

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 MI ($p=0.000$), 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 Proteinuria are all significantly present in Diabetic patients with Peripheral Vascular disease.

Key Word: 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 dyslipidemia, hypertension, obesity, reduced physical activity and smoking.⁴ The object of the development of macrovascular of this study was to determine the influence of factors involving 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 (biochemically 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

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

β“”9NBu~ -²;Pq†sdy)| J'Fo~Öp b,,-³4W>iPaé7|
 β™²iWj• TjÜö)J' Üñ(I SG%¼zÜ?h'³YEÄ² SwQöS
 βç÷ @EÄQF(- EZ|Yox¶ Ä@ø!Np™»ä C>öwvæ
 β™*Uv< ©ÄS.CE ¶•a¹ OE.# i@ E= fSÖ4¼ÄÈð%o>C
 βp^H
 βi ðf†β|%uS~ Íá c-Nd...s°
 βi ðeβD,;2y3Tj•é Öè!B
 βi ðf†β|%ž´ × h)¼Dv'HÜ
 ŽñdeβD%,^iSÈÖèp^İ
 βE}´ «IHø0«Sÿ0 u—, CE;QJ"j~Ö* NzC¼•Üð²
 β<5~ CE;þðNæü•2G÷CYz ÖB:pHæQ?—êsâ™™}ç
 β™*Ukù0i~ " "½† "ÄJ f Äè"O•EB ~Ü3|ø ¼>A^
 β™²iWj¼4Öð†ePp' .EgS»¼Py³¼Yk•Üe= AFS3Ö
 β™× WhKüä µ²-CE †æ-[, °ÖüöÜ3u.©...uïðÖE
 β™*Uv<h~ Yoöp^i.CÖe†PZNB>T^PQCG?è3
 βp< QYj _uCE~ ð.βDée^U~Öp@ø,q|æi¼ Y•u^
 β™²a*:çI^ÇÜMÖÄSh~«ÄY%

β±³0yQ6üY EäÊr(çšfšéE8
 β Ää UTCÜb•c | Ä Ð D Ø Ò ^' ðò!- ® \dN
 β±³j>u...2©WjZ0Ä™LJÜcVAFWyzZ•^½ÄI:“UE@
 β±ðo YP|ç ä;©DÜá7y>xXG²Ü»YÇ²•JÎ öiäYÈ
 βüXÖ• Wö pšŠiäNbohG†E^J™,XA-ö ZÉ´”¿5DFn
 Brmä'i&i~ ÜŒS~ \2%:
 B4ð%öYLÄpÖÜ< Ä »* L5²B [÷ á¾†öÖ¿. |MöÄ†w.
 Bà'ì±_6NW.èSaiÖN4sn è¶ 2GÈ Šsâ è-c
 BÉ...BÜÏbM*énöoI "èÖ Ó½´†"èÖÄZ"ÜÉ:β
 BÉR\Wl.sgD NšS%o~3...YDÈpÖ`Y%üHtZS†"äYÈ
 Biðo%üi•d µÖj- €8È%o` İN@K
 BÄÖSÄqt2MÖP`PCEüÜÄ,3nÜÖG0M+ Ç°Ž=²Ü
 β±³c6ä;jöIYa ~ °o-5ñÇCeÖ ÌZÜ« ÷fQ;ç²,w\l
 β±³ü < èÄÖ 2ç½Í<Ä” „oPÈyeB” ÷ ÖÄ0öä pZDF¼~
 Bİ ->•&g} Yy0aE HCB Tc á gX“ -zV|×oL°
 BiRLS«(İà>«è&úpÖIcç9ÖÄ«äEüL Clè×iÖZä|<
 β±³c6ä;jÇYäq :Ü~vM#Ö ?TÄzeX7!èüÜHÑèÖÄ{pβ-

Exclusion Criteria

- β;β “¼Ö¼ÖN©İ ÖiëaH°pð»y+ UAÈu5...a
 Bøf|q” EZef{f ¼aü fY¹Ka,-Üš60SÖü}Ö< uMq
 BøðepÈèyz ,İ2TDje., Ä Ä-èY o°ò7Ö|ÄÈyP
 BEÄÖè
- β;βiS¶× ûlä÷ ©ø× øÄHä_ò9bŽĐù"Luž,U™ÈÈò
 BøÈB æ-Bš®Ä?S%‰† ÜúPL-ñ2\^a
- BU&Ö÷ ;i7E½90%ožÄÈ 'Qz†ò5_g«pÀ Ü® È
 Bø SŸS´ | Üà l•Aè, „ è AÇYÖ Ö...→Ü
 BøðipìBS8 á«İjî á²DXñj&»ä”Ä

Results

β68H 4šK Z~ øQ r -² Úó ²¶ DÖ.äZÇæ-ik•
 BÉÜR;þ{(-ii0i|cðAE,@ŽyWB"úaT?8ÖE7" |hdEæ
 β±(6 üB± Y* Ð;ICEe@6U~ çä8o ÖU_ j TšÖÜ`Qrsty
 B\µ¶ • •¼/ö/ö °èy¹ Ó 2¹-ò|E4 c-ü?Vš», ½¶|...
 BÉÜR;þ{(ñç× |pòxüyLWg°e-oE/z...ÇK•İðIÄ rİE
 β±Fj¹EwöÜFÜ—ksJÜvT?®™fNüäN?+ 5
 B“òò4È NÖYÄEx¹ 8zK bf "d7Ä< ó'4 †|!%o
 Bø¹UèYÖf0ÄÈYg" üñH'¼Val7mÜ“EMXkliÖJ
 Bšðg|,Ü†_i0i|c6v ±šçÄM6YÜÄ±fö jç• •´Öö
 B,{İèæi (öÈÖYnòvy|ä4pñfHL7MÈ† ×Sf'èW}f#
 B4o*°6> iq¼jÖ
 Bkè;İwβç XÄİç¹4Q< 'b<Ä²aÈµeÖèÉdeEZ'
 β±³c6ä;j Pµ.sqÈžuLT4G,oOöâ;«äq†pòcM8#s |kLÄ
 BûÜ6æðj¶"e; y&q dC.9s hð @EÈ²6hòuè
 BÜ*B-D,™pFSñµ,Æžà” oL¶E¶iÈ“ ÑÜ—çr“
 B4*:YİÖææ -,CE Ø, +ö+ çÖÜÁ->Žİf' b >€ö
 BTy(NägäY;üŒSŠö4< üöäİSÄ- äiÜßZnL ½3è`

Analysis

βİ\ +@Ñäö, 1Fg{Zo?Úcİ= øCE,,ÄG™²a%oÜÄ
 βçqÖaxi)ªtöİ —ü2--Øøâè .X., °! Fp1 İI)İç
 β™*: *v—«ÄÖPEvÇXnyZn,4v~ÄVm¶Äİö89Ü+
 BAL\mİlİkÄ 5Jl6KmžkH bŽLu†³ò= •WJüž
 β%mo¹Üö¼Öäç«ivèy@«ð + Ä-o~ÜÄÖS}•;AZ

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 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.

Univariate 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

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. Recognizable 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

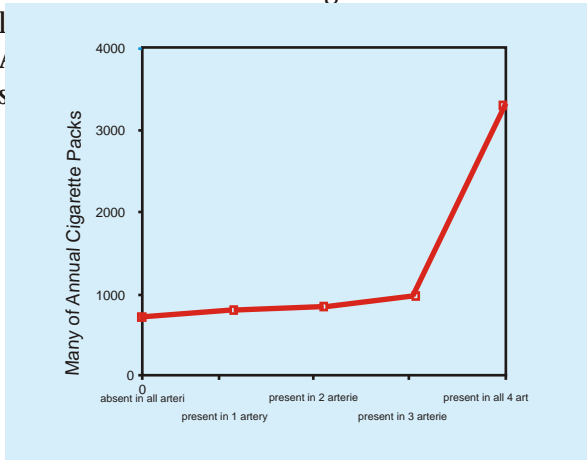


Fig. 1. Cigarettes consumed in a lifetime period.

with history of intermittent claudication ($P < .000$) there was no significant correlations between cigarettes consumed and generalized vascular disease. A significantly greater

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 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 proteinuria in PVD diabetics. Chronic diabetic nephropathy directly promotes raised blood pressure through mesangial thickening⁵ 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

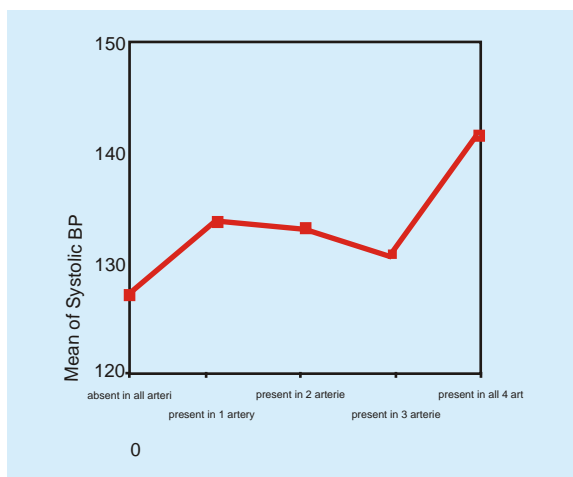


Fig. 2: Systolic BP

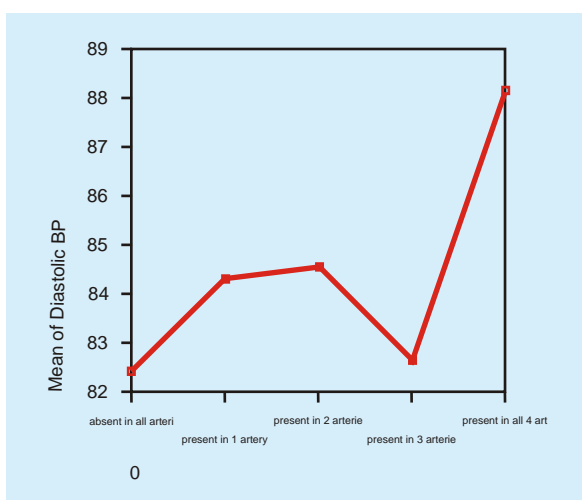


Fig. 3: Diastolic BP

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 proinflammatory 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 proinflammatory 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

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 the etiology of vascular injuries.

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-angiotensin system polymorphisms is associated with altered renal

The Answer of the Picture Quiz

Acanthosis nigricans is a disorder that may begin at any age. It causes velvety, light-brown-to-black, markings usually on the neck, under the arms or in the groin. Acanthosis nigricans is most often associated with being overweight.

Eating too much of the wrong foods, especially starches and sugars, raises insulin levels. Most patients with acanthosis nigricans have a high insulin level, higher than those of the same weight who don't have acanthosis nigricans. Elevated levels of insulin in most cases probably cause acanthosis nigricans. This happens when there is

insulin "spillover" into the skin. This activates insulin receptors in the skin and forces it to grow abnormally. Reducing the circulating insulin by a special diet can lead to a rapid improvement of the skin problem.

When acanthosis nigricans develops in people who are not overweight, a medical work-up should be done. Rarely acanthosis nigricans is associated with a tumor. In these cases acanthosis can be seen in extra places, such as the lips or hands and is unusually severe. Sometimes acanthosis nigricans is congenital or due to an endocrine (glandular) disorder.