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Colour Doppler Evaluation of Central Retinal and Ophthalmic arteries in Diabetes patients and Comparing it with Normal Individuals

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Abstract

Aim: *Aim of the study is to evaluate the ocular blood flow haemodynamics in patients with diabetes mellitus with no ocular symptoms and comparison of the same with normal controls by Doppler imaging.*

Materials and Methods: *Colour Doppler evaluation of 73 diabetic patients (146 eyes) and 73 healthy controls (146 eyes) were done with Voluson GE machine with High frequency probe (7.5 Mega Hertz). Doppler spectral analysis of ophthalmic arteries (OA) and central retinal arteries (CRA) were done. The peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI) and S/D ratio were calculated. PSV, EDV, RI were measured in normal controls and in diabetics in both the eyes and they were compared. Differences within the groups were evaluated by paired-t- test. A value of less than 0.05 were considered as statistically significant.*

Results: *The average mean RI of CRA in controls on right side is 0.71+/- 0.02 and 0.69+1-0.02.on left side. The average mean RI of OA in controls on right side is 0.77+1-0.15 and 0.76 +1- 0.02. on left side. In diabetics the average mean RI of CRA on right side is 0.77+1- 0.03. and 0.76+/-0.11 on left side. The average mean RI of OA in diabetics on right side is 0.79 +1-0.02 and 0.79 +1- 0.23 in left side. The PSV of CRA in diabetics was significantly reduced (p=<0.05) when compared to controls. The EDV of CRA in diabetics was also significantly reduced (p=<0.05) compared to normal controls. The RI is significantly increased compared to normal controls (p=<0.05). 95% confidence interval is observed in PSV, EDV, RI of CRA in diabetics. The PSV, EDV and RI of OA has no significant difference between normal controls and diabetics.*

Conclusion: *There were statistical significant difference between the PSV, EDV and RI of CRA in normal and in diabetics. This significant difference could be due to the circulatory changes in blood vessels in diabetics. No significant difference was made in OA between normal controls and in diabetics. This study concludes that retinal haemodynamic changes were present even before the clinical manifestations of retinopathy in diabetics*

Keywords: *Colour Doppler, diabetes, central retinal artery, ophthalmic artery, haemodynamics, resistance.*

Introduction

Diabetes is a disease in which the pancreas is not producing the insulin properly or the body is not utilizing the insulin properly. This leads to increased concentration of glucose in the blood (hyperglycemia). Throughout the world as of

2010, around 285 million people had diabetes and 90% of the cases were type 2 . The incidence of diabetes is increasing and it is estimated to almost double by 2030. The prevalence is expected to occur more in Asia and Africa.

Types

Type 1: Also known as insulin dependent diabetes mellitus. Loss of insulin producing beta cells in pancreas. Children and adolescent groups are most often affected. It is less common type and requires lifelong insulin injections.

Type 2: Also known as Non— Insulin-dependent Diabetes mellitus (NIDDM). It is due to insulin resistance or combined with decreased insulin secretion. Usually occurs in adult hood and can be related to obesity, lack of physical activity and unhealthy diet. It is more common type.

Gestational diabetes: Hyperglycemia occurring during pregnancy.

Complications of diabetes mellitus

Complications occur in all forms of diabetes mellitus who have no control of blood sugar levels or who are diabetics for longer duration ie 10 -20 yrs. Complications can be microvascular or macrovascular. Macrovascular complications includes cardiovascular disease such as heart attacks, strokes and insufficiency of blood flow to legs. Microvascular complications are due to damage to small blood vessels. It can affect the eyes, kidneys and nerves.

Ocular complications in diabetes

The primary part affected in eye is retina. Retinopathy is the leading cause of blindness in adults.

Anatomy Of Retina Retina is a sensory tissue which lines the back of the eye. It is multilayered (10 layers) and contains photoreceptors namely rods and cones. The rods and cones convert light energy into signals which are then carried to brain through optic nerves and interprets the signal as visual images. Tiny blood vessels in retina take the oxygen and essential nutrients to the walls of the retina. In the centre of the retina, there is a simple dimple called fovea, which is responsible for the sharp vision in eye. Optic nerve is a collection of nerve fibres which carries electric signals from retina to brain. Retina is supplied by central retinal artery which supplies the inner retinal layer and choroidal arteries which supplies the outer retinal layers. Central retinal artery is a branch of ophthalmic artery. Choroidal artery is a branch of posterior ciliary arteries.

Retinal Microvascular Dysfunction In Diabetes Mellitus

Microvascular changes occurs early in diabetes mellitus, before the development of disease in succeptible end organs like kidneys and eyes. Microvascular leakage occurs and occlusion of inner-blood retinal barrier occurs. Alterations of haemodynamic parameters in diabetic patients has clinical significance in early diagnosis and treatment of diabetes mellitus microangiopathy. The tissue and nerve cells nourished by small blood vessels are damaged by increasing blood sugar levels.

Retinal complications of diabetes mellitus

Long standing diabetes can damage the retina leading to blindness. Damage to retina may begin to develop even before the diagnosis of diabetes mellitus. Apart from retinopathy, diabetes mellitus can cause cataract and glaucoma at younger age.

Types of retinopathy

According to national eye institute, diabetic retinopathy has 4 stages. Mild non prliferative retinopathy-It is an early stage in which tiny blood vessels in the retina swells like a balloon. Moderate non — proliferative retinopathy — some blood vessels which supply the retina are blocked. Severe — non — proliferative retinopathy — The retinal blood vessels which are blocked were disrupted and signals the body to produce new blood vessels. Proliferative retinopathy — New blood vessels form either at disc or elsewhere.

In stage 1,2 and sometimes even in stage 3, patients may not have clinical symptoms, but microvascular haemodynamic alterations have occurred in retina even before the symptoms develops. Microvascular changes can be identified

by standard procedures like fundus examination. But in case of cataract or vitreous haemorrhage fundus examination may not be possible. In a study it was found that longer the duration of diabetes, more is the risk for developing retinal complications. After 5 years — 25% of IDDM has some retinopathy. After 10 years — 60% have retinopathy. After 15 years — 80% have retinopathy.

Retinal artery ultrasound

Colour Doppler imaging was first used to image various organ systems in 1979. Later in 1989, colour Doppler imaging in orbit was described by Erick son. Eye is located superficially and cystic in nature. The normal anatomy and vasculature can be clearly seen by high frequency transducers. Colour Doppler imaging of eye is a non-invasive procedure. It allows to visualize the grey scale imaging and colour coded imaging both at the same time.[[1]-[3]] The (peak systolic and end diastolic velocities of the ophthalmic and central retinal arteries can be measured using Doppler. The resistive index can then be calculated using peak systolic and end diastolic velocities. Orbital blood flow velocity can be qualitatively and quantitatively measured by colour Doppler imaging.[[4]-[7]] Orbital blood flow in normal and in diseased condition can be evaluated. As Doppler shift detection sensitivity is higher than conventional grey scale resolution, evaluation of very small vessels supplying the orbit can be done non invasively. Wolfgang E. Lieb et al examined 40 normal eyes and they were able to locate the central retinal artery (CRA), posterior ciliary arteries (PCA) and ophthalmic arteries (OA) in all patients. Using Doppler spectrum, the blood flow velocity in these vessels are assessed quantitatively.[[8]-[10]]

Materials and Methods

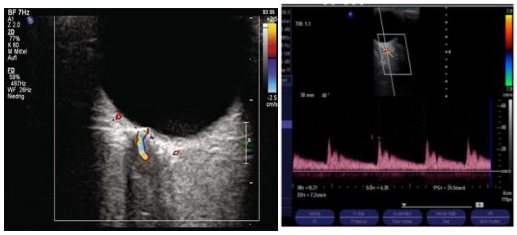
Inclusion Criteria

This study consists of 73 diabetic patients (146 eyes) and 73 healthy controls.(146 eyes). 73 diabetic patients, with deranged glucose tolerance test were the cases for the study. 73 normal persons with normal glucose tolerance without ocular complaints were considered controls. Informed consent were obtained from all the participants and the study protocol was approved by institutional ethics committee.

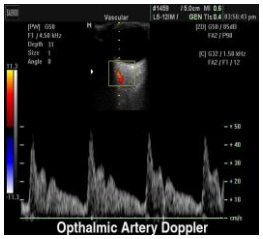
All diabetic patients were receiving the antidiabetic drugs as usual on the day of scan. Ultrasound examination performed with subjects in supine position. GE voluson machine with 7.5 mega hertz probe was used. Ultrasound probe was positioned gently on closed eyelids in transverse position. Colour Doppler mode was used to identify the central retinal artery (CRA) and ophthalmic artery (OA).

Optic nerve is localized to examine CRA, which runs in centre of the optic nerve along with central retinal vein. Ophthalmic artery OA is situated either above or below the optic nerve in the posterior orbit. Real time identification of CRA and OA was done. Doppler spectral analysis of OA and CRA was done. Sample volume was estimated by placing the cursor along the course of CRA, 3mm behind the optic disc surface. Sample volume was adjusted to 10mm or below. Angle of insonation is adjusted to be < 30 degree preferably 0 degree. The threshold level was set to optimise sensitivity without producing excessive noise. The peak systolic velocity, end diastolic velocity, resistive index and S/D ratio were calculated. Cross sectional area of CRA and OA were not done because the diameter of these vessels were too small. Peak systolic velocity, End diastolic velocity and Resistive index were measured in normal controls and in diabetics in both the eyes and they were compared.[11]

Central Retinal Artery and its Normal Wave Form Pattern



Ophthalmic Artery And Its Normal Wave Form pattern



GROUP-2 CASES (DIABETES)

AGE_GROUP

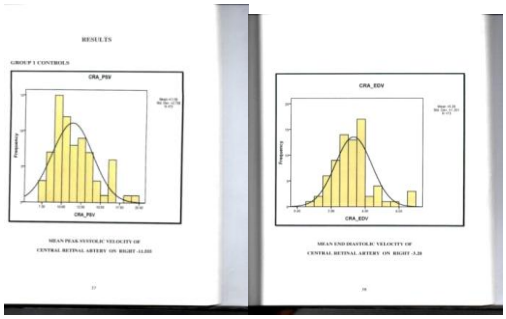
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	10 - 30	1	1.4	1.4	1.4
	31 - 50	14	19.2	19.2	20.5
	51 - 70	50	68.5	68.5	89.0
	71 - 90	8	11.0	11.0	100.0
	Total	73	100.0	100.0	

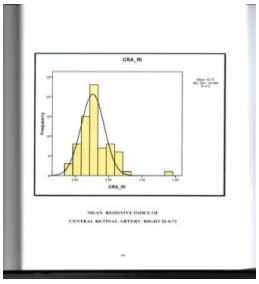
SEX

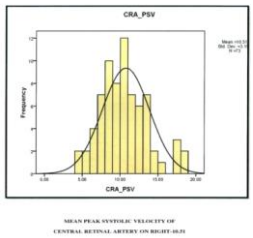
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	FEMALE	30	41.1	41.1	41.1
	MALE	43	58.9	58.9	100.0
	Total	73	100.0	100.0	

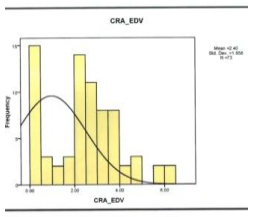
Histogram

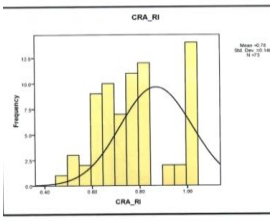
Results-Group 1 Controls

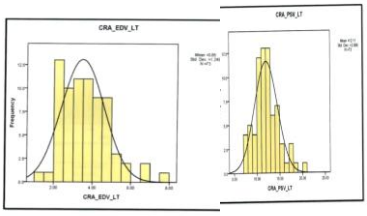


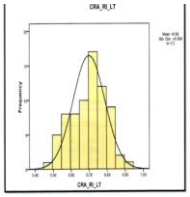


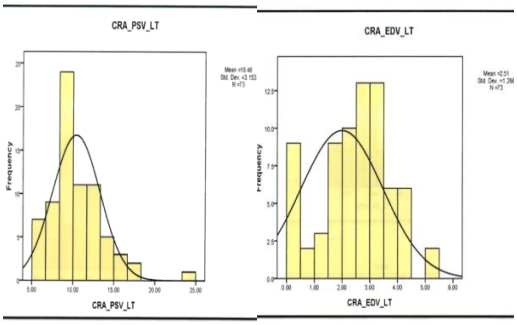


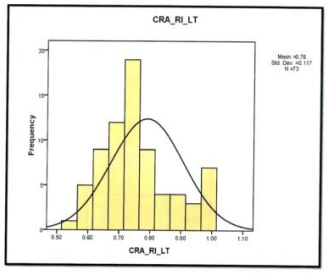












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	Cases Used	Statistics are based on all cases with valid data.

MEAN RESISTIVE INDEX OF CENTRAL RETINAL ARTERY ON LEFT -0.76

INDEPENDENT SAMPLES TEST

		Levene's Test for Equality of Variances		t-test for Equality of Means				
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
CRA_PSV RT	Equal variances assumed	.984	.323	2.125	144	.035	1.03712	.48802
	Equal variances not assumed			2.125	141.073	.035	1.03712	.48802
CRA_EDV RT	Equal variances assumed	6.888	.010	3.647	144	.000	.87384	.23960
	Equal variances not assumed			3.647	131.246	.000	.87384	.23960
CRA_SD RT	Equal variances assumed	5.167	.025	-.533	144	.595	-.51082	.95874
	Equal variances not assumed			-.533	77.578	.596	-.51082	.95874
CRA_RI RT	Equal variances assumed	15.789	.000	-2.823	143	.005	-.05795	.02053
	Equal variances not assumed			-2.830	125.170	.005	-.05795	.02048
OA_PSV RT	Equal variances assumed	.828	.364	.177	144	.860	.26616	1.50267
	Equal variances not assumed			.177	140.473	.860	.26616	1.50267
OA_EDV RT	Equal variances assumed	.323	.571	.945	144	.346	.40726	.43106
	Equal variances not assumed			.945	143.996	.346	.40726	.43106
OA_SD RT	Equal variances assumed	3.092	.081	-1.604	144	.111	-.58644	.36552
	Equal variances not assumed			-1.604	129.254	.111	-.58644	.36552
OA_RI RT	Equal variances assumed	.164	.686	-1.230	144	.221	-.01411	.01147
	Equal variances not assumed			-1.230	143.012	.221	-.01411	.01147
CRA_PSV_LT	Equal variances assumed	.818	.367	3.395	144	.001	1.64589	.48479
	Equal variances not assumed			3.395	140.446	.001	1.64589	.48479

GROUP STATISTICS

GROUP		N	Mean	Std. Deviation	Std. Error Mean
CRA_PSV	1.00	73	11.5516	2.72778	.31926
	2.00	73	10.5145	3.15362	.36910
CRA_EDV	1.00	73	3.2778	1.20093	.14056
	2.00	73	2.4040	1.65791	.19404
CRA_SD	1.00	73	3.9607	1.58304	.18528
	2.00	73	4.4715	8.03709	.94067
CRA_RI	1.00	72	.7196	.09639	.01136
	2.00	73	.7775	.14555	.01704
OA_PSV	1.00	73	27.9459	8.32815	.97474
	2.00	73	27.6797	9.77130	1.14364
OA_EDV	1.00	73	6.1055	2.61068	.30556
	2.00	73	5.6982	2.59784	.30405
OA_SD	1.00	73	4.9541	1.79707	.21033
	2.00	73	5.5405	2.55416	.29894
OA_RI	1.00	73	.7762	.06635	.00777
	2.00	73	.7903	.07211	.00844
RA_PSV_LT	1.00	73	12.1093	2.68583	.31435
	2.00	73	10.4634	3.15326	.36906
A_EDV_LT	1.00	73	3.6485	1.24874	.14615
	2.00	73	2.5132	1.28802	.15075

		Levene's Test for Equality of Variances		t-test for Equality of Means				
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
CRA_EDV_LT	Equal variances assumed	.004	.950	5.407	144	.000	1.13534	.20997
	Equal variances not assumed			5.407	143.862	.000	1.13534	.20997
CRA_SD_LT	Equal variances assumed	6.021	.015	-1.308	144	.193	-.69562	.53180
	Equal variances not assumed			-1.308	87.800	.194	-.69562	.53180
CRA_RI_LT	Equal variances assumed	.484	.488	-3.647	144	.000	-.06507	.01784
	Equal variances not assumed			-3.647	139.995	.000	-.06507	.01784
OA_PSV_LT	Equal variances assumed	3.857	.051	-1.394	144	.166	-2.20575	1.58272
	Equal variances not assumed			-1.394	130.861	.166	-2.20575	1.58272
OA_EDV_LT	Equal variances assumed	2.490	.117	.490	144	.625	.23274	.47497
	Equal variances not assumed			.490	142.104	.625	.23274	.47497
OA_SD_LT	Equal variances assumed	1.067	.303	-.463	144	.644	-.21603	.46690
	Equal variances not assumed			-.463	142.191	.644	-.21603	.46690
OA_RI_LT	Equal variances assumed	.434	.511	-1.629	144	.105	-.02712	.01665
	Equal variances not assumed			-1.629	143.949	.105	-.02712	.01665

GROUP		N	Mean	Std. Deviation	Std. Error Mean
CRA_SD_LT	1.00	73	3.6971	1.43665	.16815
	2.00	73	4.3927	4.31062	.50452
CRA_RI_LT	1.00	73	.6947	.09825	.01150
	2.00	73	.7597	.11655	.01364
OA_PSV_LT	1.00	73	28.7960	7.90323	.92500
	2.00	73	31.0018	10.97287	1.28428
OA_EDV_LT	1.00	73	6.4814	2.69874	.31586
	2.00	73	6.2486	3.03075	.35472
OA_SD_LT	1.00	73	5.1614	2.65693	.31097
	2.00	73	5.3774	2.97563	.34827
OA_RI_LT	1.00	73	.7673	.10153	.01188
	2.00	73	.7944	.09964	.01166

GROUP1-CONTROL
GROUP2-CASES(DIABETES)

INDEPENDENT SAMPLES TEST

	t-test for Equality of Means	
	95% Confidence Interval of the Difference	
	Lower	Upper
CRA_PSV RT	.07251	2.00173
	.07234	2.00190
CRA_EDV RT	.40024	1.34743
	.39985	1.34782
CRA_SD RT	-2.40585	1.38421
	-2.41970	1.39805
CRA_RI RT	-.09854	-.01737
	-.09847	-.01743
OA_PSV RT	-2.70398	3.23631
	-2.70462	3.23695
OA_EDV RT	-.44477	1.25929
	-.44477	1.25929
OA_SD RT	-1.30892	.13604
	-1.30962	.13674
OA_RI RT	-.03678	.00856
	-.03678	.00856
CRA_PSV_LT	.68766	2.60412
	.68746	2.60432
CRA_EDV_LT	.72032	1.55036
	.72032	1.55036
CRA_SD_LT	-1.74676	.35553
	-1.75250	.36126

	t-test for Equality of Means	
	95% Confidence Interval of the Difference	
	Lower	Upper
CRA_RI_LT	-.10033	-.02980
	-.10034	-.02980
OA_PSV_LT	-5.33412	.92261
	-5.33678	.92527
OA_EDV_LT	-.70608	1.17156
	-.70618	1.17166
OA_SD_LT	-1.13889	.70683
	-1.13899	.70693
OA_RI_LT	-.06003	.00579
	-.06003	.00579

		95 % CI FOR GROUP 1 (Normal)		95 % CI FOR GROUP 2 (Diabetes)
CRA_PSV RT	±0.62	10.93 to 12.18	±0.72	9.79 to 11.23
CRA_EDV RT	±0.28	2.99 to 3.55	±0.38	2.02 to 2.78
CRA_SD RT	±0.36	3.6 to 4.32	±1.84	2.63 to 6.31
CRA_RI RT	±0.02	0.69 to 0.73	±0.03	0.74 to 0.8
OA_PSV RT	±1.91	26.03 to 29.85	±2.24	25.43 to 29.91
OA_EDV RT	±0.6	5.5 to 6.7	±0.59	5.1 to 6.28
OA_SD RT	±0.41	4.54 to 5.36	±0.56	4.96 to 6.12
OA_RI RT	±0.15	0.62 to 0.92	±0.02	0.77 to 0.81
CRA_PSV_LT	±0.61	11.49 to 12.71	±0.72	9.74 to 11.18
CRA_EDV_LT	±0.28	3.36 to 3.92	±0.29	2.22 to 2.8
CRA_SD_LT	±0.33	3.36 to 4.02	±0.99	3.4 to 5.38
CRA_RI_LT	±0.02	0.67 to 0.71	±0.03	0.72 to 0.78
OA_PSV_LT	±1.81	26.98 to 30.6	±2.52	28.48 to 33.52
OA_EDV_LT	±0.62	5.86 to 7.1	±0.7	5.54 to 6.94
OA_SD_LT	±0.61	4.55 to 5.77	±0.68	4.69 to 6.05
OA_RI_LT	±0.02	0.74 to 0.78	±0.23	0.56 to 1.02

Discussion

Colour Doppler imaging is a new technique to assess the flow velocity in central retinal arteries and ophthalmic arteries. Doppler ultrasound has been used to evaluate the CRA and OA. It is possible to measure the PSV, EDV and RI of the orbital vessels.[[12]-[14])

The study population consists of 73 normal and 73 diabetic patients. None of them were hypertensives. All the diabetic patients were taking medications on the day of the study. Control subjects were receiving no medications and has no e/o hypertension, diabetes or retinal vascular disease. Ultrasound examinations were performed with subjects in supine position. Using high frequency probe placing over the closed eyelids, central retinal artery and ophthalmic arteries were identified using colour Doppler. PSV, EDV and RI were obtained.

RI= PSV-EDV/PSV. RI=Resistive index, PSV= Peak systolic velocity, EDV=End diastolic velocity.

RI has been used as a measure of vascular resistance in the artery.

Datas are expressed as the mean +1- SD. Differences within the groups were evaluated by paired-t- test. A value of less than 0.05 were considered as statistically significant. Among the controls 34 subjects were females and 39 of them were males. 9.59% of them were below 30yrs. 28.77% of them were 31- 50 yrs.51.37% of them were 51-70yrs.10.27% of them were 71-90yrs. Among the diabetics 43 were male and 30 were female. 19.2% (n=14) of them were 31-50 yrs.68.5% (n=50) of them were 51-70 yrs. 11% (n=8) of them were 71-90yrs.

17 patients were diabetics for more than 10 yrs. Among 73 diabetics, 72 of them were type-2 and only one patient is type-1. In controls the average mean PSV of CRA on right is 11.55+/-0.62, EDV is3.27+/-0.28 and RI is 0.71+/- 0.02. The average mean PSV of CRA on left is 12.10+/-0.61 and EDV is 3.64+/- 0.28, RI is 0.69+/-0.02. The average mean PSV of OA on righ is27.94 +1-1.91 EDV is 6.10+/-0.6 and RI is 0.77+1-0.15. The average mean PSV of OA on left is 28.79+/- 1.8 1 and EDV is 6.48+/- 0.62, RI is 0.76 +/- 0.02.

In diabetics, the average mean PSV of CRA on right is 10.51+/- 0.72, EDV is 2.40+/-0.38 and RI is 0.77+/- 0.03.The average mean PSV of CRA on left is 10.4+/-0.72, EDV is 2.51+/- 0.29 and RI is 0.76+/-0.11. The average mean PSV of OA on right is 27.67+/-2.24 EDV is 5.69+/- 0.59and RI is 0.79 +/-0.02 .The average mean PSV of OA on left is 31.00+/- 2.52 and EDV is 6.24+/-0.7, RI is 0.79 +/- 0.23.

The PSV of CRA in diabetics was significantly reduced (p=<0.05) when compared to controls. The EDV of CRA in diabetics was also significantly reduced (p=<0.05) compared to normal controls. The RI is significantly increased compared to normal controls (p=<0.05).95% confidence interval is observed in PSV,EDV,RI of CRA in diabetics.

The PSV, EDV and RI of OA has no significant difference between normal controls and diabetics.

In previous studies, by measuring the blood flow velocities in OA the severity of diabetic retinopathy was assessed.[[15]-[17]] However, in this study there is no significant difference in PSV of OA between normal controls and in diabetics . Diastolic flow was absent in 14 out of 73 diabetic patients and this could be due to increased resistance in the distal vascular bed.

Thickening of basement membrane, narrowing or obstructive changes in choroidal capillaries, diabetes duration of 2-9years plays a role in increasing the RI. HbAlc of all the diabetic patients were evaluated. Patients with levels of 7.5 and above has increased subendothelial deposition could contribute to the increased resistance in peripheral vascular bed.

Fake and his coworkers reported that blood flow velocity in retinal arteries were low even before the clinical appearance of retinopathy.

So many studies have reported altered blood flow parameters in retrobulbar bed in diabetic patients without retinopathy. Detecting microvascular changes in retina at the earliest stage is necessary, because this could allow early therapeutic interventions and disease monitoring.[18-20]

Patients with diabetes of more than 10 years has RI more than that of patients with slightly higher HbA1c value compared with diabetics who has a good control of their sugar levels with HbAl c below 6.5.All the diabetic patients were screened with fundus examination to look for retinopathy changes. Out of 73 diabetics only 2 patients had early retinopathy changes, but clinically they had no symptoms. Using colour Doppler it is shown that the peaksystolic velocity and the end diastolic velocity is significantly reduced and the resistive index is signifantly increased in diabetics compared to normal controls.

This stastically significant difference in peaksystolic velocity and the end diastolic velocity and resistive index could be due to haemodynamic alterations that occur in diabetics. This haemodynamic alteration could have

occurred in diabetic patients even before the clinical manifestations.

Advantages

Ultrasound can be done effectively in patients who are affected by cataract and intraocular haemorrhage. Sometimes OA and PCA can be inaccessible by flourescein angiography and Doppler velocimetry. During such situations colour Doppler imaging can be done.

Conclusion

By using, colour Doppler, the flow velocity in CRA and OA was calculated in diabetics and in normal controls and they were compared. There were statistical significant difference between the PSV, EDV and RI of CRA in normal and in diabetics. This significant difference could be due to the circulatory changes in blood vessels in diabetics. No significant difference was made in OA between normal controls and in diabetics. This study concludes that retinal haemodynamic changes were present even before the clinical manifestations of retinopathy in diabetics.

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