Causality relationships between coagulation factors in type 2 diabetes mellitus: path analysis approach

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Abstract

Background: Type 2 diabetic mellitus patients are amongst the most susceptible groups to vascular abnormalities, which predominantly lead to myocardial disease. The hypercoagulable state has been widely studied by researchers as being the major suspicious mechanism facilitating the consecutive chain of molecular events leading to these complications. However, there is no consensus on the definition of the hypercoagulable state with respect to coagulation quantities, their interrelations and basic factor(s) initiating this pathogenic event, by which the prognosis of myocardial complications could be determined.

Methods: Path analysis was used to study the interactions between coagulation factors as well as other factors beyond coagulation factors in relation with pathogenic events in both diabetics and healthy subjects. In the present work, coagulation factors of 40 healthy and 40 type 2 diabetics were determined experimentally. The data were then analyzed using SPSS and AMOS software. Multivariate regression analysis was done to draw path diagrams.

Results: Our results show that FII, as the main cause for hypercoagulable state, is directly induced by FX and FVIII in normal individuals and by FX, FXI, FV and VWF cofactors in diabetic patients.

Conclusion: In general, our findings showed complicated relationship between coagulation factors and their effects either separately or combined.

Keywords: Hypercoagulable State, Path analysis, vascular Complication, Myocardial Infarction, Coagulation Factors.

Introduction

Type 2 diabetes mellitus is one of the mostly incriminated conditions for the onset of atherosclerosis, endothelial, vascular and thrombotic complications (1-5). Increased concentration of coagulation factors is widely reported in type 2 diabetes mellitus (1, 6-8). Fibrinogen coagulation factor with plasma concentration of 200-400mg/dL and half-life of 4-6 days is converted to insoluble protein fibrin, by FIIa (9-10). In type 2 diabetic patients with or without vascular complications, fibrinogen concentrations do not indicate remarkable difference; hence fibrinogen may not be an important causal factor for vascular complications (11-12).

Thrombin or FIIa is a serine protease enzyme produced by proteolytic cleavage of its precursor FII (prothrombin) by FXa with aim of FV and phospholipid membrane (13-15). In diabetics, FII has been reported neither to increase in concentration (more than 10mg/dL) nor to be a risk factor for

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vascular events (15). However FX is a plasma glycoprotein with mean concentration of 1mg/dL and a half-life of 2-2.5 days. The activation pathway of FX to FXa is the committed step stands at the crossroad between intrinsic and extrinsic pathways of coagulation. Coagulation FV with 0.4-1.4 mg/dL and 0.5-1.5 days of half-life in turn is activated by FXa and FIIa. There are many reports which show no significant increase in FV in diabetic patients without prognostic importance (11, 16-17).

In the intrinsic pathway FX is activated by FIXa via formation of TENASE complex with coagulation factor VIII and calcium ions on phospholipid membranes. The plasma concentration of FIX showed no remarkable difference between normal and diabetics either with or without artery complications, although elevated FIX was reported in patients with myocardial infarction (16, 18-19). Coagulation FVIII which is activated by FIIa, tends to increase in diabetes mellitus but with no correlation with vascular complications (19-20). Some researchers hold that increased concentrations of both FVIII and its carrier vWF (von-Willebrand factor) in diabetes mellitus render them susceptible to heart attack (21-22). It has been shown that the activation of FXI and FIX is required for continued formation of FIIa (23). In diabetic patients, there are elevated concentrations of plasma FXI and FXII of which the former factor (FXI) has been shown to be involved in myocardial infarction (16, 20, 24-27). This coagulation factor exerts its pathogenic effect via FIX and FX activation (23, 28). Multivariate regression analysis showed that FXI is an independent factor for thrombotic complications (29-32). Coagulation FXII seems of no prognostic importance in vascular complication.

In extrinsic pathway, FX is activated by FVII/TF complex on phospholipid membrane in the presence of calcium ions. Coagulation FVII circulates in plasma as a zymogen of a short half-life (5-8 hours) at 0.05mg/dL concentration (33-34). High concentration of FVII acts as independent variable that correlates with ischemic heart disease (10-11, 13, 35). In contrast to FVIIa, inactivated FVII shows partial enzymatic activity at high concentration in the presence of TF, so that it may activate FIX; promote FXa formation and leads to artery problems (36-37). Tissue factor is necessary for the initiation of extrinsic coagulation pathway through FVII activation. (3, 38-39). Raised blood glucose and hyperinsulinemia in T2DM induces a marked increase in TF activity (1, 20, 40-42). There are reports showing that TF is increased in coronary complications (43-44)

Since FII is the last target of coagulation cascade either from intrinsic or extrinsic origin play a determinant role in initiation of vascular complication, this study has chosen it as a most important dependent variable in a hypothetical model or path resemble coagulation cascade to edit and verify it as a causality model for coagulation factors. The main purpose of the present study is to extract a path model using our hypothetical model and experimental data obtained for diabetics and normal individuals via multivariate regression analysis (path analysis) (45-46). The obtained model expected to be important model that gives a prospect on the path relations between coagulation factors e.g. the extent to which one factor affects other coagulation factors. This effect may be positive effect (threatening factors) or negative effect (safety factors) against vascular complications.

Methods
Subjects Selection: Forty patients with type 2 diabetes mellitus were selected based on their medical history as well as forty normal volunteers, all with no history of micro/macro vascular complications, neuropathy, nephropathy, insulin therapy, psychiatric illness or smoking. Subjects with backgrounds of any acute or chronic diseases were excluded. Chronic diseases of retinopathy were followed by regular checking of patients' visual acuity, nephropathy (rise in serum creatinine con-

centration and microalbuminurea) and foot sensation. All subjects were nominated by Dezfoul Ganjavian Hospital, Khuzestan Province, IRAN. The body mass index, BMI, was calculated to be 18 to 25 kg/m^2. The only medication used by diabetics was anti-diabetic metformin pill having no insulin.

Sample Preparation: Blood samples were collected from 12-h fasted subjects. Plasma was prepared by twice centrifugation at 1500×g for 10 min each at 15–18 °C and was then stored in polypropylene tubes at −70 °C until used for measurement. All samples were assayed in duplicate. Plasma samples showing evidence of hemolysis were discarded.

Analytical method: Fasting glucose of subjects was measured by PAD/GOD Method (CinnaGen Incorporation, Glucose Diagnostic Kit, Shahrak Ekbatan, Tehran, Iran). Duplicated glucose level of fasting blood plasma glucose of 126 mg/dL was used as criteria for type 2 diabetes mellitus in patients with at least 8h fasting with no caloric intake. The patients were selected based on their medical history with no signs of insulin resistance and no history of insulin treatment. The coagulation assay method used for the determination of vWF, Fibrinogen, II, V, VII, VIII, IX, X, XI in plasma was performed as reported previously (46). All experimental procedures involving human participants were conducted with due attention to the guidelines approved by the Research Ethical Committee of Shahid Chamran University (Ahwaz, Iran).

Statistical analysis
Coagulation Factor Correlation: The correlation between coagulation factors results were analyzed using the Statistical Package for the Social Science (SPSS-PC, version 15. SPSS, Inc., Chicago, IL). The significance level of 0.05 was used for correlation tests.

Path analysis: Path analysis was used to investigate the relation between coagulation factors in normal and diabetic individuals and to survey probable causal effects of some coagulation factors on a certain coagulation factor. Path analysis made it possible to describe and interpret the correlation between some coagulation factors and their effects on coagulation factor II of 40 diabetics and 40 normal voluntrees in a path model using **Amos16** software (Arbuckle, J. L. (2006). Amos (Version 16.0) (Computer Program). Chicago: SPSS). The obtaind structural equation models were tested and confined at the significance level of 0.05. The causality model defines some hierarchical regression models between coagulation factors and FII variable (the effect). Paths between variables are drawn from independent to dependent variables with directional arrow for every regression model (arrowhead on one end only). A two-way arrow between two variables indicates that the correlation between these two variables will remain unanalyzed. For every regression the total variance in dependent variable is theorized to be caused either by independent variables of the model or by extraneous variables (**e**) not considered in the model. An arrow from **e** indicates the influence of these extraneous variables. Hence, the total variances of dependent variable become the sum of variance caused by both independent variables and extraneous variables. Each independent variable may affect the dependent variable directly and/or indirectly, i.e. via mediation factors. Accordingly, the total effect of an independent variable on a certain dependent variable is the sum of its direct and indirect effects. Each path has a coefficient showing the standardized coefficient of regressing independent variable on dependent variable of the relevant path. A coefficient may be positive (increase of independent variable elevates dependent variable when all other independent variables are held constant) or negative (increase of independent variable decreases dependent variable). The indirect

effect was determined by multiplying the path coefficients of intervening variables (47).

Results

In order to construct path analysis model between coagulation factors we made a pair wise Pearson test between coagulation factors and only the factors showing significant 2-tailed correlations were selected as suitable for model construction. These data are shown in table 1(a-b). The best refined model for our hypothetical model obtained by path analysis calculated for healthy subjects is presented in figure 1. In this model, FX and FVIII are the only independent variables which showed direct effects on FII. FX seemed to be the determinant factor for FII and the major risk factor for vascular complications. Table 2 summarizes path coefficients of total, direct and indirect effects of coagulation factors of the model on FII. As represented in table 2, the maximum total effect exerted by FX on FII is as

Table 1. Pearson correlation of coagulation factors with 2-tailed significance in parenthesis for a, 40 normal and b, 40 diabetic groups.

Table 1-a

	VWF	VII	II	X	VIII	XI
VII	-0.226 (0.399)					
II	-0.156 (0.536)	0.480 (0.038)				
X	-0.456 (0.066)	0.736 (0.001)	0.637 (0.003)			
VIII	0.712 (0.003)	-0.285 (0.285)	0.329 (0.182)	-0.352 (0.166)		
XI	-0.205 (0.447)	-0.163 (0.532)	0.258 (0.285)	-0.050 (0.839)	0.320 (0.211)	
V	-0.624 (0.006)	-0.015 (0.952)	-0.008 (0.973)	0.334 (0.151)	-0.613 (0.007)	0.038 (0.879)

Table 1-b

	VWF	VII	II	X	VIII	FIB	XI	V
VII	0.034 (0.839)							
II	-0.178 (0.286)	0.694 (<0.001)						
X	-0.043 (0.797)	0.586 (<0.001)	0.868 (<0.001)					
VIII	0.144 (0.387)	-0.006 (0.971)	-0.046 (0.779)	0.076 (0.640)				
FIB	0.256 (0.121)	0.251 (0.119)	0.200 (0.215)	0.279 (0.081)	0.377 (0.016)			
XI	-0.008 (0.9620)	0.336 (0.036)	0.218 (0.183)	0.359 (0.025)	0.525 (0.001)	0.377 (0.018)		
V	0.303 (0.064)	0.522 (0.001)	0.485 (0.002)	0.398 (0.011)	0.206 (0.201)	0.256 (0.110)	0.428 (0.007)	
IX	0.070 (0.679)	0.546 (<0.001)	0.553 (<0.001)	0.642 (<0.001)	0.190 (0.247)	0.186 (0.257)	0.581 (<0.001)	0.341 (0.034)

Table 2. Total, direct and indirect effects of coagulation factors on FII in the best path diagram obtained from path analysis shown in figure1.

	Total effect	Direct effect	Indirect effect
V	-.170	.000	-.170
XI	.211	.000	.211
VWF	.299	.000	.299
VII	.444	.000	.444
VIII	.514	.514	.000
X	.642	.698	-.056

Table 3. The total, direct and indirect coefficients obtained in casualty model in diabetic patient extracted from multivariate regression done for 40 patients with type 2 diabetes mellitus.

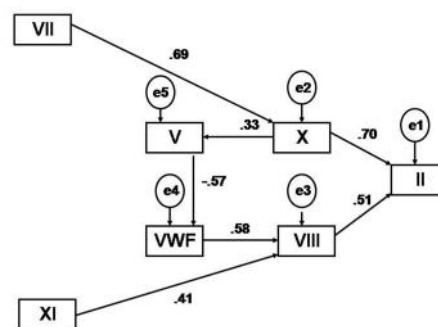|	Total effect	Direct effect	Indirect effect
VWF	-.254	-.254	.000
Glc	-.101	.000	-.101
VIII	.038	.000	.038
XI	.112	-.222	.334
VII	.232	.000	.232
V	.340	.340	.000
IX	.518	.000	.518
X	.837	.837	.000

Fig. 1. The best path diagram obtained from multivariate done for 40 normal individuals. All variable are putted in a rectangle, a single headed arrow from independent variable shows a path relation. The standardized path coefficients are calculated for direct relations between independent and dependent variables and putted over on headed arrows. The error terms that are shown by e are uncorrelated with variables of the model and with each other.

large as 0.642. This is followed by FVIII, FVII, VWF and FXI which show positive effects of 0.514, 0.444, 0.299 and 0.211 respectively. Whereas FV shows negative effect of 0.170 on FII. However only FX and FVIII show direct effects on FII while, other factors show indirect effects.

Figure 2 show the best refined model for our hypothetical model obtained by path analysis calculated for diabetic patients. In this model, FX, FV, VWF and FXI show direct effects. Table 3 summarizes the total, direct and indirect effects of coagulation factors on FII. As depicted in Table 3, FX and FV have positive effects of 0.837 and 0.340 respectively on FII but VWF and FXI have negative effects of 0.254 and 0.222 respectively. In path model for diabetic patients, as in Figure 2, all variables except FX, FXI, FV and VWF have only indirect effects on FII. The unique coagulation fac-
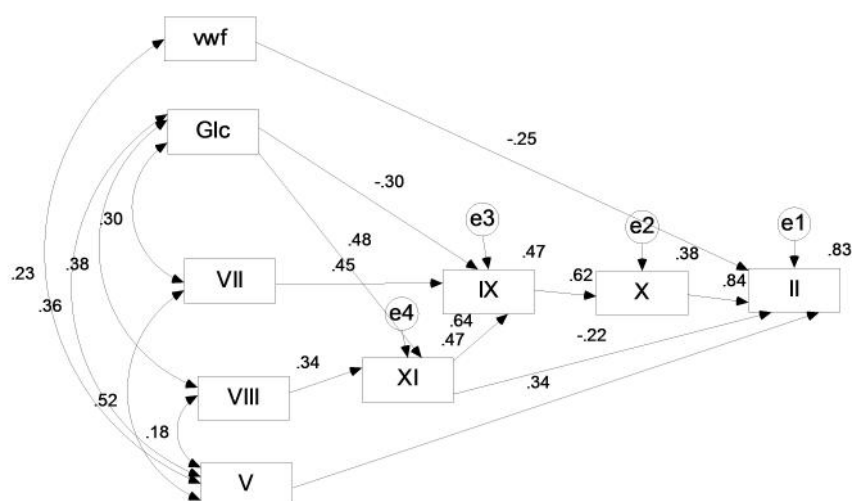

Fig. 2. The best path diagram obtained from multivariate done for 40 type2 diabetics. All variable are putted in a rectangle, a single headed arrow from independent variable shows a path relation. A double-headed arrow is connecting two variables that are merely correlated with our obvious path relations. The standardized path coefficients are calculated for direct relations between independent and dependent variables and putted over on headed arrows. The error terms that are shown by e are uncorrelated with variables of the model and with each other.

tor that affects FII by dual action of direct effects of 0.340 and indirect effects of 0.334, is FXI.

Next to coagulation factor X, Factor IX is an important factor which imposes variance on FII with positive effect of about 0.52, while, FV, FVII, FXI and FVIII are ranked at lower causative situations in terms of inducing variances on FII. This finding implies that increase in concentration of factors X, IX, V, VII, XI and VIII induce increase in FII variance and could be considered as threatening factors for cardiovascular problems given their total effects. This model shows that glucose and VWF exert negative effects on FII, counteracting the effects of other factors on vascular disease. The effect of VWF, as FVIII carrier, could be easily interpreted, since it takes up the free FVIII from plasma decreasing its active form involved in coagulation phenomenon. However, the negative effects of glucose on FII could not be so easily interpreted.

Discussion

As shown in Figures 1 and 2, the extent of correlation between coagulation factors in diabetics is more evident than in normal group i.e. in the case of diabetics, most of coagulation factors are correlated and hence the numbers of variables included in the model become higher than in the case of normal group. This may be the reason for the more hypercoagulable conditions stated in diabetic condition (46-48) .It is of great importance to remember that the main goal of the current research is to find out an acceptable model by which the biological events that lead to micro or macro vascular complication could be elucidated.

Model Fit Assessment: In order to assess how our model fits the data, we used the model to check the data fit degree. In this connection, we used some qualification parameters including (Table 4):

1. Chi-square statistic, as the first index used. This test is a single number that adds up all the differences between our actual data and the data expected if there is no difference. If the actual data and expected data (if no difference) are identical, the Chi-square value is zero. A bigger difference will give a bigger Chi-square value. The most important characteristic of this statistic is its p-value criterion. As shown, the calculated p-value exceeds 0.05. Therefore, both models (healthy normal and diabetic models) are consistent with the null hypothesis and hence according to this criterion, both models are acceptable models.

2. The second index used was GFI or the goodness of fit index. GFI says what proportion of the variance in the sample variance-covariance matrix is accounted for the model. This should exceed 0.9 for a good model. According to this index, both models are acceptable models but they are not good fit.

3. The Root Mean Square Error of Approximation or RMSEA is used as a measure of total error and estimates the lack of fitted model compared to the saturated model with all correlated factors linked to each other. RMSEA value of 0.05 or less indicates good fit, and 0.08 or less indicates adequate fit. Based on this index the model extracted here for normal individuals show a good model while the model of diabetic is a poor model.

4. Comparative Fit Index (CFI) is an index well performs well even with small size sample. This statistics ranges from 0.0 to 1.0 with values closer to 1.0 indicating good fit. Accordingly our models for healthy and diabetics show good fits (47).

Table 4. Model fit parameter extracted using AMOS 16 software for two model obtained for normal and diabetic groups.

	Chi-square	DF	P-value	GFI	RMSEA	CFI
Diabetics	28.697	20	0.094	0.893	0.106	0.949
Normal	12.302	14	0.582	0.898	0.000	0.901

Table 5. simple correlation for coagulation factors that connected with two headed arrows in diabetic model shown in figure 2.

	VII	VIII	V
vWF			0.23
GLC	0.30	0.38	0.36
VIII			0.18

However there are limitations for path models including the necessity of adequate sample size, normal distribution of the data and the presence of linear relation between studied variable which all match our data.

Bidirectional relations: Table 5 shows simple correlations between the coagulation factors due to unanalyzed relation represented by two-headed arrows which seems to add values to the extracted models. Taking into account such correlations will enable including, within the model, certain invisible relations between coagulation factors which may not be perceived immediately. As mentioned earlier, there may be one- way relations between each pair of these coagulation factors or otherwise spurious associations caused by a third factor as if it be biological one. In this context, FV tends to correlate with VWF, and glucose with FVIII in a way to construct a plausible model as in Table 5. This finding may open a new horizon of research for studying the mechanisms behind such causality relationship and beyond. The correlation which exists between FV and either VWF or glucose in diabetic model is absent in normal model. So, what is the factor behind this discrepancy between diabetics and normal individuals? The other bidirectional relations are formed with glucose in diabetic patients. Glucose tends to have bidirectional association with each of FV, FVII and FVIII. This may lead to hypercoagulable states and hence life-threatening cardiovascular events in diabetic patients.

Conclusion
Path analysis findings indicate that the analysis is a powerful method that helps to discover invisible relations between coagulation factors. Our results gave two acceptable models, which adequate fit the data for normal and diabetic patients. According to the first model for normal individuals, as shown in Figure 1 and Table 2, FX and FVIII induce the largest direct effects on FII with total effects of .642 and .514 respectively. On the other hand, FV, FXI, VWF and FVII show indirect effects on FII. While in the second model for diabetic group, as shown in Figure 2 and Table 3, the most direct effects are exerted by coagulation factors VWF, FX, FV and FXI on FII. As per this model, in addition to Glucose (Glc), FVIII and FV, factor XI also exerts indirect effect on FII simultaneously.

Our findings show that the obtained path model or diagram for coagulation factors are more complicated in diabetic patients than in normal individuals and convey that a sudden increase in the synthesis of each coagulation factors or their activation may trigger the initiation of coagulation cascade, leading to vascular clot formation with myocardial consequences.

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