

Exploring the Interrelationship Between Oxidative Stress and Metabolic, Micronutrient, Inflammatory, and Adipokine Alterations in Type 2 Diabetes Mellitus: A Serum MDA-Based Correlation Study

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with persistent metabolic disturbances accompanied by oxidative stress, inflammation, insulin resistance, and alterations in micronutrient and adipokine status. However, the interrelationships among these biochemical parameters remain incompletely characterized. The present study evaluated the association of serum malondialdehyde (MDA), an indicator of lipid peroxidation, with selected micronutrients, glycaemic control, insulin resistance, inflammation, and adiponectin in patients with T2DM.

Methods: A hospital-based observational study was conducted among 122 patients with T2DM aged 25–60 years. Fasting blood samples were analyzed for serum MDA, vitamin D, calcium, magnesium, phosphorus, iron, copper, C-reactive protein (CRP), adiponectin, fasting insulin, and glycaemic parameters. HbA1c was assessed as an indicator of long-term glycaemic control, while insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR). Serum MDA was determined using the thiobarbituric acid reactive substances method. Pearson correlation analysis was performed to evaluate the relationships between MDA and the selected biochemical variables, with statistical significance set at $p < 0.05$. **Results:** Serum MDA demonstrated significant positive correlations with HbA1c ($r = 0.63$, $p < 0.001$), CRP ($r = 0.61$, $p < 0.001$), HOMA-IR ($r = 0.59$, $p < 0.001$), and copper ($r = 0.49$, $p < 0.001$). Significant inverse correlations were observed between MDA and vitamin D ($r = -0.58$, $p < 0.001$), adiponectin ($r = -0.57$, $p < 0.001$), magnesium ($r = -0.52$, $p < 0.001$), calcium ($r = -0.34$, $p < 0.001$), phosphorus ($r = -0.31$, $p < 0.001$), and iron ($r = -0.28$, $p = 0.002$). **Conclusion:** Increased oxidative stress was significantly associated with impaired glycaemic control, insulin resistance, inflammation, altered micronutrient status, and reduced adiponectin levels in patients with T2DM. These findings highlight the interconnected nature of oxidative, metabolic, and inflammatory disturbances in T2DM and support further prospective studies to clarify their underlying biological relationships.

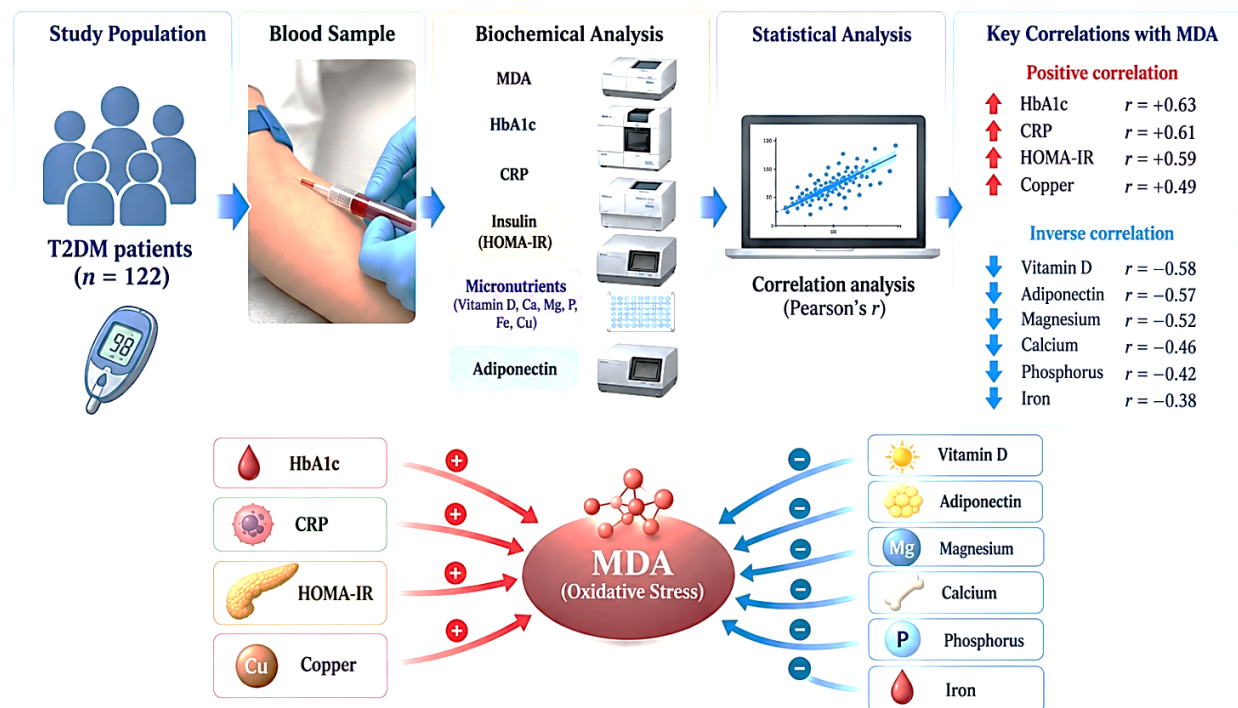
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GRAPHICAL ABSTRACT



INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and progressive metabolic disorder characterized by persistent hyperglycaemia resulting from a combination of impaired insulin secretion, insulin resistance, and progressive metabolic dysfunction. Beyond disturbances in glucose metabolism, T2DM is accompanied by alterations in lipid metabolism, chronic low-grade inflammation, endothelial dysfunction, and abnormal redox homeostasis (1). These interconnected abnormalities contribute substantially to the development and progression of diabetes-associated complications. Increasing evidence indicates that oxidative stress represents an important biochemical component of T2DM, arising when the generation of reactive oxygen species (ROS) exceeds the capacity of endogenous antioxidant defense mechanisms. A systematic review and meta-analysis of oxidative stress biomarkers reported significantly increased malondialdehyde (MDA) concentrations in individuals with T2DM compared with non-diabetic controls, supporting the involvement of lipid peroxidation in the diabetic state (2). Chronic hyperglycaemia can promote oxidative stress through several interrelated biochemical pathways, including increased mitochondrial ROS generation, glucose autooxidation, formation of advanced glycation end products, activation of protein kinase C, and disturbances in the polyol pathway. Increased oxidative burden can, in turn, interfere with insulin signaling, cellular antioxidant defenses, and vascular homeostasis (3). Thus, oxidative stress and insulin resistance may participate in a reciprocal relationship in

which metabolic dysfunction promotes ROS generation while oxidative signaling abnormalities further impair insulin action. A review of the molecular relationship between oxidative stress, insulin resistance, and T2DM has emphasized the involvement of oxidative mechanisms in insulin resistance and pancreatic β -cell dysfunction, highlighting the biological interconnection between these processes (4).

Malondialdehyde is one of the commonly investigated products of polyunsaturated fatty-acid peroxidation and is therefore frequently used as a biochemical indicator of lipid oxidative damage. Although MDA is not specific to any single oxidative pathway, its measurement can provide useful information regarding the overall lipid-peroxidative environment. In T2DM, increased lipid peroxidation may reflect the cumulative influence of hyperglycaemia, altered mitochondrial metabolism, inflammation, and impaired antioxidant protection. Importantly, oxidative stress does not operate independently of inflammatory processes (5). ROS can interact with intracellular signaling pathways involved in inflammatory responses, while inflammatory mediators can further promote oxidative imbalance. Clinical studies have reported simultaneous increases in MDA and inflammatory markers such as C-reactive protein (CRP) in patients with T2DM, supporting an association between oxidative and inflammatory disturbances (6). Micronutrients represent another potentially important component of this biochemical network. Vitamins and minerals participate in enzymatic antioxidant defense, glucose metabolism, mitochondrial function, cellular

signaling, and maintenance of redox equilibrium. Disturbances in micronutrient status may therefore coexist with or contribute to metabolic abnormalities in diabetes. Vitamin D, for example, has been investigated in relation to glucose homeostasis, insulin sensitivity, inflammation, and oxidative stress (7). An Indian study specifically examining vitamin D deficiency and oxidative stress in individuals with T2DM highlighted the potential relationship between inadequate vitamin D status and increased oxidative stress, while also emphasizing the need for further investigation of the underlying mechanisms (8). Similarly, systematic evidence has demonstrated associations between circulating vitamin D status and insulin resistance in T2DM populations, although the magnitude and clinical significance of these relationships vary among studies (9).

Mineral homeostasis may also be relevant to oxidative and metabolic disturbances in T2DM. Magnesium is required for numerous enzymatic reactions involved in glucose utilization and insulin signaling, and disturbances in magnesium status have been associated with insulin resistance and oxidative imbalance. Experimental and clinical evidence suggests that hypomagnesemia may impair glucose transporter activity, influence insulin sensitivity, and adversely affect antioxidant defenses (10). Calcium and phosphorus are similarly involved in intracellular signaling, energy metabolism, and mineral homeostasis, whereas iron participates in oxygen transport and numerous redox-related reactions. Consequently, alterations in these elements may be biologically relevant to the metabolic environment in diabetes. However, their relationships with oxidative stress are complex and may depend on the degree of metabolic disturbance, nutritional status, and other clinical factors (11). Copper deserves particular consideration because, unlike several micronutrients primarily associated with antioxidant systems, copper is a redox-active trace element capable of participating in reactions that influence ROS generation. Altered copper homeostasis has been reported in diabetes, although findings across clinical studies are not completely consistent. A systematic review and meta-analysis of serum and plasma studies demonstrated an association between circulating copper and diabetes and emphasized the involvement of copper in oxidative processes (12). Experimental evidence has additionally suggested that copper ions may facilitate ROS production under diabetic conditions, providing a possible biochemical explanation for their relationship with oxidative stress (13). These observations suggest that examining copper alongside other micronutrients may provide a more comprehensive understanding of the biochemical environment associated with oxidative stress.

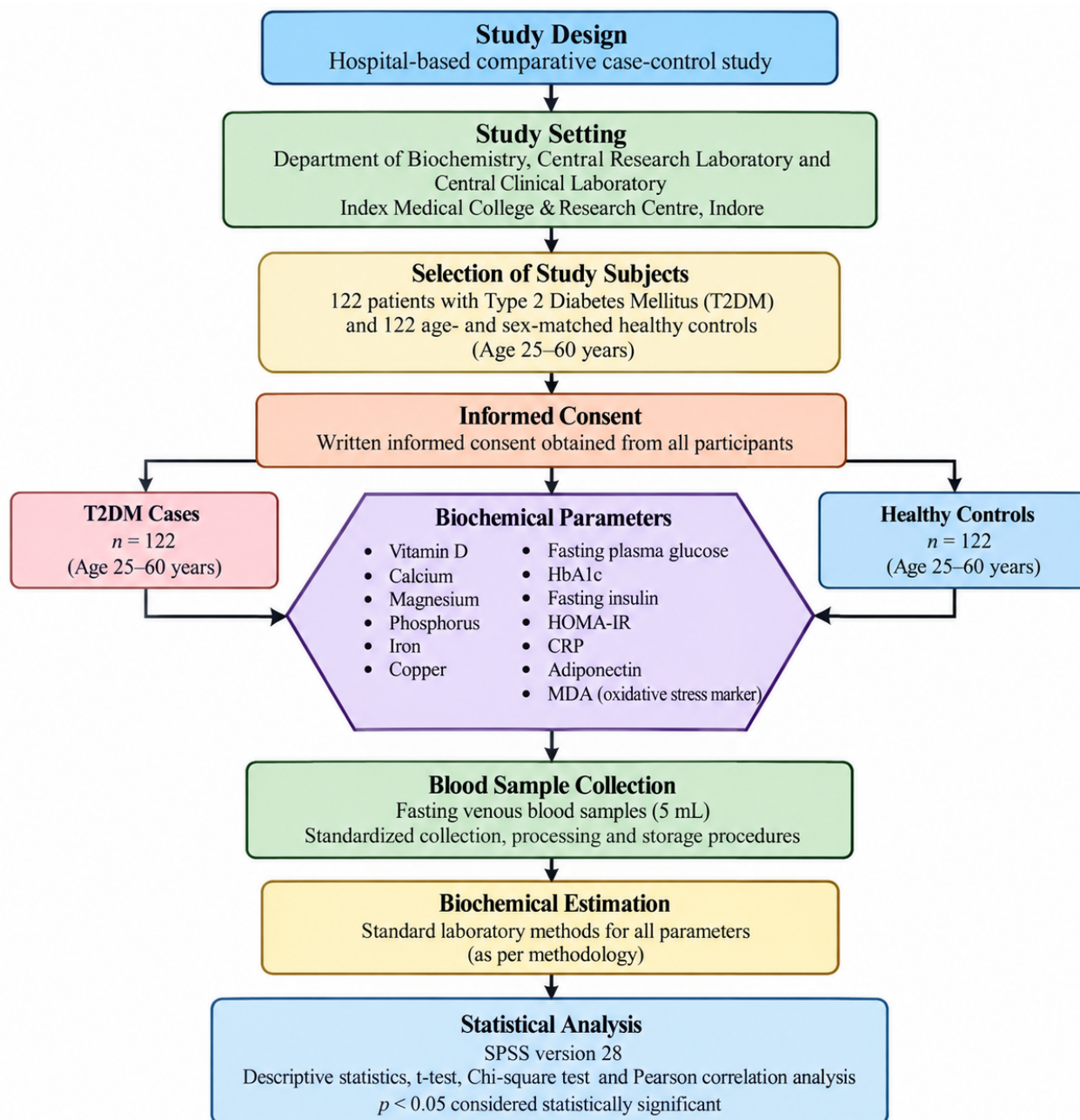
Adipokines provide another important dimension of metabolic regulation. Adiponectin, predominantly

secreted by adipose tissue, has recognized roles in glucose and lipid metabolism and is generally associated with improved insulin sensitivity and anti-inflammatory signaling. Alterations in adiponectin concentrations have been reported in metabolic disorders, including T2DM. Oxidative stress, adipose tissue dysfunction, and insulin resistance may interact through overlapping signaling pathways, suggesting that adiponectin may serve as an informative component of the metabolic–oxidative stress relationship. Previous clinical research has specifically investigated the relationship between adiponectin and oxidative stress markers in patients with T2DM, demonstrating the relevance of considering adiponectin within the broader oxidative environment (14,15). Despite substantial literature describing oxidative stress, micronutrient abnormalities, insulin resistance, inflammation, and adipokine disturbances in T2DM, an important limitation remains. Much of the existing research has examined these parameters individually or has focused on pairwise relationships, while relatively fewer studies have evaluated their integrated correlation with a common oxidative-stress marker within the same T2DM population. Studies addressing vitamin D, magnesium, copper, or adiponectin have frequently considered these variables in relation to diabetes, insulin resistance, or selected oxidative markers separately. Consequently, the simultaneous relationship of MDA with multiple micronutrients together with HbA1c, HOMA-IR, CRP, and adiponectin remains insufficiently characterized, particularly in a clinically defined Indian T2DM population. The present study was therefore designed to provide an integrated correlation-based assessment of oxidative stress and its biochemical interrelationships in patients with T2DM. A total of 122 individuals with T2DM were evaluated, with serum MDA considered the principal indicator of lipid peroxidation. Its relationship with vitamin D, calcium, magnesium, phosphorus, iron, copper, HbA1c, HOMA-IR, CRP, and adiponectin was examined using Pearson correlation analysis. The current study present investigation lies not in evaluating oxidative stress as an isolated feature of diabetes, but in examining MDA within a multidimensional biochemical framework encompassing micronutrient status, long-term glycaemic control, insulin resistance, systemic inflammation, and adipokine status simultaneously. This approach permits identification of the direction and relative strength of the associations between oxidative stress and these interconnected metabolic variables. Accordingly, the study seeks to determine whether increased lipid peroxidation is consistently associated with poorer glycaemic control, greater insulin resistance, heightened inflammatory status, altered micronutrient concentrations, and reduced adiponectin levels among individuals with established T2DM. By examining these relationships within the same study population, the investigation provides a more

integrated biochemical perspective of oxidative stress in T2DM and may help identify patterns that warrant further mechanistic and prospective investigation. Since the study is observational and correlation-based, the observed relationships are interpreted as associations rather than evidence of causality. Nevertheless, characterization of these interconnected biochemical relationships may contribute to a better understanding of the complex metabolic environment accompanying T2DM and provide a foundation for future studies investigating the

mechanistic and clinical significance of oxidative stress-related metabolic alterations. The overall study methodology and workflow are presented in **Figure 1**.

Figure 1. Schematic representation of the study methodology and workflow. The figure illustrates the study design, study setting, participant selection, biochemical parameters assessed, fasting blood sample collection, biochemical estimation, and statistical analysis performed in the study.



MATERIALS AND METHOD

2.1. Study Design and Study Population

A hospital-based observational study was conducted in the Department of Biochemistry, Central Research Laboratory, and Central Clinical Laboratory of Index Medical College & Research Centre, affiliated with Malwanchal University, Indore, Madhya Pradesh, India. The present study was designed as a correlation-based analysis to investigate the association of oxidative stress with micronutrient status, glycemic control, insulin resistance, inflammation, and adipokine status in patients with T2DM. A total of 122 patients with T2DM, aged 25–60 years, were included in the present analysis. These participants constituted the T2DM group of the study cohort. In contrast to the comparative case-control analysis, the present investigation focused exclusively on the T2DM population and examined the interrelationships among the selected biochemical variables. MDA was considered the primary marker of oxidative stress, and its association with vitamin D, calcium, magnesium, phosphorus, iron, copper, HbA1c, HOMA-IR, CRP, and adiponectin was evaluated.

2.2 Ethical Approval and Participant Selection

The study protocol was reviewed and approved by the Institutional Ethics Committee of Index Medical College & Research Centre, Malwanchal University, Indore, before initiation of the study. The study was conducted in accordance with the Declaration of Helsinki and applicable ethical principles governing research involving human participants. Written informed consent was obtained from all participants before enrolment. Patients aged 25–60 years of either sex with a documented diagnosis of T2DM were considered eligible. Individuals with type 1 diabetes mellitus, pancreatic disease, renal disease, chronic systemic illness, or conditions known to substantially influence glucose metabolism, micronutrient status, oxidative stress, or inflammatory biomarkers were excluded. Individuals receiving micronutrient supplementation or treatment likely to markedly alter the biochemical parameters investigated in the study were also excluded.

2.3 Clinical Assessment and Blood Sample Collection

Relevant demographic characteristics, medical history, diabetes-related information, and clinical findings were recorded using a structured data-collection form. Following an overnight fasting period, venous blood samples were collected from each participant under aseptic conditions by trained laboratory personnel. Approximately 5 mL of venous blood was collected using appropriate blood-collection tubes. Blood intended for serum-based biochemical and immunological investigations was collected in plain tubes and allowed to clot at room temperature for approximately 15–20 min. The samples were then centrifuged at approximately 2,000–3,000 rpm for 10 min to obtain serum. For fasting plasma glucose estimation, blood was collected into

fluoride-containing tubes, whereas EDTA-anticoagulated whole blood was used for HbA1c estimation. The separated serum was transferred into appropriately labelled aliquots. Samples intended for MDA analysis were stored at -80°C until biochemical estimation. Samples were handled carefully to minimize hemolysis, contamination, prolonged exposure to room temperature, and repeated freeze–thaw cycles.

2.4 Estimation of Fasting Plasma Glucose

Fasting plasma glucose was estimated by the GOD–POD method (16). Briefly, glucose present in the plasma was oxidized by glucose oxidase to form gluconic acid and hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide subsequently reacted with phenol and 4-aminoantipyrine to form a colored quinoneimine compound. The intensity of the developed color was directly proportional to the glucose concentration in the sample. Absorbance was measured spectrophotometrically at approximately 505 nm, and glucose concentration was calculated using the corresponding glucose standard/calibrator according to the manufacturer's instructions. Results were expressed as mg/dL.

2.5 Estimation of Glycated Hemoglobin

HbA1c was estimated using an immunoturbidimetric method. EDTA-anticoagulated whole-blood samples were first treated with the appropriate hemolysing reagent to release hemoglobin. HbA1c in the prepared sample reacted with specific antibodies directed against glycated hemoglobin, producing an immune complex and measurable turbidity (17). The degree of turbidity was proportional to the HbA1c concentration. The assay was performed using an automated biochemical analyzer and appropriate commercial reagents according to the manufacturer's instructions. Results were expressed as percentage (%) of total hemoglobin.

2.6 Estimation of Serum 25-Hydroxyvitamin D

Total serum 25(OH)D was estimated using a fluorescence immunoassay/enzyme-linked fluorescent assay (ELFA) on the Mini VIDAS platform. The assay was based on a competitive immunological reaction (18). Briefly, 25(OH)D present in the serum sample competed with a fluorescently labelled vitamin D analogue for binding to specific antibodies. Following the immunological reaction and washing steps, the fluorescence generated by the bound tracer was measured by the analyzer. Because the assay is competitive, the fluorescence signal is inversely proportional to the concentration of 25(OH)D in the specimen. Results were expressed as ng/mL.

2.7 Estimation of Serum Calcium

Serum calcium was determined using the O-cresolphthalein complexone (OCPC) method. In an

alkaline reaction medium, calcium ions present in the serum reacted with O-cresolphthalein complexone to form a colored calcium–chromogen complex (19). The intensity of the resulting, purple-colored complex was directly proportional to the calcium concentration in the specimen. Absorbance was measured spectrophotometrically at approximately 570–580 nm, and serum calcium concentration was calculated against the appropriate calibration standard. Results were expressed as mg/dL.

2.8 Estimation of Serum Magnesium

Serum magnesium was estimated by the xylidyl blue method. Under alkaline conditions, magnesium ions reacted with xylidyl blue to form a colored magnesium–xylidyl blue complex. EGTA present in the reagent system was used to minimize interference caused by calcium ions (20). The intensity of the developed color was directly proportional to the magnesium concentration. Absorbance was measured at the wavelength specified by the analytical procedure, and magnesium concentration was calculated using the appropriate magnesium standard/calibrator. Results were expressed as mg/dL.

2.9 Estimation of Serum Phosphorus

Serum inorganic phosphorus was estimated using the ammonium molybdate method. In an acidic reaction medium, inorganic phosphate present in the serum reacted with ammonium molybdate to form a phosphomolybdate complex (20). The intensity of the reaction product was measured spectrophotometrically at the wavelength specified by the commercial analytical system. Phosphorus concentration was calculated using the corresponding standard/calibrator and expressed as mg/dL. Non-hemolyzed serum was used for the analysis to minimize interference from intracellular phosphate released from erythrocytes.

2.10 Estimation of Serum Iron

Serum iron was estimated using the ferrozine colorimetric method. Under acidic conditions, iron was released from transferrin, and ferric ions (Fe^{3+}) were reduced to ferrous ions (Fe^{2+}). The resulting Fe^{2+} reacted with ferrozine to produce a colored ferrous–ferrozine complex (21). The intensity of the developed color was proportional to the concentration of iron in the sample. Absorbance was measured at approximately 560–562 nm, and serum iron concentration was calculated against the appropriate standard/calibration curve. Results were expressed as $\mu\text{g/dL}$.

2.11 Estimation of Serum Copper

Serum copper was estimated using a colorimetric assay based on the formation of a colored complex between copper ions and a specific chromogenic reagent. During

the reaction, protein-bound copper was released under the specified reaction conditions and converted into the reactive copper form required for chromogen complex formation (22). The resulting colored complex was measured spectrophotometrically at the wavelength specified by the assay system. The absorbance obtained for the sample was compared with the corresponding calibrator, and copper concentration was expressed in the appropriate concentration units.

2.12 Estimation of Serum Malondialdehyde

Serum MDA was estimated using the thiobarbituric acid reactive substances (TBARS) method, based on the procedure described by Ohkawa et al. Briefly, an aliquot of serum was subjected to reaction with thiobarbituric acid under acidic and high-temperature conditions. MDA present in the sample reacted with thiobarbituric acid to form a pink-colored MDA–thiobarbituric acid adduct. Following completion of the reaction and appropriate processing of the reaction mixture, the absorbance of the developed chromogen was measured spectrophotometrically at 532 nm against the appropriate reagent blank. MDA concentration was determined using the corresponding calibration procedure and expressed as nmol/mL (23). Because MDA is susceptible to preanalytical oxidation, serum samples were stored at -80°C before analysis, and unnecessary exposure to room temperature and repeated freeze–thaw cycles was avoided.

2.13 Estimation of C-Reactive Protein

Serum CRP was determined by a turbidimetric immunoassay. In the assay, CRP present in the serum reacted with specific anti-CRP antibodies coated on latex particles, resulting in antigen–antibody complex formation and increased turbidity. The change in turbidity produced by the immune reaction was measured photometrically at the wavelength specified by the assay system. CRP concentration was calculated using the appropriate calibration curve and expressed as mg/L (24).

2.14 Estimation of Serum Adiponectin

Serum adiponectin was quantified using a sandwich ELISA. Microplate wells coated with antibodies specific to adiponectin captured adiponectin present in the serum sample. After incubation, unbound material was removed by washing, followed by addition of an enzyme-linked detection antibody that bound to the captured adiponectin. After further washing, the appropriate chromogenic substrate, such as tetramethylbenzidine (TMB), was added. Enzymatic reaction produced a measurable color, and absorbance was recorded at approximately 450 nm after termination of the reaction. Adiponectin concentration was determined from the standard calibration curve and expressed as $\mu\text{g/mL}$ (25).

2.15 Estimation of Fasting Insulin

Fasting serum insulin was estimated using a sandwich enzyme-linked immunosorbent assay (ELISA). Serum insulin present in the sample was captured by insulin-specific antibodies immobilized on the microplate. Following incubation and washing, an enzyme-labelled detection antibody was added to form the antibody–insulin–antibody complex (26). After removal of unbound components by washing, the enzyme substrate was added and the resulting color intensity was measured using a

$$\text{HOMA - IR} = \frac{\text{Fasting glucose (mg/dL)} \times \text{Fasting insulin } (\mu\text{IU/mL})}{405}$$

The calculated HOMA-IR value was used as the index of insulin resistance for subsequent correlation analysis.

2.17 Quality Control

All biochemical assays were performed under established laboratory quality-control procedures. Commercial calibrators and quality-control materials were analyzed according to the requirements of the respective analytical systems. Instruments were calibrated using manufacturer-recommended procedures, and reagent performance, storage conditions, and expiry dates were monitored throughout the study.

Samples were handled under standardized preanalytical conditions, and precautions were taken to minimize interference from hemolysis, lipemia, contamination, inappropriate storage, and repeated freeze–thaw cycles. All assays were performed in accordance with the respective manufacturer's instructions.

2.18 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 28.0. The analysis was restricted to the 122 patients with T2DM included in the present study. Continuous variables were assessed for distributional characteristics before performing correlation analysis. The relationships between serum MDA and selected biochemical parameters representing micronutrient status, glycemic control, insulin resistance, inflammation, and adipokine status were evaluated using Pearson's correlation coefficient (*r*) for normally distributed continuous variables. Specifically, correlations were assessed between serum MDA and vitamin D, calcium,

microplate reader. Insulin concentration was calculated from the standard curve generated using known insulin standards and expressed as $\mu\text{IU/mL}$.

2.16 Calculation of HOMA-IR

Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR) (26). HOMA-IR was calculated from fasting plasma glucose and fasting serum insulin concentrations according to the following equation:

magnesium, phosphorus, iron, copper, HbA1c, HOMA-IR, CRP, and adiponectin concentrations. The correlation coefficient (*r*) was used to determine the direction and magnitude of the linear association between MDA and each investigated parameter, whereas the corresponding *p* value was used to determine statistical significance. All statistical tests were two-tailed, and a *p* value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

3.1. Study Population and Correlation Analysis

The present correlation-based analysis included 122 patients with T2DM. Unlike the comparative case-control component of the overall study, the present analysis was restricted to the T2DM group and was undertaken to investigate the interrelationships between oxidative stress and selected metabolic, nutritional, inflammatory, and adipokine parameters. Serum MDA was considered the principal indicator of lipid peroxidation and oxidative stress, while vitamin D, calcium, magnesium, phosphorus, iron, copper, HbA1c, CRP, adiponectin, and HOMA-IR were considered the associated biochemical variables. Pearson correlation analysis demonstrated statistically significant relationships between serum MDA and each of the investigated parameters. The direction and magnitude of the observed correlations indicated that MDA was positively associated with markers of poor glycaemic control, systemic inflammation, and insulin resistance, whereas significant inverse associations were observed with several micronutrients and adiponectin. The complete correlation coefficients obtained in the present analysis are summarized in **Table 1**.

Table 1. Correlation of serum MDA with selected biochemical parameters in patients with T2DM (*n* = 122)

Parameter	Pearson's <i>r</i>	<i>p</i> -value
Vitamin D	−0.58	<0.001
Calcium	−0.34	<0.001
Magnesium	−0.52	<0.001

Phosphorus	-0.31	<0.001
Iron	-0.28	0.002
Copper	+0.49	<0.001
HbA1c	+0.63	<0.001
CRP	+0.61	<0.001
Adiponectin	-0.57	<0.001
HOMA-IR	+0.59	<0.001

The results demonstrate that oxidative stress, represented by MDA, was significantly associated with multiple biochemical characteristics of T2DM. The strongest positive association was observed with HbA1c, followed by CRP and HOMA-IR, whereas vitamin D, adiponectin, and magnesium showed the strongest inverse associations. The overall pattern indicates that oxidative stress is closely interconnected with glycaemic dysregulation, inflammation, insulin resistance, micronutrient status, and adipokine alterations in the studied T2DM population (2).

3.2 Association of Serum MDA with Vitamin D and Mineral Status

Serum MDA demonstrated a significant inverse correlation with vitamin D ($r = -0.58$, $p < 0.001$). This was the strongest negative correlation observed among the micronutrients investigated. The finding indicates that patients with relatively lower serum vitamin D concentrations tended to have higher MDA levels, suggesting an association between reduced vitamin D status and increased lipid peroxidation. Vitamin D has biological functions extending beyond calcium and bone metabolism and has been implicated in the regulation of inflammatory and oxidative pathways. Altered vitamin D status may therefore coexist with an unfavourable redox environment in individuals with T2DM. Chronic metabolic disturbances associated with diabetes can increase ROS generation, while impaired antioxidant defence may facilitate oxidative damage to cellular lipids. The inverse association observed in the present study is therefore biologically plausible (27). However, the present findings should not be interpreted as demonstrating that reduced vitamin D directly causes increased oxidative stress. Vitamin D status may itself be influenced by nutritional intake, physical activity, adiposity, sunlight exposure, disease-related factors, and other metabolic characteristics. Thus, the observed correlation indicates an association within the T2DM population studied rather than a causal relationship.

Magnesium also showed a significant inverse correlation with MDA ($r = -0.52$, $p < 0.001$). This relatively strong association suggests that lower magnesium

concentrations were associated with greater lipid peroxidation. Magnesium is an important cofactor for numerous enzymatic reactions involved in energy metabolism, glucose utilization, and insulin signalling. Alterations in magnesium homeostasis have also been associated with metabolic dysfunction and impaired antioxidant defence (28). The observed inverse relationship may therefore reflect an interaction between magnesium status and the metabolic environment of T2DM. Reduced magnesium availability could coexist with insulin resistance and increased oxidative stress, while metabolic dysfunction itself may contribute to altered magnesium handling. The cross-sectional nature of the present analysis, however, does not permit determination of the temporal direction of this relationship. Significant inverse correlations were also observed for serum calcium ($r = -0.34$, $p < 0.001$) and phosphorus ($r = -0.31$, $p < 0.001$). Although these associations were weaker than those observed for vitamin D and magnesium, their statistical significance indicates that mineral status was also related to oxidative stress in the studied population (29).

Calcium participates in intracellular signalling, mitochondrial regulation, muscle function, and numerous enzymatic processes, while phosphorus is essential for ATP production, phosphorylation reactions, nucleic acid metabolism, and membrane phospholipid synthesis. Disturbances in mineral homeostasis may therefore influence cellular metabolic function and redox balance. The present findings suggest that alterations in calcium and phosphorus status may occur alongside increased lipid peroxidation in T2DM (30).

Serum iron showed a weak but statistically significant inverse correlation with MDA ($r = -0.28$, $p = 0.002$). Iron has a particularly complex relationship with oxidative stress because it is essential for oxygen transport and mitochondrial metabolism but can also participate in redox reactions capable of generating reactive species. Therefore, the observed inverse relationship should not be interpreted as evidence that higher circulating iron necessarily exerts an antioxidant effect. Instead, it may reflect the complex interaction between iron availability, nutritional status, metabolic regulation, and oxidative

processes in T2DM (31). Taken together, the findings indicate that lower concentrations of vitamin D, magnesium, calcium, phosphorus, and iron were associated with higher MDA concentrations. Among these variables, vitamin D and magnesium demonstrated the strongest inverse relationships. These observations

support the concept that micronutrient homeostasis and oxidative balance are interconnected in patients with T2DM. Serum MDA showed significant inverse correlations with vitamin D, magnesium, calcium, phosphorus, and iron, as shown in **Figure 2**.

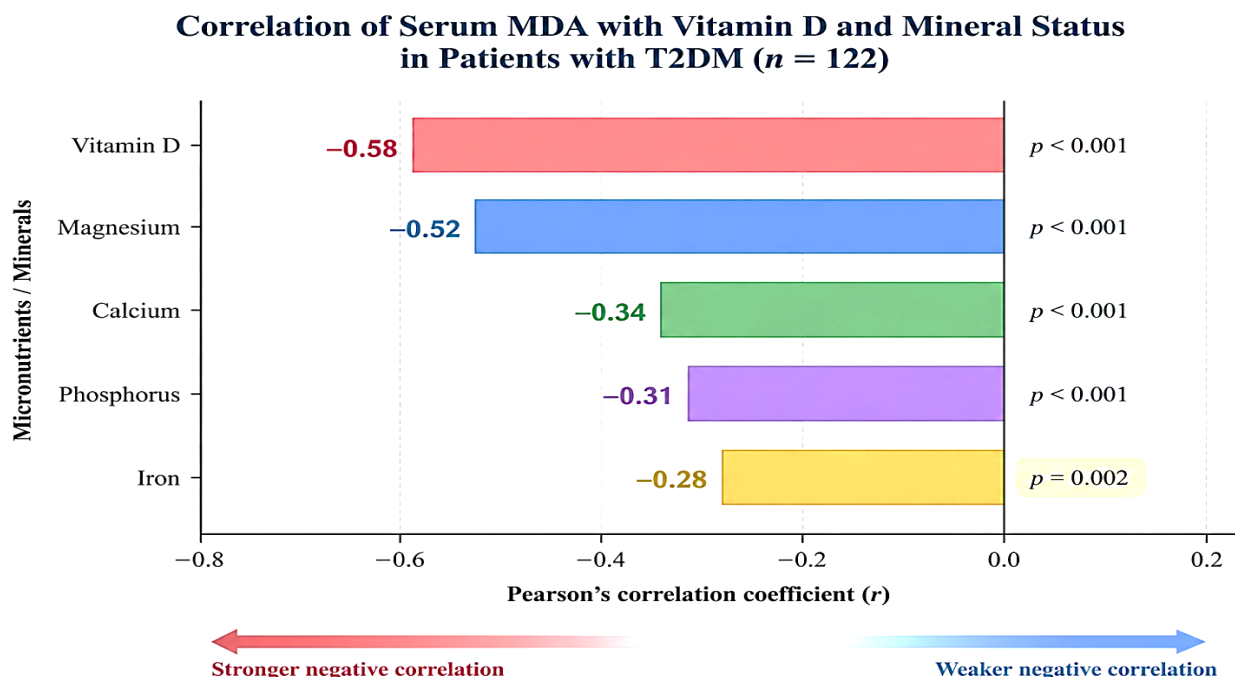


Figure 2. Correlation of serum MDA with vitamin D and mineral status in patients with T2DM ($n = 122$). Pearson's correlation coefficients (r) and corresponding p -values are shown.

3.3 Association of Serum MDA with Copper Status

In contrast to the inverse relationships observed for the other investigated micronutrients, serum copper demonstrated a significant positive correlation with MDA ($r = +0.49$, $p < 0.001$). This indicates that higher copper concentrations were associated with greater lipid peroxidation in the studied T2DM population. Copper is an essential trace element involved in several physiological processes and serves as a cofactor for important enzymes. However, because copper can undergo redox cycling, alterations in copper homeostasis may influence the generation of reactive oxygen species. Under conditions of altered metal balance, redox-active copper may participate in reactions that contribute to oxidative modification of lipids and other cellular components (32).

The positive MDA–copper association observed in the present study is therefore consistent with a possible

relationship between altered copper status and oxidative stress. The magnitude of the correlation was moderate and statistically significant, suggesting that copper status may represent an important component of the oxidative-stress profile in T2DM. Copper concentrations may be affected by nutritional status, inflammation, hepatic function, and other physiological processes. Consequently, the finding should be interpreted as an association rather than evidence of a direct pro-oxidant effect (33). The contrasting direction of the copper relationship compared with vitamin D, calcium, magnesium, phosphorus, and iron is nevertheless notable. It suggests that different micronutrients may have distinct relationships with oxidative stress in T2DM, reflecting differences in their physiological functions, regulation, and participation in redox processes (34). Serum copper showed a significant positive correlation with MDA ($r = +0.49$, $p < 0.001$), as shown in **Figure 3**.

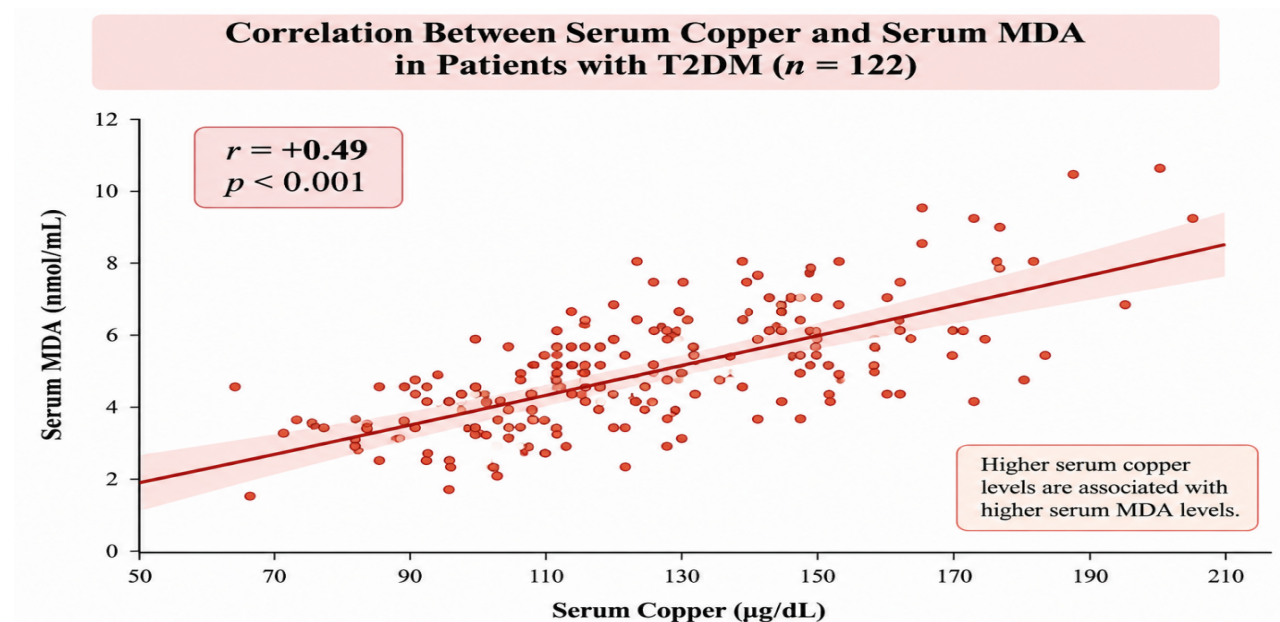


Figure 3. Correlation between serum copper and MDA in patients with T2DM (n = 122). Pearson's correlation coefficient (r) and p-value are shown.

3.4 Association of Serum MDA with Glycaemic Control

A strong positive correlation was observed between serum MDA and HbA1c ($r = +0.63$, $p < 0.001$). Among all parameters included in the Table 17 correlation analysis, HbA1c demonstrated the strongest positive association with MDA. This finding indicates that patients with higher MDA concentrations tended to have higher HbA1c values, suggesting that greater oxidative-stress burden was associated with poorer long-term glycaemic control. HbA1c represents cumulative glycaemic exposure over the preceding several weeks and therefore provides an indicator of chronic glucose dysregulation (35). The relationship between chronic hyperglycaemia and oxidative stress is biologically plausible. Persistent elevation of glucose can increase ROS production through mitochondrial dysfunction, enhanced formation of advanced glycation end products, activation of protein kinase C-dependent pathways, and other metabolic mechanisms. Increased ROS can promote

oxidation of cellular lipids, resulting in greater formation of lipid-peroxidation products such as MDA. The positive correlation observed in the present study therefore supports an association between chronic glycaemic dysregulation and oxidative stress in T2DM. It is also possible that oxidative stress contributes to further metabolic deterioration by affecting insulin signalling, mitochondrial function, and cellular homeostasis. Consequently, hyperglycaemia and oxidative stress may participate in a reciprocal cycle in which metabolic dysfunction promotes oxidative damage and oxidative stress further aggravates metabolic dysfunction (3). Importantly, because the present analysis is correlation-based, the direction of this relationship cannot be established. The observed association should therefore be described as a relationship between poor glycaemic control and increased lipid peroxidation rather than as evidence that elevated HbA1c directly causes increased MDA. Serum MDA showed a strong positive correlation with HbA1c ($r = +0.63$, $p < 0.001$), as shown in **Figure 4**.

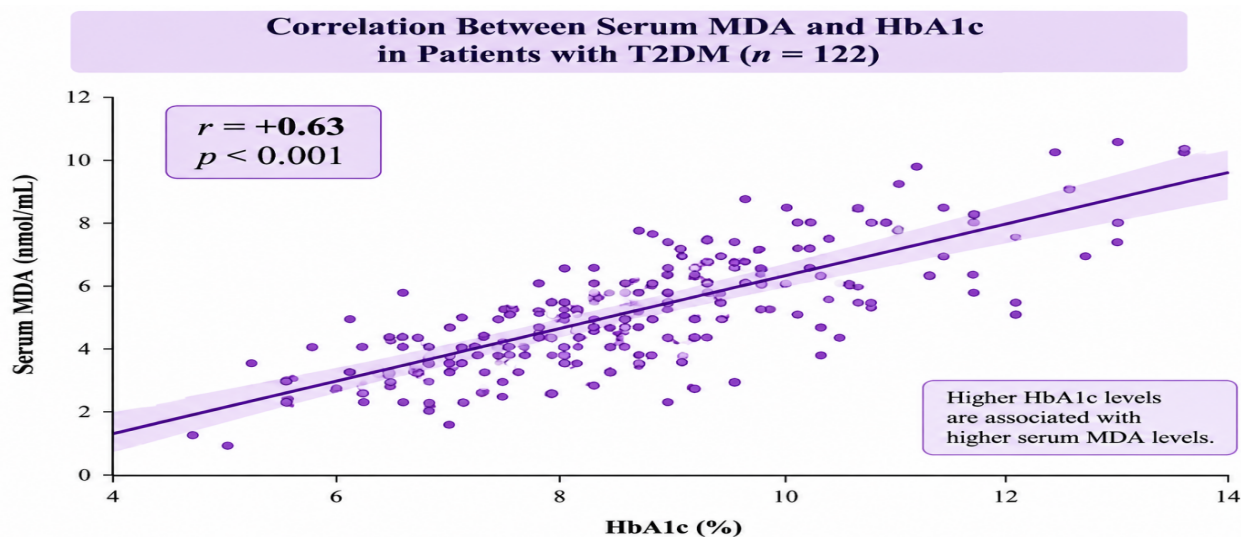


Figure 4. Correlation between serum MDA and HbA1c in patients with T2DM (n = 122). Pearson's correlation coefficient (r) and p-value are shown.

3.5 Association of Serum MDA with Inflammation and Adiponectin

Serum CRP demonstrated a strong positive correlation with MDA ($r = +0.61$, $p < 0.001$). This finding indicates that higher oxidative-stress burden was associated with greater systemic inflammatory activity among patients with T2DM. Oxidative stress and inflammation are closely interconnected biological processes. Excessive ROS production can activate intracellular inflammatory pathways, whereas inflammatory responses can further promote ROS generation. This reciprocal relationship may contribute to the persistence of both oxidative and inflammatory abnormalities in chronic metabolic disease (36). The significant MDA–CRP relationship observed in the present study therefore suggests that lipid peroxidation and systemic inflammation coexist in the

T2DM population. The magnitude of the correlation, with an r value of +0.61, indicates a relatively strong linear association. This finding is particularly relevant because CRP represents a systemic inflammatory marker, whereas MDA reflects lipid oxidative damage, allowing the two measurements to provide complementary information regarding the metabolic environment. However, CRP is not specific to diabetes-related inflammation and can be affected by infection, obesity, cardiovascular disease, and other inflammatory conditions. Therefore, the present result demonstrates an association between MDA and CRP but does not identify a specific inflammatory pathway responsible for the relationship (37). Serum MDA showed a strong positive correlation with CRP and a significant inverse correlation with adiponectin, as shown in **Figure 5**.

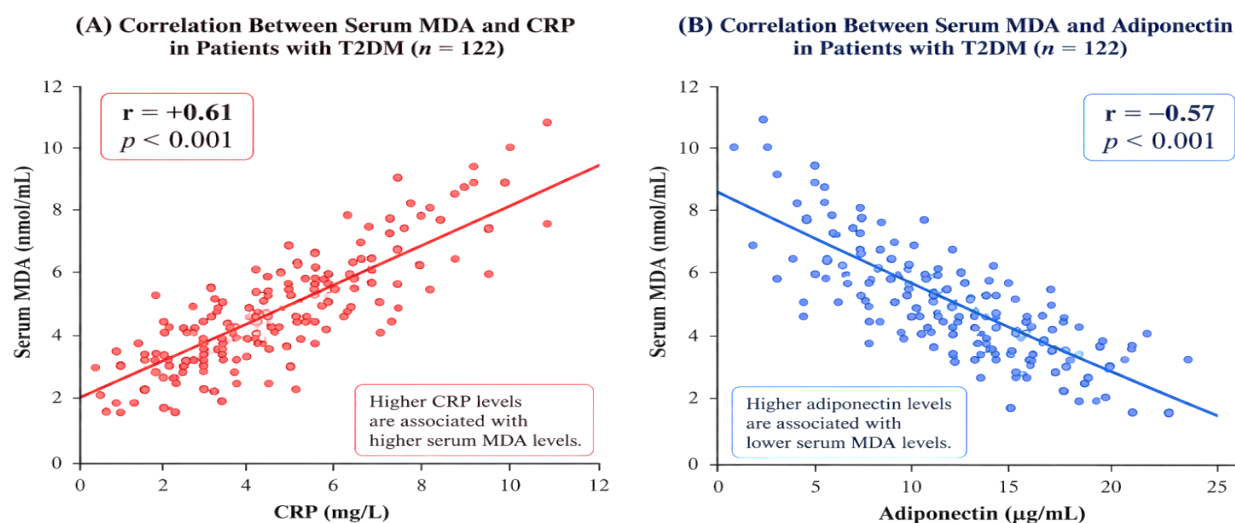


Figure 5. Correlation of serum MDA with CRP and adiponectin in patients with T2DM (n = 122). Pearson's correlation coefficients (r) and p-values are shown.

In contrast, adiponectin showed a significant inverse correlation with MDA ($r = -0.57$, $p < 0.001$). Thus, patients with lower adiponectin concentrations tended to have higher MDA concentrations. Adiponectin is an adipose-derived hormone involved in glucose and lipid metabolism, insulin sensitivity, and inflammatory regulation. Reduced adiponectin concentrations are commonly associated with an adverse metabolic phenotype characterized by insulin resistance and chronic inflammation. The inverse association between adiponectin and MDA is therefore consistent with the broader metabolic pattern observed in the present study. Reduced adiponectin may coexist with increased oxidative and inflammatory activity, while oxidative and inflammatory stress may also influence adipose-tissue function and adipokine secretion. The relationship may consequently represent reciprocal interactions between adipose dysfunction, insulin resistance, inflammation, and oxidative stress. The relatively strong inverse correlation between adiponectin and MDA further supports the importance of adipokine status when considering oxidative stress in T2DM. Nevertheless, as with the other correlations, the present analysis does not establish causality or determine whether changes in adiponectin precede or follow increases in oxidative stress (38).

3.6 Association of Serum MDA with Insulin Resistance

Serum MDA demonstrated a significant positive correlation with HOMA-IR ($r = +0.59$, $p < 0.001$). This finding indicates that higher levels of lipid peroxidation were associated with greater estimated insulin resistance among the patients with T2DM. Insulin resistance and oxidative stress are closely interconnected features of

metabolic dysfunction. Increased availability of metabolic substrates and impaired mitochondrial function can increase ROS generation, whereas excessive ROS may interfere with insulin receptor signalling and downstream pathways involved in glucose uptake and metabolism. Persistent insulin resistance can also promote further metabolic abnormalities that contribute to oxidative stress. The observed positive MDA-HOMA-IR relationship therefore provides evidence of a close association between oxidative stress and insulin resistance in the studied population. The correlation coefficient of +0.59 indicates a substantial positive relationship, although it was slightly lower than the correlations observed between MDA and HbA1c and between MDA and CRP (39). The present finding is also consistent with the observed positive correlation between MDA and HbA1c. Poor glycaemic control and insulin resistance frequently coexist in T2DM, and both may contribute to an increased oxidative burden. The simultaneous associations of MDA with HbA1c and HOMA-IR therefore suggest that oxidative stress is closely linked with the metabolic abnormalities underlying impaired glucose regulation. HOMA-IR is, however, a surrogate estimate of insulin resistance derived from fasting glucose and insulin concentrations. It does not directly measure cellular insulin sensitivity. Therefore, the present result should be interpreted as an association between MDA and estimated insulin resistance (40). Serum MDA showed a significant positive correlation with HOMA-IR ($r = +0.59$, $p < 0.001$), as shown in **Figure 6**.

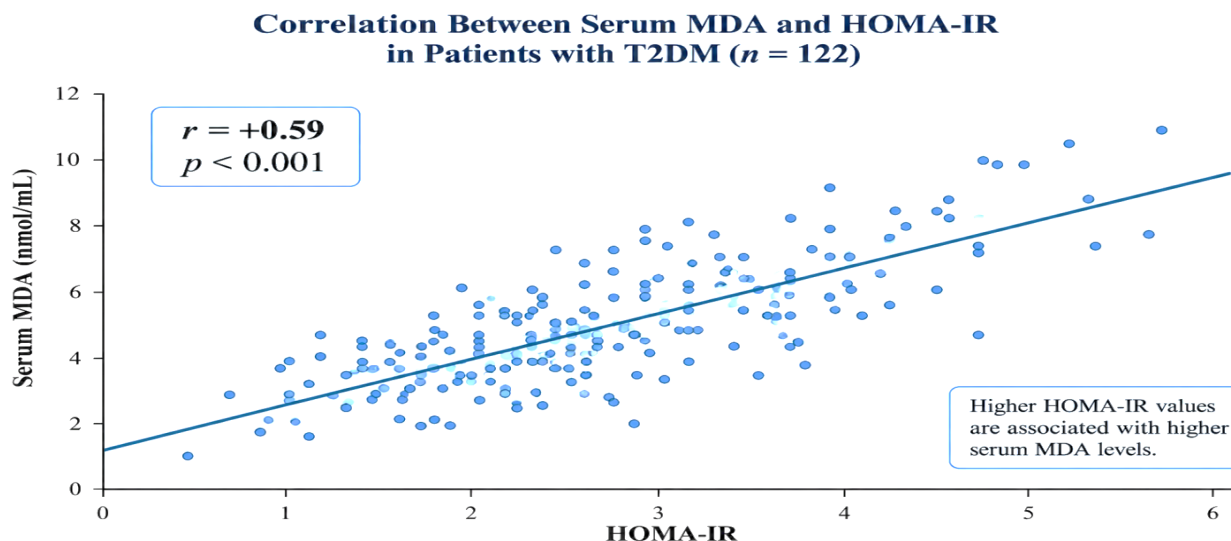


Figure 6. Correlation between serum MDA and HOMA-IR in patients with T2DM (n = 122). Pearson's correlation coefficient (r) and p-value are shown.

Figure 6. Correlation between serum MDA and HOMA-IR in patients with T2DM (n = 122). Pearson's correlation coefficient (r) and p-value are shown.

3.7 Integrated Relationship of Oxidative Stress with Metabolic and Biochemical Alterations

The combined correlation analysis demonstrated a consistent relationship between oxidative stress and multiple biochemical characteristics of T2DM. Serum MDA was positively associated with HbA1c, CRP, HOMA-IR, and copper, while significant inverse associations were observed with vitamin D, calcium, magnesium, phosphorus, iron, and adiponectin. The correlation pattern is summarized in Figure/Table X. The strongest positive association was observed between MDA and HbA1c ($r = +0.63$, $p < 0.001$), followed by CRP ($r = +0.61$, $p < 0.001$) and HOMA-IR ($r = +0.59$, $p < 0.001$). These findings collectively suggest that greater oxidative-stress burden was associated with poorer long-term glycaemic control, greater systemic inflammatory activity, and higher estimated insulin resistance.

Conversely, vitamin D showed the strongest inverse association with MDA ($r = -0.58$, $p < 0.001$), followed by adiponectin ($r = -0.57$, $p < 0.001$) and magnesium ($r = -0.52$, $p < 0.001$). Calcium, phosphorus, and iron showed weaker but statistically significant inverse relationships. These findings suggest that nutritional and endocrine-metabolic factors may also be closely related to oxidative-stress status in T2DM.

The overall pattern can be interpreted within an interconnected metabolic framework. Chronic hyperglycaemia may promote ROS generation and lipid peroxidation, leading to increased MDA formation. Oxidative stress may simultaneously impair insulin signalling and contribute to inflammatory activation.

Inflammation can further increase oxidative burden, while insulin resistance can contribute to additional metabolic disturbances. At the same time, altered micronutrient status may influence enzymatic reactions, antioxidant defence, cellular metabolism, and redox regulation. Reduced adiponectin concentrations may reflect an adverse metabolic state characterized by insulin resistance, inflammation, and increased oxidative stress (41). Thus, the present findings suggest that oxidative stress in T2DM is not an isolated biochemical phenomenon but is closely integrated with metabolic dysregulation, inflammation, insulin resistance, micronutrient status, and adipokine alterations. It is important to emphasize that the present analysis was restricted to the 122 patients with T2DM. Therefore, these correlations describe the relationships among biochemical variables within the diabetic population and should not be interpreted as case-control differences. The findings provide information about the biochemical heterogeneity of oxidative stress among patients already diagnosed with T2DM (42).

CONCLUSION

The present study provides evidence of a significant interrelationship between oxidative stress and multiple metabolic, inflammatory, micronutrient, and adipokine parameters among patients with T2DM. Serum MDA, used as an indicator of lipid peroxidation and oxidative stress, demonstrated significant associations with all investigated biochemical variables. MDA showed positive correlations with HbA1c, CRP, HOMA-IR, and

copper, while significant inverse correlations were observed with vitamin D, calcium, magnesium, phosphorus, iron, and adiponectin. These findings indicate that increased oxidative stress in T2DM occurs within a broader biochemical environment characterized by impaired glycemic regulation, insulin resistance, inflammation, altered micronutrient status, and changes in adipokine profile. The positive association of MDA with HbA1c suggests that poorer long-term glycaemic control is accompanied by greater lipid peroxidation. Similarly, the significant positive relationships between MDA and HOMA-IR and between MDA and CRP support the close association of oxidative stress with insulin resistance and systemic inflammatory status in T2DM. In contrast, the inverse relationships of MDA with vitamin D, magnesium, calcium, phosphorus, iron, and adiponectin suggest that altered micronutrient and adipokine profiles may accompany increased oxidative burden. The positive association observed with copper further highlights that individual micronutrients may have distinct relationships with oxidative processes, potentially reflecting their involvement in redox-regulating pathways. Taken together, these findings support the concept that oxidative stress is closely interconnected with the metabolic and biochemical disturbances characteristic of T2DM rather than representing an isolated abnormality. The observed correlations may provide a useful framework for understanding the relationship between lipid peroxidation, metabolic dysfunction, inflammation, micronutrient status, and insulin resistance in individuals with established diabetes. However, the cross-sectional and correlation-based nature of the analysis does not establish causality or determine the temporal direction of these associations. Moreover, potential influences of diabetes duration, nutritional status, adiposity, dietary patterns, physical activity, medication use, and other clinical factors should be considered when interpreting these relationships.

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Authors contribution

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List of abbreviations

1. T2DM = Type 2 Diabetes Mellitus
2. MDA = Malondialdehyde
3. HbA1c = Glycated Haemoglobin
4. CRP = C-Reactive Protein
5. HOMA-IR = Homeostatic Model Assessment of Insulin Resistance
6. ROS = Reactive Oxygen Species
7. TBARS = Thiobarbituric Acid Reactive Substances
8. FPG = Fasting Plasma Glucose
9. ELISA = Enzyme-Linked Immunosorbent Assay
10. SPSS = Statistical Package for the Social Sciences
11. ATP = Adenosine Triphosphate
12. NF-κB = Nuclear Factor Kappa B
13. AGEs = Advanced Glycation End Products
14. PKC = Protein Kinase C
15. SD = Standard Deviation
16. r = Pearson's Correlation Coefficient
17. p = Probability Value