The Effect of Metformin on Coagulation Profiles in Type II Diabetes Mellitus: A Tertiary Care Hospital of Nepal

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ABSTRACT

Background:

Type II Diabetes Mellitus (T2DM) is associated with a prothrombotic state due to altered coagulation and fibrinolysis. Metformin, the first-line treatment for T2DM, may influence coagulation parameters, but this effect is underexplored in the Nepalese population. The purpose of this study was to assess how metformin affected the levels of D-dimer, prothrombin time (PT), and activated partial thromboplastin time (APTT) in patients with type 2 diabetes.

Method:

Glycemic control and metformin use were used to group 120 T2DM patients and 120 healthy controls in a cross-sectional study. PT, APTT, D-dimer, and platelet count tests were performed on blood samples and the effects of raising glucose concentrations with and without metformin were evaluated using an in vitro model.

Result:

PT, APTT, and D-dimer levels were significantly higher in T2DM patients ($p<0.05$), with more noticeable changes in those with poorly controlled diabetes. Patients receiving metformin showed some degree of normalization which indicate that Metformin partially reversed the effects of high glucose on coagulation markers in vitro.

Conclusion:

Metformin may enhance coagulation profiles, which would support its use in conjunction with glycemic control and lower the risk of thrombosis.

Keywords: Type II Diabetes Mellitus, Coagulation Profile, Metformin, Hyperglycemia, D-dimer, Prothrombin Time, APTT, Thrombosis, Platelet Function, AMPK.

Introduction

It is widely acknowledged that type 2 diabetes mellitus (T2DM) contributes to a hypercoagulable condition known as "diabetic thrombophilia" in addition to its metabolic effects."[1] The imbalance between the fibrinolytic and coagulation systems, which is made worse by persistent hyperglycemia, insulin resistance, and systemic inflammation, is the cause of this prothrombotic tendency. Many studies have shown that people with diabetes have hypercoagulability, which is indicated by shortened activated partial thromboplastin time (APTT), increased D-dimer, and elevated fibrinogen levels.[1],4 The risk of myocardial infarction, stroke,

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and venous thromboembolism (VTE) is increased by these pathological causes. Despite this, little is known about how commonly used anti-diabetic medications, especially metformin, affect coagulation parameters in South Asian settings, such as Nepal.[6]

Materials and Methods

240 participants ,120 T2DM patients and 120 healthy controls were chosen from the outpatient department of Manmohan Memorial Hospital in Kathmandu for this descriptive cross-sectional study. The method used to choose participants was convenience sampling. Metformin use and HbA1c levels were used to classify diabetic patients. Individuals with recent surgery, coagulation disorders, liver/renal disease, anticoagulant use, or pregnancy were excluded. Blood samples were analyzed for fasting glucose, HbA1c, lipid profile, platelet count, PT, APTT (Sysmex CA-101), and D-dimer (CLIA, Maglumi). In vitro, whole blood (n=5 per group) was incubated with 5%, 10%, or 20% glucose, and a separate group with 20% glucose plus 20 mM metformin. After 2 hours at 37°C and centrifugation, plasma was analyzed for glucose, PT, APTT, and D-dimer.

Results

Out of 120 diabetic patients, 70 (58%) were male and 50 (42%) were female, indicating a higher prevalence of Type II Diabetes Mellitus among males (Figure 1).

The majority of patients (61.7%) were in the 40–55 age group, followed by 33.4% in the 25–40

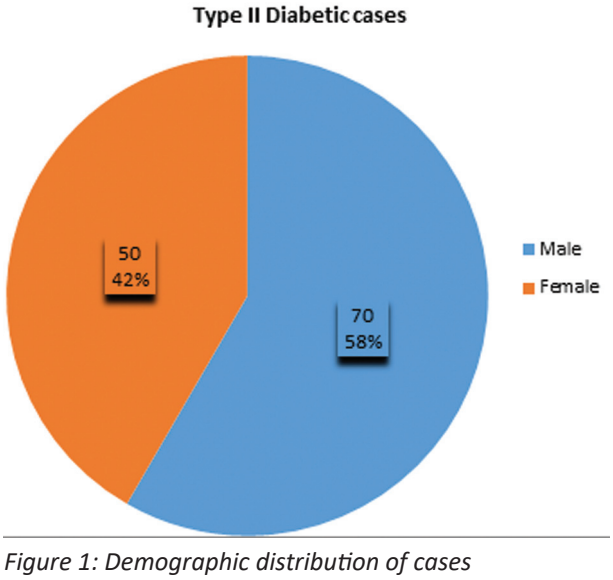

Figure 1: Demographic distribution of cases

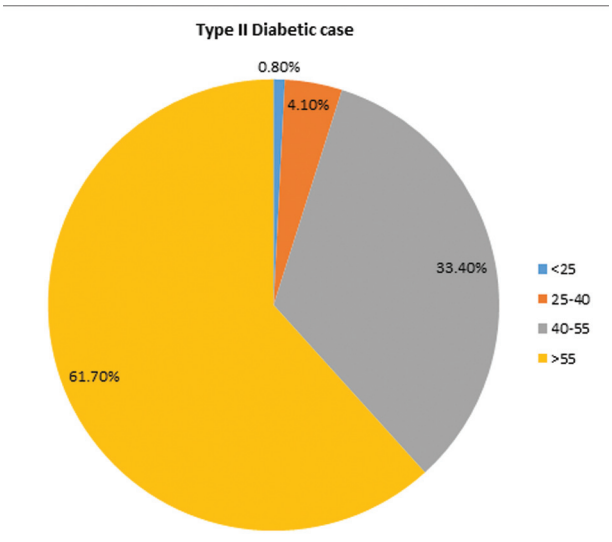

Figure 2: Distribution according to age in year

age group. Only 4.1% were under 25 years, and 0.8% were above 55, indicating that middle-aged individuals (especially 40–55) are the most affected by T2DM in this study population (Figure 2).

"Diabetic patients showed significantly shorter prothrombin time (PT) and activated partial thromboplastin time (APTT) compared to healthy controls ($p<0.01$), indicating a potentially hypercoagulable state. D-dimer levels were also elevated in the diabetic group, suggesting increased

Table 1 Comparison of biochemical parameter between controls (N=120) and cases (N=120)

Parameter	Healthy control N=120 Mean± SD	Diabetes cases N=120 Mean± SD	P value
Platelet (millions/ul)	2.21±0.50	2.31±0.71	0.186
D-dimer (mg/L)	0.19±0.75	0.29±0.13	**0.001*** **
PT(sec)	13.19±0.54	12.84±1.34	**0.002** **
APTT(sec)	31.50±10.0	30.53±1.94	**0.002** **

Table 2: Comparison between good control N=40 and poor control N=80 diabetic patient based on HbA1c

Parameter	Good control (N=40) Mean± SD	Poor control (N=80) Mean± SD	P value
Platelet(lakh/cumm)	2.19±0.53	2.39±0.74	0.086
D-dimer(mg/L)	0.20±0.75	0.23±0.14	**0.023** **
PT(sec)	13.02±0.65	12.51±1.47	**0.022** **
APTT(sec)	31.43±1.52	30.18±2.02	**0.018** **

Table 3: Comparison between Metformin Treated (and Untreated Diabetes Patients

Parameters	Metformin treated N=76 Mean± SD	Untreated Cases N=44 Mean± SD	P value
Platelet (lakh/cumm)	2.16±0.59	2.28±0.81	**0.004****
D-dimer(mg/L)	0.22±0.90	0.25±0.14	**0.008****
PT(sec)	13.11±1.52	12.36±0.73	**0.032***
APTT(sec)	31.10±1.64	29.55±2.06	**0.025***

fibrin turnover and a higher risk of thrombosis. However, no statistically significant difference was observed in platelet count between the diabetic and control groups as shown in Table 1.

Above table (table 2 compares hematological parameters between diabetic patients with good and poor glycemic control based on HbA1c levels. While platelet counts showed no significant difference between the two groups (P=0.086), patients with poor control exhibited significantly higher D-dimer levels (P=0.023) and lower prothrombin time (PT) (P=0.022) and activated partial thromboplastin time (APTT) (P=0.018) compared to those with good control. These results point to altered coagulation patterns in persons with poorly managed diabetes. All data were within clinically recognized normal ranges, despite statistically significant changes in PT, APTT, and D-dimer levels between subgroups. These results shows that although there might be minor changes in coagulation patterns, they might not have any clinical significance.

Metformin-treated patients had significantly lower platelet counts (P=0.004) and D-dimer levels (P=0.008) compared to untreated cases. Furthermore,the metformin-treated group had significantly higher prothrombin time (PT) and activated partial thromboplastin time (APTT) (P=0.032 and P=0.025, respectively).These findings suggest that metformin may have a positive impact on diabetic patients' coagulation profiles. It is important that the difference between statistical and clinical significance. Although the differences were statistically significant, their clinical implications were limited because they lies within the normal physiological range.

In vitro experiments demonstrated that high glucose (20%) exposure resulted in prolonged prothrombin time (PT), elevated D-dimer levels, and reduced activated partial thromboplastin time

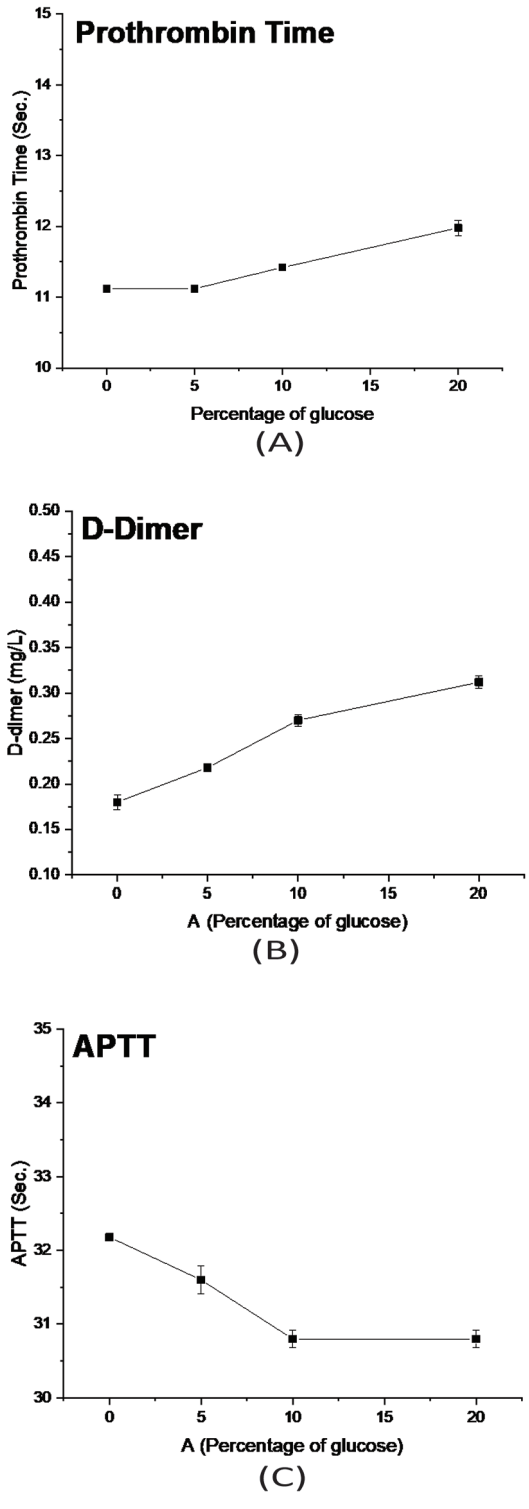

Figure 3 : *Dose-dependent change in coagulation parameters (n=5) by high glucose treatment in which percentage corresponding to 5%=328.5±3,2 mg/dl, 10%=541±1.9 mg/dl and 863±2.4 mg/dl after incubation for 2 hours.(A) Prothrombin time is increased significantly with increasing dose of glucose p=0.04. (B) APTT is significantly decreased with increasing dose of glucose, p=0.03. (C) D-dimer is significantly increased with increasing dose of glucose p=0.02.*

(APTT). However, co-treatment with metformin reversed these effects, normalizing PT and APTT values and decreasing D-dimer levels, indicating a restored fibrinolytic balance as shown in figure 3 and figure 4.

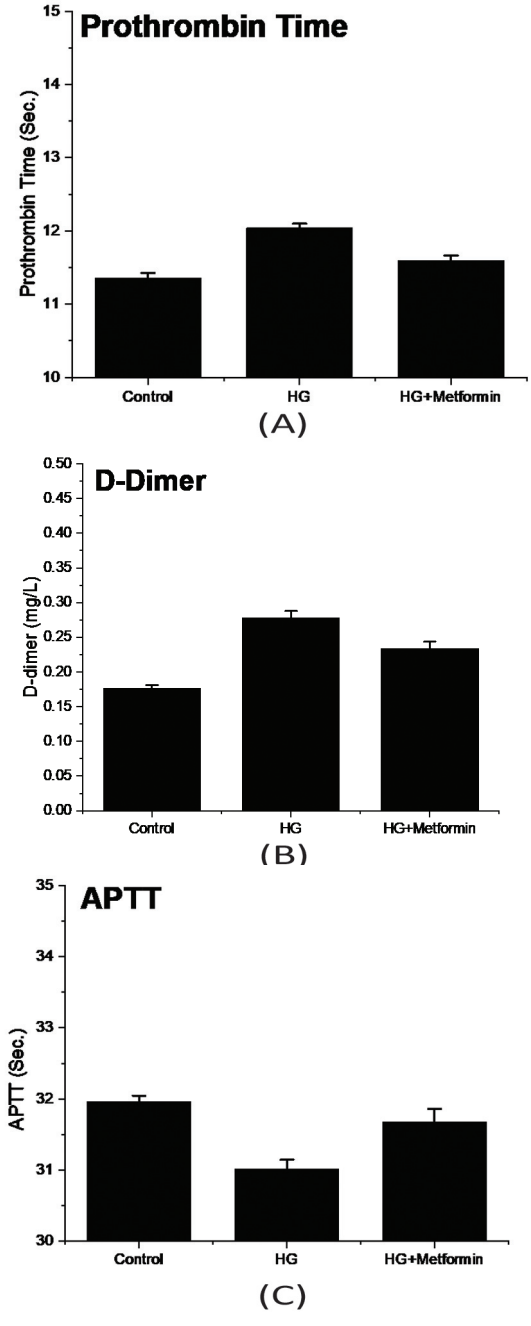

Figure 4 (A, B & C): *Effect of metformin dose (1.5 µmol/ml) in high-glucose-induced change in coagulation parameters. Glucose 20% corresponding to dose mean 863±2.4 mg/dl is treated for 2 hours with and without treatment of metformin. (A) Prothrombin time is significantly decrease or restored by metformin p=0.512. and consistently high glucose-induced change in APTT (B) , p=0.512. and D-dimer p=0.082. (C) also normalized by metformin treatment is significantly increased with increasing dose of glucose.*

Discussion:

The relationship between type 2 diabetes mellitus (T2DM) and a hypercoagulable state is well documented, with poor glycemic control further exacerbating the risk of thrombosis. This is supported by findings of shortened prothrombin time (PT) and activated partial thromboplastin time (APTT) in patients with HbA1c levels ≥7%, indicating accelerated clot formation. Chronic hyperglycemia contributes to this prothrombotic environment through several mechanisms. Hyperglycemia induces mitochondrial hyperpolarization and reactive oxygen species overload in platelets, which enhances their adhesion and aggregation. Furthermore, platelet sensitivity to agonists like adenosine diphosphate (ADP) is increased by insulin resistance. Dense fibrin clots that are resistant to fibrinolysis are created when fibrinogen undergoes non-enzymatic glycation. Concurrently, the endothelium's ability to prevent thrombosis is compromised by decreased nitric oxide bioavailability. Particularly in poorly managed diabetes, elevated levels of plasminogen activator inhibitor-1 (PAI-1) further contribute to hypofibrinolysis. [7,8,9.]

Metformin has significant antithrombotic effects in addition to lowering blood sugar by blocking mitochondrial complex I, it modifies platelet activity by lowering P-selectin expression, normalizing calcium flux. By stimulating AMP-activated protein kinase (AMPK), which increases nitric oxide synthesis, metformin also improves endothelial function. Metformin also increases the porosity of fibrin fibers. Metformin modifies the coagulation cascade by lowering thrombin generation potential, even though it has no direct effect on coagulation times like PT or APTT or the levels of coagulation factors II. [10,11,12].

These results are corroborated by in vitro research, which shows that metformin at concentrations of 5–10 mM inhibits platelets' ability to produce ATP within 48 hours. Crucially, clinical research indicate that these antithrombotic effects happen without extending bleeding times, indicating that metformin has a good safety profile when used in thromboprophylaxis. Metformin's superior cardiovascular outcomes when compared to other glucose-lowering agents may be explained by its

dual action in reducing hypercoagulability and controlling hyperglycemia [13, 14, 15]. Divergent effects were observed in vitro: APTT decreased with high glucose and slightly increased with metformin, while PT increased with high glucose but normalized with metformin. This conflicting pattern calls for more mechanistic investigation.

Conclusion

This study shows that patients with type 2 diabetes with poor glycemic control, show notable small but statistically significant changes.None of the values showed a hypercoagulable state because they were all within normal clinical ranges. Although patients receiving metformin showed better coagulation profiles, a causal relationship cannot be established due to limited the cross-sectional design of this study.

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