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Evaluation of Endothelial Dysfunction in Relation with Glycaemic Control in Type 2 Diabetes Patients Using FMD (Flow Mediated Vasodilation) : A Non Invasive Technique

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Abstract
Objective:*To study the prevalence of Endothelial Dysfunction in patients with type 2 Diabetes and its correlation with Glycaemic control.*
Materials and Methods:*It was an open label, randomized, comparative, cross sectional study conducted on 120 patients with type 2 diabetes divided into two groups depending on the glycaemic control as well controlled type 2 diabetes and uncontrolled type 2 diabetes respectively based on HbA1c levels (well controlled type 2 diabetes group HbA1c <7.0 and uncontrolled type 2 diabetes group HbA1c > 7.0). Brachial artery FMD (Flow Mediated Vasodilation) was studied in all these patients. Results obtained were statistically aanalyzed with appropriate methods.*
Results:*Out of 120 patients Endothelial dysfunction (FMD < 4.5%) was seen in 26 patients of which 21 patients belonged to the uncontrolled type 2 diabetes group with mean HbA1c of (11.46±2.49) and mean FMD of (5.43±1.82) and endothelial dysfuncton was seen in 5 patients in well controlled group with mean FMD of (8.39±2.14) and mean HbA1c of 6.91±0.23). The FMD was more in well controlled group suggesting preserved endothelial function with good glycaemic control.*
Conclusion:*Our data showed that endothelial function directly correlate with glycaemic control in type 2 diabetes. Endothelial dysfunction as measured by FMD can be a reliable indicator of macrovascular complications in type 2 diabetes mellitus.*
Keywords:*Endothelial dysfunction, Diabetes Mellitus, Atherosclerosis, Flow mediated vasodilaton (FMD),*

I. Introduction

The world today is witnessing an epidemic of diabetes globally and nationally. Diabetes mellitus with its complications has become the most important contemporary and challenging health problems .The prevalence of Diabetes in India is 11 – 15% with urban prevalence of 12.1.[1] The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly.[2]

Hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes mellitus. Although the mechanisms underlying this phenomenon are likely to be multifactorial. Insulin resistance has been described in several diseases that increase cardiovascular risk and mortality, such as diabetes, obesity, hypertension, metabolic syndrome, and heart failure.Endothelial dysfunction is an early event in atherosclerosis and is known to occur long before structural atherosclerotic changes. Increasing evidence suggests that the progression of insulin resistance to type 2 diabetes parallels the progression of endothelial dysfunction to atherosclerosis. Insulin resistance is closely linked with visceral adiposity and early data suggested that free fatty acids were responsible for this association several studies have demonstrated that nitric oxide (NO) mediated vasodilation is abnormal in patients with type 2 diabetes.[3]Early detection of endothelial dysfunction can help in the detection of macrovascular complications which are likely to occur in future in type 2 diabetes and thus planning primary and secondary preventive strategy in these patients.The International task force on brachial artery reactivity has endorsed the brachial artery FMD (flow mediated vasodilation) as standard test for screening endothelial dysfunction.[5]

II. Materials And Methods

The present study included 120 patients with type 2 diabetes. The patients were divided into two groups of 60 each as well controlled type 2 diabetes and uncontrolled type 2 diabetes dependimg on glycaemic control based on HbA1c values <7.0 and >7.0 respectively.The conditions likely to affect endothelial function such as Coronary artery disease (CAD), hypertension, peripheral vascular disease, cerebrovascular disease, chronic alcoholism, and high output states like thyrotoxicosis, vit B1 defeciency were excluded from the study.

Study design: Randomized, open label, comparative cross sectional study

Duration: The study was study carried across two years from October 2014 to September 2016

Details of visit and study: Patients with diagnosed type 2 diabetes on oral anti diabetics (OAD) and Insulin were screened and included in the study.

Parameters of control: Glycaemic control was evaluated by measuring HbA1c (glycosylated haemoglobin) levels. The patients were grouped according to their HbA1c levels as well controlled type 2 diabetes (HbA1c <7.0) and uncontrolled type 2 diabetes (HbA1c >7.0).Brachial artery FMD(flow mediated vasodilation) was studied in all patients using a 7.0 MHz phased array linear transducer attached to MEDISON SONOACE USG Doppler machine. The medial epicondyle was used as an anatomical landmark for brachial artery.

To create flow stimulus in the brachial artery, a sphygmomanometric (blood pressure) cuff is first placed above the ante cubital fossa. A baseline rest image is acquired, and blood flow is estimated by time-averaging the pulsed Doppler velocity signal obtained from a mid-artery sample volume. Thereafter, arterial occlusion is created by cuff inflation to supra systolic pressure. Typically, the cuff is inflated to at least 50 mm Hg above systolic pressure to occlude arterial inflow for a standardized length of time (1 min).[4]This causes ischemia and consequent dilation of downstream resistance vessels via autoregulatory mechanisms. Subsequent cuff deflation induces a brief high-flow state through the brachial artery (reactive hyperemia) to accommodate the dilated resistance vessels. The resulting increase in shear stress causes the brachial artery to dilate. The longitudinal image of the artery is recorded immediately after cuff release and at 1 min after cuff deflation.[4,5,6,7]

FMD was calculated as

FMD % = $D_2 – D_1 / D_1$

D_2 – brachial artery diameter at 1 min post deflation

D_1- baseline brachial artery diameter

Endothelial dysfunction is said to be present if FMD calculated is < 4.5%.[7]

Statistical analysis: Student ‘t’ test was applied for statistical significance between two groups on metric parameters, chi-square test was used to find the significance of study parameters on categorical scale between two groups.

III. Results

The patients in both the groups were age and sex matched, the endothelial function i.e. FMD (flow mediated vasodilation) in both the groups shown in table 1 and graph. Table 2 shows he FMD% across two groups and table 3 shows the prevalence of endothelial dysfunction n both the groups.

Table 1: Comparison of Diameters of Brachial arteries at baseline and post dilation

Diameter of brachial artery in mm	**Well controlled diabetes**	**Uncontrolled diabetes**	**P value**
Baseline	3.430±0.236	3.393±2.73	0.714
After 1 min of deflation	3.716±0.245	3.576±0.288	0.018*

Table 2:FMD % distribution of patients studied

FMD %	**Well controlled diabetes**	**Uncontrolled diabetes**
<8	23(38.3%)	53(88.3%)
8-12	35(58.3%)	7(11.7%)
>12	2(3.3%)	0(0%)
Total	60(100%)	60(100%)
Mean ± SD	8.39±2.14	5.43±1.82

P<0.001**

Table 3: Endothelial dysfunction (FMD < 4.5%) in two groups

Endothelial dysfunction	**Well controlled diabetes**	**Uncontrolled diabetes**
No	55(91.7%)	39(65%)
Yes	5(8.3%)	21(35%)
Total	60(100%)	60(100%)

P=0.001**, significant

Endothelial dysfunction was seen in a total of 26 patients in the study which is 21.6% of which 21 patients belonged to the uncontrolled type 2 diabetes group.

The mean FMD% of two groups were (8.39±2.14) and (5.43±1.82) in the well controlled and uncontrolled groups respectively. The above data clearly shows that endothelial function is significantly affected in the uncontrolled type 2 diabetes group in comparison with well controlled type 2 diabetes group.

IV. Discussion

Endothelial dysfunction has received increasing attention as a potential contributor to the pathogenesis of vascular disease in diabetes mellitus. Hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes mellitus. Endothelial dysfunction is an early event in atherosclerosis and is known to occur long before structural atherosclerotic changes.[8] Atherosclerosis normally remains undetected for many years, due to lack of clinicalSymptoms. The uncontrolled state of diabetes produces changes in the vascular tone due to reduced NO production and formation of advanced glycation end products with result the vasodilation of 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 FMD.[9]The mean FMD% across two groups were (8.39±1.34) and (5.43±1.89) in the well controlled and uncontrolled type 2 diabetes respectively with mean HbA1c values of (6.91±0.23)% and (11.46±2.49)%.The endothelial function in the group with good glycaemic control is better compared to th uncontrolled group. Endothelial dysfunction precedes structural atherosclerotic changes hence this stage is reversible ad tight regulation of blood sugar should be the target to improve FMD% so as to retard or delay the development of macrovascular complications in diabetes.

V. Conclusion

Endothelial function is directly linked with thglycaemic control in patients with type 2 diabetes and FMD can be an important non-invasive tool to assess endothelial dysfunction.

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