Anthropometric Measurements as a Determinant and Predictor of Peripheral Vascular Disease in a Cohort of Diabetic Patients

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Background: Diabetes leads to a dysmetabolic state in the body. A cluster of bio chemical and anthropometeric factors have been found to cause pro inflammatory state in vascular endothetium. The role of anthropomeric measures in development of atheroselerosis in patients with cardiovascular disease has been extensively studied. The aim of this study is to assess the influence of these factors in peripheral vascular disease.
Materials & Methods: Queries were run on a cohort of diabetic patients and anthropometric measurements were made. Peripheral vascular disease was assessed by presence or absence of pulses.
Results: The factors found to be significantly different in patients with peripheral vascular diseases versus those without peripheral vascular disease include waist circumference and waist Hip ratio, diastolic, systolic bloodpressure and delayed wound healing.
Conclusion: Distribution of adipose tissue and its possible endocrine control plays a significant role in subsequent development of vascular injury and atherosclerosis in Diabetics.
Key Words: Metabolic Syndrome, Waist Hip Ratio, Hypertension & Waist Circumference.

Introduction

Vascular disease carries the maximum burden of mortality and morbidity in Diabetics. A cluster of biochemical, clinical and humoral factors have been associated with impaired insulin action in glucose metabolism. Hyperinsulinemia Hypercoaguable states central obesity, essential Hypertension, dyslipedimia, hyperuricemia, endothelial markers of inflammation have all been implicated as typical components of metabolic syndrome.[1] According to clinical trials, people with metabolic synolerome, have 2 to 4 fold increase in risk for coronary Heart disease.[2] 1 Data from NHANES Epidemiological follow up study indicate a coronary heart disease incidence associated with a medical history of diabetes of 8.7% in African American women and 6.1 % in European American women.[3] Exact statistics regarding peri-pheral vascular disease and its prevalence in diabetics are not available. This study was conducted on a cohort of individuals, suffering from Diabetes Mellitus with a broader objective to determine the overall vascular disease picture that develops in individuals with metabolic syndrome.

Objectives

We aimed to study the prevalence of peripheral vascular disease and ascertain its predisposing etiological and epidemiological risk factors in a population of diabetic individuals and correlate its presentation with the larger vascular disease picture in diabetics. Can we identify any physical or biochemical markers that can help us in identifying possible high-risk patients earlier in the course of the disease?

In what fashion does altered metabolism promote or augment vascular pathology? Whether peripheral artery disease followed the same pattern, set of risk factors and indicators as macrovascular disease in other tissue fields. If so, whether the independent risk factors of similar magnitude can be predicted to cause the same degree of disease or its determinants and outcomes are different?

Methods

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

The research plan and policy was approved by the Ethics Committee of PGMI and fully followed the ethical guidelines developed by NIH and PMRC for human subjects research.

We developed a query from the database, which included most of the suspected or known determinants of disease, physical characteristics, biochemical indicators and other indicators of macro

Table 1: Descriptive statistics comparison of cases and controls.

	Controls		Cases	
	Mean	Std. Deviation	Mean	Std. Deviation
Height	159.22	9.51	159.16	9.50
Weight	68.40	15.72	69.55	15.40
BMI	27.04	6.00	27.56	6.04
Waist circumference	88.97	13.65	92.62	12.84
Hip circumference	96.85	12.50	96.55	12.31
WHADD	185.82	24.56	189.19	23.84
WHRATIO	.91	9.15	.96	.10
Triceps FT	18.43	8.52	18.24	8.52
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

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 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
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.

Weight and hip circumference was added together in the variable "whadd". Waist circumference in cm was divided by hip circumference in the variable "whratio". Mean BP was taken as an average of Systolic and Diastolic BP.

Exclusion Criteria

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

Analysis

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

Five hundred eighty 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 blood pressure measurements, 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

Body measurements and obesity measures revealed a varied relationship. Most of these measures were not significantly different in PVD cases vs PVD controls like BMI [P= 0.142], height [P= .927], weight [P=0.208], and Triceps circumference [P= 0.070] (All greater than cut off value of 0.025).

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

	t	Sig. (2-tailed)	95% Confidence Interval of the Difference Lower	Upper
Height	-.092	.927	-1.15	1.05
Weight	1.261	.208	-.64	2.95
BMI	1.470	.142	-.17	1.22
Waist circumference	4.690	.000	2.13	5.19
Hip circumference	-.409	.682	-1.73	1.14
WHADD	2.369	.018	.58	6.18
WHRATIO	7.456	.000	3.14	.79
Triceps SFT	-.386	.700	-1.18	5.39
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.
Height	.766	1	.766	.008	.927
Weight	384.849	1	384.849	1.590	.208
BMI	78.369	1	78.369	2.162	.142
Waist circumference	3862.872	1	3862.872	21.995	.000
Hip circumference	25.802	1	25.802	.168	.682
WHADD	3287.224	1	3287.224	5.610	.018
WHRATIO	.526	1	.526	55.595	.000
Triceps SFT	10.778	1	10.778	.149	.700
Systolic BP	14043.359	1	14043.359	38.011	.000
Diastolic BP	1307.135	1	1307.135	10.136	.001
Mean NBP	5872.939	1	5872.939	29.126	.000

Interestingly Waist circumference [P= .000 (C.I. 2.13 to 5.19)] Whadd [P=0.018 (C.I. 0.58 to 6.18)] and Whratio [P=0.000 (C.I. .0031 to .0054)] were all significantly different in subjects with PVD than in controls that did not had 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].

ANOVA (table 2) was employed to confirm the results as a more robust test. Almost all results tallied with the results obtained by Student's T test. Diabetics with peripheral vascular disease showed a statistically significant difference between Waist circumference (P=.000), whartio (P=.000), whadd (P= .018) Systolic BP (P=.0010), Diastolic BP (P=.001) and Mean BP (P=.000) at a cut off value of 0.05 as compared to diabetics without PVD.

Univaraite analysis between various models of diabetes duration and blood pressures revealed non-significant results.

Discussion

The diabetic individuals suffering form peripheral vascular disease had a significant and consistent difference in specific body measurements as compared to diabetics that did not had peripheral vascular disease. The physical measurements that were different in PVD subjects as compared to "Non-Pvd diabetics" included waist circumference and waist hip ratio (obtained by dividing the waist circumference by hip circumference). Both these measurements were significantly greater in the defined cases as compared to defined controls. It is interesting to note that composition of adipose tissue in and around the waist area is mostly white adipose tissue. It is larger deposition of such adipose tissue that increases the waist circumference more than other adipose tissue across the body. Waist circumference and waist hip ratio can be taken as a surrogate marker for insulin resistance and they signify the larger deposition of white adipose tissue in the waist area as compared to other areas.[2] Intraabdominal fat or visceral fat mainly comprising of white adipose tissue is more active metabolically and as such is more associated with The Metabolic Syndrome. This syndrome has been associated with higher prevalence of hypertension, hyperglycemia, low high-density lipoprotein (HDL) cholesterol, hyperinsulinaemia, raised apolipoprotein B, and small dense low-density lipoprotein (LDL) cholesterol particles.[3-5]

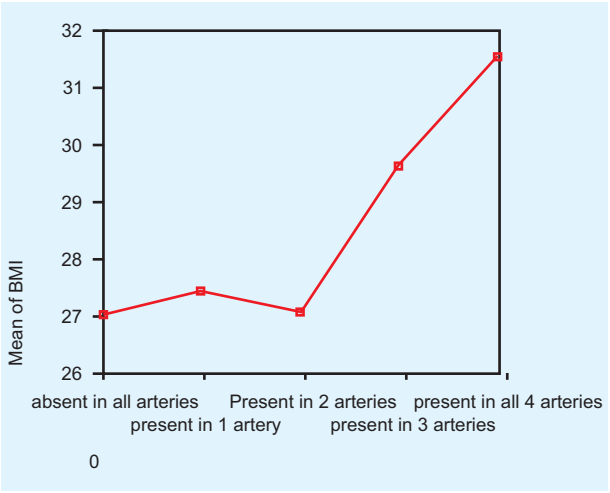


Fig. 1: BMI.

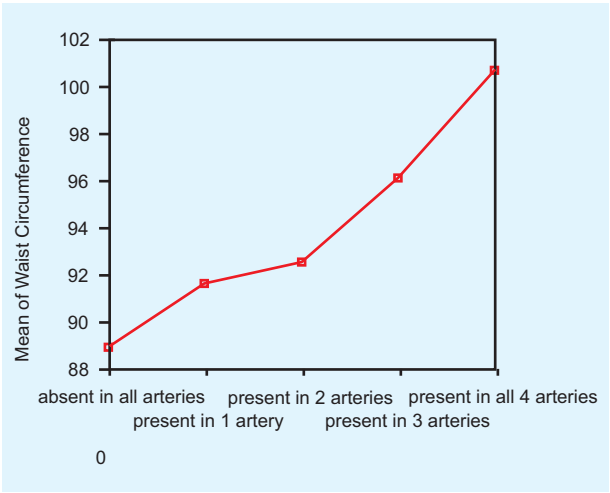
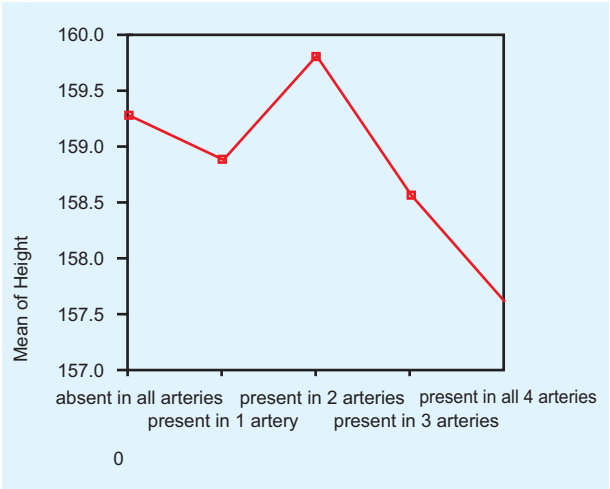


Fig. 2: Waist circumference.



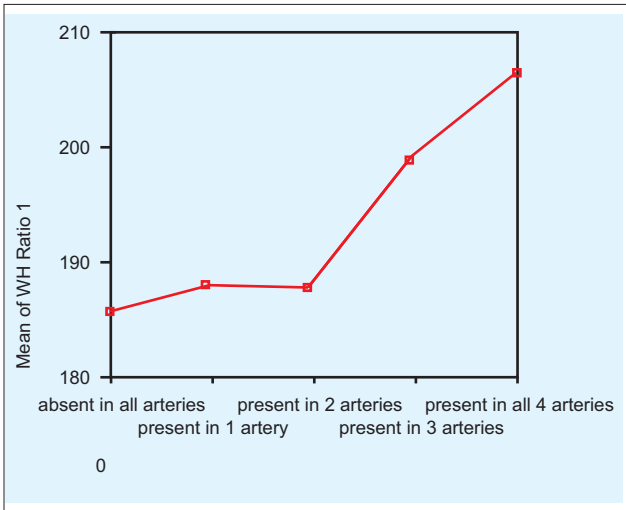


Fig. 4: Height.

Yamashita et al concluded in his study on the association of insulin resistance with body fat distribution that central body distribution (measured by visceral and subcutaneous fat measurements on CT scans) especially in the waist area had significant positive correlations with plasma glucose, serum triglyceride level, and total cholesterol level as well as systolic or diastolic blood pressure. Visceral fat distribution was more frequently associated with coronary artery disease than subcutaneous fat distribution suggesting that insulin resistance may be more specifically present in such individuals. Furthermore, visceral fat accumulation was also associated with all the above-mentioned complications even in non-obese subjects.[6] The results of Yamashita et al and our study hint out that central body fat deposition may predispose the diabetic patients towards increased risk of altered metabolic state that promotes metabolic homeostatic pathology over a period of time. In previous segments of this study we concluded that vascular pathology in one tissue field predicted vascular pathology in other tissue fields (coronary, cerebral) and vice versa.

The factors that promote vascular pathology may bear a direct relationship to insulin resistance. The exact nature of relationship between insulin resistance, obesity and vascular end organ complications needs to be further teased out. It is possible that gross vascular pathology in various tissue fields may bear a direct and etiological role with insulin resistance and central body fat distribution, while both of these indicate a common underlying genetic / environmental susceptibility that promotes diabetes and subsequent altered metabolism in the first place. The finding of a strong differential relationship of waist circumference with diabetes and raised blood pressures hints towards a possibly etiological / pathological role of white adipose tissue and central adiposity in pathogenesis of vascular pathology possibly by promoting a generalized dysmetabolic state. Only central adiposity relationship with vascular pathology was more consistent out of all other indicators of body fat measurements like BMI, hip circumference, or triceps circumference. This emphasizes the differential nature and specific role of white adipose tissue around the waist area.

Insulin resistance may be the central phenomenon causing central body fat deposition along with poor glycemic control and altered blood pressures. Obesity and diabetes have been linked together through Resistin (a substance with autocrine and endocrine effects primarily expressed in adipocytes.[7] Resistin inhibits insulin stimulated glucose uptake and antibodies against resistin enhance glucose transport in adipocytes. Increased expression of Resistin in recent reviews have been implicated with insulin resistance, poor glycemic control and increased differentiation of adipocytes through a positive feedback cycle.[15] Is "resistin" the missing link of that specific genetic tendency that promotes the phenomenon of altered glycemic and lipid control?

As previously discussed there was a significant difference in levels of Systolic BP and Diastolic BP in PVD diabetics as compared to non-PVD diabetics. This finding may simply represent incidental coexistence of hypertension in diabetics with peripheral vascular disease or its presence as an independent disease? But here the specific presence of raised systolic BP, 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. The cause of raised BP may be poorly controlled diabetes, insulin resistance, obesity or a combination 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.[9]

Almost similar results were mentioned by *Siani A et al* in his study conducted on 768 men as a follow up of Olivetti Heart Study.

Multivariate analysis showed that waist

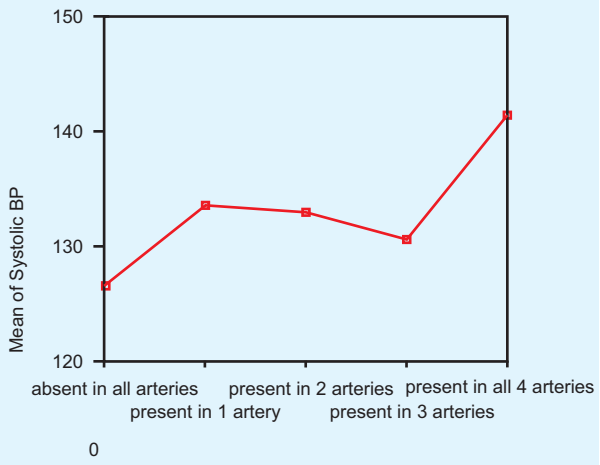


Fig. 5: Systolic BP.

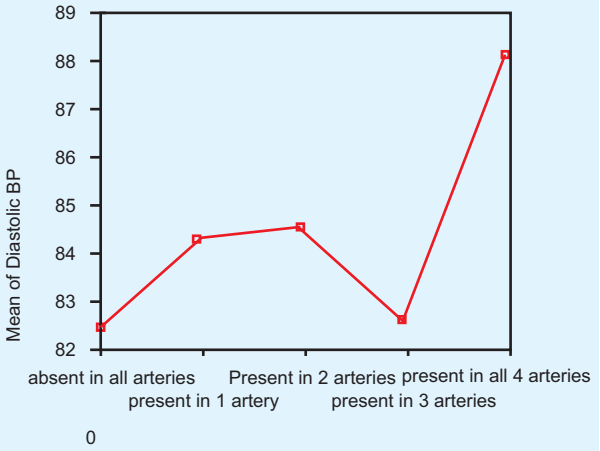


Fig. 6: Diastolic BP

predictor of BP after adjustment for confounders. Significant increases of systolic and diastolic pressure, heart rate, and postload serum insulin were observed across increasing subsections of waist circumference in the selected cohort.[10]

Conclusively our results and those of Yamashita et al and Siani et al point out towards a the pathological role of white adipose tissue / central adiposity or its mere coexistence along with altered glycemic control and raised blood pressures. But it probably seems more than just incidental coexistence. It hints towards a concurrent underlying pathology that may predispose individuals suffering with diabetes to a whole spectrum of pathological manifestations, which include obesity, insulin resistance, abnormalities of lipid profile, various endocrine changes, abnormalities of coagulation factors, abnormalities of ventricular function and vascular compliance. The exact order in which these pathological phenomenons follow each other still needs to be determined.

It is highly plausible that genetic tendency with insulin resistance and non-utilization of glucose leads to conversion of carbohydrates into FFA and triglycerides, which eventually raises VLDL and LDL levels that promote central fat deposition.

Infectious and autoimmune etiologies have also been cited as the cause of vascular injury but the disease spectrum in diabetics seems to be more of a genetic, metabolic and endocrine etiology. Central obesity may only be an indicator of a genetic predisposition that leads to an altered expression of *ProFat* cytokines like resistin that promote insulin resistance and obesity. The homeostatic imbalance also adversely affects the overall vascular condition in the vascular endothelium and creates a pro-inflamatory hypercoagulable state alongside raised blood pressures. This eventually leads to a proatherogenic state and culminates in athero-sclerotic disease affecting the coronary, cerebro-vascular, and peripheral vascular fields.

Conclusion

Presence of peripheral vascular disease in diabetics is significantly associated with increased waist circumference, waist hip ratio, raised systolic BP, diastolic BP, and delayed wound healing.

It would be interesting to know if etiologic pathology of hypertension and diabetes overlap in specific patient populations and if various risk factors for cardiovascular disease emanate from the same genetic susceptibilities with a synergic contribution by the environment or dietary habits.

Further analysis and a string of discoveries is awaited before we can fully ascertain the distribution of adipose tissue, role and regulation of fat cells; its possible endocrine role and the underlying relationship of adipose cells with carbohydrate metabolism and insulin resistance and their specific roles in producing a hypertensive proinflamatory phase and subsequent phenomenon of vascular injuries and atherosclerosis. Successfully answering these questions might prove to be the most significant step in preventing the vascular morbidity and mortality burden associated with diabetes.

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Answer of the Picture Quiz

This lady shows typical facies of Cushing's syndrome. Please note the moon shape face and striae on the legs. On investigation she was found to have big adrenal tumor which was operated. Steroids were started and continued for 6 months and later tapered off. She was completely well one year after the operation.

Cushing's syndrome, also called hypercortisolism, is a rare endocrine disorder caused by chronic exposure of the body's tissues to excess levels of cortisol. Exposure to too much cortisol can occur from long-term use of synthetic glucocorticoid hormones to treat inflammatory illnesses. Pituitary adenomas (benign tumors of the pituitary gland) that secrete increased amounts of ACTH can also spur overproduction of cortisol. Tumors of the adrenal gland and ectopic ACTH can cause similar problems with cortisol balance. Common symptoms of Cushing's syndrome include upper body obesity, severe fatigue and muscle weakness, high blood pressure, backache, elevated blood sugar, easy bruising, and bluish-red stretch marks on the skin. In women, there may be increased growth of facial and body hair, and menstrual periods may become irregular or stop completely. Neurological symptoms include difficulties with memory and neuromuscular disorders.