



## A STUDY OF ENDOTHELIAL DYSFUNCTION IN PREDIABETICS AS EVIDENCED BY FLOW MEDIATED VASODILATION IN COLOR DOPPLER OF BRACHIAL ARTERY

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**ABSTRACT** Endothelial dysfunction is an early event and it precedes atherosclerosis. Does endothelial functional assessment can provide valuable insight into "PRE-INTRUSIVE" phase of atherosclerosis. Flow mediated dilation is known to depend on ability of endothelium to release nitric oxide in response to shear stress and can be used to estimate reliably endothelial function.

"PRE-DIABETIC PATIENTS" have endothelial dysfunction due to HYPER GLYCAEMIA and INSULIN RESISTANCE. This study was undertaken in pre diabetics to know the occurrence of endothelial dysfunction. Endothelial dysfunction was assessed Non - Invasively by Doppler Ultrasound of brachial artery of pre diabetic patients who had impaired "Fasting Plasma Glucose".

Flow mediated dilatation was calculated as percentage increase in brachial artery diameter in response to increase in brachial artery flow.

The importance of unravelling mechanistic link between early insulin resistance and accelerated atherosclerosis is underscored by recent finding even in adolescents mild insulin resistance is associated with increased cardio vascular risk. Decreased nitric oxide bio- availability in endothelium is of particular relevance in pre-diabetics.

This study was done with that hypothesis that insulin resistance is a substrate for accelerated atherosclerosis depicted by endothelial dysfunction. The findings in our study are that mild insulin resistance is associated with accelerated endothelial dysfunction.

### KEYWORDS :

#### Criteria Of Pre Diabetes :

1. Impaired fasting glucose .. 100-125mg/dl
2. IFG WHO Guide lines .. 110-125mg/dl
3. Impaired Glucose .. 140-199mg/dl (tolerance test after 2 Hrs post)
4. HBA1C ..... 5.7-6.4%

#### Pre Diabetes And Cardiovascular Disease :

1. IFG(100-125 mg/dl)CVD Risk 1.18
2. IFG(110-125mg/dl)CVD Risk 1.20
3. Impaired Glucose Tolerance CVD Risk 1.20

#### Endothelial Cell Dysfunction :

It is described as imbalance between :

1. Relaxing factors and constructing factors
2. Anti-Coagulant mediators and Pro-coagulant mediators
3. Growth inhibiting factors and growth promoting factors

#### Endothelial Cell Dysfunction In Pre Diabetics:

Modulation of vascular tone , regulation of vessel inflammation and inhibition of thrombosis is impaired in pre diabetes , creating a permissive environment for atherogenesis

#### 1. Vasomotor function

Increased production of reactive oxygen species , decreased (NO) nitric oxide bioavailability of endothelium - derived NO

#### 2. Inflammation

Insulin resistance increases inflammation , the "T" cells migrate to vascular intima.They secrete cytokines and chemokines recruiting monocytes and smooth muscle cells. Leading to fatty streaks.

#### 3. Thrombosis

Pre diabetic endothelial cells augment production of tissue factor , leading to thrombus formation.

#### Biomarkers of endothelial cell Dysfunction :

1. Elevated levels of plasma cellular adhesion molecules (E-selectin , I CAM 1 and V CAM 1) , it raises relative risk of CVD in pre diabetes and diabetes by 1.5 - 7.5 fold.
2. Increased levels of inflammatory cytokines especially TNF , IL-6 , CRP.

#### Assessment Of Flow Mediated Dilation In Brachial Artery By Color Doppler Ultrasonography :

The brachial artery flow mediated Doppler was performed in all subjects using 7.5MHz transducer. Test was done after overnight fasting. The B.P cuff was tied to the right arm in the supine position.

The Brachial artery was imaged in right cubital fossa and its diameter measured. (From intima media with electronic calipers) at end -

systole. Systolic and diastolic velocity time integrals were measured. The arm was then occluded by raising pressure in BP cuff to atleast 50mm above the systolic pressure. The Systolic and Diastolic velocity time integrals were measured within 15 seconds of release of pressure in the cuff. The brachial artery diameter was measured again at 1 minute to assess the flow mediated dilation. The ultrasound of brachial artery was continuously recorded before , during and up to 2 minutes after release of occlusion.

#### The flow in the brachial artery calculated as :

Base line flow =  $\pi * d1^4 / 4 * HR1 * (VTIS1 + VTID1)$   
 Reactive hyperemia flow =  $\pi * d2^4 / 4 * HR2 * (VTIS2 + VTID2)$   
 {measured immediately after release of cuff}  
 $d1, d2$  = diameter of Brachial artery  
 $HR1, HR2$  = heart rate  
 $VTIS1, VTIS2$  = VTI Systolic  
 $VTID1, VTID2$  = VTI diastolic

#### Percentage increase in brachial artery flow was calculated as :

% Reactive hyperemia =  $(\text{Reactive hyperemia flow} - \text{baseline flow}) * 100 / \text{baseline flow}$

#### Flow mediated dilation :

$FMD = (d3 - d1) * 100 / d1$  ;  
 where  $d3$  is brachial artery diameter at 1 minute of cuff release.

#### Clinical Relevance Of Endothelial Dysfunction :

Atherosclerosis remains undetected for many years , due to lack of clinical symptoms. Once a clinical manifestation sets in , of atherosclerosis , the intervention remains essentially restricted to an improvement of symptoms and retardation of disease process.

It is therefore of particular importance to intervene at the stage of endothelial dysfunction before the development of atherosclerosis.

#### METHODOLOGY

50 patients with impaired glucose levels

#### Inclusion Criteria :

1. Age 15-65 years
2. Subjects with impaired fasting glucose (100-125mg/dl)

#### Exclusion Criteria :

1. Below 15 years and above 65 years
2. Diagnosed DM1 and DM2
3. Subjects with vascular diseases
4. Febrile illnesses
5. Subjects on drugs which alter flow mediated dilation of endothelium.

**Investigations Done :**

Haemoglobin , total count , differential count , ESR , FPG , Lipid profile , ECG , Color Doppler Ultrasonography.

**Inference:**

1. Endothelial dysfunction is seen 2 males and 1 female
2. Smoking is significantly associated with endothelial dysfunction
3. Obese people have increased risk
4. Males with waist / hip ratio greater than 1 have higher risk of premature atherosclerosis
5. High LDL and low HDL strongly correlated to impaired flow mediated vasodilatation and thus endothelial dysfunction.

**RESULTS:**

In this study endothelial dysfunction is observed in 3 patients ( 6%) out of 50 pre diabetics , out of them 2 were males (4.65%) , 1 was a female (14.85%). People with greater BMI and HBA1C greater than 6 % and males with waist / hip ratio greater than 1 were having greater chance of endothelial dysfunction.

**CONCLUSION**

In this study out of 50 pre diabetics , endothelial dysfunction was seen in 6% subjects , found more commonly in pre diabetic females (14.85%) than in males (4.65%).

**Risk factors associated with endothelial dysfunction were :**

1. Increased BMI
2. Waist to hip ratio greater than 1
3. High LDL and low HDL
4. HBA1C greater than 6%
5. Pre diabetics who smoke
6. Obesity in pre diabetics

**Table 2: Distribution Of Subjects Based On BMI**

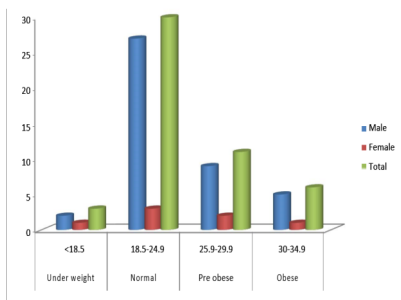
Weight categories	BMI	cases			controls		
		Male	Female	Total	male	female	Total
Under weight	<18.5	2	1	3	4	2	6
Normal	18.5-24.9	27	3	30	37	3	40
Pre obese	25-29.9	9	2	11	2	2	4
Obese	30-34.9	5	1	6	0	0	0

- In this study both males 27 (62.7%) and females 3 (42.85%) have their major subject distribution in normal BMI range.
- Among males 9(20.93 %) and females 2( 28.57%) are pre obese
- 5(11.63%) males and one female (14.28%) are obese
- Mean BMI and S.D(24.3±4.23)

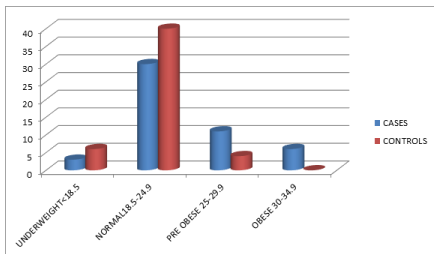
**STATISTICAL SIGNIFICANCE:**

- BMI between (25.9 -34.9) is a strong predictor for occurrence of endothelial dysfunction

P value<0.004



**Graph 2: Distribution Of Subjects Based On BMI**



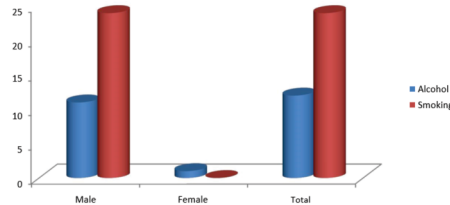
**Graph 3: Distribution Of Subjects Based On BMI**

**Table 3: Distribution Of Subjects By Personal Habits**

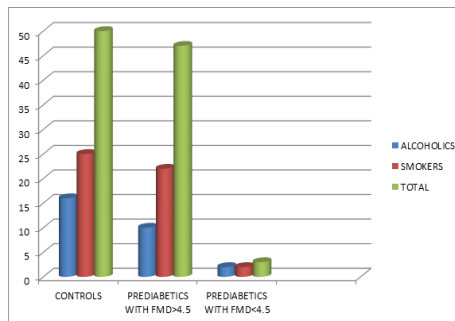
	Male	Female	Total
Alcohol	11	1	12
Smoking	24	0	24

**Table 4: Distribution Of Subjects By Personal Habits**

	CASES			CONTROLS		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
ALCOHOLICS	11	1	12	14	2	16
SMOKERS	24	0	24	25	0	25



**Graph 4: Distribution Of Subjects By Personal Habits**



**Graph 5: Distribution Of Subjects By Personal Habits**

In this study 24(55.81%) are smokers and all are males.

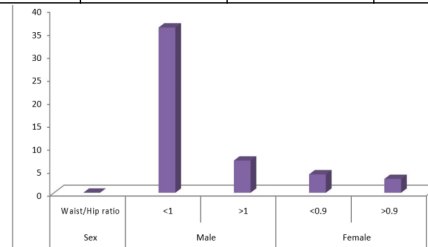
- Among alcoholics 11 are males one is female.

**Statistical Significance:**

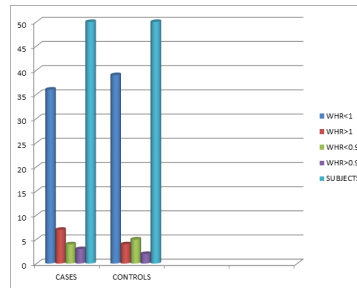
- Smoking is associated with significant endothelial dysfunction with P value 0.0469
- Alcohol intake is not associated with endothelial dysfunction P value 0.186

**Table 5: Distribution Based On Waist/hip Ratio**

Sex	Waist/Hip ratio	CASES Total	CONTROLS
Male	<1	36	39
	>1	7	4
Female	<0.9	4	5
	>0.9	3	2



**Graph 6: Distribution Based On Waist/hip Ratio**



**Graph 7: Distribution Based On Waist/hip Ratio**

In this study 16.2% of males have waist/hip ratio >1

- 42.87% females have waist/hip ratio >0.9
- STATISTICAL SIGNIFICANCE:
- Waist / hip ratio >1 among MALES is a significant contributor to endothelial dysfunction.

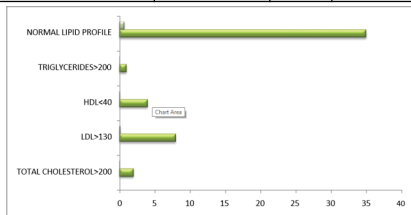
THIS ASSOCIATION IS NOT SEEN IN FEMALES

P value 0.023 in males  
P value 0.429 in females

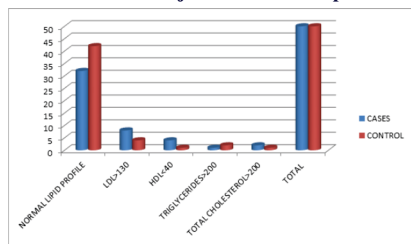
Hence pre diabetic MALES with WAIST/HIP>1 has HIGHER RISK of developing ENDOTHELIAL DYSFUNCTION

Table 6: Disturbation Based On Abnormal Lipid Profile

Abnormal lipid profile	CASES		CONTROLS	
	NO.OF SUBJECTS	%	NO.OF SUBJECTS	%
TOTAL CHOLESTEROL>200	2	4%	1	2%
LDL>130	8	16%	4	8%
HDL<40	4	8%	1	2%
TRIGLYCERIDES>200	1	2%	2	4%
NORMAL LIPID PROFILE	35	70%	42	84%



Graph 8: Distribution Of Subjects Based On Lipid Profile



Graph 9: Distribution Of Subjects Based On Lipid Profile

In this study total cholesterol > 200mg/dl is seen in 2(4%)

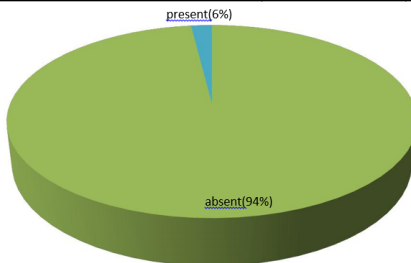
- LDL > 130mg/dl is seen in 8(16%) with MEAN±S.D(106.8±22.3)
- HDL < 40 mg/dl is seen in 4(8%) with MEAN±S.D(51.68± 2.87 )
- Triglycerides > 200mg/dl is seen in one subject with MEAN ±S.D(2%)
- Majority have their lipid profile normal 35(70%).

**STATISTICAL SIGNIFICANCE:**

LDL >130 mg/dl ; P value <0.023  
HDL <40 mg/dl ; P value <0.014  
TRIGLYCERIDES .200mg/dl; P value 0.060

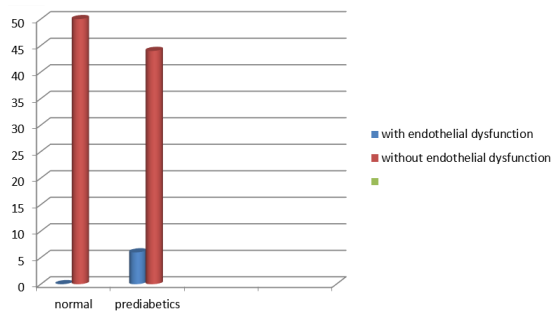
Table 7: Distribution Of Subjects Base On Endothelial Dysfunction

Endothelial Dysfunction FMD>4.5%	No. of subjects	Total %
absent >4.5	47	94%
present <4.5	3	6%
Total	50	100%



Graph 10: Distribution Of Subjects Based On Endothelial Dysfunction

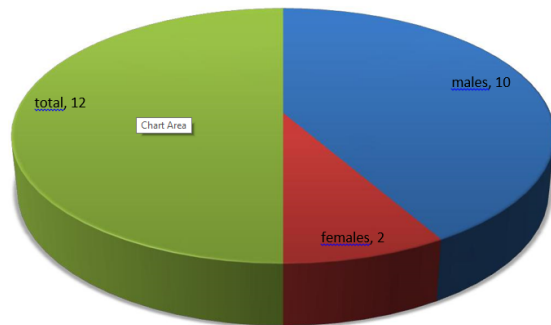
• Endothelial dysfunction is observed in 6% subjects



Graph 11: Distribution Of Subjects Based On Endothelial Dysfunction

Table 8: Distribution Based On HbA1c Levels HbA1c

HbA1c	CASES			Controls		
	Males	females	TOTAL	Males	Females	TOTAL
>6%	10	2	12	0	0	0
<6%	33	5	38	43	7	50



Graph 12 : Distribution Of Subjects Based On Hba1c

- Out of 12 subjects with HbA1c >6% endothelial dysfunction is noted in 3 (25%)
- 33 subjects have their HbA1c <6%

**Statistical Significance:**

- HbA1c >6% is significantly associated with endothelial dysfunction with P value < 0.011

Table 10: Distribution Of Endothelial Dysfunction By Various Risk Factors

Risk factors	FMD<4.5% (n=3)	FMD>4.5% (n=43)	p value
1.Age	40.3±6.72	39.7±7.13	0.217
2.Sex	males(4.65%)	males(81.3%)	0.017
	females(14.85%)	females(85.71%)	
3.Smoking	2(8.33%)	22( )	0.046
4.Alcohol	0	0	0.186
5.BMI			
Pre obese	27.5	27.64	0.047
Obese	(33.15±3.16)	(30.8±3.9)	0.004
6.Abnaormal lipid profile			
High LDL	(133.99±01.09)	(102.4±38.07)	0.004
Low HDL	(38±10.13)	(51.58±7.98)	0.014
High triglycerides	(169±28.9)	(155.4±27.03)	0.060
7.Severity by ECG	1	0	0.078
8.Abnormal waist/hip ratio	males(1.25±0.32)	males(0.82±0.45)	Males 0.023 Females 0.429
	females(1.0±0.28)	females(0.76±0.32)	
9.HbA1c	25%	75%	0.011

**INFERENCE:**

- Endothelial dysfunction is seen in 2(4.65%) males and one female(14.29%).
- Smoking is significantly associated with occurrence of endothelial dysfunction.
- Alcohol intake is not related to the development of endothelial

dysfunction.

- Obese male and female have increase risk of developing atherosclerosis in future.
- Males with waist/hip ratio>1 have higher risk of having pre mature atherosclerosis and vascular complications.
- High LDL and low HDL is strongly correlated to impaired flow mediated vasodilatation and thus endothelial dysfunction.

**Table 11 : Measured Parameters Of Fmd In Prediabetic Subjects**

STUDY VARIABLES	MEAN	STANDARD DEVIATION	NORMAL VALUES
Base line diameter	3.8	0.51	3.76±0.54
Base line flow	645	218.2	631.62±222.41
Reactive hyperemic flow	890.1	366.7	780.58±356.57
Hyperemic flow %	81.65	74.94	122.39±55.39
FMD %	10.38	10.53	17.12±10.13

Hyperemic flow % and FMD% were significantly altered in pre diabetics when compared with standard values.

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