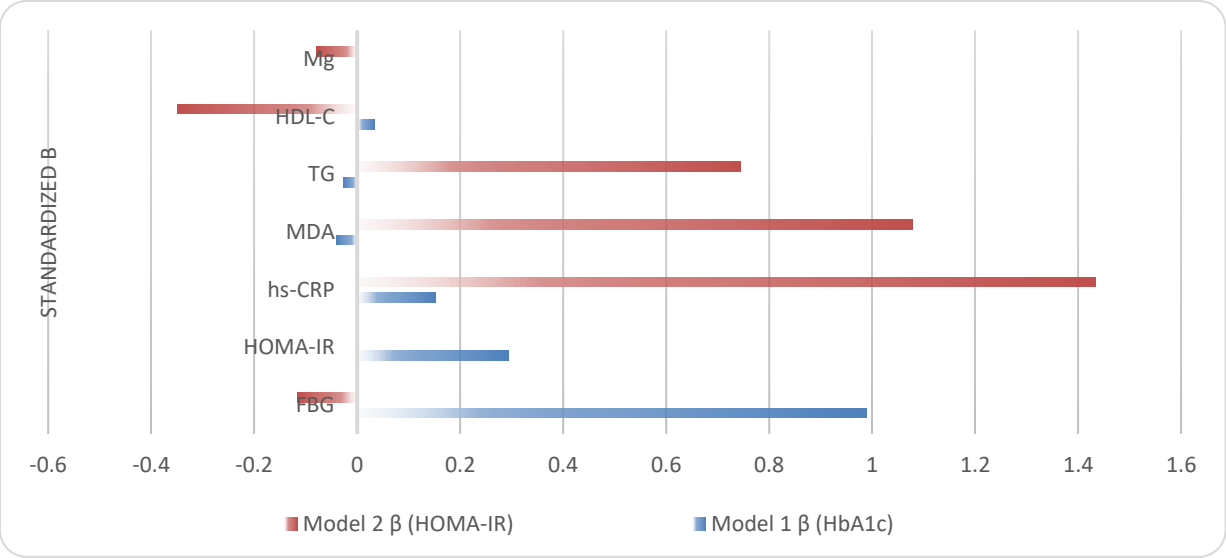

Figure 4: Standardized β-Coefficients for the Relationships between HbA1c, HOMA-IR, and Metabolic Biomarkers

4.12 Principal Component Analysis

Exploratory PCA of 12 standardized biochemical parameters yielded five components collectively accounting for 95.2% of total variance (Table 7). The first main component (PC1; eigenvalue = 8.375; 68.9% of variance) that attracted substantial loadings from FBG, HOMA-IR, hs-CRP, MDA, and TG, define a main axis of shared change spanning glycaemic, inflammatory, and oxidative stress markers. PC2 (10.0%) was defined principally by loadings on LDL-C, T-CHO, and HDL-C, reliable with a discrete lipid co-variance domain, while PC3 (7.8%) exhibited cross-loadings from of GSH, MDA, and hs-CRP. It must be emphasized that PCA components are inherently statistical constructs reflecting patterns of shared variance among measured variables; any biological interpretation remains speculative and should not be conflated with established physiological or regulatory axes.

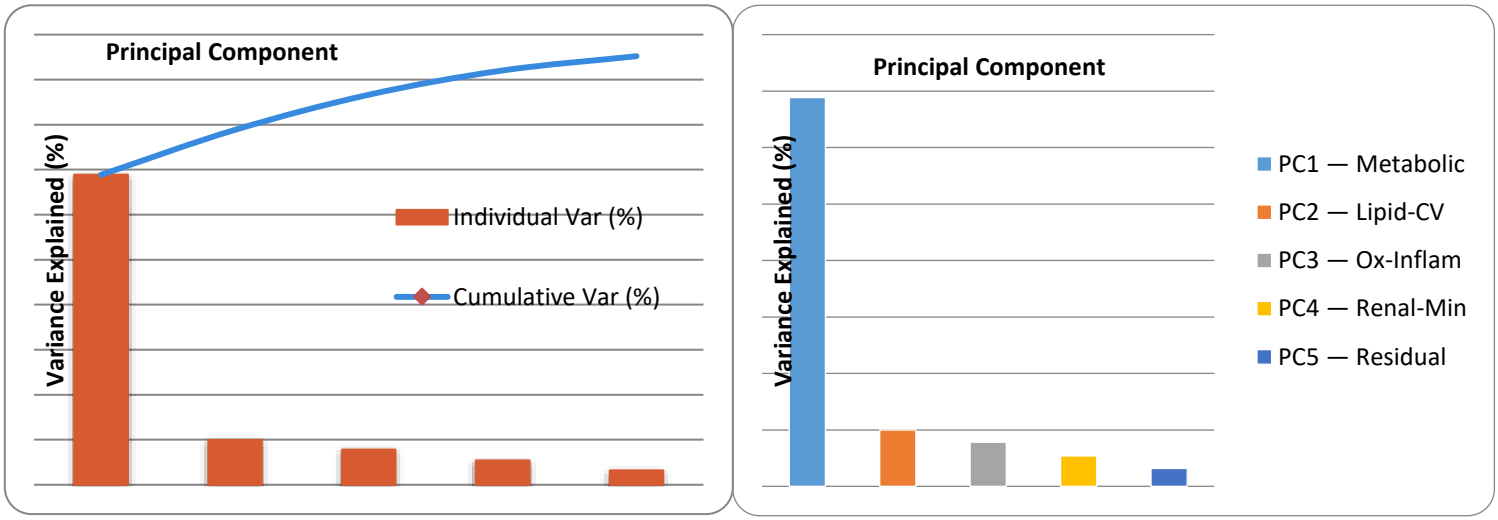

Figure 5: Scree Plot and Cumulative Variance Explained by Principal Components

Table 7. The Chief component analysis with variance, eigenvalues, and biological reading.

Component	Eigenvalue	Variance (%)	Cumulative (%)	Top Variables
PC1	8.375	68.86	68.86	FBG, HOMA-IR, MDA, hs-CRP
PC2	1.214	9.98	78.84	LDL-C, T-CHO, HDL-C
PC3	0.950	7.81	86.65	GSH, MDA, hs-CRP
PC4	0.655	5.39	92.04	Creatinine, Mg
PC5	0.385	3.17	95.21	Residual

PCA performed on standardized (z-scored) values of 12 key biochemical parameters. Eigenvalue > 1.0 criterion applied for component retention. Cumulative variance explained by 5 components = 95.2%.

Discussion

The strong harmonization among fasting blood glucose and HbA1c ($r = 0.974$, $p < 0.001$) is consistent with the established mathematical relationship between these glycaemic indices as documented in the ADAG study (Nathan et al., 2008), and supports the internal consistency of the dataset. The reliability in the ADA 2023 glycaemic classification practical to this cohort is further reinforced by the rigorous exclusion of conditions known to distort HbA1c validity — specifically hemolytic anaemia, haemoglobinopathies, and chronic kidney disease — jointly lending internal validity to the glycaemic stratification strategy employed.

The HOMA-IR gradient across the blood sugar layers is 1.18 ± 0.58, 2.02 ± 0.78, and 6.68 ± 3.98 in normoglycemic, prediabetic, and intradiabetic participants, respectively where the amplification represents 5.7-fold of the severity of insulin resistance across the blood sugar chain. It is also noteworthy and important that the average prediabetic group of 2.02 already exceeds the threshold of 1.73–2.0 that traditionally determines insulin resistance in the European population (Bonora et al., 2000), which means that the accumulation of cardiac metabolic risks is underway long before the development of explicit diabetes mellitus. This pathway aligns with HOMA-IR distributions stated in Middle Eastern populations (Al-Daghri et al., 2013; Esteghamati et al., 2010) and is consonant with the accelerated beta-cell exhaustion model projected by Butler et al. (2003), who recognized a 40–60% reduction in beta-cell mass at the point of T2DM diagnosis. The visible HOMA-IR raise between prediabetic and diabetic strata most believably reflects the transition from compensated to decompensated insulin resistance (DeFronzo & Tripathy, 2009) the explication regionally confirmed by Al-Nimer et al. (Bugger & Abel, 2014), who reported a comparable mean HOMA-IR of approximately 5.8 among newly diagnosed Iraqi patients with T2DM (Al-Obadi et al., 2025).

The lipid results signify a mechanistically coherent manifestation of insulin resistance–driven atherogenic dyslipidaemia: a 72.7% rise in triglycerides (122.45 to 211.47 mg/dL), a 26.9% decline in HDL-C (57.82 to 42.28 mg/dL), modest LDL-C elevation, and a near-doubling of VLDL-C (24.49 to 42.31 mg/dL). The HOMA-IR–TG ($r = 0.915$) and HOMA-IR–HDL-C ($r = -0.828$) correlations are well-replicated in cardiometabolic research and are mechanistically grounded in selective hepatic insulin resistance, whereby SREBP-1c–driven hepatic lipogenesis persists despite failure of the IRS-1/PI3K/Akt pathway

(Brown & Goldstein, 2008). the simultaneously suppression of lipoprotein lipase activity additional they reduce peripheral TG clearance (Klop et al., 2013), and the parallel VLDL-C elevation confirms that the dyslipidaemia experiential in this cohort is predominantly hepatogenic rather than dietary in origin.

The HDL-C tilt carries significance besides its quantitative dimension in the insulin-resistant states,also HDL particles undergo qualitative they remodeling enrichment with serum amyloid A and depletion of apoA-I ,that renders them dysfunctional and pro-inflammatory (Rye & Barter, 2014). These findings are confirm by Al-Rubeaan et al. (2015), who study the hypertriglyceridaemia prevalence excess 50% in a large Saudi T2DM cohort, and by the study (Gannagé-Yared et al., 2008), whose Lebanese diabetic patients exhibited a mean HDL-C of 42.1 mg/dL they practically identical to the 42.28 mg/dL observed in our study. The comparatively higher HDL-C values reported in Western European cohorts most likely reflect variances in dietary composition, ingrained physical activity, and genetic determinants of lipid metabolism (Superko et al., 2012).

Oxidative Stress: The MDA–GSH Redox Axis

The strong inverse association between MDA and GSH ($r = -0.951$; $p < 0.001$) comprise the most potent bivariate correlation in the dataset, coherent with the well-characterised reciprocal relationship amid lipid peroxidation substitute and antioxidant indices across glycaemic strata. The 86.4% difference in MDA and 24.3% reduction in GSH between normoglycaemic and diabetic participants indicate significant divergence in these redox-related indices.

Regarding the quantification of MDA specifically they contributions from dietary aldehydes and non-lipid carbonyl compounds cannot be excluded (Brownlee, 2001), and the systematic pre-analytical variability introduced by ex vivo GSH oxidation further qualifies interpretation. According to the MDA and GSH values they are the best regarded as relative indicators of oxidative burden rather than definitive quantitative measures. Nevertheless these restraints are several converging pathways that have been suggested to account for the raise of lipid peroxidation in chronic hyperglycaemia among them the polyol pathway, hexosamine pathway, PKC activation, and AGE–RAGE signalling (Brownlee, 2001, 2005) in overall endogenous antioxidant defenses of which GSH represents the most quantitatively significant non-enzymatic component (Forman et al., 2009). The terminal aldehyde product of n-6 polyunsaturated fatty acid peroxidation, MDA simultaneously marks and perpetuates cellular injury through protein cross-linking and DNA adduct formation (Esterbauer et al., 1991).

The HOMA-IR quartile analysis reveals a dose-response relationship: MDA increased by 107% from Q1 to Q4 (2.40 to 4.96 nmol/mL), while GSH declined by 27% (568.92 to 412.58 µmol/L).

The insignificantly stronger correlation of HOMA-IR with MDA ($r = 0.936$) relative to that of FBG ($r = 0.927$) tentatively suggests that insulin resistance, rather than hyperglycaemia per second, that may be interpret the primary driver of oxidative burden an explication consistent with evidence that insulin resistance independently promotes mitochondrial ROS over generation through impaired electron transport chain efficiency (Hoehn et al., 2009). The MDA and GSH values recorded in the present study agree with those reported in Egyptian (Moussa, 2008) and Pakistani (Mahreen et al., 2010) T2DM populations, and the 24.3% GSH depletion observed here falls within the 20–30% decline recognized across T2DM cohorts globally (Lutchmansingh et al., 2018). The give moderate comparatively measurement of this depletion that may be reflect the absence of severe end-organ complications in the

study population, also the factor likely to weaken the exceptional of antioxidant exhaustion seen in more clinically advanced disease.

The hs-CRP concentrations varied significantly across glycaemic strata (1.59 ± 0.55 mg/L [normoglycaemic] to 4.99 ± 1.93 mg/L [diabetic]; the Kruskal-Wallis $p < 0.001$). All diabetic participants surpass the conventional 1 mg/L cardiovascular risk threshold for hs-CRP. It is important to acknowledge, however, that hs-CRP is a non-specific acute-phase reactant essentially influencing By obesity visceral adipose tissue forms a major source of interleukin-6, which in turn drives hepatic CRP synthesis. In other hand the absence of systematically measured body mass index or waist circumference data in this cohort, the proportion of the observed between-group hs-CRP differences attributable to diabetes-specific inflammatory activation versus adiposity-driven inflammation It cannot be specified-due to the presence of material explanatory restrictions that call for explicit recognition. In addition to its role as an obvious inflammatory marker, hs-CRP is functionally involved in GAC-STAT3 and NF-CP signaling (Ridker, 2016) It works at the intersection of insulin resistance and its final consequences, and this is explained by the fact that inflammatory cytokines can weaken IRS-1 phosphorylation and GLUT4 translocation, that establishing a plausible bidirectional inflammatory–metabolic feedback relationship (Tilg & Moschen, 2008).

In the current dataset, HOMA-IR quartile analysis indicated a 3.43-fold increase in hs-CRP from Q1 to Q4, with no measurable plateau (Dinkova-Kostova & Abramov, 2015); hs-CRP–MDA ($r = 0.899$) and hs-CRP–GSH ($r = -0.875$) correlations imply that in this cohort converged inflammatory and oxidative variability. In the regression analysis, hs-CRP was the strongest independent statistical predictor of HOMA-IR ($\beta = 1.434$), in the concept of metaflammation (Hotamisligil, 2017) and therapeutically in line with the rationale for the CANTOS trial (Ridker et al., 2017). The diabetic group's hs-CRP value at 4.99 mg/L matches the values indicated by Al-Daghri et al. (2011) in Saudi T2DM patients, and the Q4/Q1 hs-CRP ratio corresponds to the 4.2-fold T2DM risk gradient by hs-CRP quartile in the Women's Health Study (Ridker et al., 2003). Importantly, however, all of the associations reported here are cross-sectional and observational; causal inference should not be made.

Serum Magnesium: An Independent Metabolic–Redox Contributor

Serum magnesium declined progressively from 2.16 ± 0.19 mg/dL (normoglycemic) to 1.98 ± 0.18 mg/dL (diabetic; $p < 0.001$), with inverse correlations against FBG ($r = -0.506$), HOMA-IR ($r = -0.533$), and MDA ($r = -0.500$). While mean magnesium levels remain within the classical reference range, the systematic decrease in the glycaemic levels and its relation to metabolic and oxidative stress markers highlight a biologically relevant trend. Magnesium itself plays an important role as a cofactor for autophosphorylation of insulin receptor tyrosine kinase, and its deficiency suppresses IRS-1–PI3K–Akt signalling by a receptor-proximal mechanism (Barbagallo & Dominguez, 2015; Volpe, 2013). Hyperglycaemia-dependent osmotic diuresis worsens this deficit by wasting magnesium in the kidney, which propagates the phenomenon of magnesium depletion, sustaining the cycle to the present state (Simmons et al., 2010). Moreover, when magnesium levels are insufficient, there is a decrease in glutathione peroxidase activity as well, which diminishes antioxidant activity and promotes lipid peroxidation (Rosique-Esteban et al., 2018), forming possibly a mechanistic basis for the reciprocal Mg–MDA relationship observed in this cohort. These observations are consistent with those reported by the meta-analysis of Dibaba et al. ($n > 600{,}000$) where a 15% decrease in the risk of T2DM associated with

one 100 mg/day dietary magnesium (Dibaba et al., 2014) and Guerrero-Romero and Rodríguez-Morán randomized trial (Guerrero-Romero & Rodríguez-Morán, 2011) reported ∼20% decreases in HOMA-IR after magnesium supplementation in a placebo-controlled study among hypomagnesaemic adult subjects. Although small by comparison, independent magnesium in Model 2, at $\beta = -0.078$, endorses its use in comprehensive metabolic risk assessment systems.

Total CK was positively associated with HOMA-IR ($r = 0.734$) and LDH to MDA ($r = 0.625$; both $p < 0.001$), and the difference in LDH between diabetic participants compared with normoglycaemic groups was large (203.01 ± 32.09 vs. 170.76 ± 21.54 U/L; $p < 0.001$). Neither CK nor LDH is a cardiac-specific enzyme, and their primary clinical roles are due to necrosis of skeletal muscle and hepatocellular damage. All parameters stay within reference ranges; however, the elevations observed at higher glycaemic levels are consistent with metabolic stress in skeletal muscle and hepatic tissues that is found in subclinical patients and are plausibly attributable to lipid overload, mitochondrial dysfunction, and oxidative damage (Bugger & Abel, 2014). The elevation of LDH is presumably correlated with an anaerobic glycolytic switch due to oxidative stress–induced mitochondrial dysfunction in cardiomyocytes (Abel et al., 2008), as the LDH–MDA association links cellular energy metabolism with lipid peroxidation. The HOMA-IR–CK association is more plausible with insulin resistance–mediated intramyocellular lipid aggregates and sarcolemmal instability (Goodpaster et al., 2001), and the absence of clinically significant CK-MB and troponin I differences confirms a skeletal, and not cardiac, contribution to the elevated CK values observed. The serum creatinine and urea did not vary significantly between glycaemic strata, but the diabetic subgroup showed numerically higher values for both parameters and thus the two markers clustered into a separate principal component (PC4; 5.4% of variance), indicating a biologically coherent renal sub-axis. Given the small diabetic subgroup ($n = 26$), it presumably limited the statistical power to detect early between-group differences, and the lack of microalbuminuria and eGFR measurements is a known limitation of the study.The absence of overt renal dysfunction nonetheless confirms that the elevated MDA and hs-CRP values observed cannot be attributed to uraemic confounding. Future studies should incorporate urinary albumin-to-creatinine ratio and cystatin C to characterize early diabetic nephropathy within the broader metabolic-redox-inflammatory framework.

Model 1 achieved an Adj. $R^2 = 0.952$ for HbA1c prediction, with FBG as the dominant statistical associate ($\beta = 0.989$). The independent associations of HOMA-IR ($\beta = 0.293$) and hs-CRP ($\beta = 0.153$) suggest that HbA1c variation is not purely glycaemia-dependent in this observational model, consistent with contextualising HbA1c interpretation within the broader cardiometabolic context in this exploratory cross-sectional sample, though these associations do not permit causal inference. Model 2 identified hs-CRP ($\beta = 1.434$) and MDA ($\beta = 1.078$) as the strongest independent statistical associates of HOMA-IR, consistent with the convergence of inflammatory and oxidative biomarker variance on the insulin resistance dimension in this cross-sectional sample. These associations do not permit mechanistic attribution or establishment of causal precedence; the concept that insulin resistance is a consequence of converging inflammatory-oxidative perturbations, whilst supported by experimental evidence [17], requires prospective validation in human cohort data before such inference is warranted from observational studies.

Exploratory PCA revealed a dominant PC1 — with substantial loadings for FBG, HOMA-IR, MDA, and hs-CRP — explaining 68.9% of total variance across 12 biochemical parameters, proportionally consistent with factor-analytic metabolic syndrome studies reporting a dominant glycaemic-inflammatory-lipid

factor explaining 55–75% of variance [38, 39]. A distinct PC3 capturing GSH, MDA, and hs-CRP co-variation (7.8% of variance) indicates a partially separable oxidative-inflammatory variance domain, while PC4 (5.4%) co-loaded magnesium and renal function markers [33]. These components are statistical constructs and should not be reified as discrete biological regulatory axes; their interpretation is exploratory and requires external replication in independent cohorts.

Conclusion

This cross-sectional multi-biomarker study identified concurrent associations among glycaemic indices, insulin resistance, dyslipidaemia, oxidative stress markers, and systemic inflammation across the glycaemic spectrum. The direction and magnitude of the observed inter-biomarker associations are consistent with the published cross-sectional literature, and quartile-based analysis revealed a progressive relationship between insulin resistance severity and inflammatory–oxidative biomarker burden. Exploratory PCA further elaborated on three principal types of general statistical dimensions of shared variance that can broadly represent metabolic, lipid-cardiovascular, and oxidative-inflammatory co-variance patterns. These findings are hypothesis-generating and should be treated within the constraints of a cross-sectional design where causal inference, mechanistic attribution, and temporal sequence determination remain not within scope. The analytical non-specificity of the TBARS-based MDA assay and the pre-analytical instability of serum GSH measurement add to the interpretive constraints of oxidative stress data. The lack of anthropometric data systematically collected — specifically BMI and waist circumference — precludes adiposity-adjusted interpretation of the hs-CRP associations, a limitation that materially qualifies the inflammatory findings. Longitudinal prospective studies using analytically specific oxidative biomarkers with objectively characterised anthropometrics, detailed medication records, and external validation cohorts are necessary before the clinical translational significance of these associations can be responsibly assessed. In light of that, the MDA/GSH ratio and hs-CRP merit special mention as potentially informative integrative biomarker indices whose utility in metabolic risk stratification needs to be confirmed in appropriately powered prospective designs.

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Data Availability Statement: The anonymized dataset supporting the findings of this study is available from the corresponding author upon reasonable request.

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