

Clinical Characteristics of Diabetic Patients with Diabetic Retinopathy

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Abstract: *Background:* Proliferative diabetic retinopathy is a consequence of retinal ischemia due to capillary occlusion resulting from damage to the retinal endothelium, and is associated with increased risk of cardiovascular morbidity and mortality.

Methods: We randomly assigned seventy three patients with DM type II and grouped them according to their retinal proliferative disease (Group A - 25 patients [12 males], mean age 62.8±10.8 years, no diabetic retinopathy; Group B - 25 patients [19 males], mean age 61.9±9.4 years, non-proliferative retinopathy; and Group C - 23 patients [13 males], mean age 59.2±10.3 years, proliferative retinopathy). Twenty three healthy subjects (14 males; mean age 44.3±11.6 years) served as the control group. We studied their retinal vasculopathy status, height, weight, body mass index (BMI), waist circumference, age, endothelial function (flow mediated diameter [FMD%] percent change) and their peripheral artery disease (ankle brachial index [ABI]).

Results: A significant difference was found between the duration of length of DM type II between patients without retinopathy [group A] (9±6 years) and patients with non-proliferative retinopathy [group B] (17±9 years) (p=0.001). No difference in length of diabetes was observed between patients with non-proliferative retinopathy [group B] and patients with proliferative retinopathy [group C] (19±6 years) (p=0.30). A significant difference was observed in HgA1C% between group A (7.1±2.7%) and group B (8.5±1.5%) (p=0.02). No such difference was noted between group B and group C (8.5±1.6%) (p=0.98). Only 6 patients (out of 23) used insulin treatment in group A compared with 16 group B (out of 25) and 17 in group C (out of 25) (p=0.004). All three groups of diabetic patients were older (62.8±10.8, 61.9±9.4, 59.2±10.3 years, respectively) than volunteers (44.3±11.6 years) (p≤0.001), had a lower stature (1.65±0.09, 1.68±0.07, 1.65±0.09 meters, respectively) compared with controls (1.73±0.08 meters) (p≤0.05), had a larger waist circumference (110.04±14.17, 108.88±13.00, 109.30±13.49 cm, respectively) than controls (93.43±11.66 cm) (p≤0.001), and larger BMIs (30±6, 29±4, 30±5) compared with controls (25±4) (p≤0.001). All diabetic patients had severe endothelial dysfunction measured by FMD% (-1.9±7.4, -3.3±9.2, -3.1±6.6 %, respectively) compared with the control group (16.5±7.5%) (p≤0.001). ABI was within normal range in all patient (0.97±0.18, 1.14±0.24, 1.03±0.28, respectively), and in volunteers (1.06±0.18) (p≥0.05). There was no significant change within the 3 subgroups of diabetic retinopathy patients in age, height, weight, BMI, or FMD%.

Conclusions: All patients with DM type II had severe endothelial dysfunction, higher BMIs, lower statures, larger waist circumferences; however they all had normal ABIs.

Keywords: Endothelial function, diabetic retinopathy, ABI.

INTRODUCTION

The earliest clinical signs of diabetic retinopathy are microaneurysms [1] and after 20 years of disease they are present in nearly all patients with DM type I [2] and in 80% of patients with DM type II [3]. Proliferative diabetic retinopathy involves the formation of new blood vessels, and this process carries an ominous prognosis for vision [1]. Patients who have had the disease for 15 years may develop proliferative retinopathy in up to 50% of patients with DM type I [2] and in 10% of patients with DM type II [3]. Epidemiological studies have shown that proliferative retinopathy predicts cardiovascular mortality and morbidity in both DM type I [4-7] and DM type II [8-12] populations. There is data suggesting that non-proliferative retinopathy could predict mortality (all

cause and cardiovascular) only in women with DM type II [13] while another study that followed 2103 DM type II patients for 7 years showed that only diabetic retinopathy (especially in its more advanced stages) is associated with an increased cardiovascular disease incidence independent of other known cardiovascular risk factors [14]. The mechanism of the association between diabetic proliferative retinopathy and increased incidence of cardiovascular morbidity and mortality raises questions about the ability to predict vascular disease progression (micro- and macro-vascular) by non invasive means or by clinical parameters.

Our aim was to find an association between diabetic retinopathy staging (no-retinopathy, non-proliferating retinopathy, and proliferating retinopathy) and clinical characteristics and/or severity of systemic vascular responsiveness that will define each group and may assist in early detection of microvascular complications

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that eventually lead to blindness and cardiovascular events.

METHODS

We randomly assigned seventy three patients with DM type II (25 patients [12 males], mean age 62.8 ± 10.8 years, without diabetic retinopathy [group A], 25 patients [19 males], mean age 61.9 ± 9.4 years, with non-proliferative retinopathy [group B], and 23 patients [13 males], mean age 59.2 ± 10.3 years, with proliferative retinopathy [group C]) that came for a routine follow up visit in the ophthalmologic outpatient clinic. Twenty three healthy subjects (14 males; mean age 44.3 ± 11.6 years) served as the control group. On entry to the study an experienced ophthalmologist diagnosed retinopathy by fundoscopy after papillary dilatation, using a clinical disease severity scale [15]. Retinopathy was classified as follows: Group A - no retinopathy; Group B - non-proliferative retinopathy; Group C - proliferative retinopathy with intra-retinal hemorrhage and/or hard exudates. Twenty three healthy volunteers served as the control group. The study was approved by the internal review board of the hospital, and all participants signed a consent form before enrolment to the study.

Clinical Characteristics

Included age, gender, height, weight, Body Mass Index (BMI), (calculated by dividing weight in kilograms by height in meters squared), waist circumference (was measured at the level of the umbilicus), hemoglobin A1C% (HbA1C %), length of disease, and the need for insulin treatment. Vascular responsiveness was assessed by measuring endothelial function and using the ankle brachial index.

Flow Mediated Diameter Percent Change (FMD %)

All measurements of brachial artery diameter and FMD were performed early in the morning, in a quiet and dark room and at controlled ambient temperatures between 20°C and 26°C . Studies were conducted after an overnight fast of at least 10 hours (water was permitted), with the subjects supine and after 10 minutes of rest. The subject's right arm was comfortably immobilized in the extending position, allowing for ultrasound scanning of the brachial artery 5–10 cm above the antecubital fossa. In each examination, recording of vessel images were followed by inflation of a cuff to supra-systolic pressure (40 to 50 mmHg above systolic pressure) for 5 minutes. Then the

cuff was deflated and the brachial artery diameter was imaged and recorded for 3 minutes. FMD% more than 10% is considered a normal response. Lower than 10% FMD% reflect endothelial dysfunction, which means a high likelihood to develop cardiovascular event in the future. Subjects with negative FMD% results (the artery is constricted after stress and not dilated as was expected) have the worst prognosis.

Ankle-Brachial Index (ABI)

An ABI was performed while the patient was supine and measurement of the systolic blood pressure in all four extremities was done. To measure an ankle systolic pressure, a standard adult blood pressure cuff was placed around the ankle just above the malleoli. While using the Doppler flow-meter to monitor the signal from the posterior of the anterior tibial artery, distal to the cuff, the cuff was inflated to a pressure approximately 30 mm Hg above the systolic pressure to occlude flow temporarily. As the cuff was slowly deflated (2 to 5 mm Hg/s), the pressure at which the Doppler flow signal was first heard and recorded was the ankle systolic pressure. An ABI was calculated by dividing the ankle systolic blood pressure by the greater of the two systolic upper extremity systolic blood pressures. An ABI of >1.0 was normal. An ABI of 0.5 to 0.9 was indicative of injury to a single arterial segment. An ABI of <0.5 was indicative of severe arterial injury or injury to multiple arterial segments.

Statistical Analysis

Students' T test and Chi square test were used for categorical variables and one way ANOVA was used for continuous variables to compare differences between patients in different stages of diabetes mellitus. T-tests included two tailed distribution with paired and two sample unequal variance.

RESULTS

Seventy three DM type II patients were recruited to the study after signing a consent form. We grouped them according to the ophthalmologic examination (fundoscopy) after papillary dilatation, using a clinical disease severity scale [15]. There were 25 patients in Group A (12 male, mean age 62.8 ± 10.8 years), 25 patients in Group B (19 males, mean age 61.9 ± 9.4 years), and 23 patients in Group C (13 male, mean age 59.2 ± 10.3 years). In the control group there were 23 healthy subjects (14 male, mean age 44.3 ± 11.6 years) ($p \leq 0.001$) (Table 1). Patients had a lower stature

Table 1: Clinical Characteristics

	Controls	Group A	Group B	Group C
No.	23	25	25	23
Men	14(60%)	12(48%)	19(76%)	13(56%)
Age (years)	44.3±11.6	62.8±10.8	61.9±9.4	59.2±10.3
P-value**		≤0.001	≤0.001	≤0.001
Height (cm)	173±8	165±9	168±7	165±9
P-value**		≤0.001	0.046	≤0.001
BMI	25±4	30±6	29±4	30±5
P-value**		0.001	≤0.001	≤0.001
Waist Circumference	93±12	110±14	109±13	109±13
P-value**		≤0.001	≤0.001	≤0.001
Insulin Rx		6	16	17
P-value*		0.004	0.80	
Duration of DM (y)		9±6	17±9	19±6
P-value*		0.001	0.30	
HBgA1C%		7.1±2.7	8.5±1.5	8.5±1.6
P-value*		0.02	0.98	

BMI – body mass index.

DM – diabetes mellitus type II.

HBgA1C%-hemoglobin A 1 C %.

P-value* - comparison between the groups of patients.

P-value** - comparison between each group and the control group.

P-value***- comparison between group 3 and group 1.

(165±9 cm, 168±7 cm, 165±9 cm, respectively) compared with controls (173±8 cm) ($p \leq 0.05$), a larger waist circumference (110±14 cm, 109±13 cm, 109±13 cm, respectively) than controls (93±12 cm) ($p \leq 0.001$), and a larger BMI (30±6, 29±4, 30±5, respectively) compared with controls (25±4) ($p \leq 0.001$) (Table 1). A significant difference was found in diabetes mellitus duration between patients without retinopathy [group A] (9±6 years) and patients in the non-proliferative retinopathy group [group B] (17±9 years) ($p = 0.001$). No difference in length of diabetes was found between the

non-proliferative retinopathy group [group B] and the proliferative group [group C] (19±6 years) ($p = 0.30$) (Table 1). A significant difference was observed in HgA1C% between group A (7.1±2.7%) and group B (8.5±1.5%) ($p = 0.02$). No such difference was noted between the non-proliferative group (group B) and the proliferative group (group C) (8.5±1.6%) ($p = 0.98$) (Table 1). Only 6 patients in group A (out of 23) used insulin treatment, while 16 patients (out of 25) (group B) and 17 patients (out of 25) (group C) used it ($p = 0.004$) (Table 1). All diabetic patients had severe

Table 2: Vascular Measurements

	Controls	Group A	Group B	Group C
Baseline Brachial	36±6	41±9	38±7	38±7 Diameter (mm)
P-value**		0.01	0.20	0.26
FMD (%)	16.5±7.5%	-1.9±0.18%	-3.3±9.2%	-3.1±6.6%
P-value**		≤0.001	≤0.001	≤0.001
ABI	1.06±0.18	0.97±0.18	1.14±0.24	1.03±0.28
P-value*		0.01	0.17	

FMD (%) – Flow Mediated Diameter percent change.

ABI – Ankle Brachial Index.

P-value* - comparison between the groups of patients.

P-value** - comparison between each group and the control group.

endothelial dysfunction measured by FMD% ($-1.9\pm 7.4\%$, $-3.3\pm 9.2\%$, $-3.1\pm 6.6\%$, respectively) compared with the control group ($16.5\pm 7.5\%$) ($p\leq 0.001$) (Table 2). ABI was within normal range in all groups (0.97 ± 0.18 , 1.14 ± 0.24 , 1.03 ± 0.28 , respectively) with no significant difference from the volunteers' ABI (1.06 ± 0.18) ($p\geq 0.05$) (Table 2). No significant change was observed within the 3 groups of diabetic retinopathy patients in age, height, weight, BMI, waist circumference and FMD% ($p=NS$ for all) (Tables 1 & 2).

DISCUSSION

We found that all patients with DM type II had severe endothelial dysfunction, higher BMIs, lower statures and larger waist circumferences; however they all had normal ABIs.

Diabetic Retinopathy and Vascular Disease Progression

Population based studies have shown that microvascular complications predict cardiovascular disease mortality in DM type I [15, 16] and type II [17-20]. An 18 years follow up study found that proliferative retinopathy in both sexes and background retinopathy in women predicted all-cause, cardiovascular disease, and coronary heart disease death. These associations were independent of current smoking, hypertension, total cholesterol, HDL cholesterol, glycemic control of diabetes, duration of diabetes, and proteinuria. This suggests the presence of common background pathways for diabetic microvascular and macrovascular disease other than those included in the conventional risk assessment of cardiovascular disease [21]. There have been several theories that tried to explain the vascular damage associated with DM because hyperglycemia alone could not explain it by itself [21-25]. Hyperfunction of platelets in diabetic patients with good glycemic control has been demonstrated and increased platelet protein kinase C levels have been implicated in the pathogenesis of diabetic complications [26]. Diabetic patients with retinopathy produce more superoxide anion compared with DM patients without retinopathy. Stimulated leukocytes from diabetic patients with proliferative retinopathy generated superoxide anion at significantly higher rates than did those from diabetics with non-proliferative retinopathy. These results suggest that reactive oxygen species produced by leukocytes may play a role in the progression of diabetic retinopathy [27, 28]. Recent evidence suggests that high levels of bone marrow

derived circulating endothelial progenitor cells contribute to the pathological neovascularization of ischemic tissues and are a critical risk factor for the development of these complications [29].

Endothelial Function

We found severe endothelial dysfunction in all 3 groups of patients with DM type II. There was no statistical difference between the groups, and all patients had a negative result (vasoconstriction) of the brachial artery diameter and the brachial artery diameter flow-mediated percent change. We could not use this test to discriminate and characterize any of the diabetic groups, neither the non-proliferative nor the proliferative retinopathy groups. Endothelial function is too sensitive (but without specificity) for discrimination between the different stages of diabetic retinal vasculopathy. The association between microvascular and macrovascular disease is not clear in diabetes mellitus; microangiopathy and macroangiopathy in DM type II frequently coexist. In order to study this association the intima media thickness (IMT) of the carotid artery and the endothelial function (flow mediated dilatation percent change [FMD%] of the brachial artery) were examined, and levels of von Willebrand factor (vWF) and soluble intercellular adhesion molecule 1 (sICAM-1) were measured in patients with DM type II. IMT was higher in diabetic patients with retinopathy compared with patients without retinopathy, FMD% was lower (worse endothelial dysfunction) in the retinopathy group compared with patients without retinopathy; however, levels of s-ICAM-1 and vWF were not different between the 2 groups. In a multiple regression analysis diabetic retinopathy predicted increased IMT and decreased FMD% (worse endothelial dysfunction), and impaired endothelial function was suggested as a common denominator of pathogenesis of microvascular complications and atherosclerosis in patients with DM type II [30]. Endothelial dysfunction was significantly more severe post acute coronary syndrome in patients with DM type II compared with patients without DM type II, 3 days and 6 months after the acute event [31]. An association was found between endothelial dysfunction and microalbuminuria, and in a logistic regression analysis FMD% was the only variable independently related to microalbuminuria [32].

Height and Diabetes Mellitus

Patients with diabetes mellitus were shorter than the control group; however, no height difference was

observed within the diabetic patients' groups. A cross sectional analysis 7424 adults aged 40-74 years (from the NHANES III survey 1988-1994) showed that the shorter height and leg length and lower leg-to-height ratio were associated with higher percent body fat, especially in women. The relative rate of diabetes mellitus type 2 was higher among shorter individuals [33]. Other studies established an association between short stature and risk of insulin resistance [34, 35] and glucose intolerance [36, 37]. In the Finnish Diabetic Nephropathy (Finndiane) study, patients with type I diabetes mellitus that were in the lowest quartile of adult height had increased risks of prevalent diabetic nephropathy and laser treated retinopathy [38]. In the Diabetes Control and Complications Trial (DCCT) patients with type II diabetes mellitus who were in the lowest quartile of adult height had increased risks of incident diabetic nephropathy and proliferative retinopathy [38]. Impaired growth and development in utero and during early childhood may lead to metabolic diseases in adulthood, with features of insulin resistance, thereby providing a possible link between growth, final stature, and diabetic complications [33]. There are three potential pathways linking impaired pre-pubertal growth to the risk of obesity and diabetes mellitus in middle age: 1. Being breast fed and higher energy intake at 4 years of age are associated with longer leg length in adulthood [39]. Being breast-fed may also lower the long-term risk of obesity and diabetes mellitus type II [40]. 2. Hormonal factors relevant to growth, like Insulin-growth factor-I (during fetal and childhood growth), that appears to predict a lower risk of diabetes in adulthood [41]. 3. The intrauterine environment, which could influence both stature and the subsequent risk of diabetes *via* fetal programming of metabolism [42].

Study Limitations

The relatively small group of patients and the significantly younger age of subjects in the control group limit our ability to have firm conclusions. Larger studies with more age-matched controls should be sought and pursued in the near future.

SUMMARY

All patients with DM type II in our study had severe endothelial dysfunction, higher BMIs, lower stature, and larger waist circumferences. We could not find clinical markers and vascular responsiveness markers that could distinguish between subgroups of patients with Diabetes Mellitus that could help define staging of

diabetic retinopathy or could predict future microvascular disease progression.

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