

Evaluation of Endothelial Function and Effect of Glycemic Control (Excellent Vs Poor / Fair Control) on Endothelial Function in Uncontrolled Type 2 Diabetes Mellitus

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Abstract

Objective: To evaluate the endothelial functions before and after glycemic control in type II diabetes mellitus.

Material and Methods: It was an open, randomized and comparative study on 30 patients of type 2 diabetes mellitus. The study was of 12 weeks spread over 5 visits. The initial visit (visit 1) is for screening of patients. Other visits (visits 2 to 5) constituted the follow up of patients. The primary efficacy parameters included blood sugar (fasting and postprandial) done on each visit and glycosylated hemoglobin (HbA1c) done at visits 1 and 5. Based on glycosylated hemoglobin (HbA1c) only poorly controlled and fairly controlled patients were included in the study. Brachial artery flow mediated vasodilatation (FMD) was studied in all these patient at visits 1 and 5 to see the effect of glycemic control on endothelial functions. Results obtained were statistically analyzed with appropriate method.

Results: There was a significant improvement in endothelial functions in patients with fair, good and excellent control of diabetes. During uncontrolled state (HbA1c 10.08 ± 0.48 %) FMD was lowest i.e. 2.88 ± 0.53 at 1st week which improved to 11.94 ± 3.33 at 12th week with control of diabetes (HbA1c 6.74 ± 0.16 %). The FMD in patients who had fair control (HbA1c 8.45 ± 0.30 %) in the beginning was 6.74 ± 2.43 % and after excellent control in these patients FMD rises to 12.81 ± 3.16 %.

Conclusion: Our data showed that the endothelial functions improved sequentially with control of diabetes from fair to good to excellent glycemic control.

Introduction

Diabetes mellitus has assumed epidemic proportion in the new millennium. The W.H.O. has projected that global prevalence of type-II diabetes mellitus will tremendously increase to more than double from 135 million in 1995 to 300 million by 2025.¹ The American Diabetes Association recently designated type-II diabetes mellitus as a major risk factor for cardiovascular diseases.² Atherosclerosis which is a precursor for macro-vascular disease involves both functional as well as structural changes in the vasculature. Functional changes involve abnormalities in endothelium, vascular smooth muscle cells and platelet functions.^{3,4} Endothelial function is the earliest to be affected in this cascade of events leading to atherosclerotic plaque formation.^{3,5}

The metabolic abnormality in type-II diabetes mellitus provokes various molecular mechanisms which contribute to endothelial dysfunction^{3,4,6,7} due to which vessels are unable to dilate sufficiently in response to appropriate stimuli and ultimately tissue perfusion diminishes gradually. This endothelial dysfunction is followed by structural changes in vasculature and

atherosclerotic plaque formation leading onto macrovascular complications.^{5,6,8} Endothelial dysfunction is a reversible process⁹ but uncontrolled diabetes mellitus and unchecked endothelial dysfunction ultimately leads to irreversible structural changes in the vasculature, so by preventing the development of endothelial dysfunction or reversing it after development will prevent or delay the macro-vascular complications. Therefore, early detection of endothelial dysfunction can help in the detection of macrovascular complications which are likely to occur in future in type-II diabetics^{10,11} and thus help in planning primary and secondary preventive strategy in these patients.^{8,9}

The International Task Force on brachial artery reactivity has endorsed the brachial artery flow-mediated vasodilatation (FMD) as standard test for screening of endothelial dysfunction.^{12,13} Using this technique several studies conducted during the past decade demonstrated the link between endothelial dysfunction, impaired glucose tolerance and type-II diabetes mellitus.¹⁴⁻¹⁷ A recently concluded study on endothelial dysfunction and diabetic foot ulcer risk endorsed that a fundamental defect in endothelial function reflected in flow-mediated dilatation is the basis of microvascular complications in diabetic subjects.¹⁸ Scanty literature exists on the effect of glycemic control on endothelial dysfunction in type-II diabetes mellitus. Hence, the present study was conducted to evaluate the endothelial function and effect of glycemic control (excellent vs poor/fair control) on endothelial function in uncontrolled type 2 diabetes mellitus.

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Table 1 : Grouping of the patients based upon the glycemic control

Patient groups	HbA1c	No. of patients	Level of glycemic control
Group I	>9%	18	Poor
Group II	8-8.9%	12	Fair
Group III	7-7.9%	None	Good
Group IV	<7%	None	Excellent

Table 2 : Comparison of baseline endothelial function in patients and controls

Parameters	Patients	Controls	p value
Glycosylated hemoglobin (HbA1c) % Mean ± S.D.	9.43 ± 0.91%	5.78 ± 0.30%	<0.001
Flow mediated vasodilatation (FMD) % Mean ± S.D.	4.43 ± 2.47%	13.39 ± 3.09%	<0.001

Material and Methods

30 patients with uncontrolled type-II diabetes mellitus were included in the study and 10 normal healthy subjects served as controls. The conditions/diseases likely to affect endothelial functions such as coronary artery disease, hypertension, peripheral vascular disease, cerebrovascular disease, chronic illnesses, chronic alcoholism and patients on statin therapy were excluded from the study.

Study design: It was an open, randomized and comparative clinical study.

Duration of study: The total duration of study was 12 weeks. All the patients were advised to follow dietary as well as drug interventions for strict control of diabetes mellitus.

Details of visits: The study comprised of 5 visits.

Visit 1 (Initial visit) was meant for screening the patients for inclusion in the study.

The 2nd, 3rd and 4th visits were follow up visits on the 2nd, 4th and 6th week respectively. Finally the 5th visit was on the 12th week of study.

Parameters of Control

Short-term glycemic control was evaluated by measuring fasting and postprandial blood sugar levels on each visit and long term glycemic control was evaluated by measuring Glycosylated hemoglobin (HbA1c) on the initial and the last visits. The patients included in the study were grouped as per their glycosylated haemoglobin levels in four groups (Table 1).

We only included poorly controlled and fairly controlled diabetics in this study so as to evaluate the effect of glycemic control.

Brachial artery flow mediated vasodilatation (FMD) was studied in all patient after overnight fasting (8 hours) using 7.5 Hz phased array linear transducer. The medial epicondyle was used as anatomical landmark for brachial artery. Flow mediated vasodilatation (FMD) was calculated as:-

$$\text{FMD (\%)} = \frac{d_2 - d_1}{d_1} \times 100$$

d2 - Brachial artery diameter at 1 min post deflation

d1 - Base line brachial artery diameter

Table 3 : Endothelial function in Group I patients before and after control

Parameters	Stages of control	
	Poor control (Visit 1)	→ Excellent control (Visit 5)
Glycosylated hemoglobin (HbA1c) % Mean ± S.D.	10.08 ± 0.48 %	6.74 ± 0.16%
Flow mediated vasodilatation (FMD) % Mean ± S.D.	2.88 ± 0.53%	11.94 ± 3.33%
Statistical analysis (p value)	<0.001	<0.001

Table 4 : Endothelial function in Group II patients before and after control

Parameters	Stages of control	
	Fair control (Visit 1)	→ Excellent control (Visit 5)
Glycosylated hemoglobin (HbA1c) % Mean ± S.D.	8.45 ± 0.30 %	6.72 ± 0.20 %
Flow mediated vasodilatation (FMD) % Mean ± S.D.	6.74 ± 2.43%	12.81 ± 3.16%
Statistical analysis (p value)	<0.001	<0.001

Target Parameters

Two target parameters [glycosylated haemoglobin (HbA1c) and brachial artery flow mediated vasodilatation (FMD)] were performed twice i.e. at first visit to establish basal values and thereafter at the 12th week to study the effect of control.

Statistical analysis- Student "t" test was applied for statistical significance. Paired "t" test was used for intra group comparison and unpaired "t" test was used for comparison between groups.

Results

The patients and control included in this study were age and sex matched. The initial endothelial functions in patients and controls are shown in Table 2.

All the patients included in this study had highly significant mean glycosylated haemoglobin (HbA1c) 9.43 ± 0.91% as compared to control i.e. 5.78 ± 0.30% and FMD was significantly reduced to 4.43 ± 2.47% in patients with respect to healthy controls i.e. 13.39 ± 3.09. This fact indicated that endothelial dysfunctions occurred in the patients with uncontrolled diabetes (p<0.001). Endothelial functions evaluated further in two groups (Group I and Group II) are depicted in table 3 and 4 respectively. The patients of Group I (HbA1c 10.08 ± 0.48 %) had lowest FMD e.g. 2.88 ± 0.53 % indicating severe endothelial dysfunction during first visit. The endothelial function improved serially with control of diabetes and FMD reached to 11.94 ± 3.33 % at visit 5 when excellent control was achieved (HbA1c 6.74 ± 0.16%).

Discussion

Endothelial dysfunction appears early as a key event in atherogenesis, long before the structural changes and hyperglycemia is a major determinant factor for reduced flow mediated vasodilatation.^{3,13,19} The endothelial functions, hence, are likely to improve with control of hyperglycemia.^{14,16,19} The uncontrolled state of diabetes produces changes in the vascular tone due to reduced nitrous-oxide production and formation of advanced glycation product with the result the vasodilatation of the arteries suffer. This stage is reversible with control of diabetes because structural changes of atherosclerosis have not been still initiated. Endothelial dysfunction is the earliest marker of macrovascular complications and can be assessed by Flow-

mediated vasodilatation. Flow-mediated vasodilatation (FMD) in our patients during uncontrolled state (HbA1c 10.08 ± 0.48 %) was 2.88 ± 0.53 at visit 1 which improved to 11.94 ± 3.33 at visit 5 with control of diabetes (HbA1c 6.74 ± 0.16 %). It is a known fact that the endothelial functions improve in parallel with the glycaemic control^{13,16,17} but to what extent is still not known. Based on this concept, the FMD was measured in patients with poor control (group-I), it was 2.88 ± 0.53 % at visit 1 which improved to 11.94 ± 3.33 % at visit 5 with excellent control. This fact clearly indicated that improvement in endothelial functions occurred in parallel with the achievement of glycaemic control, a fact not highlighted in the literature. This fact further has been highlighted by our findings in group-II. The FMD in patients who had fair control (HbA1c 8.45 ± 0.30 %) in the beginning was 6.74 ± 2.43 % indicating that it was already better as compared to group-I (poor control). It itself strengthens the fact that FMD improves serially with achievement of various stages of control. These patients showed further improvement and FMD rises to 12.81 ± 3.16 % equal to excellent control achieved in group-I. Thus, now, we have established that there is scope of improvement in FMD at every stage of control though the literature is silent on this aspect. Finally, we emphasize that excellent control should be the target to achieve maximum improvement in FMD so as to retard or delay the development of macrovascular disease in diabetic patients.

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