The Effect of Age and Lipid Profiles on Peripheral Vascular Disease in a Cohort of Diabetic Patients

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Background: Vascular disease carries the maximum mortality and morbidity burden in diabetic patients. Peripheral vascular disease is generally considered to be similar in its etiology and pathology to vascular disease in other tissue fields and its risk factors are also believed to be a part of larger atherogenic vascular picture.
Methods: The study was conducted on a cohort of individuals suffering from Diabetes Mellitus registered at the "The Diabetes Management Center". A total of 1160 cases were selected on the basis of presence or absence of peripheral artery disease with an aim to study the prevalence of peripheral vascular disease in diabetic and ascertain if total cholesterol, age and duration of diabetes play a role in the development of peripheral vascular disease.
Results: Our study showed that presence of peripheral vascular disease in diabetics is significantly associated with increased age, increased duration of diabetes, history of intermittent claudication, delayed wound healing and increased area of skin ulcers. There is no significant difference in total cholesterol level, LDL, HDL, and triglyceride levels amongst those diabetics that developed PVD than those who did not. The role of genetic susceptibilities leading to altered metabolism with due contribution by environmental factors may come to light by further analysis of other variables involved in artery disease picture.
Conclusion: Presence of peripheral vascular disease in diabetics is significantly associated with increased age, increased duration of diabetes and history of intermittent claudication, delayed wound healing and increased area of skin ulcers. There is no significant difference in total cholesterol level, LDL, HDL, and triglyceride levels amongst those diabetics that developed PVD than those who did not.
Key Words: Diabetes Mellitus, Peripheral Vascular Disease, Serum Lipid.

Introduction

The study was conducted on a cohort of individuals suffering from Diabetes Mellitus and who are registered with "The Diabetes Management Center" at the Services Hospital Lahore as a randomized cross sectional retrospective analysis. This study was a part of series of studies being conducted by the Diabetes study group at the Services Hospital. The broader objective of this endeavor was to determine the overall vascular disease picture that develops in dia-betics specifically in individuals with the metabolic syndrome. Among many complications of diabetes vascular disease carries the maximum mortality and morbidity burden. Exact statistics regarding peri-pheral vascular disease and its prevalence in diabetics are not available; although data from NHANES I epidemiological follow up study indicate a coronary heart disease incidence associated with a medical history of diabetes 8.7% in African American women and 6.1% in Europe American women. Medical history of diabetes was a significant predictor of CHD incidence and mortality in American women and explained the excess coronary incidence in younger African American as compared to European American women.

Material And Methods

In this portion we aimed to study the prevalence of peripheral vascular disease in diabetics and ascertain if total cholesterol, age and duration of diabetes play a role in the development of peripheral vascular disease picture in such patients. More specifically if cholesterol and its constituent levels are substantially different in individuals with diabetes suffering from peripheral vascular disease than in those diabetics who do not suffer from peripheral vascular disease as a part of continuing, broader atherogenic process. Whether increasing age and duration of diabetes play any role in the development of peripheral vascular disease. Can quantifying these factors predict the future development of PVD in specific sets of patients and if a common underlying biochemical etiology or markers existed indicative of the develop-ment of peripheral vascular disease?

Queries were developed from a first visit record of 4482 consecutive diabetic patients being treated as regular patients at "The Diabetes Management

database holds information regarding all diabetic patients who have been diagnosed with diabetes and are being treated as outdoor patients at this particular hospital.

We developed a query from the database which included many suspected or known determinants of disease. We included physical characteristics, biochemical indicators related to cholesterol levels and other indicators of micro vascular and macro vascular disease for this segment of the study.

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 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 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.

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 and
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.

Total skin ulcer area was calculated by multiplying horizontal, vertical measurements and depth of the ulcer area. All areas were added together in the variable "Ulcerttl".

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 tests and ANOVA with post hoc

Table 1: Descriptive statistics comparison of cases and controls.

	Controls		Cases	
	Mean	Std. Deviation	Mean	Std. Deviation
Total cholesterol	194.28	34.77	194.40	37.70
LDL	100.86	22.65	108.77	34.28
HDL	40.64	9.10	41.76	8.04
Triglycerides	220.53	99.27	254.48	287.09
DM duration(years)	6.77	6.43	9.07	7.20
Ulcers	0.24	1.78	1.01	5.22

disease as a dependent variable and all other risk factors as covariates.

Univariate linear analysis was also performed between factors like cigarettes packets smoked per year, diabetes duration 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

The results of Student t test between various covariates are shown in Table number 1. Total cholesterol and its constituents had no significant difference between those diabetics with peripheral vascular disease and those without peripheral vascular disease Total Cholesterol [P=0.987(C.I. 14.33 to 14.57)], (LDL P=0.297), HDL (P=0.608) and Triglycerdies (P=0.465). Although means of LDL and Triglycerides in cases were higher than means of controls and the variances for cases were significantly wide [for LDL 108 ± 34.28 cases vs 100.86 ± 22.65controls] and [for TGs 254.48 cases ± 287.09 vs 220.53 ± 99.27controls].

Importantly DM duration in years and age were significantly different in individuals who had peripheral vascular disease than in subjects who did not had peripheral vascular disease [P=0.000 (C.I. 1.51 to 3.09)] and [P= .000 (C.I. 3.75 to 6.54)] respectively. Age and duration of diabetes probably show the chronic pathologic progression of altered glycemic controls involved with increasing time span and its direct relationship with the end organ complications both in reality representing the same underlying pathological phenomenon.

The total area of foot ulcers (calculated by multiplying the longitudinal and horizontal breadth and depth of the ulcer area) was significantly different in PVD subjects than in subjects without PVD [P=.000 (C.I. 0.33 to 1.39)].

Other significant differences between PVD diabetics and non PVD diabetics were history of Intermittent claudication [P=.000], delayed wound healing [P=.008] and the presence of protienurea in diabetics with PVD [P=.000]. Presence of proteinurea 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

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

	t	Sig. (2-tailed)	95% confidence interval of the difference Lower	Upper
Age	7.255	.000	3.75	6.54
Total cholesterol	.016	.987	-14.33	14.57
LDL	1.051	.297	-7.14	22.97
HDL	.515	.608	-3.23	5.48
Triglycerides	.734	.465	-58.06	125.95
DM duration (years)	5.728	.000	1.51	3.09

Table 3: Statistical analysis according to ANOVA.

	Sum of Squares	df	Mean Square	F	Sig.
Age	7676.083	1	7676.083	52.633	.000
Total cholesterol	.356	1	.356	.000	.987
LDL	974.337	1	974.337	1.105	.297
HDL	19.325	1	19.325	.265	.608
Triglycerides	25054.555	1	25054.555	.538	.465
DM duration (Years)	1528.945	1	1528.945	32.812	.000
Ulcers	487.46	1	487.46	15.23	.000

Obtained by Student T test tallied with ANOVA results. Age (P= .000), DM duration (P=.000), were significantly different in diabetics with Peripheral vascular disease than in diabetics without peripheral vascular disease. While Total Cholesterol (P=.987), LDL (P=0.297), HDL (P=0.608), Triglycerides (P=0.465), had no significant difference in diabetics with PVD as compared to diabetics without PVD.

Univaraite analysis between various models of age, diabetes duration and size of ulcers revealed non significant results.

Discussion

Our results prove little or no association of traditional risk factors like high cholesterol levels, increased triglyceride levels or increased LDL levels with the presence of peripheral vascular disease in diabetic subjects as compared to those diabetics who do not have peripheral vascular disease. Peripheral vascular disease is generally considered to be similar in its etiology and pathology to vascular disease in other tissue fields and its risk factors are also believed to be a part of larger atherogenic vascular picture. We can't totally prove or disprove the presence or absence of cholesterol factor in the disease causation picture by our results but still there was no statistically significant difference in Total Cholesterol, LDL, HDL and even Triglycerides levels in diabetic subjects with peripheral vascular disease as opposed to those without peripheral vascular disease. Specifically the effects of LDL have been documented to be detrimental in vascular disease and its decrease has generally been considered to decrease endpoint mortality and morbidity in various intervention trials conducted through out the world. A known example is the "Heart protection study trial" conducted in UK on 20, 536 adults reported decrease in mortality, cerebrovascular and cardiovascular events with use of Statins.[2,3] Still we did not find any specific difference in cholesterol and its constituent's levels in PVD diabetics as compared to non PVD diabetics.

In most of these studies lowering cholesterol level has been shown to increase survival and decrease morbidity irrespective of initial cholesterol level. In another randomized intervention trial conducted at University of Queensland Australia; Fathi R et al employed aggressive and normal lipid lowering strategies vs placebo and measured actual LDL levels, episodes of angina and atheroma burden (showed by carotid intima media thickness). Results were compared between Aggressive lipid lowering group (Atrovastatin 80 mg/day), usual lipid lowering group and placebo group. After 12 weeks of treatment patients had significant decrease in LDL levels and angina score but atheroma burden (carotid intima media thickness) between aggressive therapy normal therapy and placebo group showed no difference.

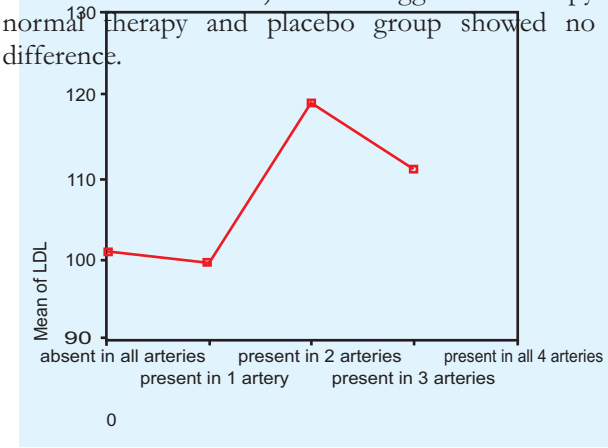


Fig. 1: LDL.

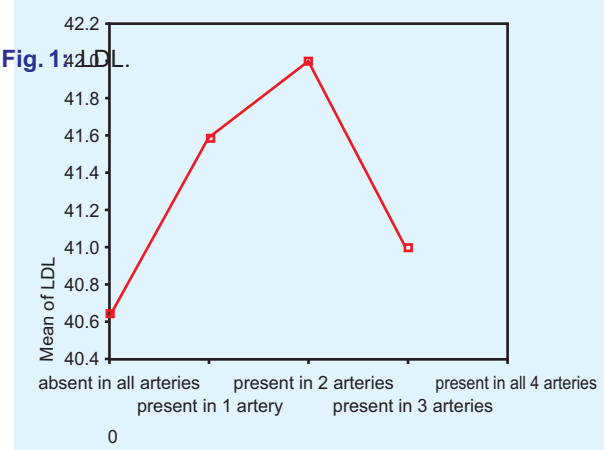
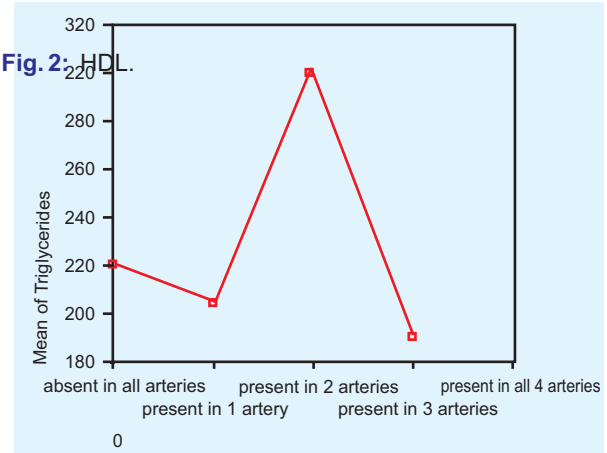


Fig. 2: HDL.



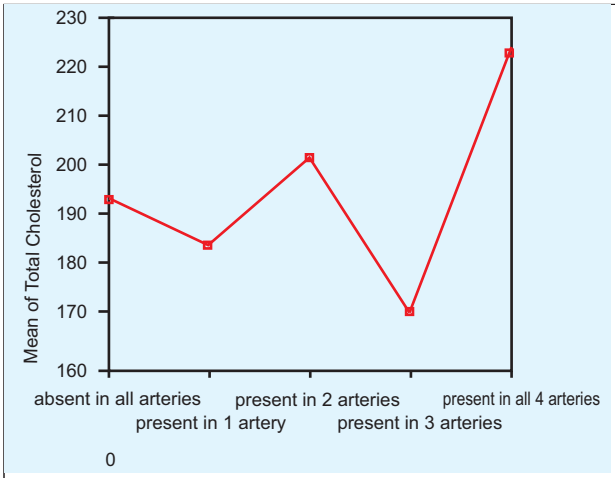


Fig. 4: Total cholesterol.

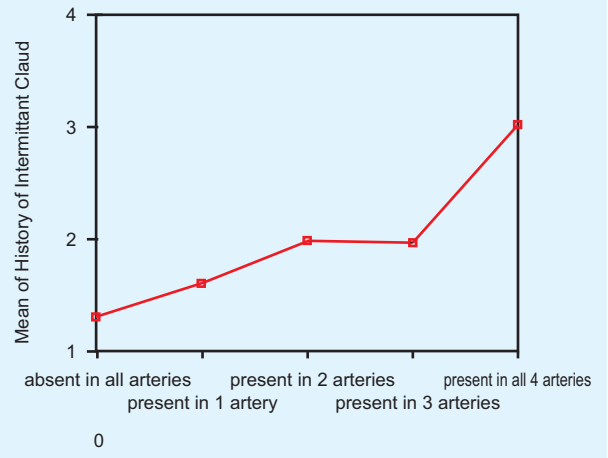


Fig. 5: Intermittent claudicating.

Although aggressive lipid reduction may actually decrease the deposition of further cholesterol in the vascular fields but they cannot flatten/ cure the already build atheromas (which still carry risk of rupture, blockage and thrombus formation) as demonstrated by *Fateh et al*. If we are only altering cholesterol and LDL from further deposition than we are only trying to rectify the outcomes of a metabolic imbalance which might have gone wrong from a much primary stage. We may be focusing less on the initial cause while trying to prevent the final outcome and complications. It is entirely possible that lipid levels may have more of a synergic contributory role than a primary etiological role in development of peripheral vascular disease. Can we totally prevent these atheromas from developing in the first place and identify why these particular sites or these specific metabolically altered conditions predispose these sites to have bad cholesterol deposits thus drastically reducing coronary and cerebrovascular disease mortality in high risk patients? Is it the initial dysmeytaboic state of altered carbohydrate and lipid metabolism or poor diabetic control superimposed with this altered state which predisposes these individuals to increased risk of coronary and other vascular events. Treating the basic metabolic imbalance / disturbance may actually help in totally preventing these atheromas.

Other results form our study also signify that various measures of tissue injury in the lower limbs were also significantly greater in diabetics with PVD as opposed to matching controls. The total ulcer size (obtained by multiplying breadth, length and depth of a specific ulcer) was much greater in PVD diabetics as opposed to non PVD diabetics, History of intermittent claudication and delayed wound healing etc although subjectively measured were also significantly greater in PVD diabetics as opposed to matching controls. All these findings offer a ready explanation of increased injury measures due to reduced tissue perfusion over prolonged time. We may also be able to quantify a future risk for tissue injury in lower limbs by degree of occlusion in various arteries just as it is done for more recognized tissue fields like the coronary or cerebral fields. Another significant difference between PVD diabetics and non PVD diabetics was that age and duration of diabetes were greater in diabetics with PVD as compared to diabetics without PVD. Age and duration of diabetes actually directly represent increased duration of the altered metabolic imbalance that predisposes these individuals to vascular injury eventually. This pathologic imbalance may represent poor glycemic control only. Since our study was more cross-sectional in nature than being prospective we cannot definitely comment on what degree of poor glycemic control actually causes the disease. There was a minimal chance of a systematic bias causing selection of longer suffering diabetics with PVD only; since our source population was spread across various social and educational stratas referred from a number of practices and hospitals at various stages of disease ranging from newly diagnosed to those with end organ complications and was evenly spread across cases and controls. Is it the poor glycemic control only or a more basic underlying pathology related to diabetes that is manifested as the end organ complications and vascular pathology. There is a high plausibility in the hypothesis that diabetic state in itself predisposes to vascular injury directly while more insult is to a susceptible cell line is added with poor glycemic control. The phenomenon of insulin resistance may also be complacent in the

overall vascular disease picture?

Understanding this phenomenon may help in identifying and quantifying the appropriate. Biomarkers and help in identifying the most susceptible populations amongst diabetics.

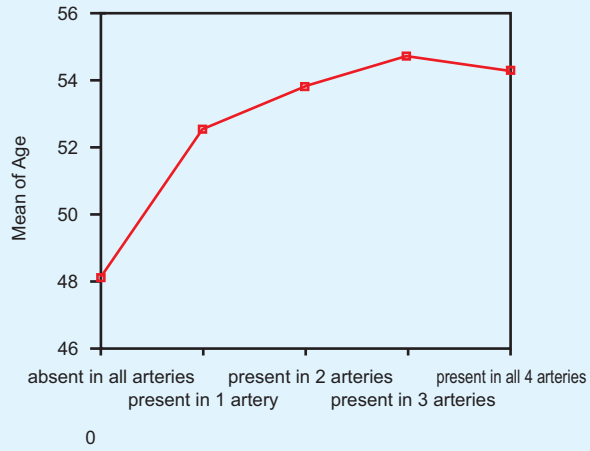


Fig. 6: Mean of age.

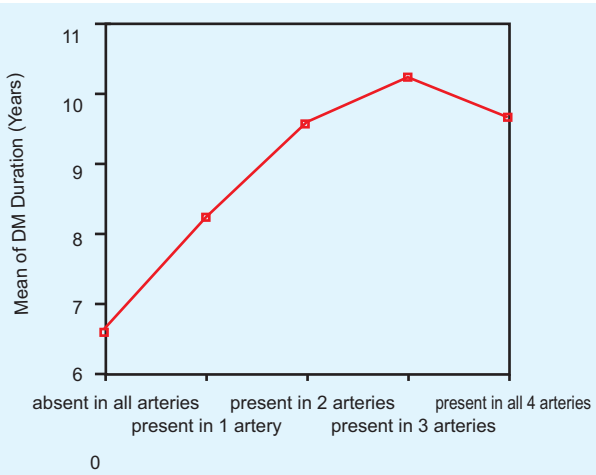


Fig. 7: DM duration.

Insulin resistance may promote vascular injury by promotion of a dysmetabolic state as well as a hyeprcoaguable state. Individual markers of this phenomenon have yet to be established fully but certain phopsholipases and soluble ICAM's and VCAM's have been identified in recent reviews as being raised in those individuals who have artery pathology in the cerebral and coronary vascular fields.[5,6,7,8,9] The raised levels of these lipases and cellular adhesion molecules could just represent a generalized inflammatory phenomenon only. It is indeed plausible that these makers can actually be utilized to predict future vascular disease or they may at least serve as valid markers for the dysmetabolic state. The pathological state could be as simple as altered glycemic control or it may involve complex intricacies of altered lipid and protein metabolism along with altered carbohydrate metabolism

There is definitely something more consistent than altered lipid level that stays on course steadily throughout the duration of diabetes eventually promoting vascular pathology. The initial genetic susceptibility may directly promote an unfavorable metabolic state with altered utilization of carbohydrates. As a consequence of this altered state or as an independent factor, risk markers like raised VLDL and LDL may add further insult to the already susceptible endothelium. Chronic prolonged unfavorable state along with further deposition of LDL like substances will lead to thickening, rupture and subsequent narrowing of lumen.

This study was important as it proves that at least one traditional risk factor of vascular disease namely altered lipid profile (increased LDL, decreased HDL and increased triglycerides) is not significantly different in the vascular disease picture happening in the peripheral vascular field. The cross reactivity of vascular disease in the peripheral arteries needs to be further analyzed with reference to vascular disease in the cerebral and coronary artery fields. If indeed our results are reproducible than this may signify that at least in case of diabetics there could be more primary, underlying change/alteration in metabolism that leads to non-homeostatic proinflamatory phase that promotes vascular injury.

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 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 increased age, increased duration of diabetes and history of intermittent

claudication, delayed wound healing and increased area of skin ulcers. There is no significant difference in total cholesterol level, LDL, HDL, and triglyceride levels amongst those diabetics that developed PVD than those who did not. The role of genetic susceptibilities leading to altered metabolism with due contribution by environmental factors may come to light by further analysis of other variables involved in artery disease picture. All these observations and discoveries would be important in answering questions regarding the etiology of vascular disease in diabetics

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