

Can Vascular Pathology in Cerebral and Coronary Fields Predict Peripheral Artery Disease in a Cohort of Diabetic Patients ?

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Objective: To find out whether peripheral artery disease followed the same pattern, set of risk factors and indicators as macro vascular disease in the coronary arteries and cerebral arteries disease. **Study design:** This was a randomized cross sectional retrospective analysis. **Place and duration:** Study was carried out at The Diabetes Management Center at The Services Hospital Lahore, during June 1999 to June 2001. **Patients and methods:** A total of 580 patients were selected from the diabetic data base that had absent pulsations in the any of the four arteries of the lower limbs. Another set of 580 diabetics with presence of pulsations in all the arteries of the lower and upper limbs was randomly selected to match the cases. **Results:** Diabetics with peripheral vascular disease had a significant positive history of past CVA and past MI. **Conclusion:** Presence of peripheral vascular disease is significantly associated with presence of history of past CVA and past MI, raised systolic BP, diastolic BP, and mean BP and increased proteinuria.

Key words: Peripheral artery disease, Cerebral vascular pathology, Coronary vascular pathology

Among many complications of diabetes, vascular disease carries the maximum mortality and morbidity burden. Exact statistics regarding peripheral vascular disease and its prevalence in diabetics are not available; although data from NHANES I epidemiological follow up study indicates a coronary heart disease incidence associated with a medical history of diabetes as 8.7% in African American women and 6.1% in European American women¹. Medical history of diabetes was a significant predictor of chronic heart disease incidence and mortality in American women and explained the excess coronary disease incidence in younger African American as compared to European American women.

The present study evaluates various predictors of the peripheral artery disease with reference to macro vascular disease in the coronary and cerebral arteries.

Material and methods:

The study was conducted at The Diabetes Management Center at Services Hospital Lahore as a randomized cross sectional retrospective analysis. All those individuals suffering from diabetes mellitus and being treated as regular outpatients at the center were entered into the study.

Cases were selected on the basis of absence or presence of peripheral artery disease. An artery disease index was created on the basis of absence or presence of pulse in arteries of the lower legs. The included arteries were: 1). Right posterior tibial and 2). Left posterior tibial, 3). Right dorsalis Pedis and 4). Left dorsalis Pedis. The index was assigned a value of 1 or 0 on absence or presence of pulsations in that particular artery respectively. For example if a patient had absent pulsation in all four arteries he was assigned an index score of 4. Similarly a patient who had pulses present in all four arteries was assigned an index score of 0. All patients who suffered from traumatic injuries to the lower limb resulting in

dysfunction or amputation of any part of lower limb below knees, individuals with graft replacement of any artery segments of the lower limbs and also the individuals who had been diagnosed with arteritis in lower limbs related to any connective tissue disease category were excluded from the study.

A proforma was developed which included all suspected or known determinants of past vascular disease, biochemical indicators, cross sectional blood pressures and other indicators of micro vascular and macro vascular disease.

A total of 580 cases were selected from the diabetic database which fulfilled the above mentioned criteria and had an absent pulsation in any of the four arteries included in the artery disease index.

Another group of 580 diabetics without any history of peripheral vascular disease and with the presence of pulsations in all arteries of lower and upper limbs on their first visits were randomly selected to match the cases.

SPSS version 10.0 was used for analysis of this dataset. Student t test and ANOVA with post hoc analysis using Scheffé were performed using artery disease as a dependent variable and all other risk factors as covariates.

Univariate linear analysis was also performed between factors like cigarette packets smoked per year etc to see if these variables gave an explanation regarding the dose response relationship or a time factor based relationship between artery disease and its possible risk factors.

Results:

Most of these cases had been referred from other practices, hospitals and locations. Some of these patients had just been diagnosed and others came at advanced stages of the disease with end organ complications. Ascertaining the duration of the disease since it was first diagnosed (biochemically or therapeutically) gave this

study an independent and diverse review about the prevalent diabetic control, history of disease and various therapeutic strategies employed by a range of practicing physicians in different setups. The varied diabetic control in these patients gave this study a unique cross-sectional picture.

Past history of cerebrovascular accidents was significantly associated with peripheral vascular disease in any of the four arteries [P= 0.002 (C.I. .0017 to .0072)]. Past history of MI (myocardial infarction) was also significantly associated [P= 0.000(C.I. .0024 to .0086)] with the presence of peripheral vascular disease. Table 1 Blood pressure measurements were also significantly different in subjects with PVD than in subjects without PVD (peripheral vascular disease). Systolic B.P. [P= .000 (C.I. 4.75 to 9.19)] and diastolic BP [P=0.001 (C.I. 0.82 to 3.44)].

Although there seemed to be a difference between total packs of cigarettes consumed in a lifetime, between PVD diabetics and non PVD diabetics. (cases 954 +-3690 vs. controls 796.20 +-3381.72). mean cumulative packs smoked were not statistically significant between PVD cases and controls [P=0.463 (C.I. -264.22 to 580.67)]. Total cigarette packs consumed depicted cumulative lifetime dose consumed by an individual. Although there was a lack of association otherwise but cumulative lifetime packs of cigarettes were significantly associated with absence of pulse in right posterior tibial artery specifically [P=0.006(C.I. 229.98 to 1365.03)].

Other significant results were history of chest pain [P=.001] and the presence of proteinuria in diabetics with PVD [P=.000]. Presence of proteinuria may be directly correlated with increased duration of diabetes.

ANOVA (table 2) was employed to confirm the results as a more robust test. Most of the results obtained by Student T test tallied with ANOVA results. In diabetic cases with PVD Past CVA (P=.002), past MI (P=.000), systolic BP (P=.0010), diastolic BP (P=.001) and mean BP (P=.000) were all significantly different at a cut off value of 0.05 as compared to diabetics without PVD.

Table 1. Independent samples T Test.

	t	Sig. (2- tailed)	95% confidence interval of the difference	
			Lower	Upper
Annual cigarette packs	.735	.463	-264.22	580.67
Past CVA	3.175	.002	1.71E-02	7.25E-02
Past MI	3.492	.000	4.42E-02	8.62E-02
Systolic BP	6.165	.000	4.75	9.19
Diastolic BP	3.184	.001	.82	3.44
Mean BP	5.397	.000	2.87	6.15

Univariate analysis between various models of total packs of cigarettes consumed and blood pressures revealed non-significant results.

Table 2. ANOVA

	Sum of square	df	Mean square	F	Sig
Annual cigarette packs	6771613.58	1	6771613. 586	.540	.463
Past CVA	.583	1	.583	10.080	.002
Past MI	.883	1	.883	12.195	.000
Systolic BP	14043.359	1	14043.35	38.011	.000
Diastolic BP	1307.135	1	1307.135	10.136	.001
Mea BP	5872.939	1	5872.939	29.126	.000

Discussion:

Results of the study indicate that diabetics with peripheral vascular disease had a significant positive history of past CVA and past MI. This association was statistically significant as compared to the diabetics without PVD. The assessment of presence or absence of past CVA and MI was based on documentation of diagnostic or therapeutic intervention or documentation of positive history, physical signs and positive diagnostics related to a vascular event. Repeat diagnostic procedures or labs were not carried again but accurate documentation provided the desired accuracy for the study. The accurate future prediction of vascular events was limited because of the retrospective cross-sectional nature of the study. Nevertheless it is more or less widely accepted fact that past vascular events in cerebral or coronary fields are a good predictor of future events in these fields individually and other wise thus predicting future morbidity and mortality. Hence it may be fairly concluded that PVD is strongly correlated with past cerebrovascular and cardiovascular disease events and when properly quantified can be possibly utilized to predict the future occurrence of events in these or other tissue fields or vice versa as well. The results depict that vascular disease more or less has the same predictive factors across the body and shows cross reactivity.

Other researchers have also reported same results on the association of peripheral artery disease, cerebrovascular disease and acute coronary syndromes.² It was noted that patients with prior extra cardiovascular disease (vascular disease outside the coronary perfusion field) events often had coronary multivessel disease and these patients had more often angina pectoris as compared to Q wave infarctions in patients that did not have prior history of extra cardiovascular disease. This signifies that patients with extra cardiovascular disease had a generalized tendency of the coronary vascular network to clot, narrow or contract across the cardiac tissue. Although Q wave infarctions also represent atheromatous rupture in one major artery resulting in complete blockage of tissue perfusion; but still the association of coronary multivessel disease with cerebrovascular disease and peripheral

vascular disease may emphasize a generalized vascular pathological process going on in these vessels.

In another study, Uehara et al reported comparable findings for peripheral artery disease and carotid artery disease associations. In their study MRI evaluation of 151 consecutive patients scheduled for non emergency coronary artery bypass grafting revealed that more than fifty percent stenosis in the cervical carotids was present in 16.6% of the subjects and similarly more than fifty percent intracranial artery stenosis was detected in 21.2% of the subjects. Multiple linear regression analyses identified peripheral vascular disease and infarcts in the basal ganglia as significant and independent predictors of cervical carotid arterial stenosis.

All these studies most likely hint towards a process of vascular pathology that is proceeding rather homogeneously across the body although some areas manifest earlier than others based on their environmental or genetic influences and eventually some tissue fields cause more morbidity and mortality than others. Whether the readily identified group of coronary syndromes which have adverse risk influences like increased cholesterol, cigarette smoking etc also represent a segment of this generalized vascular pathology group or otherwise would need to be further substantiated. Recognizably, manifestations or time period involved may be different in different tissue fields but still artery disease in one field can predict artery disease in other tissue fields and vice versa. Eventually it may be manifested as cardiovascular disease in cerebral, coronary and peripheral vascular fields.

With more intervention trials this cross reactivity of vascular pathology in various tissues may become more quantifiable.

Interestingly there was no significant correlation between total cigarettes consumed in a lifetime and absence of pulses in the lower limbs. Although total life time cigarettes consumed were strongly correlated with history of intermittent claudication ($P < .000$), there was no significant correlation between cigarettes consumed and generalized vascular disease.

Significantly greater proteinuria levels between PVD diabetics and non PVD diabetics was also present and it may signify the generally increased duration of diabetes and the gross pathology that it promotes in other tissue fields like kidneys.

A significant difference in the levels of systolic BP and diastolic BP in diabetes with PVD was observed as compared to diabetics without PVD. This finding may simply represent incidental independent coexistence of hypertension in diabetics with peripheral vascular disease or rather its presence as a dependent disease. In this case the specific presence of raised systolic, diastolic and mean BP in diabetics with PVD as compared to diabetics without PVD hints to its pathological presence in association with diabetics rather than its presence as an independently existing condition.

It is also possible that our dataset of patients had a higher prevalence of diabetic nephropathy as well signified by significant proteinuria in PVD diabetics. Chronic diabetic nephropathy directly promotes raised blood pressure through mesangial thickening³ and possibly through concurrent production of increased levels of angiotensin leading to eventual vasoconstriction. But it is also a clinical experience that weight loss in obese patients provides better blood pressure control and outcomes⁴. Can obesity be directly related to higher blood pressures as it is directly related to poor glycemic control? Can the loss of overall homeostasis regulation due a certain set of genetic and environmental susceptibilities promote and augment all of these pathological manifestations together or these are mere manifestations of an altered process that has gone wrong from the very beginning.

Studies report strong correlations of waist circumference with blood pressure and insulin resistance measures⁵. Univariate and multivariate analysis showed that waist circumference remained the strongest independent predictor of BP after adjustment for confounding factors. Significant increases of systolic and diastolic BP, heart rate, HOMA index and post load serum insulin was observed across increasing subsections of waist circumference in the selected cohort. Greater degrees of central adiposity were strongly associated with higher prevalence of elevated BP values and insulin resistance⁶.

Some researchers have even put the name "hypertension syndrome" to the set of cardiovascular risk factors ranging from insulin resistance to lipid abnormalities to problems with arterial compliance and raised blood pressure. It is quite possible that a common underlying pathology may predispose individuals suffering with diabetes to a whole spectrum of pathological manifestations that include obesity, insulin resistance, abnormalities of lipid profile, various endocrine changes, abnormalities of coagulation factors and vascular compliance. From the results of this study it may be fairly assumed that diabetics having PVD with a central distribution of body fat are more prone to have a raised BP leading to end organ complications and possibly other cardiovascular risk factors independently of body mass index.

Waist circumference is an important indicator of insulin resistance which may have a more central role in the diabetic picture than previously thought. Waist circumference may be labeled as a marker for insulin resistance.⁶ The strong correlation of waist circumference with a strong fit in a regression model as proposed by Siani et al⁵ signifies that insulin resistance may have a direct effect on altered blood pressure and hypertension along side causing altered glycemic control. If this association is reproducibly significant then it means a common underlying pathology for diabetes and hypertension in at least insulin resistant or obese diabetics.

Insulin resistance and poor glycemic control in itself may promote a dysmetabolic state leading to central adiposity, altered lipid metabolism and also cause a proinflammatory phase aggravated or augmented by nephrological end organ complications and subsequently raised sympathomimetics causing a generalized vasospasm. Further clinical evidence generated with biomarker variables based studies may be required to substantiate this hypothesis fully.

Conclusion:

Presence of peripheral vascular disease in diabetics is significantly associated with presence of history of past CVA and past MI, raised systolic BP, diastolic BP, and mean BP and increased proteinuria.

It is possible that altered glycemic control may directly promote hypertension due to homeostatic pathology. Possibly both diabetes and hypertension may represent end results of a purely metabolic mechanism gone wrong at the very beginning or being promoted by specific genetic influences in specific patient populations that emanate along with other risk factors for vascular disease in these specific set of patients with a synergic contribution by the environment or dietary habits.

Further trials with a focus on variables that unfold this particular aspect of altered glycemic control would indeed be an important step forward in understanding

altered metabolic responses and their role in the etiology of vascular injuries.

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