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Coagulation Profile In Diabetes Mellitus And Its Association with Microvascular Complications in Uncontrolled and Controlled Diabetes at Edo Specialist Hospital, Benin-City, South-South, Nigeria

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Abstract: Diabetes mellitus induces coagulopathies by glycating haemoglobin, prothrombin, fibrinogen, and other proteins involved in the clotting mechanism. Shortened PTTK and PT represent a hypercoagulable state related to an elevated thrombotic risk and a negative cardiovascular effect, both of which can lead to the onset and progression of microvascular and macrovascular problems. The study aims to compare the coagulation profile in diabetes-related microvascular complications in clients with uncontrolled and controlled diabetes at an Edo specialty hospital in Benin City. A hospital-based case-control study was carried out at ESH in Benin City. Two hundred eighty individuals were recruited for the study, including 215 diabetes patients (55 type I diabetes, 160 type II diabetes, and 65 non-diabetics) attending the outpatient department of ESH in Benin City. Blood was drawn for coagulation and biochemical assays. Diabetes patients had significantly lower levels of PT and PTTK compared to non-diabetes controls ($p<0.05$). Fibrinogen and D-dimer levels were considerably higher ($p<0.05$). The PTTK level was much lower in type 2 diabetes than in type 1 diabetes, and there was a significant difference in platelet count between type 1 and type 2 diabetes. Female diabetes patients had lower levels of PTTK and PT than male diabetic patients. Furthermore, in diabetes with complications, the levels of PTTK and platelet count were lower (p0.05). It was discovered that insulin treatment decreased platelet count, whereas sulfonylurea increased fibrinogen levels in people with diabetes. Diabetes may increase the risk of clotting, as indicated by shorter PTTK, PT, and higher fibrinogen and D-dimer levels compared to controls. The coagulation profile should be evaluated as a regular screening test in diabetes patients to reduce the incidence and prevalence of vascular burden and to improve quality of life.
Keywords: Diabetes mellitus; coagulation; vascular complication

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INTRODUCTION

Diabetes Mellitus (DM) is a complex metabolic condition that affects carbohydrate, lipid, and protein metabolism. India has the most diabetic patients (31.7 million), followed by China (20.8 million) and the United States (17.7 million) (Kaveeshwar, 2014). The global prevalence of diabetes is 6.7%, with Nigeria having a 3.74% prevalence in adult cases (International Diabetes Federation, 2022) The frequency in Nigeria has recently been assessed to be 1.7% of the overall population (International Diabetes Federation, 2017). According to the most recent predictions, the global prevalence of Diabetes is anticipated to reach 592 million by 2035 (Forouhi, 2014). Diabetes mellitus is characterized by persistent hyperglycemia, which affects various organs due to microvascular and macrovascular complications such as neuropathy, retinopathy, nephropathy, and so on (Kharroubi, 2015). Atherogenic dyslipidaemia, hypertension, glucose intolerance, and a prothrombotic state are frequent metabolic abnormalities in diabetic individuals (Grundy,1998). This prothrombotic condition is a more recently discovered component of the metabolic syndrome; persons with metabolic syndrome have a pattern of coagulation factors that promote thrombosis or retard thrombolysis (Grundy,1998; Nolan,1996). The most prevalent manifestation of diabetic macrovascular consequence is cardiovascular disease. Diabetics are at a 2- to 4-fold greater risk of developing coronary artery disease. Diabetic patients with poor glycemic control, as well as those with other co-morbid illnesses such as hypertension and obesity, have a higher prevalence of microvascular problems. Microvascular consequences include retinopathy, nephropathy, and neuropathy. (Luscher, 2013). Diabetics have a higher risk of thrombotic problems due to hyperglycemia, which causes platelet hyperreactivity, hyperfibrinogenemia, increased thrombin production, and decreased fibrinolysis (Schneider, 2009).

This study evaluated the coagulation profile in diabetes related with microvascular complications in uncontrolled and controlled diabetes clients, as well as the effect of anti-diabetes medicines on the coagulation profile of diabetes subjects at an Edo specialist hospital in Benin-City.

The underlying causes for increased thrombosis risk in diabetes are complex and involve numerous routes. Diabetes patients have early atherosclerosis and more widespread vascular disease, which predisposes them to plaque rupture and thrombus formation. Furthermore, these patients have an enhanced thrombotic tendency due to platelet hyper-reactivity and increased activation of prothrombotic coagulation factors, as well as impaired fibrinolysis. Elevated fibrinogen levels (Imperatore,1998), increased plasminogen activator inhibitor (PAI)-1 (Byberg et al.,1998), and other abnormalities in platelet function characterize the prothrombotic condition (Nolan,1996). Diabetes individuals have varying coagulation patterns, according to research. Acang and Jalil (1993) discovered that diabetic patients had shorter prothrombin times (PTs) and partial thromboplastin times with kaolin (PTTK). In contrast, Collier**,**1992 discovered normal PTs in type 2 diabetic patients. Erem**,** (2005) reported normal PTs and APTTs in diabetics. Despite the fact that Sub-Saharan Africa has the greatest prevalence of diabetes, there are paucity of data on coagulation profile on diabetes in study area, therefore it is necessary to evaluation of coagulation profile of people with Diabetes Mellitus in a specialist hospital in Benin City, Edo State.

MATERIALS AND METHODS

This hospital-based case-control research was conducted at the Edo specialist hospital in Benin City between April and October 2022. The hospital serves as the primary referral centre for Benin and its neighbouring State and is the largest healthcare facility in Benin City. According to the 2006 Nigerian census, Benin City, the capital and largest city of Edo State, has a population of 1,050,000; located at a longitude 6.30N and latitude 5.60E and has a total area of 1204km^2.

The objective of the study was to assess the coagulation profile in diabetes-related microvascular complications in patients with uncontrolled(HbA1c>7.0%) and controlled(HbA1c<7.0%) diabetes at a 200-bed Edo specialist hospital in Benin City. For the study, 280 individuals were gathered from the outpatient department of ESH in Benin City, including 215 diabetes patients comprising (160 patients with type II diabetes and 55 type I) and 65 non-diabetics.

One of the glycaemic recommendations for persons with diabetes is an HbA1c of 7.1% or below (ADA,2018). HbA1c <7.1% is a sign of good glycemic management (Mclntosh et al.,2001). The study excluded individuals with septicaemia, bleeding issues, liver illness, cancer, pregnancy, postoperative patients, and individuals taking anticoagulants.

The Edo State Ministry of Health (ethical code 1525/205, dated 15th April 2022) approved the study. Participants were given a detailed description of the study's protocols before being asked for informed consent. Results and documentation were rigorously kept private. A well-designed questionnaire was utilized to gather data on each participant's clinical history.

10 ml of blood were taken from each participant who gave their consent, of which 5 ml were placed in a fluoride oxalate tube after 15 hours fasting; for fasting blood glucose, 1.4 ml were placed in an EDTA tube, and 3.6 ml were placed in a plastic buffered tri-sodium citrate tube containing 380ul of 3.2% buffered tri-sodium citrate. Centrifuging the sample in tubes containing 3.2% buffered trisodium citrate and fluoride oxalate for 15 minutes at 1500 rpm separated the plasma for PT/APTT and plasma glucose assays, respectively.

Sysmex Haematology Analyzer was used to assess platelet count (Sysmex XT-2000i, Kobo, Japan). Venous blood treated with sodium citrate to prevent clotting was used to estimate prothrombin time and partial thromboplastin time with kaolin, fibrinogen, and D-dimer. Using the glucose oxidase/peroxidase technique, fasting plasma glucose was calculated (Barham,1972). The results are shown as mean ± standard error of the mean (SEM). SPSS version 23.0 was used to analyze the data. Using the student's t-test and one-way ANOVA, the mean values for diabetes and control were compared. Statistics were judged significant at $P<0.05$.

RESULTS AND DISCUSSION

The coagulation profiles of patients with and without diabetes mellitus are displayed in table 1. Prothrombin time and partial thromboplastin time with kaolin, fibrinogen, D-dimer, and platelet levels were shown to be statistically significant ($p< 0.05$) when compared to the control. Type 1 and type 2 diabetes coagulation profiles are displayed in Table 2. When compared, it was shown that type 1 diabetes had a low platelet count, and type 2 diabetes had a shorter duration for PTTK ($p< 0.05$). The coagulation profile of male and female diabetic individuals is displayed in Table 3. When compared to males, it was found that females had statistically substantially lower levels of PTTK and platelet count ($p> 0.05$) but higher levels of PT and D-dimer ($p > 0.05$).

The coagulation profile of glycaemic control is displayed in Table 4. In subjects with poor glycemic control (HbA1C>7%), the PTTK time was shown to be shorter ($p<0.05$). Diabetes with complications (retinopathy and nephropathy) was displayed in Table 5. together with diabetes without complications. It was shown that the PTTK duration was shorter, and the platelet count was lower ($p< 0.05$). When compared, the levels of fibrinogen and D-dimer were not statistically different ($p>0.05$). Multiple comparisons of the impact of anti-diabetes medications on the coagulation profile were included in Table 6. It was shown that subjects using metformin and daonil had shorter PTTK times (p 0.05), subjects using insulin and daonil had lower platelet counts ($p<0.05$), subjects using sulfonylurea had shorter PTs ($p>0.05$). Subjects using metformin and daonil had higher fibrinogen levels ($p>0.05$).

Table 1. Coagulation Profile in Diabetes Mellitus

	Diabetes Mellitus n =215	Non-Diabetes n =65	P-Value
PT(Sec)	12.64±0.46	14.51±0.12	P=0.029
PTTK(Sec)	25.13±0.44	29.84±0.22	P=0.001
Fibrinogen(g/L)	2.39±0.06	1.96±0.07	P=0.001
D-dimer(g/L)	0.19±0.02	0.13±0.01	P=0.002
Platelets count(cell/L)	177.22±2.19	195.62±3.21	P=0.001
FBS(mg/dl)	191.58±3.28	97.89±2.20	P=0.001
AGE(years)	53.44±1.10	36.95±1.00	P=0.001

Value are expressed in mean±SEM, PT- Prothrombin time, PTTK- Partial thromboplastin time with kaolin,FBS-Fasting blood sugar, $p<0.05$- Significant, $p>0.05$- Non-significant

Table 2. Coagulation Profile among Type I Diabetes Mellittus and Type II Diabetes Mellitus

	Type I DM n =55	Type II DM n =160	P-Value
PT(Sec)	13.34±1.21	12.41±0.46	P=0.471
PTTK(Sec)	28.41±1.20	24.00±0.39	P=0.001
Fibrinogen(g/L)	1.92±0.14	1.96±0.07	P=0.758
D-dimer(g/L)	0.14±0.02	0.12±0.01	P=0.369
Platelets count(cell/L)	155.96±3.29	184.52±2.47	P=0.001
FBS(mg/dl)	170.40±6.78	198.86±3.58	P=0.001

Value are expressed in mean±SEM, PT- Prothrombin time, PTTK- Partial thromboplastin time with kaolin,FBS-Fasting blood sugar, $p<0.05$- Significant, $p>0.05$- Non-significant

Table 3. Coagulation Profile among Male and Female Diabetes Mellitus

	Males n =65	Females n =150	P-Value
PT(Sec)	13.64±1.08	12.21±0.47	P=0.228
PTTK(Sec)	27.92±1.09	23.92±0.38	P=0.001
Fibrinogen(g/L)	1.93±0.12	1.96±0.08	P=0.802
D-dimer(g/L)	0.13±0.12	0.12±0.01	P=0.583
Platelets count(cell/L)	154.98±2.87	186.85±2.51	P=0.001
FBS(mg/dl)	177.80±6.53	197.55±3.67	P=0.010

Value are expressed in mean±SEM, PT- Prothrombin time, PTTK- Partial thromboplastin time with kaolin,FBS-Fasting blood sugar, p<0.05-Significant, p>0.05- Non-significant

Table 4. Coagulation Profile among Controlled and Uncontrolled Diabetes

	HbA_1C <7.0% n =45	HbA_1C >7.0% n =170	P-Value
PT(Sec)	12.38±1.31	12.71±0.47	P=0.766
PTTK(Sec)	28.82±1.45	24.16±0.38	P=0.001
Fibrinogen(g/L)	1.96±0.16	1.96±0.01	P=0.988
D-dimer(g/L)	0.13±0.02	0.12±0.01	P=0.756
Platelets count(cell/L)	156.31±3.44	182.75±2.45	P=0.001
FBS(mg/dl)	151.80±4.58	202.11±3.56	P=0.001
AGE(years)	53.44±1.10	36.95±1.00	P=0.001

Value are expressed in mean±SEM, PT- Prothrombin time, PTTK- Partial thromboplastin time with kaolin,FBS-Fasting blood sugar, p<0.05-Significant, p>0.05- Non-significant.

Table 5. Coagulation Profile among Diabetes with Complication and Without Complication

	Diabetes With Complication N =75	Diabetes Without Complication N =140	P-Value
PT(Sec)	13.68±0.97	12.09±0.48	P=0.102
PTTK(Sec)	23.90±0.40	27.42±0.97	P=0.001
Fibrinogen(g/L)	1.89±0.11	1.98±0.08	P=0.530
D-dimer(g/L)	0.13±0.02	0.12±0.01	P=0.660
Platelets count(cells/L)	155.67±2.67	188.76±2.56	P=0.001
FBS(mg/dl)	193.93±3.63	187.19±2.56	P=0.328

Value are expressed in mean±SEM, PT- Prothrombin time, PTTK- Partial thromboplastin time with kaolin,FBS-Fasting blood sugar, p<0.05-Significant, p>0.05- Non-significant

Table 6. Coagulation Profile Among Diabetes On Different Anti-Diabetic Drugs

	Melformin/ Daonil N =100	Insulin/ Daonil N =55	Sulfonylurea N =60	F-Value	P-Value
PT(Sec)	$12.78±0.59^a$	$13.34±1.21^a$	$11.78±0.74^a$	0.78	P=0453
PTTK(Sec)	$23.38±0.47^a$	$28.42±1.20^b$	$25.05±0.67^a$	11.68	P=0.001
Fibrinogen(g/L)	$1.92±0.10^a$	$1.92±0.14^a$	$2.05±0.13^a$	0.41	P=0.663
D-dimer(g/L)	$0.11±0.01^a$	$0.14±0.02^a$	$0.12±0.02^a$	0.47	P=0.623
Platelets count(cells/L)	$177.38±3.18^a$	$155.96±3.29^b$	$196.43±3.40^c$	28.66	P=0.001
FBS(mg/dl)	$191.42±4.11^a$	$170.40±6.78^b$	$211.26±6.38^c$	11.34	P=0.001

Value are expressed in mean±SEM, PT- Prothrombin time, PTTK- Partial thromboplastin time with kaolin,FBS-Fasting blood sugar, p<0.05-Significant, p>0.05-Non-significant, Superscript that are same show non-significant among the group while superscript with difference show significant difference among the group.

Diabetes mellitus (DM) is a major public health issue and one of the leading causes of death globally; more than half of people with diabetes, predominantly type 2, go untreated. This is due to insulin insufficiency or relative insulin receptor insensitivity. Without an early diagnosis, the complication rate continues to climb. According to WHO, 70% of people with diabetes live in underdeveloped nations, including Nigeria (Oyakhire, 2021). The fundamental barrier against thrombosis, vascular endothelium, is abnormal in diabetes. In hyperglycemia, nitric oxide generation is decreased by preventing the activation of endothelial Nitric Oxide Synthase (eNOS) and high amounts of reactive oxygen species, most notably superoxide anion. The superoxide anion reacts with the nitric oxide ion to create the peroxynitrite ion. Peroxynitrite inhibits the formation of prostacyclin, a vasodilator. Increased adipose tissue synthesis of free fatty acids due to insulin resistance impairs nitric oxide generation (Beckman, 2002).

Diabetes improves coagulation capacity. In Type 2 diabetes, elevated levels of plasminogen activator inhibitor-1 hinder fibrinolysis. Diabetes is characterized by increased expression of tissue factor and coagulation factors, as well as a decrease in endogenous anticoagulants such as protein C and antithrombin- 3. Thus, people with Type 2 diabetes have an increased proclivity for coagulation as well as impaired fibrinolysis (Beckman, 2002). The current study compared the coagulation profile in diabetes associated with microvascular complications in the deregulated (HbA1C>7%) and regulated (HbA1C7%) groups. The study also looked at the effect of diabetes medications on the coagulation profile.

In this study, it was discovered that prothrombin time (PT) and partial thromboplastin time with kaolin (PTTK) were shorter in diabetes participants compared to non-diabetes ($p<0.05$). In contrast, platelet count was lower, and fibrinogen and D-dimer levels were higher ($p<0.05$). Interleukin-6 levels have been demonstrated to encourage hepatocytes to generate fibrinogen, demonstrating an important relationship between inflammation and hypercoagulation (Ajjan & Grant, 2006). A second pathway involves insulin resistance, a critical pathogenic factor in T2DM and is related to increased hepatic fibrinogen synthesis in response to insulin, as opposed to T1DM and healthy controls (Barazzoni, 2003; Tessari**,** 2006). Increased fibrinogen production has also been observed postprandially in T2DM but not in healthy controls, implying that fibrinogen synthesis is dysregulated in this state due to hepatic dysregulation (Tessari,2006). Sapkota, (2013) proposed that in diabetes, free radicals trigger thrombin production, implying that oxidative stress could be a relationship between hyperfibrinogenaemia and diabetes. Arpaci, (2015) concluded that no significant changes in PT, PTTK, and fibrinogen levels were seen in diabetic individuals belonging to the controlled diabetic group (HbA1c< 7.0%) and the uncontrolled diabetes group (HbA1c >7.0%).

Although improvement in glycemic management does not necessarily lead to a reduction in fibrinogen levels, as demonstrated in this study, a link between plasma glucose and fibrinogen levels have been documented, directly implicating glycaemia in modifying fibrinogen levels (Becker,2003). However, it should be noted that the kind of hypoglycaemic therapy can affect fibrinogen levels since metformin use has been linked to lower fibrinogen levels than sulfonylurea use, which has been linked to higher fibrinogen levels (Fanghanul, 1998).

In this study, it was discovered that people with diabetes with poor glycemic control (HbA1C>7%) had higher mean platelet counts than people with diabetes with adequate glycemic control (HbA1C<7%), a statistically significant finding ($P<0.05$). Due to the thrombopoietin and nitric oxide produced during diabetes, the platelet

count has increased (Jabeen, 2013). In a study conducted in 2014 by Shetty A et al., (2014) it was found that platelet count varied with rising glycemic levels. On the other hand, a study by Kaur, (2019), demonstrated that the patient's glycaemic levels did not impact platelet counts.

This study found no differences in PT between people with diabetes with HbA1C< 7% (12.38±1.31 sec) and diabetics with HbA1C >7% (12.71±0.47Sec) ($p>0.05$), which is consistent with findings from Arpaci, (2015) who found no differences in PT between individuals in the regulated diabetic group (HbA1c< 7.0%) and those in the deregulated diabetic group (HbA1c>7%).

In this study, the amount of platelet count was found to be higher in type 2 diabetes as compared to type 1 diabetes ($p<0.05$), which could be attributable to endothelial dysfunction, which promotes platelet activation by decreasing the production of nitric oxide (NO), which reduces platelet reactivity. Oxidative stress amplifies this impact by decreasing NO activity and increasing platelet activation. Inflammation and platelet activation are mutually exclusive. It was also discovered that subjects with control hyperglycemia have lower platelet reactivity and better antiplatelet effects. Platelets from insulin-resistant people are less sensitive to the activities of nitric oxide and prostacyclin (Anfossi et al.,1998). The intact endothelium produces nitric oxide and prostacyclin, which slow platelet activation by increasing intra-platelet concentrations of cyclic nucleotides, cyclic guanosine monophosphate, and cyclic adenosine monophosphate. As a result, resistance to the actions of these medicines promotes enhanced platelet reactivity. As a result, insulin resistance reduces the tonic antagonism of platelet activation, increasing platelet reactivity.

The prothrombin time was decreased in diabetes patients compared to controls in this study, which contradicted the findings of Abdulrahaman and Dallatu (2012), who found that PT was enhanced in untreated diabetics compared to treated diabetics. Furthermore, in diabetes with complications, there was an increase in PT. The conversion of dormant factor VII to active factor VII causes an increase in PT. This study found no significant difference in fibrinogen levels between controlled and uncontrolled glucose diabetic subjects ($p>0.05$), which is consistent with the findings of Arpaci,2015, who found no significant increase in fibrinogen levels between people in the regulated diabetic group (323.42 mg/dL) and people in the dysregulated diabetic group (342.36 mg/dL).

In this study, the d-Dimer levels of individuals with managed glucose (0.13±0.02g/L) and uncontrol glucose (0.12±0.01g/L) did not significantly differ among diabetic participants ($p>0.05$). Increased fibrin clot production and disintegration are thought to cause elevated levels of d-Dimer (Nwose, 2007). In their study, Nwose,(2007), found that the transition from prediabetes to diabetes and diabetes with complications was accompanied by a progressive rise in plasma d-Dimer levels.

In this study, participants with uncontrolled diabetes had shorter PTTK times than those with controlled diabetes ($p< 0.05$), likely caused by increased factor VIII activity. The integrity of the intrinsic route is shown by PTTK (Mard-Soltani,2011). Since factor VIII is a cofactor for factor IXa in the intrinsic route, an increase in factor VIII may affect the PTTK's response time. Diabetes-related endothelial abnormalities play a role in the rise of factor VIII. In contrast to this study, Abdulrahaman and Dallatu (2012) found that untreated diabetics had a considerable increase in PTTK levels (58.460±4.146) compared to treated diabetics (43.260±5.587) and non-diabetic controls (41.3804.295), albeit the exact mechanism is unknown.

This study supports the shorter PTTK measured by Acang and Jalil (1993). Still, it supports the findings of Zhao, (2011), who found that individuals with type 2 diabetes in a case-control study at Zhejiang University in China had insignificantly shorter PT values. Also, in 2010, Madan,(2010) did not discover any variations in PT among people with type 2 diabetes. The variations in coagulation test findings could be brought on by variations in sample size, race, and geographic location.

In agreement, our investigation found no differences in fibrinogen levels between diabetic individuals with and without vascular problems ($p>0.05$), which is consistent with Asakawa,(2000). Uncertainty exists regarding the pathogenetic mechanism behind the stimulation of clotting in diabetes. Hyperglycemia causing decreased biological activity of the anticoagulant protein AT-III in diabetic and non-diabetic patients is one example of how hyperglycemia can affect anticoagulant system components (Ceriello,1993).

This study found that metformin treatment for diabetes patients had a shorter PTTK than other anti-diabetes medications. In contrast, insulin had a higher impact on platelet count, and sulfonylurea increased fibrinogen levels ($p >0.05$). The function of sulfonylurea in modifying coagulation factor levels/activity is mostly unknown. Gliclazide has been demonstrated to decrease clot permeability, resulting in the formation of prothrombotic clots with fibrinolysis-resistant structures (Dhall & Nair, 1994). Contrarily, when diabetes and insulin resistance are present, the use of insulin is linked to prothrombotic alterations because it raises fibrinogen levels, as was observed in this study.

The discrepancies in the results of the coagulation tests (Platelet Count, PT, PTTK, Fibrinogen, and d-Dimer) seen between studies may be the consequence of variances in sample size, racial makeup, and geographic location. The precise cause of the discrepancy between the various investigations is unknown.

CONCLUSIONS

According to the results of the investigation, people with diabetes with HbA1c levels below 7% had significantly different coagulation profiles from those with levels above 7%. While no substantial difference was seen in PT, fibrinogen, and D-dimer, significant, consistent changes were detected in PTTK platelet count. Patients with diabetes had shorter PTTK and PT, a lower platelet count, higher levels of fibrinogen, and higher D-dimer levels than non-diabetics. Diabetes patients have a higher risk of thrombosis, as evidenced by the significant differences in PTTK, PT, platelet count, fibrinogen, and D-dimer between diabetic patients and non-diabetics. In diabetic individuals who have had the condition for a long time, coagulation profile analysis should be prioritized. Increased hypercoagulability is indicated by a decrease in coagulation profile in diabetes, and thromboembolic consequences are indicated by an increase in fibrinogen levels. The coagulation profile should be taken into consideration as one of the standard screening tests in diabetes patients to decrease the incidence and prevalence of vascular burden and to improve quality of life.

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CONFLICT OF INTEREST

There are no stated conflicts of interest by the authors.

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