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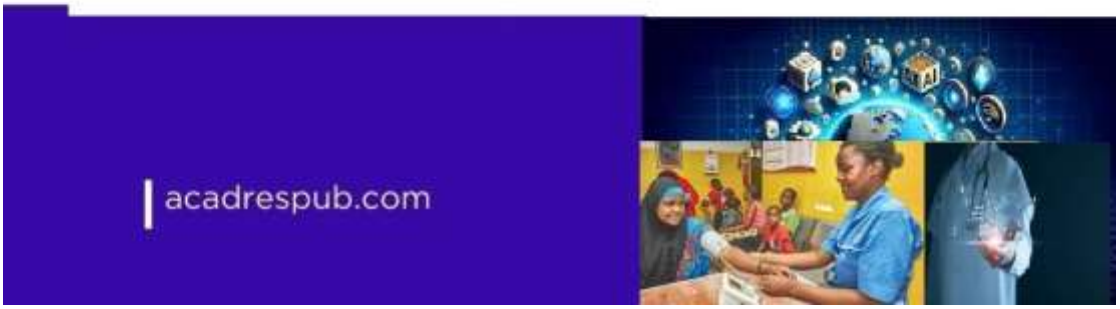

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MERCURY AND ARSENIC EXPOSURE AS POTENTIATORS OF OXIDATIVE DNA DAMAGE AND METABOLIC DYSFUNTION IN TYPE 2 DIABETES MELLITUS: A CASE-CONTROL STUDY IN EDO SOUTH, NIGERIA

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is increasingly recognized as a multifactorial metabolic disorder driven not only by genetic predisposition and lifestyle factors, but also by environmental toxicants capable of disrupting cellular metabolism and redox homeostasis. In Sub-Saharan Africa, rapid urbanization, industrial pollution, artisanal mining activities, contaminated water systems, and unsafe waste disposal practices have intensified human exposure to heavy metals such as mercury (Hg), arsenic (As), lead (Pb), and cadmium (Cd). These toxicants are known to induce oxidative stress, mitochondrial dysfunction, inflammatory activation, and pancreatic β-cell injury, yet their contribution to diabetes pathogenesis remains insufficiently characterized in Nigerian populations.
Objective: This study investigated the association between heavy metal exposure, oxidative DNA damage, inflammatory activation, and antioxidant defense responses among individuals with T2DM in Edo South, Nigeria.

Methods: A hospital-based case–control study was conducted involving 240 participants comprising 140 clinically diagnosed T2DM patients and 100 apparently healthy controls. Serum concentrations of oxidative DNA damage biomarker 8-hydroxy-2′-deoxyguanosine (8-OHdG), inflammatory cytokines (TNF-α, IL-6, hs-CRP), antioxidant enzymes (SOD, CAT, GPX), lipid peroxidation marker malondialdehyde (MDA), adiponectin, and heavy metals (Hg, As, Pb, Cd) were quantified using standard biochemical and toxicological techniques. Comparative analyses were performed using Student's t-test, while Pearson correlation and multivariate linear regression were employed to identify independent predictors of fasting blood sugar (FBS).

Results: T2DM patients demonstrated significantly elevated oxidative DNA damage, with serum 8-OHdG levels markedly higher than controls (5.74 \pm 0.81 ng/mL vs. 1.62 \pm 0.56 ng/mL; $p < 0.001$). Inflammatory biomarkers including hs-CRP, TNF-α, and IL-6 were also significantly increased, indicating persistent low-grade systemic inflammation. Marked elevations in antioxidant enzymes (SOD, CAT, GPX) were observed in diabetic subjects, suggesting an adaptive compensatory response to excessive reactive oxygen species (ROS) generation. Furthermore, MDA levels were significantly elevated, confirming enhanced lipid peroxidation and oxidative injury.

Heavy metal profiling revealed that 60.7% of T2DM participants exhibited elevated mercury concentrations, while 50% demonstrated elevated arsenic levels; in contrast, all controls remained within normal reference ranges. Multivariate regression analysis identified mercury exposure (β= -0.52 = -0.52, $p < 0.001$), GPX activity (β= -2.63, $p < 0.001$), and age (β= -0.45, $p < 0.001$) as significant independent predictors of glycemic dysregulation.

Conclusion: This study provides compelling evidence that environmental heavy metal exposure particularly mercury and arsenic is strongly associated with oxidative DNA damage, chronic inflammation, and metabolic dysfunction in T2DM patients in Edo South, Nigeria. The findings support the emerging concept that environmental toxicants constitute important non-traditional drivers of diabetes pathogenesis. Integrating environmental health surveillance, toxicological screening, and oxidative stress management into diabetes care may improve disease prevention and therapeutic outcomes in vulnerable populations.

Introduction

Type 2 Diabetes Mellitus (T2DM) has emerged as one of the most significant public health challenges of the 21st century, accounting for substantial morbidity, mortality, and economic burden worldwide(Ruze et al., 2023). The International Diabetes Federation estimates that the prevalence of diabetes will continue to rise dramatically, with developing countries bearing the greatest proportion of disease expansion due to rapid urbanization, dietary transitions, reduced physical activity, and socioeconomic inequalities(Lin et al., 2020). In Nigeria, the burden of T2DM has increased considerably over the past two decades, with many cases remaining undiagnosed until complications develop(Adeleye, 2021).

Although obesity, sedentary behavior, poor dietary habits, and genetic susceptibility remain classical determinants of T2DM, increasing evidence suggests that environmental toxicants may significantly contribute to metabolic dysregulation(Kumar et al., 2020). Heavy metals such as mercury, arsenic, cadmium, and lead have attracted growing scientific attention because of their capacity to disrupt endocrine signaling, impair mitochondrial function, induce oxidative stress, and interfere with glucose metabolism(Javaid et al., 2021).

Oxidative stress is a central pathogenic mechanism in T2DM. Persistent hyperglycemia promotes excessive production of reactive oxygen species (ROS) through several pathways including glucose auto-oxidation, activation of the polyol pathway, advanced glycation end-product (AGE) formation, and mitochondrial electron transport chain dysfunction. When ROS generation exceeds endogenous antioxidant capacity, oxidative damage occurs to lipids, proteins, and nucleic acids(González et al., 2023; Jomová et al., 2023).

Among available biomarkers of oxidative DNA damage, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is widely regarded as one of the most reliable indicators of oxidative nucleic acid injury(Jomová et al., 2023). Elevated 8-OHdG levels reflect hydroxyl radical-mediated guanine oxidation and have been associated with chronic inflammatory conditions, carcinogenesis, aging, and diabetes-related complications. However, few studies in Nigeria have comprehensively evaluated the relationship between environmental heavy metal exposure and 8-OHdG levels in T2DM patients(Graille et al., 2020; Wang et al., 2020).

Mercury and arsenic are particularly important because of their documented diabetogenic potential. Mercury can bind sulfhydryl groups in proteins, impair antioxidant enzyme function, and disrupt pancreatic β-cell integrity(Ma et al., 2020). Arsenic interferes with insulin receptor signaling, inhibits glucose uptake, and alters mitochondrial respiration. Chronic exposure to these toxicants may therefore accelerate oxidative stress and metabolic dysfunction(Djordjević et al., 2020; Lin & Yin, 2022; Pánico et al., 2022).

In addition to oxidative injury, chronic low-grade inflammation is increasingly recognized as a hallmark of T2DM. Pro-inflammatory cytokines such as TNF-α and IL-6 impair insulin signaling pathways and promote insulin resistance. Elevated high-sensitivity C-reactive protein (hs-CRP) further reflects systemic inflammatory activation associated with vascular complications and endothelial dysfunction(Stanimirović et al., 2022; Zhao et al., 2023).

Despite these mechanistic insights, there remains limited data integrating toxicological exposure, oxidative DNA damage, antioxidant responses, and inflammatory status among diabetic populations in Sub-Saharan Africa. Edo South, Nigeria, presents a particularly relevant setting because of increasing industrialization, environmental contamination, and population exposure to potentially hazardous pollutants(Gorini et al., 2021; Goriuc et al., 2024; Yousef et al., 2023).

This study therefore aimed to:

1. Evaluate serum heavy metal profiles among T2DM patients and healthy controls;
2. Determine the extent of oxidative DNA damage using 8-OHdG;
3. Assess inflammatory and antioxidant biomarkers associated with metabolic dysfunction; and
4. Identify independent predictors of glycemic dysregulation in T2DM.

We hypothesized that T2DM patients would demonstrate significantly elevated heavy metal

burden, oxidative DNA damage, and inflammatory activation compared with healthy individuals, independent of conventional demographic factors.

Methodology

Study Design and Setting

This study employed a hospital-based case–control design conducted in Edo South Senatorial District, Nigeria. The study adhered to the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Population

A total of 240 participants were recruited for the study, comprising:

- 140 clinically diagnosed T2DM patients (test group), and
- 100 apparently healthy age-independent controls.

Participants with acute infections, malignancies, chronic inflammatory disorders, renal failure, liver disease, or current antioxidant supplementation were excluded to minimize confounding effects.

Ethical Considerations

Ethical approval was obtained from the appropriate institutional ethics review committee. Written informed consent was obtained from all participants before sample collection and data acquisition.

Sample Collection

Venous blood samples were collected under aseptic conditions following overnight fasting. Samples were centrifuged, and sera were separated and stored at appropriate temperatures pending biochemical and toxicological analyses.

Biochemical and Toxicological Analyses

Glycemic Assessment

Fasting Blood Sugar (FBS) was measured using standardized enzymatic methods.

Oxidative DNA Damage Marker

8-OHdG concentrations were quantified using enzyme-linked immunosorbent assay (ELISA) techniques.

Inflammatory Biomarkers

The following inflammatory markers were analyzed:

- High-sensitivity C-reactive protein (hs-CRP),
- Tumor Necrosis Factor-alpha (TNF-α), and
- Interleukin-6 (IL-6).

Antioxidant and Oxidative Stress Biomarkers

- Oxidative stress and antioxidant status were evaluated using:
- Superoxide Dismutase (SOD),
- Catalase (CAT),
- Glutathione Peroxidase (GPX), and
- Malondialdehyde (MDA).

Heavy Metal Determination

Serum concentrations of mercury, arsenic, lead, and cadmium were quantified using validated toxicological analytical methods.

Statistical Analysis

Data were expressed as Mean ± Standard Deviation (SD). Comparative analyses between groups were performed using Student's t-test. Pearson correlation analysis evaluated relationships among oxidative stress markers, inflammatory parameters, and glycemic indices. Multiple linear regression models were constructed to determine independent predictors of fasting blood sugar. Statistical significance was set at $p < 0.05$.

Results

Demographic and Glycemic Characteristics

The T2DM group was significantly older than the control group (55.21 ± 7.53 years vs. 23.84 ± 3.28 years; $p < 0.001$). Fasting blood sugar was markedly elevated among diabetic subjects (172.93 ± 27.93 mg/dL) relative to controls (70.24 ± 8.51 mg/dL; $p < 0.001$), confirming poor glycemic regulation within the test population.

Oxidative DNA Damage and Inflammatory Biomarkers

A profound increase in oxidative DNA damage was observed in the T2DM cohort, as demonstrated by significantly elevated serum 8-OHdG concentrations.

- 8-OHdG=5.74±0.81 ng/mL (T2DM)vs1.62 ± 0.56 ng/mL (Control)

Similarly, inflammatory markers including hs-CRP, TNF-α, and IL-6 were significantly elevated among diabetic participants, indicating persistent systemic inflammatory activation associated with insulin resistance and endothelial dysfunction.

Reduced adiponectin levels observed in the T2DM group further support the presence of metabolic dysregulation and impaired insulin sensitivity.

Oxidative Stress and Antioxidant Responses

Significant elevations in SOD, CAT, and GPX activities were observed among T2DM patients. Although antioxidant enzymes are traditionally considered protective, the marked increase observed likely reflects an adaptive compensatory response to overwhelming oxidative burden.
The concurrent rise in MDA concentrations strongly indicates excessive lipid peroxidation and ROS-mediated cellular injury.

A strong positive correlation between MDA and GPX activity ($r = 0.96$, $p < 0.01$) suggests that antioxidant systems were upregulated in response to heightened oxidative stress rather than representing improved redox equilibrium.

Table 1. Comparative Biochemical and Oxidative Profiles

Variable	Control (n=100)	T2DM (n=140)	t-value	p-value
8-OHdG (ng/mL)	1.62 ± 0.56	5.74 ± 0.81	46.38	<0.001
hs-CRP (mg/L)	1.76 ± 0.46	4.17 ± 0.56	36.27	<0.001
Adiponectin (μg/mL)	18.4 ± 4.5	11.52 ± 4.22	12.11	<0.001
SOD (U/mL)	59.95 ±10.39	102.46 ± 6.51	36.15	<0.001
MDA (nmol/mL)	142.7 ± 13.14	216.43 ± 31.69	24.72	<0.001

Heavy Metal Distribution

Heavy metal analysis demonstrated a striking disparity between diabetic and non-diabetic participants. Elevated mercury concentrations were identified in approximately 60.7% of T2DM subjects, while elevated arsenic concentrations occurred in 50% of diabetic participants. Conversely, all control subjects remained within normal toxicological reference ranges.

These findings strongly implicate environmental toxicant exposure as a possible contributor to metabolic dysregulation in the study population.

Multivariate Regression Analysis

Multivariate regression analysis revealed that mercury exposure, GPX activity, and age were significant independent predictors of fasting blood glucose among T2DM participants.
$FBS=\beta 0-0.52\,(Hg)-2.63(GPX)-0.45(Age)+\varepsilon$

The adjusted coefficient of determination ($R^2_{adj}=0.32$) indicates that these variables collectively explained approximately 32% of the variation in glycemic status.

Discussion

The present study demonstrates a strong association between Type 2 Diabetes Mellitus, oxidative DNA damage, chronic inflammation, and heavy metal exposure among individuals in Edo South, Nigeria. The findings contribute important regional evidence supporting the growing recognition of environmental toxicants as significant non-traditional contributors to metabolic disease.

One of the most striking findings was the substantial elevation of serum 8-OHdG among T2DM patients. As a sensitive biomarker of oxidative DNA injury, elevated 8-OHdG reflects extensive ROS-mediated nucleic acid damage resulting from chronic hyperglycemia and

mitochondrial dysfunction(Ma et al., 2020). Persistent oxidative DNA damage may contribute to accelerated cellular senescence, vascular injury, and diabetic complications including nephropathy, neuropathy, and cardiovascular disease(Jomová et al., 2023; Li et al., 2023).

The elevated levels of hs-CRP, TNF-α, and IL-6 further emphasize the inflammatory nature of T2DM. TNF-α is known to impair insulin receptor substrate signaling through serine phosphorylation, thereby reducing insulin sensitivity(Sharif et al., 2021; Varra et al., 2024). IL-6 contributes to hepatic glucose overproduction and chronic immune activation, while elevated hs-CRP reflects systemic inflammatory burden associated with endothelial dysfunction and atherogenesis(Lee et al., 2021; Zatterale et al., 2020).

A particularly important contribution of this study is the characterization of heavy metal profiles among diabetic patients. The observation that over 60% of diabetic participants exhibited elevated mercury levels, with half also demonstrating arsenic toxicity, strongly suggests environmental exposure as a major pathogenic influence(Riaz et al., 2020). Potential sources of exposure in the region may include contaminated groundwater, industrial emissions, artisanal refining activities, pesticide residues, fish consumption, and improper waste disposal practices(Virolainen et al., 2022; Xu et al., 2022).

Mercury exerts toxic effects primarily through high-affinity binding to sulfhydryl-containing proteins, resulting in depletion of glutathione reserves and disruption of antioxidant defenses. It can also impair mitochondrial oxidative phosphorylation, increase ROS generation, and induce β-cell apoptosis(Tsvetkov et al., 2022). Arsenic has similarly been implicated in impaired insulin signaling, altered glucose transporter activity, and dysregulated pancreatic function(Hu et al., 2020).

Interestingly, antioxidant enzymes such as SOD, CAT, and GPX were significantly elevated among T2DM subjects. This apparent paradox likely reflects a compensatory physiological response to excessive oxidative stress rather than effective protection. Sustained ROS production stimulates transcriptional upregulation of endogenous antioxidant systems; however, prolonged exposure may eventually overwhelm these protective mechanisms, resulting in cumulative oxidative damage(Jomová et al., 2023; Tauffenberger & Magistretti, 2021).

The strong positive correlation between MDA and GPX supports the notion of adaptive antioxidant activation in response to lipid peroxidation(Al-Hakeim et al., 2022). Elevated MDA concentrations indicate severe membrane lipid oxidation, which may compromise cellular integrity and insulin-responsive tissues(Ma et al., 2020; Yousef et al., 2023).

The multivariate regression findings further strengthen the biological significance of environmental toxicants in diabetes pathogenesis. Mercury exposure emerged as an independent predictor of glycemic dysfunction even after adjustment for age and antioxidant variables. This suggests that heavy metal toxicity may directly influence glucose metabolism beyond conventional metabolic risk factors(Javaid et al., 2021; Yimthiang et al., 2022).

Collectively, these findings support a mechanistic framework in which environmental heavy metals amplify oxidative stress, provoke inflammatory activation, impair insulin signaling, and promote progressive metabolic dysfunction.

Clinical and Public Health Implications

The findings of this study have important implications for diabetes prevention and management in developing countries.

- First, environmental toxicology should be increasingly recognized as a component of non-communicable disease surveillance. Routine assessment of environmental exposure history may improve identification of individuals at elevated metabolic risk.

- Second, antioxidant and anti-inflammatory therapeutic strategies may provide additional benefits in T2DM management, particularly in environmentally exposed populations.

- Third, public health interventions aimed at reducing heavy metal contamination in food, water, and occupational

environments may contribute to lowering diabetes burden.

Finally, healthcare systems in Sub-Saharan Africa may benefit from integrating environmental medicine into chronic disease management frameworks.

Strengths and Limitations

Strengths

- Comprehensive integration of toxicological, inflammatory, oxidative, and metabolic biomarkers;
- Evaluation of oxidative DNA damage using the highly sensitive 8-OHdG biomarker;
- Focus on an underrepresented African population with significant environmental exposure risk.

Limitations

- The case–control design limits causal inference;
- Age mismatch between groups may introduce confounding effects;
- Exposure duration and environmental sources of heavy metals were not directly quantified;
- Dietary and occupational exposure histories were not extensively characterized.

Conclusion

This study demonstrates that T2DM patients in Edo South, Nigeria exhibit a convergence of oxidative DNA damage, chronic inflammatory activation, antioxidant dysregulation, and significant heavy metal exposure. Mercury and arsenic emerged as major environmental toxicants associated with metabolic dysfunction and impaired glycemic regulation.

The findings support the concept of a “triple pathogenic burden” in T2DM consisting of:

- Environmental toxicant exposure,
- Persistent oxidative stress and DNA injury, and
- Chronic systemic inflammation.

Addressing environmental pollution may therefore represent an important but underappreciated strategy in diabetes prevention and management. Future longitudinal investigations exploring detoxification strategies, environmental remediation, and antioxidant-targeted interventions are warranted to further elucidate the role of toxic metals in the progression of T2DM.

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