Study of Prothrombotic Changes in Metabolic Syndrome

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Abstract The metabolic syndrome is a complex disorder of various metabolic risk factors in a single individual having central obesity and commonly associated with diabetes and cardiovascular diseases. The aim of our study was to study the relationship between coagulation abnormalities and metabolic syndrome. We performed a prospective cross-sectional study in a tertiary care hospital. A total of fifty cases of metabolic syndrome and fifty age & sex matched controls were selected. These two groups were investigated for Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen levels, Plasminogen Activator Inhibitor 1 (PAI1) levels and Factor VIII levels. In cases with metabolic syndrome, significantly increased levels of Fibrinogen, Factor VIII and Plasminogen Activator Inhibitor1 (PAI1) were observed. PT & APTT were shorter in cases with metabolic syndrome. The coagulation parameters studied, correlated significantly with the components of metabolic syndrome. Metabolic syndrome is a hypercoagulable state and further studies are required for further evaluation of the consequences of this hypercoagulable state. There is a need for clinical trials evaluating prophylactic anticoagulation for prevention of venous thrombosis in patients with metabolic syndrome.

Keywords Metabolic syndrome · Coagulation · Prothrombin time (PT) · Activated partial thromboplastin time (APTT) · Fibrinogen · Plasminogen activator inhibitor-1 (PAI-1) · Factor VIII

Introduction

The Metabolic syndrome is a complex disorder characterized by the presence of a clustering of metabolic risk factors including presence of central obesity and a strong association with diabetes and cardiovascular diseases [1].

According to the International Diabetes Federation Consensus definition [2], for a person to be defined as having the metabolic syndrome, all of the following criteria must be met: Central obesity (defined as waist circumference more than ethnicity specific values; for Indian males ≥ 90 cm & for Indian females ≥ 80 cm; if BMI is > 30 kg/m², central obesity can be assumed and waist circumference does not need to be measured) Plus any two of the following four factors: 1) Raised triglycerides ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality 2) Reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males & < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality 3) Raised blood pressure systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension 4) Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

The prevalence of metabolic syndrome has been increasing in economically developed and developing countries and it is associated with increased risk of cardiovascular morbidity and mortality [3]. It is a complex pathological condition, associated with endothelial

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dysfunction, increased activity of coagulation factors, hyperactivity of platelets and decreased fibrinolysis [4]. Alterations of the coagulation and/or fibrinolytic system are the key pathogenic components of the atherothrombotic process which underlies acute coronary or cerebrovascular events in metabolic syndrome [5]. The impairment of haemostatic balance identified in subjects with metabolic syndrome includes alterations of both intrinsic and extrinsic pathways of coagulation with alteration in the levels of coagulation and/or fibrinolytic system [5]. However there is paucity of data looking at objective lab evidence of hypercoagulable state in patients with metabolic syndrome. Our study is aimed at comprehensively studying the relationship of coagulation abnormalities with metabolic syndrome.

Materials and Methods

This was a prospective cross-sectional study, carried out in a tertiary care hospital over a two years period. Patients with Metabolic Syndrome & age and sex matched Controls were investigated for Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen levels, Plasminogen Activator Inhibitor 1 (PAI 1) levels and Factor VIII levels.

Blood samples of patients with metabolic syndrome from outpatient Department of Medicine & Endocrinology were obtained.

The study was approved by the institutional ethics committee. Informed consent, from patients & normal controls were obtained as per guidelines of the institutional ethics committee.

Inclusion criteria: Patients age > 18 yrs with metabolic syndrome defined according to the International Diabetic federation Criteria [2] for metabolic syndrome were included. Age and sex matched controls were included who did not satisfy the criteria for metabolic syndrome.

Exclusion criteria: Patients with (1) Renal disorders (2) Thyroid disorders (3) Hepatic disorders (4) Drugs causing hypercoagulability (5) Pregnancy (6) Malignancy (7) Congenital hypercoagulable states were excluded

Peripheral blood samples of patients were collected in 3.2% Sodium Citrate vacutainers. All these coagulation investigations were performed on Compact Ceveron Alpha Automated Coagulation Analyzer (Compact Bio-Sciences Ltd), based on clotting, Chromogenic & Turbidimetric analysis.

Statistical Methods

Categorical variables were presented in number and percentage (%) and continuous variables were presented as

mean $\pm$ SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-

- (1) Quantitative variables were compared using Unpaired *t* test/Mann–Whitney Test (when the data sets were not normally distributed) between the two groups and Anova/Kruskal–wallis test (for non parametric data) between more than two groups.
- (2) Qualitative variables were compared using Chi Square test/Fisher's exact test.
- (3) Univariate and multivariate linear regression was used to assess the association of PT, APTT, Fibrinogen, PAI1 and Factor VIII with components of metabolic syndrome.

A *p* value of < 0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0

Results

Clinical Characteristics of the Patients:

Table 1 shows the clinical characteristics of the included patients and controls in our study.

Results of Coagulation Investigations:

Table 2 shows the results of our coagulation investigations.

PT & APTT values were decreased in cases of Metabolic Syndrome as compared to normal controls. The levels of fibrinogen, PAI1 & Factor VIII were increased in cases of Metabolic Syndrome in comparison with normal controls (Table 2).

Table 3 summarizes the Univariate & Multivariate analysis of these coagulation parameters.

Univariate analysis of individual metabolic parameters with PT & APTT, demonstrated an inverse correlation with waist circumference, fasting plasma glucose, serum triglycerides and systolic blood pressure while a positive correlation was seen with HDL levels and the results were statistically significant with *p* value of < 0.0001 (Table 3).

Multivariate analysis of individual metabolic parameters with PT demonstrated a significant inverse correlation with systolic blood pressure and a significant positive correlation with HDL & multivariate analysis of individual metabolic parameters with APTT demonstrated a significant inverse correlation with systolic blood pressure, serum triglycerides and a significant positive correlation with HDL (Table 3).

Table 1 shows clinical characteristics of patients

Parameter	Cases	Controls	<i>P</i> value
Median age	51.7 Yrs	51.02 Yrs	<0.311
BMI	33.43 ± 2.68 kg/m ²	24.33 ± 1.83 kg/m ²	<0.001
Waist Circumference	102.68 ± 6.92 cm	87.6 ± 7.53 cm	<0.001
FBG	116.68 ± 17.99 mg/dl	92.46 ± 12.07 mg/dl	<0.001
TG Levels	35.98 ± 51.9 mg/dl	51.84 ± 5.69 mg/dl	<0.001
Hypertension			
SBP	139.39 ± 11.83 mm	124.2 ± 10.2 mm	<0.001
DBP	84.14 ± 8.19 mm	79.08 ± 5.65 mm	<0.001

Table 2 shows results of coagulation parameters

Parameter	Cases	Controls	<i>P</i> value
PT	9.79 ± 0.74 s	12.04 ± 0.7 s	<0.001
APTT	28.96 ± 0.92 s	32.6 ± 1.34 s	<0.001
Fibrinogen	402.24 ± 66.92 mg/dl	261.5 ± 4.195 mg/dl	<0.001
PAI 1	49.99 ± 5.34 ng/ml	36.75 ± 3.35 ng/ml	<0.001
Factor VIII	152.66 ± 7.54 IU/dl	131.44 ± 6.24 IU/dl	<0.001

Table 3 summarizes the Univariate & Multivariate analysis of these coagulation parameters

Coagulation parameter	Metabolic factor	Univariate analysis		Multivariate analysis	
		Beta coefficient (95% CI)	<i>P</i> value	Beta coefficient (95% CI)	<i>P</i> value
PT	Waist circumference	− 0.075(− 0.096–0.054)	<.0001	− 0.017(− 0.038–0.004)	0.109
	Fasting glucose	− 0.037(− 0.049–0.026)	<.0001	− 0.008(− 0.018–0.003)	0.155
	SBP	− 0.059(− 0.076–0.043)	<.0001	− 0.029(− 0.044–0.014)	0.0003
	S.TG	− 0.025(− 0.031–0.019)	<.0001	− 0.005(− 0.012–0.003)	0.210
	HDL	0.096(0.076–0.116)	<.0001	0.051(0.025–0.078)	0.0002
APTT	Waist circumference	− 0.117(− 0.151–0.083)	<.0001	− 0.001(− 0.028–0.027)	0.962
	Fasting glucose	− 0.061(− 0.08–0.043)	<.0001	− 0.013(− 0.028–0.001)	0.064
	SBP	− 0.087(− 0.114–0.06)	<.0001	− 0.029(− 0.05–0.009)	0.005
	S.TG	− 0.047(− 0.055–0.039)	<.0001	− 0.015(− 0.025–0.005)	0.005
	HDL	0.181(0.154–0.207)	<.0001	0.115(0.08–0.15)	<.0001
Fibrinogen	Waist circumference	5.181(3.803–6.559)	<.0001	2.323(0.762–3.884)	0.004
	Fasting glucose	2.546(1.775–3.317)	<.0001	0.943(0.14–1.747)	0.022
	SBP	3.542(2.396–4.689)	<.0001	1.355(0.2–2.51)	0.022
	S.T.G	1.458(1.019–1.897)	<.0001	0.097(− 0.471–0.664)	0.736
	HDL	− 5.559(− 7.062–4.056)	<.0001	− 2.289(− 4.278–0.3)	0.0246
PAI	Waist circumference	0.437(0.311–0.563)	<.0001	0.1(− 0.029–0.229)	0.127
	SBP	0.32(0.218–0.42)	<.0001	0.105(0.009–0.2)	0.032
	Fasting glucose	0.24(0.173–0.307)	<.0001	0.093(0.026–0.159)	0.007
	S.TG	0.15(0.114–0.186)	<.0001	0.037(− 0.01–0.083)	0.125
	HDL	− 0.555(− 0.679–0.431)	<.0001	− 0.26(− 0.424–0.096)	0.0022
Factor VIII	Waist circumference	0.806(0.624–0.988)	<.0001	0.443(0.232–0.654)	0.00007
	Fasting glucose	0.34(0.229–0.451)	<.0001	0.135(0.027–0.244)	0.015
	SBP	0.378(0.203–0.552)	<.0001	0.007(− 0.149–0.163)	0.925
	S.TG	0.213(0.152–0.274)	<.0001	0.007(− 0.07–0.083)	0.865
	HDL	− 0.869(− 1.068–0.671)	<.0001	− 0.444(− 0.712–0.175)	0.0015

Univariate analysis of individual metabolic parameters with levels of fibrinogen, PAI1 & Factor VIII, showed a positive correlation with waist circumference, blood pressure, serum triglyceride level, fasting plasma glucose while there was an inverse correlation with HDL and the results were statistically significant with p value of < 0.0001 (Table 3).

Multivariate analysis of individual metabolic parameters with fibrinogen demonstrated a significant positive correlation with waist circumference, fasting glucose and systolic blood pressure and a significant inverse correlation with HDL. Amongst all of the coagulation parameters, fibrinogen levels had the highest correlation with metabolic syndrome derangements. Multivariate analysis of individual metabolic parameters with PAI1 demonstrated a significant positive correlation with fasting glucose and systolic blood pressure and a significant inverse correlation with HDL. Multivariate analysis of individual metabolic parameters with Factor VIII demonstrated a significant positive correlation with waist circumference, fasting glucose and a significant inverse correlation with HDL (Table 3).

Discussion

This cross sectional study was done to evaluate coagulation profile parameters in patients with metabolic syndrome as compared to normal controls to identify hypercoagulable derangements in patients with metabolic syndrome.

We observed significantly lower prothrombin time, a functional determination of the extrinsic (tissue factor) pathway of coagulation, in patients with metabolic syndrome as compared to matched controls. Similarly we also observed lower levels of APTT, a test of the intrinsic coagulation pathway, in patients with metabolic syndrome as compared to matched controls.

Shortened PT & APTTs are reflective of a procoagulant state as has been observed in previous studies. Acang et al. [6] reported shorter PT & APTT with hypercoagulable state in diabetes mellitus. Zhao et al. [7] and Sakpota et al. [8] also observed decreased PT and APTT values in diabetic patients. Fu et al. [9] and Asrat et al. [10] reported shortened APTT median among diabetic patients.

We observed elevated levels of fibrinogen in patients with metabolic syndrome & ANOVA analysis showed that levels of fibrinogen increased with increase in the number of components of metabolic syndrome. Our results are consistent with previous studies by Ford et al. [11] and Mahendra et al. [12] who reported elevated plasma fibrinogen levels in patients with diabetes mellitus. Our results are also consistent with the previous study done by Imperatore et al. [13] who correlated elevated fibrinogen

levels with BMI, waist-to-hip ratio, systolic and diastolic blood pressure, plasma total cholesterol, LDL cholesterol, triglycerides, insulin, and HDL cholesterol [13]. Fibrinogen levels had statistically significant correlation with the most number of metabolic parameters on multivariate analysis. Thus levels of fibrinogen can be considered as the most sensitive coagulation parameter for metabolic syndrome in our study.

We also observed higher levels of PAI in patients with metabolic syndrome. High PAI levels are associated with increased production of several inflammatory cytokines including TNF alpha. [14–17]. Increased factor VIII levels and vWF levels are some of the other findings associated with chronic inflammation as well as increased circulating levels of various cytokines [18].

There are several important implications of our study. Our study demonstrates that metabolic syndrome is associated with hypercoagulable state. Currently there are no guidelines for recommending prophylactic anticoagulation for patients with metabolic syndrome. However our study adds to the literature for association of hypercoagulable state and metabolic syndrome and thus necessitating need for clinical trials prospectively evaluating prophylactic anticoagulation in patients with metabolic syndrome. Long term follow up of patients with metabolic syndrome is needed to assess for venous or arterial thrombosis particularly unprovoked thrombosis events.

Our study has important limitations that merit consideration. Our study had a small sample size. As a result significant differences between several metabolic parameters and coagulation derangements were not observed on multivariate analysis. However in spite of a limited sample size, we were able to assess differences in the coagulation profile of patients with metabolic syndrome as compared to matched normal controls.

Conclusion

Metabolic syndrome is a hypercoagulable state and further studies are required for evaluation of the consequences of this hypercoagulable state.

Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interests.

Informed Consent Informed consent was obtained from all individual participants included in this study.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or National research committee and with the

1964 Helsinki declaration and its later amendments or comparable ethical standards.

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