Can Vascular Pathology In Cerebral And Coronary Fields Predict Peripheral Artery Disease In A Cohort Of Diabetic Patients?

Ambreen Butt, Kamran. K. Chima, Bilal Saulat & Faisal Masud

Background: Diabetes mellitus, a metabolic disorder of absolute or relative insulin deficiency, is characterized by micro and macro-vascular complications. This process of vascular pathology proceeds at a uniform rate throughout the body. Eventually it may be manifested as atherosclerotic changes in cerebral, coronary and peripheral arteries Variables like central adiposity, altered metabolism, elevated blood pressure, proteinuria causes resistance.
Methods: A retrospective cross-sectional study was carried out on 4482 diabetic patients attending the "Diabetes Management Center" Services Hospital, Lahore. Known determinates of past vascular disease PVD were assessed. An artery disease index was formulated by the presence or absence of lower limb pulses.
Results: Past history of CVA was significantly associated with PVD with a p-value of 0.002. Similarly past history of M1 (p=0.000), hypertension (p=0.000), proteinuria (p=0.000) were all significantly present in patients with PVD. There was lack of association between cigarette smoking (p= 0.463) and PVD.
Conclusion: Past history of CVA and MI, Hypertension and Protienuria are all significantly present in Diabetic patients with Peripheral Vascular disease.
Key Workd: Atherosclerosis, Microvascular Complications, Macrovascular Coronary Circulation Peripheral Vascular Disease.

Introduction

Atherosclerosis is the leading cause of occlusive arterial disease of extremities in patients over 40 years of age.[1] Diabetes plays a major role in development of atherosclerosis. There is a risk increase from one to five fold for cardiovascular complications and a three fold increase in stroke due to atherosclerosis in diabetic patients.[2] An increased prevalence of atherosclerotic disease has also been found in diabetic individuals. Chronic hyperglycemia plays an important role in development of microvascular complications.[3] Macrovascular complications are however more affected by other factors including dyslipedimia, hypertension, obesity, reduced physical activity and smoking.[4] The objectd in the development of macrovasculive of this study was to determine the influence of factors involvear complications on the overall vascular disease picture that develops in diabetics, specifically in individuals with metabolic syndrome.

Methods

Queries were developed from a first visit record of 4482 consecutive diabetic patients being treated as regular patients at " Diabetes Management Center", Services Hospital, Lahore. The Diabetic database holds information regarding all diabetic patients who have been diagnosed with diabetes and are being treated as outpatients at this particular hospital.

We developed a query from the database 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.

The query encompassed the complete status of patients on their first visits to "The Diabetes Management Center". 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 (biochemicaly or therapeutically) gave us an disease and various therapeutic strategies employed by a range of practicing physicians in different setups. The varied diabetic control in these patients gave us a unique cross-sectional picture. In such cases where treatment was not uniform across the board only those independent variables would be significant which have a consistent correlation with natural diabetic history and progression. Any treatment differences in such diabetics would be automatically randomized and would not add bias towards the end results.

Table 1: Descriptive Statistics Comparison of Cases and Controls.

	Controls		Cases	
	Mean	Std. Deviation	Mean	Std. Deviation
Annual cigarette packs	796.20	3381.72	954.42	3690.30
Past CVA	3.97	.20	8.45	.28
Past MI	5.17	.22	.11	.31
Systolic BP	126.72	16.81	133.69	21.35
Diastolic BP	82.40	10.68	84.53	11.99
Mean BP	104.59	12.83	109.11	15.43

Inclusion Criteria

Cases were selected on the basis of presence or absence of peripheral artery disease. An artery disease index was created by the absence of pulse in arteries of the lower legs. The included arteries were

1. Right posterior tibial
2. Left posterior tibial
3. Right dorsalis pedis
4. Left dorsalis pedis

The index was assigned a value of 1 or 0 on presence or absence of pulsations in that particular artery respectively. For example if a patient had absent pulsation in all four arteries he was assigned an index of 4. One who has absent pulsation in 3 arteries out of 4 was assigned an index of 3. One who had pulses present in all 4 arteries was assigned an index score of 0.

Exclusion Criteria

- All patients who suffered from traumatic injuries to the limb resulting in dysfunction or amputation of any part of lower limbs below knees
- All individuals with graft replacements of any artery segments of the lower limbs.
- Individuals who have been diagnosed with arteritis in lower limbs related to any connective tissue disease category

Analysis

580 cases were selected form the diabetic database that fulfilled the above mentioned criteria and had an absent pulsation in any of the following four arteries of the lower limb. Right posterior tibial, left posterior tibial, right dorsalis pedis and left dorsalis pedis.

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 Scheffe 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 us an explanation regarding the dose response relationship or a time factor based relationship between artery disease and its possible risk factors.

Results

Past history of CVA 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 was also significantly associated [P=0.000(C.I .0024 to .0086)] with the presence of peripheral vascular disease.

Blood pressure measurements were also significantly different in subjects with PVD than in subjects without PVD. 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 cigarettes 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)].

Table 2: Statistical analysis according to independent samples t test.

	t	Sig. (2-tailed)	95% Confidence Interval of the Difference Lower	Upper
Annual cigarette packs	0.735	.463	264.22	580.67
Past CVA	3.175	.002	1.71	7.25
Past MI	3.492	.000	2.42	8.62
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

Table 3: Statistical analysis according to ANOVA.

	Sum of Squares	df	Mean Square	F	Sig.
Annual cigarette packs	6771613.586	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	14043.359	38.011	.000
Diastolic BP	1307.135	1	1307.135	10.136	.001
Mean BP	5872.939	1	5872.939	29.126	.000

Other significant results were history of chest pain [P=.001] and the presence of protienuria 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.

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

Discussion

The results of the study indicate that there is a statistically significant positive history of past CVA and past MI in diabetics with peripheral vascular disease as compared to diabetics without peripheral vascular disease. Assessment of past CVA and past MI was based on documentation of diagnostic or therapeutic interventions positive family history, physical signs and positive diagnostics related to a vascular event. The accurate future prediction of vascular events was limited because of the retrospective cross-sectional nature of the study.

However 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. Our results depict that vascular disease more or less has the same predictive factors across the body and shows cross reactivity.

Other researchers like Cotter G et al reported similar results on the association of peripheral artery disease, cerebrovascular disease and acute coronary syndromes. It was noticed during their study that Patients with prior extracardiovascular disease (vascular disease outside the coronary perfusion field) events often had coronary multivessel disease and these patients more often had angina pectoris as compared to Q wave infarctions in patients that did not have prior history of extra cardiovascular disease.[4] This signifies that patients with extarcardiovascular disease had a generalized tendency of the coronary vascular network to clot, narrow or contract across the cardiac tissue (porbably more so at specific points). 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.

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 lifetime cigarettes smoked were strongly correlated

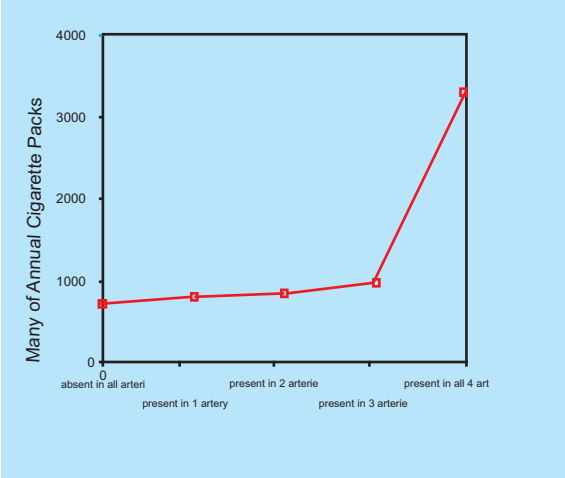

Fig. 1. Cigarettes consumed in a lifetime period.

with history of intermittent claudication (P<.000) there was no significant correlations between cigarettes consumed and generalized vascular disease. A significantly greater proteinurea 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 levels of Systolic BP and Diastolic BP in Diabetics 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. Can insulin resistance or dysmetabolic state cause an altered arterial structure in any way? Or the homeostatic environment is disturbed resulting in the emergence of a cumulative picture of injury to the vascular endothelium.

It is also possible that our dataset of patients had a higher prevalence of diabetic nephropathy as well signified by significant proteinurea in PVD diabetics. Chronic diabetic nephropathy directly promotes raised blood pressure through mesangial thickening[5] and possibly through concurrent production of increased levels of angiotensin leading to eventual vasoconstriction. Seemingly this explanation may give a clue about higher blood pressures in this dataset of patients or diabetics as a whole. But it has also been observed with clinical experience that weight loss in obese patients provides better blood pressure control and outcomes.[6] 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 to 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 metabolic process that has gone wrong from the very beginning.

Siani A et al in his study conducted on 768 men as a follow up of Olivetti Heart Study reported strong correlations of waist circumference with blood pressure and insulin resistance measures. 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 Factors. Significant increases of systolic and diastolic Pressure, heart rate, HOMA index and post load serum insulin were observed across increasing subsections of waist circumference in the selected cohort. Greater degrees of central adiposity was strongly associated with higher prevalence of elevated BP values and insulin resistance.[7] The cause of raised BP may be poorly controlled diabetes, insulin resistance, obesity or a combination

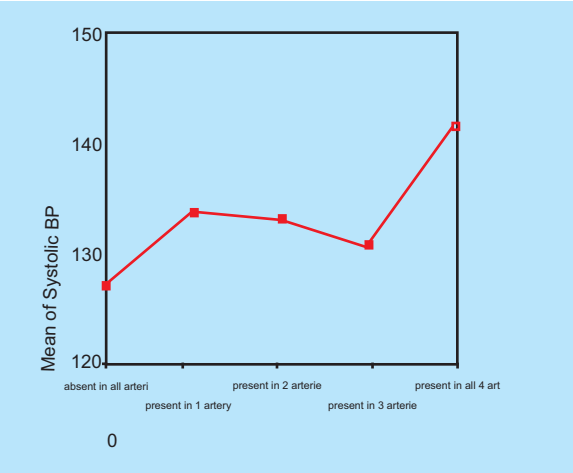

Fig . 2: Systolic BP

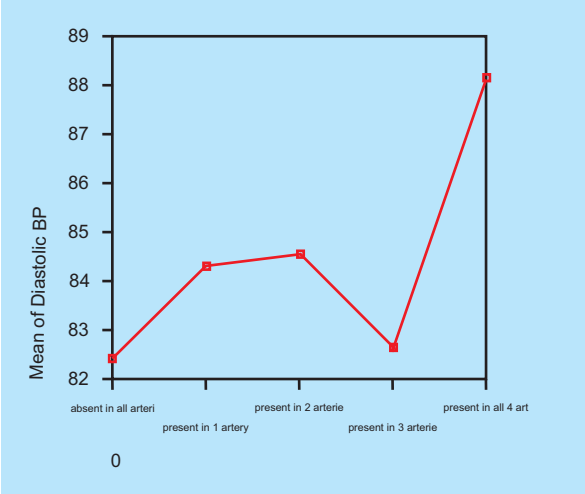

Fig. 3: Diastolic BP

of all of these factors in addition to the overall vascular pathology that they promote. 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. What may be the first step in the chain of events that promotes diabetes, hypertension and obesity? It is either baltered glycemic control or altered fat metabolism that leads to the other as a subsequent step. Can one specific genetic malfunction explain the manifestations of obesity, diabetes and hypertension in specific set of patients?

All these findings point out towards a common underlying pathology that 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 our results and the results of Siani A et al 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 can be labeled as a marker for insulin resistance.[8] The strong correlation of waist circumference with a strong fit in a regression model as proposed by Siani et al 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 than 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 proinflamatory phase aggravated or augmented by nephrologic end organ complications and subsequently raised sympathomimetics causing a generalized vasospasm. This spasm in itself or with other environmental and metabolic intermediates may cause injury at prone endothelial sites. Considering the raised blood pressure as a related event there could be a chronic prosympathomimetic phase being aggravated by long standing diabetes along with diabetic nephropathy and mesangial thickening leading to raised blood pressure measurements with a subsequent proinflamatory phase as a result of this longstanding unfavorable metabolic state leading to endothelial injury. Further clinical evidence generated with biomarker variables based studies may be required to substantiate this hypothesis fully.

Control of Biases:

The diabetic database consisted of 4482 consecutive visiting patients to the Diabetes Management Center, selection bias was reduced by defining peripheral vascular disease in detail and including all cases of peripheral vascular disease in the analysis. Controls were selected randomly out of the remaining diabetics by random number selection from the same diabetic database. Thus cases and controls had all characteristics comparable, except for presence or absence of peripheral vascular disease. Lead time bias was also reduced due to random selection of comparable cases and controls independent of disease history or duration.

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 protienurea.

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 the etiology of vascular injuries.

Division of Pulmonary Medicine and Critical Care
Medical Unit III, Services Hospital
Post Graduate Medical Institute, Lahore, Pakistan.

theesculapio@hotmail.com

References

1. Braunwald E.Disorders of the Cardiovascular system. In: Braunwald E. Fauci S.A, Kasper LD, Stephen L.H, Long L.D, Jameson L, (eds). Harrisons Principles of Internal Medicine. 15th ED. New York: McGraw-Hill 2001: 1435.
2. Powers AC.Diabetes Mellitus.In: Braunwald E. Fauci S.A, Kasper LD, Stephen L.H, Long L.D, Jameson L, (eds). Harrisons Principles of Internal Medicine. 15th ED. New York: McGraw-Hill 2001: 2124.
3. Powers AC.Diabetes Mellitus.In: Braunwald E. Fauci S.A, Kasper LD, Stephen L.H, Long L.D, Jameson L, (eds). Harrisons Principles of Internal Medicine. 15th ED. New York: McGraw-Hill 2001:2124.
4. Cotter G, Cannon CP, McCabe CH, Michowitz Y, Kaluski E, Charlesworth A et al. Prior peripheral arterial disease and cerebrovascular disease are independent predictors of adverse outcome in patients with acute coronary syndromes: are we doing enough? Results from the Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 study. Am Heart J.2003; 145: 622-7.
5. Makino H, Nakamura Y, Wada J. Remission and regression of diabetic nephropathy. Hypertens Res 2003; 26: 515-9.
6. Valsamakis G, Chetty RK, Kumar S. The management of obesity in type 2 diabetes mellitus. Curr Med Res Opin. 2002; 18: 75-81.
7. Siani A, Russo P, Paolo Cappuccio F, Iacone R, Venezia A, Russo O et al. Combination of renin-angio-tensin system polymorphisms is associated with altered renal sodium handling and hyper-tension. Hypertension 2004; 43: 598-602.
8. Gasteyger C, tremblay A. metabolic impact of body fat distribution. J Endocrinal invest 2002; 25: 876 83.