Inflammatory and Metabolic Biomarker Alterations Associated with Long-Term Metformin and Glibenclamide Therapy in Type 2 Diabetes

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ABSTRACT

Objective: To evaluate inflammatory cytokine profiles and key metabolic enzyme activities in T2DM patients receiving long-term metformin or glibenclamide therapy, with a view to identifying biochemical signatures associated with altered metabolic responsiveness.

Methods: This comparative cross-sectional study evaluated inflammatory cytokines and metabolic enzyme activities in adults with T2DM receiving long-term metformin or glibenclamide therapy. A total of 125 participants aged ≥30 years were recruited from the Endocrinology Clinic of the University of Benin Teaching Hospital, Nigeria. Subjects had received either metformin or glibenclamide for a minimum of three months. Age and sex matched non-diabetic individuals served as controls. Serum interleukin-1β (IL-1β) and interleukin-6 (IL-6) concentrations were quantified using enzyme-linked immunosorbent assay (ELISA). Erythrocyte glucose-6-phosphate dehydrogenase (G6PDH) and serum lactate dehydrogenase (LDH) activities were determined using standardized enzymatic assays. Statistical analyses were performed using appropriate parametric tests, with significance set at $p < 0.05$.

Results: Male patients receiving metformin or glibenclamide exhibited significantly higher IL-1β concentrations compared with non-diabetic controls ($p < 0.05$), while IL-6 levels showed no consistent significant differences across treatment groups. G6PDH activity was significantly reduced in male patients on both therapies, whereas LDH activity was significantly elevated in both male and female patients, indicating altered redox balance and increased metabolic stress during long-term oral antidiabetic therapy.

Conclusion: Long-term metformin or glibenclamide therapy in individuals with T2DM is associated with measurable alterations in inflammatory and metabolic biomarkers. Elevated IL-1β levels, reduced G6PDH activity and increased LDH activity particularly among male patients, suggest the presence of chronic metabolic stress and inflammatory activation during prolonged oral antidiabetic therapy.

Keywords: metformin, glibenclamide, Inflammatory, Metabolic Biomarker Alterations, Type 2 Diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from insulin resistance, impaired insulin secretion, or a combination of both (Donath & Shoelson, 2011; American Diabetes Association, 2024). The global prevalence of T2DM continues to rise, posing a significant public health burden, particularly in low-income countries. Beyond glycemic dysregulation, chronic low-grade inflammation and oxidative stress are now recognized as central contributors to disease progression and the development of long-term complications.

Metformin and sulfonylureas, including glibenclamide, remain among the most frequently prescribed oral antidiabetic agents worldwide (DeFronzo & Norton, 2017; Baker & Rasouli, 2021; American Diabetes Association, 2024). Metformin primarily improves insulin sensitivity and suppresses hepatic gluconeogenesis, while glibenclamide enhances pancreatic insulin secretion through ATP-sensitive potassium channel inhibition. Despite their clinical effectiveness, many patients experience a gradual decline in glycaemic control during prolonged therapy, commonly described as secondary treatment failure. The molecular and biochemical processes underlying this phenomenon remain incompletely understood.

Inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) have been implicated in insulin resistance, β-cell dysfunction, and metabolic inflammation (Donath & Shoelson, 2011; Hotamisligil, 2017; Prentki & Nolan, 2020). Concurrently, metabolic enzymes including glucose-6-phosphate dehydrogenase (G6PDH), a key regulator of cellular redox homeostasis, and lactate dehydrogenase (LDH), an indicator of altered glycolytic flux and cellular stress, may reflect underlying metabolic perturbations associated with chronic hyperglycaemia and prolonged pharmacotherapy.

Although previous studies have examined inflammatory and oxidative markers in T2DM, data linking long-term metformin and glibenclamide use to specific inflammatory and metabolic enzyme alterations remain limited, particularly in the African populations. This study therefore aimed to evaluate inflammatory cytokine profiles and key metabolic enzyme activities in T2DM patients receiving long-term metformin or glibenclamide therapy, with a view to identifying biochemical signatures associated with altered metabolic responsiveness.

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MATERIALS AND METHODS

Study Design and Participants

This comparative cross-sectional study was conducted at the Endocrinology Clinic of the University of Benin Teaching Hospital (UBTH), Nigeria. Adult patients aged 30 years and above with a clinical diagnosis of T2DM and receiving either metformin or glibenclamide monotherapy for at least three months were eligible for inclusion.

Exclusion criteria included insulin therapy, acute or chronic inflammatory diseases, renal or hepatic impairment, active infections, and antioxidant supplementation.

A total of 125 participants were recruited and categorized into three groups: (i) T2DM patients on metformin therapy, (ii) T2DM patients on glibenclamide therapy, and (iii) apparently healthy non-diabetic controls matched for age and sex.

Ethical Considerations

Ethical approval for the study was obtained from the Health Research Ethics Committee of the University of Benin Teaching Hospital (UBTH) (Approval No.: **ADM/E 22/A/VOL. VII/148217**). Written informed consent was obtained from all participants prior to enrolment.

Sample Collection

Venous blood samples were collected under aseptic conditions following an overnight fast. Serum and erythrocyte fractions were separated and stored at appropriate temperatures until analysis.

Biochemical Analyses

Serum IL-1β and IL-6 concentrations were quantified using commercially available ELISA kits in accordance with the manufacturers' protocols. Erythrocyte G6PDH activity and serum LDH activity were determined using standardized enzymatic assay kits following established procedures.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using Student's t-test or one-way analysis of variance (ANOVA) as appropriate. Statistical significance was

defined as $p < 0.05$. All analyses were conducted using standard statistical software.

RESULTS

Comparative analyses revealed significant alterations in inflammatory cytokine levels and metabolic enzyme activities among T2DM patients receiving long-term oral antidiabetic therapy. Male patients on metformin or glibenclamide exhibited significantly elevated IL-1β concentrations compared with control subjects ($p < 0.05$). IL-6 concentrations did not demonstrate consistent statistically significant differences across treatment groups.

G6PDH activity was significantly reduced in male patients receiving either metformin or glibenclamide relative to controls ($p < 0.05$), whereas female patients showed no significant reduction. In contrast, LDH activity was significantly increased in both male and female patients receiving either therapy ($p < 0.05$), suggesting enhanced glycolytic flux and cellular stress.

Table 1: Serum pro-inflammatory cytokine levels in patients with type 2 diabetes receiving Metformin therapy.

Variable	Control (Mean ± SD)	Metformin (Mean ± SD)
Male		
Interleukin-1β (pg/mL)	2.350 ± 1.626	10.94 ± 1.071**
Interleukin-6 (pg/mL)	2.100 ± 0.871	3.495 ± 0.095
Female		
Interleukin-1β (pg/mL)	7.950 ± 1.876	8.513 ± 1.559
Interleukin-6 (pg/mL)	3.300 ± 0.496	4.547 ± 0.331

***Significantly higher than control at p < 0.05.*

Table 2: Serum pro-inflammatory cytokine levels in patients with type 2 diabetes receiving glibenclamide therapy

Variable	Control (Mean ± SD)	Glibenclamide (Mean ± SD)
Male		
IL-1β (pg/mL)	2.35 ± 0.63	7.60 ± 1.19*
IL-6 (pg/mL)	2.10 ± 0.87	3.40 ± 1.57
Female		
IL-1β (pg/mL)	7.95 ± 1.88	9.10 ± 1.41
IL-6 (pg/mL)	3.30 ± 1.50	3.12 ± 1.42

**Significantly different from control (p < 0.05).*

Table 3: G6PDH and LDH activities in patients with type 2 diabetes receiving metformin therapy.

Variable	Control (Mean ± SD)	Metformin (Mean ± SD)
Male		
LDH (U/L)	263.3 ± 13.8	277.9 ± 18.3*
G6PDH (U/gHb)	2.06 ± 1.28	0.86 ± 0.08*
Female		
LDH (U/L)	269.8 ± 11.3	275.8 ± 16.0*
G6PDH (U/gHb)	1.11 ± 0.01	1.11 ± 0.04

**Significantly different from control (p < 0.05).*

Table 4: G6PDH and LDH activities in patients with type 2 diabetes receiving glibenclamide therapy

Variable	Control (Mean ± SD)	Glibenclamide (Mean ± SD)
Male		
LDH (U/L)	263.3 ± 23.8	279.8 ± 29.0*
G6PDH (U/gHb)	2.06 ± 0.28	0.69 ± 0.34*
Female		
LDH (U/L)	269.8 ± 21.3	290.5 ± 28.3*
G6PDH (U/gHb)	1.11 ± 0.91	1.07 ± 0.92

**Significantly different from control (p < 0.05)*

DISCUSSION

The present study demonstrates that long-term metformin and glibenclamide therapy in T2DM is associated with distinct inflammatory and metabolic enzyme alterations, with notable sex-specific differences, consistent with reports linking chronic inflammation and metabolic stress to secondary treatment failure (Donath & Shoelson, 2011; Brooks, 2020; Prentki &Nolan, 2020).

Elevated IL-1β levels observed particularly in male patients are consistent with the role of IL-1β in metabolic inflammation, insulin resistance, and β-cell dysfunction. These findings support accumulating evidence linking chronic inflammation to reduced metabolic responsiveness in T2DM.

The observed reduction in G6PDH activity among male patients suggests impaired NADPH generation and compromised antioxidant defense, potentially predisposing cells to oxidative stress a mechanism previously described in diabetic metabolic dysregulation (Sharma et al., 2017; Brooks, 2020). G6PDH deficiency has previously been associated with poor glycaemic control and increased susceptibility to oxidative damage in diabetic states. Conversely, elevated LDH activity across treatment groups may reflect altered glycolytic metabolism and increased cellular stress associated with chronic hyperglycaemia and prolonged pharmacotherapy.

Sex-specific differences observed in this study may reflect hormonal modulation of inflammatory and metabolic pathways, as well as differences in drug adherence, pharmacokinetics, and lifestyle factors. Most importantly, the findings do not imply classical pharmacological drug resistance but rather suggest biochemical adaptations that may contribute to secondary treatment failure over time.

CONCLUSION

This study demonstrates that long-term metformin or glibenclamide therapy in individuals with T2DM is associated with measurable alterations in inflammatory and metabolic biomarkers. Elevated IL-1β levels, reduced G6PDH activity and increased LDH activity particularly among male patients, suggest the presence of chronic metabolic stress and inflammatory activation during prolonged oral antidiabetic therapy. These findings underscore the potential utility of inflammatory cytokines and metabolic enzymes as adjunct biomarkers for monitoring therapeutic responsiveness and guiding long-term diabetes management strategies.

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