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The Association Between Type 2 Diabetes Mellitus and Stroke, Coronary Artery Disease and Thromboembolism

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Abstract

Background: *The incidence of cerebrovascular disease in diabetic patients is 6 times higher than nondiabetic patients. Approximately 85% of these patients die because of the cardiovascular diseases. DM is an independent risk factor for cardiovascular diseases, and this risk increased much with accompanying dyslipidemia. In diabetic patients, increased triglyceride and decreased HDL cholesterol accelerate atherosclerosis. In stroke patients, increased plasma Pro-BNP levels are associated directly with stroke severity and mortality.*

Method: *Following the approval of Dicle University Medical Faculty Ethics Committee, the randomly selected patients admitted to the emergency department with the following thromboembolic complaints were investigated prospectively for 6 months study period. The patients were classified into 4 groups. Group 1: type 2 Diabetes Mellitus (DM) without thromboembolic complications; group 2: type 2 DM with thromboembolic complications; group 3: thromboembolism without DM; group 4: healthy volunteers. The coagulation factors, lipid profiles and pro-BNP levels were measured in all patients.*

Results: *Systolic tension arterial (STA) and diastolic tension arterial (DTA) levels were significantly higher in group 2 as compared to group 1 and control groups ($p<0,05$). Among groups, there were statistically significant differences in glucose, urea, creatinine, fibrinogen, factor 7, factor 8, pro-BNP, triglyceride, HDL, VLDL levels ($p<0,05$).*

Conclusion: *DM is a factor that increases STA and DTA levels. In type 2 diabetes, fibrinogen and coagulation factors such as factor 7 and factor 8 increase, anticoagulant factors decrease, HDL cholesterol levels decrease, triglyceride levels and VLDL cholesterol levels increase and pro-BNP levels increase. As a result, the risk of arteriosclerosis and thromboembolism associated with ischemic stroke, peripheral and coronary artery disease and mortality increase.*

Keywords: *Type 2 diabetes mellitus, stroke, coronary artery disease, thromboembolism*

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Introduction

Diabetes mellitus (DM) is the most common endocrine disease in the world. The absolute and relative deficiency of endogenous insulin or peripheral ineffectiveness result in a syndrome consisting of chronic hyperglycemia, disturbance of carbohydrate, protein and lipid metabolism, changes of capillary membrane and accelerated arteriosclerosis. After the discovery of the insulin and oral antidiabetic drugs, the life expectancy of the diabetic patients is prolonged markedly. Therefore, the incidence of the chronic complications increases with the prolonged diabetic life-span. These complications are the most important reasons for the mortality and morbidity in the diabetic patients (1).

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted mainly in the ventricles in response to end-diastolic volume expansion and pressure overload, BNP plasma levels increase in the patients with coronary cardiac disease, hypertension, diabetes or other vascular diseases, the high risk of left ventricle systolic or diastolic dysfunction. In the stroke patients, a high plasma level of Pro-BNP is associated directly with stroke severity and mortality (2). In other meta-analyses, pro-BNP levels increased for 72 hours in the patients with cardioembolic stroke (3).

Atherosclerosis is a macrovascular disease that involves the intima of large and medium vessels, and constricts the lumen (4). Its frequency increases with age. DM accelerates the development of macroangiopathy (5). Namekata et al. showed that the incidence and severity of arteriosclerosis in type 2 DM patients above 40 years old was significantly higher as compared to the same age group without diabetes (6). The incidence of cerebrovascular disease in diabetic patients is 6 times higher as compared to nondiabetic patients. 85% of these patients die because of the cardiovascular diseases (7). Diabetes is an independent risk factor for cardiovascular diseases and this risk increased with the accompanying dyslipidemia (8). In diabetic patients, increased triglyceride and decreased HDL cholesterol accelerate atherosclerosis. This dyslipidemia form in type 2 DM was generally present before the development of diabetes (9).

In our study, we aimed to evaluate the role of DM on thromboembolism development and mortality by comparing diabetic and non-diabetic patients admitted to emergency department due to a thromboembolic reason.

Materials and Methods

Patients

Following the approval of Dicle University Medical Faculty Ethics Committee, the randomly selected patients admitted to our emergency department with the following thromboembolic complaints were investigated prospectively for 6 months' study period. Diabetic patients diagnosed at least for 5 years were recruited in terms of chronic complications. The patients with DM and/or thromboembolic complications were classified into 4 groups to evaluate the effects of coagulation factors, lipid profile and pro-BNP on diagnosis and mortality. Group 1: type 2 DM without any thromboembolic complications; group 2: type 2 DM with any of thromboembolic complications; group 3: isolated thromboembolism without DM; group 4: healthy volunteers without DM and thromboembolism history.

Inclusion and exclusion criteria

i. Inclusion criterias

1. The patients diagnosed with DM without thromboembolic complications
2. >15 years old patients with type 2 DM admitted to the emergency department
3. The patients who approved to participate to the study
4. >15 years old patients without DM, but admitted to the emergency department due to acute coronary syndrome
5. >15 years old patients without DM, but admitted to the emergency department due to cerebrovascular thromboembolism

ii. Exclusion criterias

1. Increased serum pro-BNP levels
    a. Intracerebral haemorrhage,
    b. Subarachnoid haemorrhage,
    c. Congestive cardiac failure
2. The patients who did not approve to participate to the study
3. The factors that may affect coagulation tests
    a. Hepatic failure
    b. Warfarin and similar anticoagulant treatments

All patients gave the standard study form and written informed consent form in the emergency department following the first intervention and treatment.

Statistical analysis

The results were presented as mean±SD. Univarite statistical analyses were performed by chi-square test for the categorical variables and by student-t test for the continuous variables. Oneway Anova test was used for inter-groups comparisons and Bonferonni test was used to determine the group which differentiates. $p<0.05$ value was considered as statistically significant.

Result

Clinical and demographical features

Total of 96 patients were included in the study. 68 (70,84%) of them were in patient group, 28 (29,16%) of them were in control group. Among the included 96 patients, 50 of them (52,08%) were male, 46 of them (47,92%) were female, the median age was 56,76±15,60 (30–81 year).

Among groups, no differences in female/male ratio, median age and BMI were found (Table I)

Table I: Age and sex distribution among groups

		Group 1 n=23	Group 2 n=22	Group 3 n=23	Control n=28	P Value
Age (Year; mean±SD)		61,70±13,62	63,59±8,36	64,48±9,82	58±6,17	0,155
Gender	**Male**	13(%56,52)	11(%50,00)	14(%60,87)	16(%57,15)	0,133
	Female	10(%43,48)	11(%50,00)	9(%39,13)	12(%42,85)	0,152
BMI		28,65±6,88	29,09±5,44	32,60±6,47	30,43±3,80	0,084

The levels of systolic tension arterial (STA) and diastolic tension arterial (DTA) were significantly higher in group 2 as compared to group 1 and control group ($p<0,05$). (Table II)

Table II: The comparison of systolic tension arterial (STA) and diastolic tension arterial (DTA) among groups

Variants	**(Mean+SD)**	**N**	**(Mean+SD)**	**N**	**P Value**
STA	Control (117±7)	28	Group 1 (123±28)	23	1,000
	Control (117±7)	28	Group 2 (143±39)	22	0,004*
	Control (117±7)	28	Group 3 (129±19)	23	0,624
	Group 1 (123±28)	23	Group 2 (143±39)	22	0,045*
	Group 1 (123±28)	23	Group 3 (129±19)	23	1,000
	Group 3 (129±19)	23	Group 2 (143±39)	22	0,436
DTA	Control (74±7)	28	Group 1 (71±15)	23	1,000
	Control (74±7)	28	Group 2 (85±20)	22	0,021*
	Control (74±7)	28	Group 3 (80±12)	23	1,000
	Group 1 (71±15)	23	Group 2 (85±20)	22	0,008*
	Group 1 (71±15)	23	Group 3 (80±12)	23	0,245
	Group 3 (80±12)	23	Group 2 (85±20)	22	1,000

Biochemical parameters

The pooled analyse results of the median biochemical parameters, lipid panel and coagulation factors in the control and patient groups were presented in table III.

Among groups, statistically significant differences were found in glucose, urea, creatinine, fibrinogen, factor 7, factor 8, pro-BNP, triglyceride, HDL, VLDL levels ($p<0.05$).

Table III: The median values and standard deviations of biochemical parameters, lipid panel and coagulation factors among groups

Parameters (Mean±SD)	**Group 1**	**Group 2**	**Group 3**	**Control**	**P Value**
Glucose (mg/dl)	407,48±315,406	330,45±198,628	122,13±32,558	102,14±20,609	0,000*
Urea (mg/dl)	66,91±42,932	63,14±29,185	47,83±38,916	34,29±11,045	0,002*
Creatinine (mg/dl)	1,283±0,5758	1,551±0,8583	0,974±0,5941	0,871±0,2355	0,000*
Sodium (mmol/L)	133,04±6,765	135,32±4,156	138,74±3,583	139,43±2,602	0,512
Potassium(mmol/)	4,365±0,8386	4,168±0,8758	4,309±0,7977	3,986±0,4759	0,276
Calcium (mg/dl)	8,670±0,6342	9,027±0,7330	8,878±0,7090	8,714±0,6676	0,274
Prothrombin Time (sec)	12,08±1,990	12,41±2,016	12,65±1,613	11,86±1,380	0,394
INR (INR)	0,996±0,1364	1,002±0,1290	1,030±0,2265	0,986±0,1008	0,766
Fibrinogen (mg/dl)	375,74±145,405	398,55±126,835	382,35±86,510	279,14±77,783	0,001*
Pro-BNP (pg/ml)	1439,8±1888,9	11954,9±13715,3	4571±8202,2	86,14±40,92	0,000*
Factor 7 (%)	83,55±42,086	73,95±25,636	87,52±24,845	147,00±87,570	0,000*
Factor 8 (%)	172,00±76,266	139,00±44,395	157,61±38,018	121,29±27,029	0,003*
Factor 12 (%)	79,70±36,770	76,23±32,199	94,70±29,619	83,86±20,493	0,187
HbA1c (%)	9,639±3,7240	7,873±2,3845	4,087±0,7332	4,000±0,7698	0,000*
Cholesterol (mg/dl)	172,39±55,140	163,36±37,875	171,65±39,677	181,43±52,516	0,612
Trigliserit (mg/dl)	200,43±122,086	149,82±86,770	144,70±67,943	87,43±35,872	0,000*
HDL (mg/dl)	34,91±16,265	37,45±14,070	40,35±12,550	51,57±8,724	0,000*
LDL (mg/dl)	95,13±34,639	101,14±32,647	116,48±42,592	111,86±41,159	0,212
VLDL (mg/dl)	41,26±25,187	31,95±21,637	26,22±12,979	17,34±7,151	0,000*
Protein C (%)	89,00±30,150	95,86±23,839	101,57±11,524	97,43±17,637	0,265

Comparison of biochemical data differentiating significantly among groups

Blood glucose levels were significantly higher in group 1 and group 2 as compared to group 3 and control group ($p<0.05$). Blood urea levels were significantly higher in group 1 and group 2 as compared to control group ($p<0.05$). Blood creatinine were significantly higher in group 1 and group 2 as compared to control group ($p<0.05$) and significantly higher in group 2 as compared to group 3 ($p<0.05$). (Table IV)

Table IV: Comparison of biochemical data differentiating significantly among groups

Variants	(Mean±SD)	N	(Mean±SD)	N	P Value
Glucose	Control (102,14±20,609)	28	Group 1 (407,48±315,406)	23	0,000*
	Control (102,14±20,609)	28	Group 2 (330,45±198,628)	22	0,000*
	Control (102,14±20,609)	28	Group 3 (122,13±32,558)	23	1,000
	Group 1 (407,48±315,406)	23	Group 2 (330,45±198,628)	22	0,957
	Group 1 (407,48±315,406)	23	Group 3 (122,13±32,558)	23	0,000*
	Group 3 (122,13±32,558)	23	Group 2 (330,45±198,628)	22	0,001*
Urea	Control (34,29±11,045)	28	Group 1 (66,91±42,932)	23	0,003*
	Control (34,29±11,045)	28	Group 2 (63,14±29,185)	22	0,013*
	Control (34,29±11,045)	28	Group 3 (47,83±38,916)	23	0,827
	Group 1 (66,91±42,932)	23	Group 2 (63,14±29,185)	22	1,000
	Group 1 (66,91±42,932)	23	Group 3 (47,83±38,916)	23	0,282
	Group 3 (47,83±38,916)	23	Group 2 (63,14±29,185)	22	0,682
Creatinine	Control (0,871±0,2355)	28	Group 1 (1,283±0,5758)	23	0,049*
	Control (0,871±0,2355)	28	Group 2 (1,551±0,8583)	22	0,001*
	Control (0,871±0,2355)	28	Group 3 (0,974±0,5941)	23	1,000
	Group 1 (1,283±0,5758)	23	Group 2 (1,551±0,8583)	22	0,784
	Group 1 (1,283±0,5758)	23	Group 3 (0,974±0,5941)	23	0,476
	Group 3 (0,974±0,5941)	23	Group 2 (1,551±0,8583)	22	0,009*

Comparison of coagulation factors differentiating significantly among groups

Fibrinogen levels and factor 7 level were significantly higher in group 1, group 2 and group 3 as compared to control group ($p<0.05$). When group 1, group 2 and group 3 were compared in terms of fibrinogen and factor 7 levels, no significant differences were found ($p>0.05$). When factor 8 levels were compared among groups, the levels were significantly higher in group 1 as compared to control group ($p<0.05$). No significant differences were found in the other groups ($p>0.05$). (Table V)

Table V: Comparison of coagulation factors differentiating significantly among groups

Variants	(Mean±SD)	N	(Mean±SD)	N	P Value
Fibrinogen	Control (279,14±77,783)	28	Group 1 (375,74±145,405)	23	0,016*
	Control (279,14±77,783)	28	Group 2 (398,55±126,835)	22	0,002*
	Control (279,14±77,783)	28	Group 3 (382,35±86,510)	23	0,008*
	Group 1 (375,74±145,405)	23	Group 2 (398,55±126,835)	22	1,000
	Group 1 (375,74±145,405)	23	Group 3 (382,35±86,510)	23	1,000
	Group 3 (382,35±86,510)	23	Group 2 (398,55±126,835)	22	1,000
Factor 7	Control (147,00±87,570)	28	Group 1 (83,55±42,086)	23	0,000*
	Control (147,00±87,570)	28	Group 2 (73,95±25,636)	22	0,000*
	Control (147,00±87,570)	28	Group 3 (87,52±24,845)	23	0,001*
	Group 1 (83,55±42,086)	23	Group 2 (73,95±25,636)	22	1,000
	Group 1 (83,55±42,086)	23	Group 3 (87,52±24,845)	23	1,000
	Group 3 (87,52±24,845)	23	Group 2 (73,95±25,636)	22	1,000
Factor 8	Control (121,29±27,029)	28	Group 1 (172,00±76,266)	23	0,002*
	Control (121,29±27,029)	28	Group 2 (139,00±44,395)	22	1,000
	Control (121,29±27,029)	28	Group 3 (157,61±38,018)	23	0,059
	Group 1 (172,00±76,266)	23	Group 2 (139,00±44,395)	22	0,158
	Group 1 (172,00±76,266)	23	Group 3 (157,61±38,018)	23	1,000
	Group 3 (157,61±38,018)	23	Group 2 (139,00±44,395)	22	1,000

Comparison of lipid profile differentiating significantly among groups

The triglyceride and VLDL levels were significantly higher in group 1 and group 2 as compared to control group ($p<0.05$). No significant differences were found in the other groups ($p>0.05$). HDL levels were significantly lower in group 1, group 2 and group 3 as compared to control group ($p<0.05$). No significant differences were found among patient groups ($p>0.05$). (Table VI)

Table VI: Comparison of lipid profile differentiating significantly among groups

Variants	(Mean±SD)	N	(Mean±SD)	N	P Value
Triglycerides	Control (87,43±35,872)	28	Group 1 (200,43±122,086)	23	0,000*
	Control (87,43±35,872)	28	Group 2 (149,82±86,770)	22	0,045*
	Control (87,43±35,872)	28	Group 3 (144,70±67,943)	23	0,091
	Group 1 (200,43±122,086)	23	Group 2 (149,82±86,770)	22	0,251
	Group 1 (200,43±122,086)	23	Group 3 (144,70±67,943)	23	0,143
	Group 3 (144,70±67,943)	23	Group 2 (149,82±86,770)	22	1,000
HDL	Control (51,57±8,724)	28	Group 1 (34,91±16,265)	23	0,000*
	Control (51,57±8,724)	28	Group 2 (37,45±14,070)	22	0,001*
	Control (51,57±8,724)	28	Group 3 (40,35±12,550)	23	0,017*
	Group 1 (34,91±16,265)	23	Group 2 (37,45±14,070)	22	1,000
	Group 1 (34,91±16,265)	23	Group 3 (40,35±12,550)	23	0,954
	Group 3 (40,35±12,550)	23	Group 2 (37,45±14,070)	22	1,000
VLDL	Control (17,34±7,151)	28	Group 1 (41,26±25,187)	23	0,000*
	Control (17,34±7,151)	28	Group 2 (31,95±21,637)	22	0,028*
	Control (17,34±7,151)	28	Group 3 (26,22±12,979)	23	0,470
	Group 1 (41,26±25,187)	23	Group 2 (31,95±21,637)	22	0,489
	Group 1 (41,26±25,187)	23	Group 3 (26,22±12,979)	23	0,030*
	Group 3 (26,22±12,979)	23	Group 2 (31,95±21,637)	22	1,000

Comparison of pro-BNP values among groups

Pro-BNP levels were significantly higher in group 2 and group 3 as compared to control group ($p<0,05$); significantly higher in Group 2 as compared to group 3 ($p<0,05$). (Table VII)

Table VII: Comparison of pro-BNP values among groups

Variants	(Mean±SD)	N	(Mean±SD)	N	P Value
Pro-BNP	Control (86,14±40,92)	28	Group 1 (1439±880)	23	1,000
	Control (86,14±40,92)	28	Group 2 (11954±3715)	22	0,000*
	Control (86,14±40,92)	28	Group 3 (4571±202,2)	23	0,025*
	Group 1 (1439±880)	23	Group 2 (11954±3715)	22	0,011*
	Group 1 (1439±880)	23	Group 3 (4571±202,2)	23	1,000
	Group 3 (4571±202,2)	23	Group 2 (11954±3715)	22	0,012*

Discussion

Diabetes is a metabolic and vascular disease (10). It is known that diabetes mellitus stimulates and accelerates the development of atherosclerosis (48). In diabetes, the other metabolic disorders including hyperglycemia and hyperinsulinemia as well as dyslipidemia, hypertension contribute to atherosclerotic disease. The multifactorial risks increase the disease risk exponentially (5,10). In a study performed by Calles-Escandon(11), 80% of the patients with type 2 diabetes die due to the thrombotic events. 75% of the mortality was associated with cardiovascular diseases. The other 25% of mortality was associated with peripheral vascular diseases and cerebrovascular diseases. Diabetes is a known risk factor for stroke (12). The microvascular and macrovascular complications of diabetes begin to develop (1-2 years) before the diagnoses.

In a study with healthy, middle-aged, 1998 nondiabetic male patients, the other cardiovascular risk factors including high tension, resting heart rate, cholesterol, triglyceride increased with the increase of blood glucose during the 22-years of follow-up. In the same study, high-normal levels of fasting blood glucose were reported to be an important independent marker for cardiovascular mortality (13).

In the diabetes patients, cerebrovascular diseases are more common, more severely and presents more diffuse lesions as compared to the normal population. The aggregation ability of thrombocyte increases in diabetes. The half-life of fibrinogen in diabetic patients is shortens, however, the fibrinogen levels are high; presumably the reason is the increased hepatic fibrinogen production (14). In a study performed by Timothy et al. (15), diabetes was an important risk factor for ischemic stroke. No significant differences were found in age, sex and BMI in the patients included in our study.

Arterial hypertension is a risk factor for the development and progression of diabetic micro and macroangiopathy. Hypertension increases the mortality 4-6 times in diabetes due to the renal and cardiac disorders. The risk of serious cardiovascular events in diabetes with hypertension is 2-3 times more common as compared to only diabetes or only hypertension (5). In a study performed by Beer et al. (16), the incidence of systolic and diastolic tension was significantly higher in the type 2 diabetes patients as compared to the control group. In our study, STA and DTA levels were higher in the diabetes with thromboembolism. In line with the previous studies, diabetes with hypertension increases the risk of arteriosclerosis.

In the large epidemiological studies, strict glycemic control of type 1 and type 2 DM delays the development or progression of vascular complications (17). Hyperglycemia is an important factor for the development of diabetes complications. Hence, it may be responsible for the coagulation and

fibrinolytic system vascular complications in the diabetes (18). Blood glucose levels were high in the diabetic patients with and without thromboembolism. These results suggest that nonregulated diabetic patients admitted to emergency room not only for diabetes regulation but also for complications associated with diabetes.

Diabetic nephropathy is an important cause of mortality in the diabetic patients. 5-15% of the patients with type 2 diabetic had diabetic nephropathy (19). In a study performed with Yamada et al. (20), diabetic nephropathy patients were classified into the diabetic nephropathy group if their serum creatinine levels > 145μmol/l. In our study, blood urea and creatinine levels were significantly higher in the diabetic patients as compared to the control group. In our study, blood urea and creatinine levels were significantly higher in the diabetic patients with or without thromboembolic complications as compared to the nondiabetic patients, suggesting the included diabetic patients might be in the nephropathy development process. The included patients had been diagnosed with type 2 DM for more than 5 years, their median blood glucose levels and HbA1c levels were high, resulting in increased risk of chronic diabetic complications.

In type 2 diabetes, fibrinolytic mechanisms generally decrease with hypercoagulation. Several studies showed that there is a correlation between the hyperglycemia grade, coagulation and fibrinolytic system abnormalities (18). In these studies, fibrinogen, F7, F8, F11, F12, kallikreine and Von Willebrand Factor (VWF) levels were high in the patients with type 2 diabetes (21,22,23). In a study performed by Streja et al.(24), CRP and fibrinogen levels were high in the type 2 diabetic patients with macrovascular complications. Fibrinogen levels were significantly high in the patients with microvascular patients independent of CRP. In our study, fibrinogen and factor 7 levels were higher in all diabetic patients with thromboembolic complications. Factor 8 levels were higher in diabetic patients. Fibrinogen factor 7 and factor 8 levels were high in diabetic patients without thromboembolism, suggesting diabetes is a predisposing factor for coagulation.

Type 2 DM is frequently associated with atherogenic dyslipidemia (25). It is known that the main factors defining dyslipidemia in type 2 diabetes include decrease of HDL cholesterol levels, increase of triglyceride levels and increase of VLDL cholesterol levels (9). In a study performed by Beer (16) et al., decrease of HDL cholesterol levels, increase of triglyceride and VLDL cholesterol levels were observed in the diabetic patients. In our study, as expected, triglyceride and VLDL levels were significantly higher in the diabetic patients as compared to the control group, and the HDL levels were lower. These results suggest that the risk of thromboembolism is high in DM.

Hon-Kan Yip et al. (26) reported that plasma Pro – BNP levels were very strong and independent variable for the prediction of long-term outcome in the patients with acute stroke. In a study performed by Iltimur et al (27), Pro–BNP levels were significantly high in 91% of the patients who died due to ischemic stroke. Early pro–BNP increase had been attributed to sympathetic activation and myocardial depression in this study. In a study performed by Etger et al (28), pro-BNP levels increased in 2/3 of the acute stroke patients and high blood levels were associated with increased morbidity. In a study performed by Beer et al. (16), pro-BNP levels were high in the type 2 diabetes patients with vascular complications. Among groups in our study, pro-BNP levels were significantly higher especially in the patients with thromboembolism as compared to the control group. Among thromboembolic patients, levels were much higher in the diabetic patients. In DM group, the levels were higher as compared to the control group but the difference was not statistically significant, suggesting pro-BNP levels were high in diabetes and may be an important criterion for prognosis.

Conclusion

In conclusion, diabetes is a factor that increases STA and DTA values in our study. Diabetic nephropathy is an inevitable outcome in the diabetic patients. Fibrinogen and coagulation factors including factor 7 increase in type 2 diabetes, anticoagulant factors decrease, HDL cholesterol levels decrease, triglyceride and VLDL cholesterol levels increase; pro-BNP levels increase; as a result the risk of thromboembolism and mortality increase.

Conflict of interest

The authors declare that there is no potential conflicts of interest.

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