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Endothelial dysfunction: The contribution of diabetes mellitus to the risk factor burden in a high risk population

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ABSTRACT

Background: Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in Western societies and are rapidly becoming a worldwide health problem. African-Americans have increased morbidity and mortality rates from CVD. Our study aimed to assess the effects of the CVD risk factors burden alone versus with diabetes mellitus in a high risk CVD population. Methods: The two study groups consisted of thirty seven diabetics and thirty seven non-diabetic African-Americans aged ≥55 years without clinical atherosclerosis having similar cardiovascular risk factors (age, hypertension, hypercholesterolemia, smoking, and body mass index) except for diabetes mellitus. Brachial artery flow-mediated dilation (FMD), Nitroglycerin-mediated dilatation (NMD) and carotid intima-media thickness (IMT) were recorded in all subjects. Results: Endothelial function as assessed by the brachial artery FMD was significantly impaired in the diabetic group compared to the non-diabetic group (7.8 ± 5 vs 3.3 ± 4; p = 0.0001). There were no differences in neither Nitroglycerin-mediated dilatation (NMD) nor carotid intima-media thickness (IMT) in the diabetic and non-diabetic groups. Conclusion: The contribution of diabetes to the development of endothelial dysfunction in subjects with clustering of CVD risk factors may be early as indicated by significant functional changes preceeding structural vascular changes..

Keywords: Diabetes; Endothelial Dysfunction; Cardiovascular Risk Factors

1. INTRODUCTION

Type 2 diabetes mellitus (DM) has reached epidemic levels with an adult world prevalence estimated to be at 366 million in 2011, and with an expected increase to 552 million by 2030 [1].

These alarming predictions indicate a growing economic burden among patients and society more broadly. Hypertension (HTN) and DM constitute a potent duet for the development of atherosclerotic and arteriosclerotic cardiovascular diseases. Approximately one half of patients with type 2 diabetes die prematurely of a cardiovascular cause related to accelerated atherosclerosis [2]. Consequently, there has been an increased in emphasis on understanding the underlying mechanisms orchestrating the onset of cardiovascular diseases (CVD) in diabetic individuals and identifying patients at a particular high risk for future cardiac events. Endothelial dysfunction constitutes an important early occurrence in the development of the atherosclerotic process as well as an independent predictor of poor prognosis in CVD [3,4]. The main aim of this study was to investigate the impact of DM on vascular structure and function as reflected by carotid intima-media thickness (IMT), brachial artery flow mediated dilatation (FMD) respectively. With this goal in mind, we studied 2 groups of patients without clinical atherosclerosis having similar cardiovascular risk factors (age, hypertension, hypercholesterolemia, smoking, and body mass index) except for diabetes mellitus.

The independent mechanistic contribution of diabetes mellitus to the risk factor burden for the development of arteriosclerosis and atherosclerotic lesions in a high-risk population that may result in impairment of arterial function has not been well studied.

2. METHODS

Two study groups were analyzed for this report: One group consisted of thirty seven diabetics and a second group of thirty seven non-diabetic African-Americans

aged over 55 years without clinical CAD/CVD matched for age, gender, smoking, body mass index (BMI), low density lipoproteins (LDL) and triglycerides. The study protocol was approved by the institutional review board and each subject gave written informed consent.

2.1. Flow-Mediated Dilation

Flow-mediated dilation (FMD) of the brachial artery was measured as previously described [5]. Briefly, following measurement of the baseline diameter of the brachial artery, ischemic condition was induced by inflating a blood pressure tourniquet located at the proximal forearm to at least 50 mmHg above the systolic blood pressure. After 5 minutes of pre-hyperemia ischemia, the tourniquet cuff pressure was released and 2D images of the brachial artery dilation following reactive hyperemia were recorded.

Endothelium-dependent dilatation (FMD) was defined as the percent change in arterial diameter following reactive hyperemia compared to the baseline diameter and calculated as follows:

$$\%\text{FMD} = 100 \times \frac{\left(\text{diameter during reactive hyperemia} - \text{resting diameter}\right)}{\text{resting diameter}}$$

2.2. Nitroglycerin-Mediated Dilatation (NMD)

Nitrate-mediated dilatation (NMD) capacity (endothelium independent) dilation capacity was tested to examine the vasodilatory effect of an exogenous source of nitric oxide [5]. Changes in brachial artery diameter were measured in response to administration of 0.4 mg of sublingual nitroglycerin, a direct smooth-muscle dilator. The endothelium-independent dilatation (NMD) was defined as the percent increase in arterial diameter 5 minutes following nitroglycerin compared to baseline and calculated as follows:

$$\%\text{NMD} = 100 \times \frac{\left(\text{maximum diameter} - \text{resting diameter}\right)}{\text{resting diameter}}.$$

2.3. Carotid Intima-Media Thickness

The carotid intima-media thickness (IMT) was evaluated using high resolution ultrasound. All patients were studied in a fasting state and all underwent a full clinical examination. Total cholesterol, triglycerides, and HDL cholesterol were determined by enzymatic methods, and LDL cholesterol was calculated using the Friedewald equation.

3. RESULTS

Data are expressed as means ± SD. Comparisons between groups were analyzed by the unpaired Student t-test). P-values ≤ 0.05 were accepted as statistically significant. Data processing was performed with the software modules of SPSS® (Statistical package for analysis in social sciences, Predictive analysis software release 18, SPSS Inc., Chicago, USA).

The clinical characteristics and biochemical profile of the study subjects are summarized in **Table 1**. There were no statistically significant differences between the groups in age, gender, smoking status, and BMI, however HDL was significantly higher in the non-diabetic group.

Endothelial dysfunction assessed by the brachial artery FMD was significantly impaired in diabetics compared to non-diabetics; $p < 0.01$ (**Table 2**).

The mean carotid IMT of diabetic subjects (0.92 ± 0.17 mm) was similar to that of the RF-matched group (0.94 ± 0.16 mm; no statistical difference). The NMD tended to decrease in diabetics; however, the decrease was not statistically significant.

4. DISCUSSION

Adult patients with diabetes are known to have higher rates of cardiovascular complications [6,7]. Type 2 diabetes mellitus (T2DM), hypertension (HTN), and obesity (OB) are all major risk factors for the development of cardiovascular-renal dysfunction (CVR-D). The greater

Table 1. Characteristics and metabolic profile of participants with and without DM.

Variable	Non-diabetic (n = 37)	Diabetes (n = 37)	
Age, Years	65 ± 6	65 ± 6	ns
BMI kg/m^2	31.7 ± 6	33 ± 6	ns
SBP, mmHg	128.0 ± 13	130 ± 14	ns
DBP, mmHg	77.0 ± 8	72 ± 9	<0.01
PP, mmHg	51 ± 4	58 ± 3	<0.01
HDL, mg/dl	52 ± 11	46 ± 12	<0.01

Table 2. Carotid IMT mm thickness and FMD% changes in brachial artery diameter following ischemia & nitroglycerin.

Variables	Non-diabetics (n = 37)	Diabetics (n = 37)	p
% D Change (FMD)	7.80 ± 5.00	3.30 ± 4.00	<0.01
IMT, mm	0.94 ± 0.16	0.92 ± 0.17	ns
% Nitroglycerin Change	9.90 ± 6.00	8.30 ± 6.00	ns

prevalence of CVR-D when a constellation of HTN, T2DM, and obesity are present is suggestive of synergistic effects of these risk factors on outcomes [8]. The higher incidence of vascular events in diabetics usually implies the presence of more frequent and severe cardiovascular risk factors.

Ample evidence exists that the clustering of an increasing number of cardiovascular risk factors in an individual has an impact on the morphological and functional changes of the vasculature [9-12], however, only a few studies have analyzed the differential impact of diabetes mellitus on the initiation and progression of endothelial dysfunction. Tsuchiya *et al.* [13] investigated 101 subjects with T2DM and reported that only FMD showed significant changes in diabetic subjects as risk factors accumulated as compared to other vascular parameters namely carotid IMT. They further demonstrated that insulin resistance showed the most significant association with reduced FMD. Previously published studies support the hypothesis that FMD may be one of the major determinants of development of CVD in both high and low-risk populations and may provide additional prognostic value beyond traditional cardiovascular risk factors [14-18]. On the other hand, endothelial-independent vasodilation with nitroglycerin administration was mildly reduced in diabetic subjects although this observation was not statistically significant. Such findings are consistent with the trend toward a reduced NMD response documented in earlier studies in diabetics [19-21] in which the impairment of endothelial function was much greater than that of the smooth muscle dilator response. Furthermore, while vascular smooth muscle cell dysfunction (NMD) has been previously well documented in diabetic patients compared to healthy controls [22,23], impairment of nitroglycerin responses has also been reported in adults with multiple CVD risk factors [24]. Hence, we investigated 2 groups of subjects, a diabetic and a non-diabetic group) sharing similar atherosclerotic risk factors: Age, gender, body mass index (BMI), smoking habit, hypertension, and lipid parameters. In the present study, endothelium-dependent brachial artery response to occlusion induced ischemia (FMD) was significantly diminished in diabetic patients when compared to high-risk individuals that have not manifested cardiovascular disease. These observations suggest that diabetes may be associated with reduced FMD/endothelial damage earlier than any of the traditional cardiovascular risk factors. In accordance with our findings, a recent study called attention to the fact that impaired endothelial function in diabetic patients was not related to the presence or levels of various established cardiovascular risk factors but rather to the duration of DM and found that for every 10 years of DM, FMD was reduced by 1% [25]. In a hypertension clinic, while evaluating random hypertensive patients for isolated systolic and diastolic HTN, the pulse pressure was noted to be larger in diabetics [26]. A wide pulse pressure (PP) is associated with CVR-D, and has been observed in DM patients; a comparative analysis of hypertension clinical trials including 62,712 diabetics and 108,599 non-diabetics revealed lower mean levels of diastolic blood pressure in diabetics and higher mean levels of systolic blood pressure [27].

This study has a few limitations: This study is small and multiple regression analysis was not done to determine the relative contribution of other risk factors.

5. CONCLUSION

The results of this study demonstrated that the contribution of diabetes to the development of endothelial dysfunction in subjects with clustering of metabolic factors is early, preceding structural changes, and contributes significantly to reduce FMD. Hence, FMD may be used as a sensitive marker for the early detection of atherosclerotic changes in diabetic patients with multiple cardiovascular risk factors.

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