# Ocular Pulse Amplitudes in Diabetics in South India


A dissertation submitted in partial fulfilment of

M.S. Branch III (Ophthalmology) Examination of the

TamilNadu Dr. MGR Medical University, Chennai, to

be held in March 2013

# Declaration

I hereby declare that the investigations that form the subject matter of this thesis were carried out by me under the guidance of Dr.Andrew Braganza, Professor of Ophthalmology, Christian Medical College, Vellore, Tamil Nadu. I declare that this has not been submitted to any other University in part or in full.

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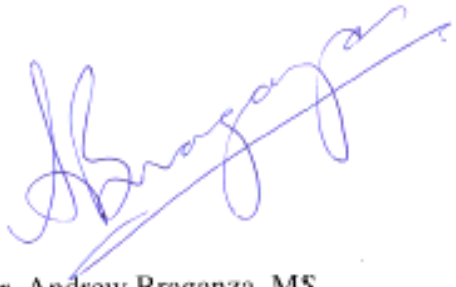
# BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "Ocular Pulse Amplitudes in Diabetics in South India" done towards fulfilment of the requirements of the Tamilnadu Dr. MGR Medical University, Chennai, for the M.S. Branch III (Ophthalmology) examination to be conducted in March 2013, is a bona fide work of the candidate Dr. Ashish George Kuruvilla, Post-Graduate student in the department of Ophthalmology, Christian Medical College, Vellore under my supervision and guidance. This dissertation has not been submitted, fully or in part to any other board or university.



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# Introduction

Diabetic retinopathy is one of the most common causes of blindness in the world. From the data collected from nationwide studies, trends show that Diabetes mellitus is steadily increasing and is now evolving into a major public health problem (1).

The problem we now face in India is that despite "modernisations" and implementing western cultures leading to an increase in sedentary life style and consumption of high fat foods, knowledge about the disease and early diagnosis is still lacking. In addition, Asians certainly have unique clinical and biochemical abnormalities like , greater abdominal adiposity, lower adiponectin levelsand increased insulin resistance. (2)

Western literature have shown that 20 years after diabetes starts, majority of patients with diabetes Type I (insulin-dependent) and more than 60% of Diabetes type II will have some degree of retinopathy.(3)

Just as Asians have certain phenotypical predispositions for developing Diabetes, this concept can be carried to other physiological characteristics such as haemodynamics, in particular our topic of interest, which is ocular blood flow and its regulation both in disease and health.

A great deal of research and resource has been poured into identifying the pathogenesis of Diabetic retinopathy. The blood supply to the outer retinal layers is from the choroidal vessels and the inner retinal layers are supplied by the retinal capillaries which are supplied by the central retinal artery. Damaging effects of chronically elevated glucose on the retinal

capillary endothelial cells and pericytes and also focal ischemia as pathogenetic factors in progression of disease have been well studied (4).

The biochemical and cellular mechanisms that cause diabetic vasoconstriction and vasodilation are also starting to be ascertained. However there are very few studies that have looked at choroidal blood flow as a prognostic or pathogenetic factor in the development and progression of Diabetic Retinopathy.

The study of the choroid is being looked into as an attempt to answer some of the questions regarding the pathogenesis of diabetic retinopathy and how these changes are brought about in the retina. The pulsatile ocular blood flow (POBF) and ocular pulse amplitude (OPA) are indirect indicators of choroidal blood flow. Though inferences have been made from the few studies that have been done on choroidal blood flow, conclusions based on each study have been contradictory to each other. With the advent of new and more accurate measurement tools, more reliable data can be obtained regarding the choroidal circulation and its perfusion.

Ocular blood flow can be indirectly measured non-invasively with the pneumotonometer, which measures the pulsatile ocular blood flow and more recently, the Dynamic Contour Tonometer which measures the ocular pulse amplitudes. These instruments provide the clinician with data that can be used to interpret the choroidal blood flow, which actually supplies 80% of the retina.(5)

Dynamic contour tonometry (DCT) is a non-invasive technique of checking the intraocular pressure. It also measures the ocular pulse amplitude of the eye being studied simultaneously. Ocular blood flow varies with systole and diastole. The pulsatile ocular blood flow (POBF) shows a peak during systole. The difference in the maximum and minimum values of pulsatile wave contour during systole and diastole gives us the ocular pulse amplitude (OPA).

In this study, we focused on documenting ocular pulse amplitudes, and indirectly the choroidal blood flow, in diabetic patients with various stages of Diabetic retinopathy. We also wanted to observe the effect of hypertension on choroidal blood flow in Diabetic patients. By carrying out this study, we may determine whether changes in choroidal blood flow play a role in either prognosticating diabetic retinopathy, or whether it proves to be a factor able to predict progression of diabetic retinopathy.

# AIM

To document the ocular pulse amplitudes in patients with various stages of Diabetic retinopathy

# OBJECTIVES

1. To document any difference in Ocular Pulse Amplitudes with increasing severity of Diabetic retinopathy

2. To document any difference in Ocular Pulse Amplitudes between Diabetics with and without systemic Hypertension

# Review of literature

**Burden of Diabetes Mellitus:**

According to WHO, 346 million people in the world have diabetes.(1) By 2030, the number is estimated to grow to 438 million ,which forms about 8% of the adult population. In 2004, around 3.4 million people died from complications related to diabetes mellitus(1). More than 80% of diabetes deaths occur within low- and middle-income countries. The World Health Organisation (WHO) says that deaths due to Diabetes will become double by 2030. Non-communicable diseases, which includes diabetes, account for 60% of all deaths worldwide.(1)

The global prevalence of diabetes is 6.4% and WHO projects that the prevalence is from 10.2% in the West to about 3.8% in Africa.(1) 70% of cases of diabetes occur within countries with low- and middle income. In India there is an estimated 50.8 million people with Diabetes.

In developing countries, for every patient who is diagnosed with Diabetes, there is one patient who has the disease but has not been screened for it (3). Therefore timely diagnosis and management are very important steps to reduce the complications due to Diabetes.

80% of type 2 diabetes is preventable by increasing physical activity, changing diet and improving the surrounding environment. Yet, the incidence of diabetes is likely to rise globally(1).

**Economic burden of disease:**

The financial burden caused by people with diabetes and their families depends on the economic status in which there are in. Unfortunately, the insurance policies are not very great for people in the poorest of countries and therefore the families have to take care of the whole financial burden of disease.

**Diabetic retinopathy in India:**

The prevalence of Diabetic Retinopathy in the Chennai Urban Rural Epidemiology **(CURES)** Eye Study in Southern India was 17.6 per cent where 1715 diabetic subjects were studied. This was a population based study done in 10 zones in Chennai, which included a representative sample of the population of 26,000 individuals. Diabetes was diagnosed based on the past medical history and also medications for diabetes. duration of diabetes, degree of glycaemic control and hyperlipidaemia were found to be the main risk factors for onset and progression of disease. (6)

Among the 1715 known Diabetics, the overall prevalence of Diabetic retinopathy was found to be 20.8 per cent, while among the newly diagnosed diabetic subjects 5.1 per cent had retinopathy. The Prevalence of Diabetic macular edema in the total diabetic population was 5 % and in the known diabetic subjects it was 6.3% and 1.1 % among the newly diagnosed diabetic subjects. (6)

In another study, **R P Agrawal et al** (7) found that out of a total of 4067 patients with Diabetes who presented to an outpatient diabec clinic, 1176 patients (28.9%) had findings of some Retinopathy . Among these, 79.8% of patients had non proliferative diabetic retinopathy (NPDR), 5.8% of patients had maculopathy and 14.6% of patients had proliferative retinopathy.(8)

**R Raman et al.** (9) did a multicentric random sampling of the population in Chennai for screening for diabetic retinopathy. The sample size was 5900. They found the prevalence of Diabetes to be 28.2% and the prevalence of diabetic retinopathy to be 3.5%. (9)

**Ramachandran A et al (9)** conducted a study among 3010 subjects (M:F 1892:1118, Mean age 52 +/- 9.7 years) attending an outpatient diabetic clinic. The study sample resembled the population sample. Retinopathy was diagnosed in 23.7% (nonproliferative retinopathy in 20.0% and proliferative in 3.7%). (10)

## Pathophysiology in Diabetic retinopathy:

Diabetic retinopathy is essentially a microangiopathy in which there is leakage in the blood – retinal barrier, resulting from damage to the walls of the arterioles supplying the retina. Hyperglycaemia can lead to a wide variety of microvascular and macrovascular

abnormalities, including abnormal autoregulation. (9) As described by Ciulla et al. , chronic hyperglycemia leads to a change in retinal vasoregulations. This increases bulk retinal blood flow with progressive retinopathy, perifoveal capillary dropout. In turn, there are retrobulbar hemodynamic abnormalities, including choroidal, central retinal arterial flow changes and ophthalmic arterial flow changes.(9) Having said that, the factors that link raised glucose levels to , vascular cell dysfunction, capillary dropout, and tissue hypoxia have not been elucidated.

## Ocular blood flow response to hyperglycemia:

With regard to the macrovascular pathophysiology, **Bursell et al (9)** found that chronic raised sugars are associated with a decrease in blood flow in the retina , but the retina is still capable of autoregulating this by increasing retinal blood flow according to the acute elevations in blood glucose. Their study with video fluorescein angiography (n=60) suggest that as compared to normal ocular blood flow, there is a reduction in ocular blood flow in diabetic patients without any retinopathy.

When patients had been exposed to acute increase in glucose levels, there was an increase in retinal blood flow within one hour. The retinal blood flow with progressively increasing sugar levels were as follows: with the glucose clamp at 100 mg/dl , the retinal blood flow was 16.3 ± 3.8 AU (arbitrary units); with the Glucose clamp at 200 mg/dl: 21.5 ± 4.7AU, with

the glucose clamp at 300 mg/dl : 25.9 ± 8.8 AU and in the Random diabetic group, it was 19.4 ± 4.6 AU. In the non diabetic group: 28.7 ± 6.4 AU. They suggest that there is an association between elevated blood sugar levels and reduced retinal blood flow. In spite of this, the retina is able to autoregulate in response to increased metabolic needs.

## Retinal blood flow studies:

Different studies have found different results of increased, decreased or no changes in the ocular blood flow in various stages of diabetic retinopathy.

**Kohner et al** (11) studied retinal blood flow 36 diabetic patients and 9 normals using video fluorescein angiography. In their studythey measured mean transit time of flourescein in the retina and estimated vessel volume by measuring vessel diameter. They found that there was increased volume flow in diabetic patients with mild or no retinopathy as compared to normals. They also found that patients with moderate retinopathy had a slight increase . Severe retinopathy patients had blood flow similar to non diabetics.

**Clermont et al** (12) showed that the retinal blood flow increased as the stage of retinopathy increased. In this study, 48 diabetic and 22 non-diabetic patients had their diabetic retinopathy levels estimated from fundus photographs according to the Early Treatment Diabetic Retinopathy Study (ETDRS). Fluorescein angiograms were recorded from the left eye by video fluorescein angiography. Retinal blood flow decreased 33% in patients with mild retinopathy compared with control patients (P = .001) and increased sequentially in

more advanced stages of retinopathy, with a strong correlation between retinal blood flow and retinopathy level ($r2 = 0.434$, $P = .001$)

The increase in perfusion of retina during pre-proliferative retinopathy probably arises from thickening of basement membrane capillaries leading to occlusive angiopathy and tissue hypoxia . This in turn increases demands further (13)(14). They also found that the retinal capacity to autoregulate is blunted in subjects with diabetes (15,16)

**Grunwald et al** (15) showed in a study using LASER Doppler Velocimetry (n=77) that breathing 100% oxygen reduces retinal blood flow. In diabetics without any retinopathy total flow decreased only 53% , 38% in patients with background retinopathy, by 61% in normal eyes, and only 24% in eyes with proliferative retinopathy. Loss of normal response to elevated PO2 suggests that the ability to decrease bulk retinal flow when there is increased oxygen delivery, is gradually reduced as the disease progresses.(16)

**Rassam et al** (17) studied the effect of hypertension on haemodynamics of the choroid and retina and studied the autoregulatory ability of the retinal vessels in the presence of normal blood sugars and also hypoglycemia. Retinal blood flow was measured in 10 normal control subjects, 10 subjects with Diabetes with blood glucose < 10 mmol/L and 10 subjects with diabetes with blood glucose > 15 mmol/l' before and after increasing the blood pressure .
Laser Doppler velocimetry was utilised. Results showed that when the mean arterial pressuer increased by 40 %, there was an increase in retinal blood flow of 32.9 + 7-1 % in controls (non diabetics). In diabetics with low blood glucose level, the increase in retinal blood flow

was significant when there was 30% increase in Mean Arterial Pressure (23.6 + 87 %, P = 0-032) and at 40 % increase (49-9 + 12-03 %, P = 0-004). Diabetics with hyperglycemia failed to show any sign of autoregulation at any of the increased levels of Mean Arterial Pressure (with 15 % increase, 27 0 + 11 1 %; with 30 % increase, 66.9 + 19.8 %; and with 40 % increase, 101 9 + 21 4 %; P < 0.022). The coefficients of autoregulation showed that in controls, retinal vascular autoregulation broke down with increases in Mean Arterial Pressure between 30 and 40 %. In diabetic subjects, it broke down between 15 and 30 % in patients with normal sugars and at less than 15 % when sugars were high. They hypothesised that there was a defect in autoregulation in response to elevated blood pressure in diabetics, even more so with hyperglycemia.

**Schemetter et al.** (18) showed that the sensitivity of the beta-adrenergic receptors of ocular vessels of diabetics is less than that of control subjects. LASER interoferometry was used. (18) Eyes (n = 214) were classified according to modified Airlee classification into 4 groups. They found that fundus pulsation amplitudes were significantly less in patients with proliferativce diabetic retinopathy (P < 0.027).

**Evans et al.** (19) studied retrobulbar blood flow velocities using color Doppler in 22 subjects, 11 of whom were diabetics with no or minimal diabetic retinopathy, and the other 11 were controls. They did so in normal air and also in hyperoxic conditions. They found that hyperoxia induced a significant change in the central retinal artery's end diastolic velocity in the control group. However in the diabetic group, this change was not appreciated. Also, the

resistance index in normals increased under conditions of hyperoxia.. They concluded that hyperoxia does reduce central retinal artery end diastolic velocity and increase resistance index in normal people and this change may not be seen in diabetics.(19)

**Patel et al**. (20) compared 24 controls with no diabetes with 76 patients who had diabetes. Among the diabetics, no retinopathy patients were 12, background diabetic retinopathy :27, pre-proliferative diabetic retinopathy :13, and proliferative diabetic retinopathy:12, and 12 were post pan retinal photocoagulation. When comparing non-diabetic and diabetic patients with no diabetic retinopathy, retinal blood flow was increased substantially in all stages of diabetic retinopathy untreated. They concluded that retinal blood flow is substantially elevated in subjects with diabetic retinopathy in comparison with normal subjects and diabetics without retinopathy.

**Mendivil et al.** (21) compared 25 eyes in 25 patients with proliferative diabetic retinopathy before LASER and 6 months and 12 months after pan retinal photocoagulation with a control group of 30 . The ophthalmic artery and central retinal vessels of all patients were eestimated. The systolic, diastolic, and mean arterial velocities were found. In both the ophthalmic artery and the central retinal artery, blood velocities were lower in the diabetics. Also, pan retinal photocoagulation significantly reduced blood flow velocities. As compared to controls, patients with proliferative diabetic retinopathy had lower ocular perfusion pressures. Those who received pan retinal photocoagulation continued to have lower blood flow velocities during the one year follow up in the study.

**Feke et al**. (22) used laser Doppler technique and monochromatic fundus photography to measure retinal circulatory parameters in 39 patients with type 1 diabetes with duration of diabetes between 7 and 20 years and 13 age-matched controls without diabetes. Blood pressure, intraocular pressure, and heart rate were measured in all subjects. Glycosylated hemoglobin was measured in the patients. Retinopathy was assessed using standardized color fundus photography and fluorescein angiography. They concluded that the retinal circulation of patients with type 1 diabetes with no retinopathy or background retinopathy is characterized by dilated major arteries with reduced blood speeds.

## Effects of diabetes on retrobulbar blood flow:

As the retina is supplied by the central retinal artery, we would expect some changes in the central retinal artery hemodynamics in patients with diabetes. **Guven et al.** (23) showed in seventy-three eyes in 37 patients with diabetes that the CRA maximum blood flow velocity levels were significantly higher in the pre-retinopathy group (9.8 +/- 2.1 cm/second) than in the non-PDR group (8.1 +/- 2.2 cm/second). Color Doppler imaging was used to quantitate peak systolic blood flow velocities of the central retinal artery (CRA). (n=37) In addition, the CRV maximum blood flow velocity levels were significantly higher in the pre-retinopathy group (5.7 +/- 0.9 cm/second) than in both the PDR group (4.8 +/- 1.5 cm/second) and the PRP group (4.9 +/- 1.7 cm/second)

**Goebel et al.** (24), using color Doppler imaging, studied 146 diabetic eyes, (61 proliferative, 59 non proliferative and 26 preproliferative retinopathy) and compared it with 126 eyes of 70 controls. He showed that proliferative retinopathy strongly correlated with decreased flow velocities in the retrobulbar vessels, mainly the central retinal artery. These findings only tell us that there is change in the retrobulbar blood flow. Whether these changes in the retrobulbar circulation are partly a cause of retinopathy or an effect of dysfunctional autoregulation is not clear.

## Choroidal changes in Diabetes- Diabetic choroidopathy:

In patients with Diabetes, the choroid undergoes changes which are not clinically picked up easily. These include an increase in the tortuosity of the vessels, localised areas of vascular dilatation and narrowing, presence of vascular loops and the formation of microaneurysms. Histological analysis of the human choroid shows areas of capillary drop outs and capillaries that are beaded. Fluorescein angiography showed delayed choroidal perfusion, and electroretinograms with abnormal oscillatory potentials in the same diabetic patients. (25)

Another study found that some of the risk factors for developing choroidopathy were the severity if diabetic retinopathy, degree of diabetic control and stringency of diabetic treatment regimen. (26)

## Studies on choroidal blood flow :

Upto 80% of the aerobic metabolism of the retina is supplied by the choroid.(5)( Retinal blood flow represents only about 4 percent of total ocular blood flow. The choroidal blood flow on the other hand ranges from 500 to 2000 ml/min/100g tissue. The mechanisms controlling ocular blood flow are of different types: systemic, local, neural, endocrine, paracrine.

Since the retinal and choroidal arterioles do not possess sphincters, blood flow in these tissues is only a function of the muscular tonus of the arterioles and possible the state of contraction of the pericytes. Vessels tonus is modulated by the interacted of multiple control mechanisms: myogenic, metabolic , neurogenic, and humoral, which are mediated by the release of vasoactive molecules by the vascular endothelium or by the glial cells surrounding the vessels.

We know that there is retinal autonomic dysregulation in diabetic retinopathy. We also know that the choroid is regulated by the autonomic nervous system. What has not been studied to a great extent though is whether there is any autonomic dysregulation of the choroidal blood flow in Diabetic patients. (9)

In normal individuals, the choroid has a linear relationship with the pulse pressures. This indicates a lack of autoregulation capacity of the choroid in response to increased pulse

pressures. In the choroid, an increase in arterial pressures causes the sympathetic nervous system to increase the peripheral resistance.(5)

Due to the recent advance in tools to measure choroidal blood flow, a great deal has been learnt about how the blood flow within the eye occurs and how it changes with various stresses in the body. POBF and OPA are indirect indicators of choroidal blood flow can be measured by techniques like laser interferometry, colour Doppler imaging, laser Doppler flowmetry and pneumotonometry.

**Polska et al** (23) found these various techniques reproducible in healthy individuals. Laser interferometry assesses fundus pulsation amplitude. Colour Doppler imaging assesses blood velocities in the ophthalmic and posterior ciliary arteries. Laser Doppler flowmetry assesses choroidal blood flow, volume, and velocity using fundus camera.

Pulsatile ocular blood flow (POBF) can be measured using the pneumotonometer (ocular blood flow) system. (28) During the measurement using the pneumatic applanation tonometer, the instrument assesses changes in the intraocular pressures caused by the cyclic filling and draining of the choroidal vessels. The maximum difference between the systolic and diastolic blood pressures during the cardiac cycle is called the pulse amplitude (PA).

Theoretically, POBF is measured from variation in intraocular pressures over time. This works on the basis that venous blood outflow from the eye is not pulsatile. Also, ocular rigidity is taken to be equal in all patients. The calculation of POBF is automatically taken from five pulsations which are most close in beat-to-beat variation. (28)

## Studies on POBF:

**Savage et al**. (29) conducted a study using the Langham pneumotonometry on patients with Non Proliferative Diabetic retinopathy. Out of the 77 diabetics, 13 had mild or no retinopathy, 36 had moderate to severe retinopathy and 28 had proliferative retinopathy. All patients with proliferative retinopathy had pan retinal photocoagulation (PRP). Patients with moderate to severe non-proliferative diabetic retinopathy (NPDR) had POBF which were 18% higher than the control group (mean ocular blood flow : 943 µL/min). IN post PRP patients, ocular blood flow was 22% below the control (mean ocular blood flow: 619 µL/min), and 34% less than the severe retinopathy group.

Diabetic patients with no retinopathy and those with mild NPDR had Ocular blood Flow which were indistinguishable from the control group (785 ul/min vs. 797 µL/min). He concluded that POBF is unaffected during the early stages in diabetic retinopathy, but gradually increases as the stages of retinopathy increases. He also found that the pulse ocular blood flow decreases after LASER pan retinal photocoagulation .(29)

**McKinnon et al**, (30) using a pneumotonometer - slit lamp arrangement, studied mean pulsatile ocular blood flow in patients with various stages of Diabetic retinopathy. Among the 82 patients studied, there were 22 controls, 20 diabetics with no retinopathy, 20 with background retinopathy, and 20 with non proliferative diabetic retinopathy. Compared to the control group, it was found that the pulsatile ocular blood flow was increased in all grades of retinopathy. The most significant of this was comparing controls versus those with background retinopathy ($p<0.05$). They also found that as the intensity of retinopathy increased, the POBF also increased. The mean pulsatile ocular blood flows were as follows: controls: 644ul/min; background retinopathy: 1015 ul.mim; no retinopathy: 818 ul.min; and preproliferative retinopathy 1097ul/min (30)

**Dimitrova et al.** (31) studied choroidal blood flow changes in diabetic patients with and without diabetic retinopathy . He used color Doppler imaging to study the end diastolic velocity and the resistance index. He found that in patients with Diabetic retinopathy, the end diastolic velocity significantly decreased (2.55+-1.08 cm/s vs 3.23+-1.08 cm/s) and the resistance index significantly increased (0.70+-0.08 vs 0.62+- 0.06) . Therefore, it was reemphasised that choroidal circulation was proven to be affected in patients with diabetic retinopathy.

**Langham et al.** (32) proposed that the cause for the decreased choroidal circulation in patients with Diabetic retinopathy was increased peripheral resistance and decreased ocular perfusion pressure.

**Nagoka et al** (33), using LASER Doppler flowmetry, determined the choroidal blood flow in the fovea of 70 patients with non insulin dependent diabetes Mellitus. There were also 36 controls. Out of the 70 patients, 33 had no Diabetes (NDR), 20 had non-proliferative retinopathy and no macular edema (NPDR-MO) and 17 had non proliferative retinopathy with edema at the macula (NPDR+MO). Foveal thickness was measured using Optical coherence tomography. They found that of all the groups, the group with NPDR with macular edema had significantly decreased choroidal blood flow compared to the controls. (13.5 vs 5.6 AU) further reiterating that choroidal blood flow is altered in diabetic retinopathy and more so in patients with macular edema.

LASER interferometry studies on fundus pulsation magnitude have been done and these fail to show any significant difference in choroidal blood flow in diabetics compared to normals. (18,34) **Guven et al**. showed that blood flow velocities in the arteries feeding the choroid are also changed by Diabetes. (23)

## Studies done on ocular pulse amplitudes:

**Schmidt et al**(25) studied OPA, using the Langham ocular blood flow (OBF) pneumotonometer system. Ocular pulse ampllitudes were measured in diabetic patients with no retinopathy (n=22) , non proliferative (n=24) and proliferative retinopathy (n=18). He found no significant difference in OPA between the sub groups and therefore concluded that the OPA does not change with the progression of retinopathy.

**Geyer et al.** (35)studied pulse amplitude (PA) and pulsatile ocular blood flow (POBF) using a pneumotonometer. Participants were grouped into 4 categories: normal controls (n=26), diabetes with no retinopathy (n=18), moderate non proliferative retinopathy (n=20) and severe non proliferative and proliferative retinopathy (n=12).

Results showed that there was an initial dip in the pulsatile ocular blood flow during early stages of Diabetic retinopathy and then in more severe stages, there was an increase in the pulse ocular blood flow.(35) Geyer observed that the ocular pulse amplitude was lower in diabetics with no retinopathy as compared to normal subjects and participants with documented diabetic retinopathy. They also found that the ocular blood flow increased as the progression of diabetic retinopathy increased. They hypothesized that the low POBF in the non-diabetic-retinopathy patients correlated with the histological features of chorio-capillaris degeneration and basal lamina deposits. In proliferative retinopathy, they hypothesise that the choroid also has an analogous condition- "Diabetic choroidopathy".

Geyer et al. showed the following in their study on OPA with the Langham OBF system. The pulse amplitudes were 2.8 , 1.8, 2.7 and 2.9 mm Hg in each of the groups controls, diabetics with no retinopathy, non proliferative diabetic retinopathy and proliferative retinopathy.

| | Control | NDR | NPDR | PDR |
|---|---|---|---|---|
| Number | 26 | 18 | 20 | 12 |
| Pulse amplitudes | 2.8 (1.0) | 1.8 (0.7) | 2.7 (0.8) | 2.9 (0.9) |
| Significance compared to ndr | P<0.001 | | P=0.55 | P=0.83 |
| Pulse ocular blood fow (ul/sec) | 13.7 (4.5) | 8.8 (3.4) | 11.7 (2.1) | 18.3 (3.8) |
| Significance compared to control | | P< 0.001 | P=0.054 | P=0.003 |

The above mentioned studies of on OPA, the OPA has been measured using the pneumotonometer. Dynamic contour tonometer (DCT) , a relatively newer instrument used to measure IOP can be also be used to measure OPA (more details elaborated later). To date there are no studies of OPA in diabetics as measured by DCT.

## Factors affecting ocular blood flow

### Effect of Pan Retinal Photocoagulation on ocular blood flow:

Pan retinal photocoagulation alters retinal and retrobulbar blood flow and these changes last for at least 2 years. There is also evidence that pan retinal photocoagulation has an affect on the choroidal circulation as there is destruction of the choriocapillaris. This theoretically can reduce the amplitude of the ocular pulse pressure.(20)(21)(29)(36)(37)

### Effect of age on ocular blood flow:

The blood flow into the eye decreases with age.(38) Also, the pulse ocular blood flow decreases as the intraocular pressures increase. (38) Having said that, in primary open angle glaucoma, the pulse ocular blood flow was shown to decrease. (39)

### Effect of gender on pulsatile ocular blood flow:

**Gekkieva et al.** (40) observed in their study comparing the ocular pulse amplitudes and ocular blood flow in men and women. They found significantly increased POBF (722.6 ±

152.8 in females versus 647.8 ± 1164.9 in males $p$=0.056) and OPA(2.3 ± 0.7 in females versus 2.0± 0.6 mm Hg in males) in females as compared to males.

**Ocular Blood flow and Hypertension:**

Blood pressures do not seem to affect the ocular pulse amplitude. (41) (42) These studies were done among normal subjects. They hypothesized that this lack of significant change in OPAs were due to the regulatory mechanisms of the baroreceptors in the carotid system before blood reached the choroidal circulation.(41) Also, in another study, they found that the presence of Hypertension altered the choroidal circulation, influencing any results that may be interpreted based on ocular pulse amplitudes in Diabetics with HYpertension. They found that in the presence of Hypertension, the choroidal blood flow increases in patients with Diabetes as compared to patients without Hypertension.(43)

**Ocular blood flow and pulse amplitude studies in India:**

The Ocular pulse amplitude has not been studied extensively within the Indian population. In New Delhi, **Agarwal et al**. found that the pulse ocular blood flow in normal Indian individuals was higher than that of the Caucasian population(7) 95 normal subjects were selected. 41 males and 54 females. The pneumotonometer OBF system was used for all the measurements. The mean pulse amplitude obtained among the normal subjects was **3.4±1.46 mm Hg.**

There is no published data on the normal range of ocular pulse amplitudes among the Indian subcontinent, nor any on the ocular pulse amplitudes of diabetic patients using the Dynamic Contour Tonometer. With this study we aim to document the above in the context of the Indian subcontinent.

**Ocular pulse amplitudes in Glaucoma:**

The variations of OPA in glaucoma has been well studied. Most studies show that there is a reduction in the ocular pulse amplitudes in patients with primary open angle glaucoma. (44)

In normal eyes in which the intraocular pressures were mechanically raised, with the raise in Intraocular pressures, the ocular pulse amplitudes increase. There is a direct relationship between the ocular pulse amplitudes and the ocular rigidity. (45)

**Relationship of ocular pulse amplitudes and axial length:**

Similarly, the variations of OPA in normal subjects have shown that OPA varies with the axial length of the eye. (46)(47) Kaufmann showed a negative correlation between OPA and axial length (0.27 mm Hg/1 mm of length; $P<.001$) (48)

**Ocular pulse amplitudes in Retinitis Pigmentosa patients:**

OPA measures by the ocular blood flow system showed a significant decrease in the OPA with increasing severity of Retinitis Pigmentosa. (49) The study was done to see if there was

a decrease in choroidal perfusion in patients with increasing severity of Retinitis Pigmentosa. Therefore, in the conducted study, patients with Retinitis Pigmentosa were not selected to be enrolled in the study.

**Ocular pulse amplitude in patients with age related macular degeneration:**

In early ARMD, there is an increase in the choroidal blood flow, and in advancing severity of age related macular degeneration, there is a reduction in the choroidal blood flow and volume. (34)

**Mori et al**. (50) in their work showed that the POBF and PA are reduced in patients with exudative type of age related macular degeneration (AMD) in comparison to normal controls and those with dry age related macular degeneration. They recruited 10 patients with dry AMD, 11 patients with exudative AMD, and 69 normals matched for age. The significance of difference in pulse amplitudes between the exudative AMD group (PA=1.2 mm Hg) and non-exudative AMD (PA=2.2mm Hg) was p= 0.04. Similarly, the significance of difference between the exudative AMD group and the controls (PA= 2.0mm Hg) was p=0.01. They concluded that the decrease in choroidal blood flow may have a pathophysiological role in developing exudative age related macular degeneration with neovascularisation.

**Ciulla et al.** (51) analysed flow velocities using color doppler in several retrobulbar vessels in 2 groups of patients: those with non exudative AMD (n=25) and those with no AMD

(n=25). They found a trend toward reduced bulk ocular blood flow in patients with non exudative AMD as compared to normals. Therefore they concluded that choroidal perfusion is altered in even non-exudative AMD.

## Dynamic Contour Tonometry:

Dynamic contour tonometry (DCT) is a new non-invasive technique of checking the intraocular pressure. It also simultaneously measures the ocular pulse amplitude of the eye being studied. Ocular blood flow varies with systole and diastole. This pulsatile ocular blood flow (POBF) shows a peak during systole. The difference in the minimum and maximum values of the pulsatile wave contour during systole and diastole gives us the ocular pulse amplitude (OPA). The OPA is an indirect indicator of the choroidal perfusion.(42)(52)

The Pascal DCT is one such device which can be installed into the optical axis of a slit lamp. The tonometer head piece consists of a cylindrical head with a surface contour which comes

into contact with the corneal surface and becomes equal to the contour of the cornea when the pressures on both sides are equalized. The sensitive part of the head is only $0.25mm^{2.}$

The Pascal software measures the intraocular pressure and its variation with every heart beat- the ocular pulse amplitude. The values are shown on an LCD display. The signals are stored in a computer via a wireless unit and the results are thus displayed and stored for further data analysis.

The intraocular pressures measured by the PASCAL dynamic contour tonometer are more accurate than the Goldmann applanation tonometer. The intra observer and inter observer variability was about 0.65 and 0.44 for the DCT and 1.11 and 2.38 mm Hg for the Goldmann applanation tonometer. This accuracy of the DCT can be accounted by the fact that the readings are electronic. (53) They also found that with DCT, the intraocular pressures reduced from the first to sixth readings. This is due to the repeated pressure over the eye as the readings are taken. Similarly, we suspect that there may be changes in the ocular pulse amplitudes of patients when repeated readings are taken, therefore an average of 3 readings are taken, with quality index 1 or 2. (54)

## Studies using dynamic contour tonometer:

**Kaufmann et al** (48) found a median value of ocular pulse amplitudes of **3.0mmHg** among the 223 eyes studied, ranging from 0.9 – 7.2 mm Hg. He observed that the following had no bearing on the ocular pulse amplitudes: central corneal thickness, corneal curvature, anterior chamber depth, age and sex. There was an association between intraocular pressures and ocular pulse amplitudes (0.12mm Hg for every 1 mm Hg in IOP) They also found that the OPA reduced with increased axial lengths (0..27mm hg for every 1 mm ).

**Hoffmann et al** described a mean ocular pulse amplitude value of **3.08± 0.92 mmHg**. (55) in his study in which Dynamic contour tonometry was used for measurement in a group of 19 eyes .

**Pourjavan et a**l (42), found a mean OPA of 2.2 +-0.7 mm Hg with a diurnal variation of 0.4 mm Hg in a prospective study with 52 eyes of 28 normal subjects. They found that there was no significant difference in the mean OPA levels at any time in the diurnal curve. Neither blood pressure nor age had a significant bearing on the readings of OPA.

To date there are no studies of OPA in diabetics as measured by DCT-. We conducted this study to look at the OPA in varying grades of diabetic retinopathy and if presence of hypertension could affect the OPA in these patients. Also, we conducted the study to have a

baseline in the ocular pulse amplitudes in this region in south India, the only other study of ocular pulse amplitudes being done in the north of India.

# Materials and Methods

**Study Design**: observational study

**Study population:**

1) Patients diagnosed to have diabetes in the Medicine/ endocrinology department of CMCH and referred to the Department of Ophthalmology, CMCH for evaluation for diabetic retinopathy.

2) Known diabetics and are undertaking treatment in the Department of Ophthalmology, CMC Vellore.

3) Patients who are not known diabetes who presented either to our outpatient facility or camp facility were screened for diabetes and were included in the diabetic/ no diabetic group as per the blood results (the inclusion criteria as given below).

**Institutional Review Board clearance:** The study was cleared by the institutional ethics and research committee of the Christian Medical College, Vellore. Ref. No: …… (appendix1)

**Location:** Department of Ophthalmology, CMC Vellore.

**Inclusion criteria:**

Patients were enrolled into the study if they belong to the following criteria:

1. **For group 1 (No DM)**, patients had no history of Diabetes or having taken medications for Diabetes in the past. TO confirm absence of Diabetes Mellitus, based on the American Diabetic Association guidelines for Diabetes diagnosis 2011 (49) . HbA1C levels were done for all patients that were enrolled for the study (HbA1C of more than equal to 6.5 mg/dl were diagnosed as diabetics). Therefore, All patients with A1C levels of < 6.5 mg /dl were selected under this group

2. **For group 2 (DM with no DR),** they required one of the following criteria before being enrolled into the study:

a. Chronic history of Diabetes, on oral hypoglycemic medications

b. Recently diagnosed Diabetics ( based on ADA guidelines)

3. **For group3 (DM with DR),** they required presence of diabetic retinopathy to be enrolled in to the study.

Hypertension was diagnosed based on the **Joint National Committee - 7 report** as patients who had blood pressure readings of more than equal to 140/90 mm Hg in two or more readings*.

**Exclusion criteria:**

1. Active retinal pathology other than diabetic or hypertensive retinopathy
2. Any intraocular surgery in the past 1 year in the eye chosen to be examined
3. No clear view to the fundus
4. History of cerebro-vascular event
5. History of connective tissue disorders and hematological disorders
6. Patients with proven glaucoma
7. Ocular hypertensives (those with corrected intraocular pressures more than 24mm Hg)
8. Suspicious discs (suggestive of glaucoma)
9. History of any chronic topical ocular medications being used.
10. Corneal disease which prevents DCT measurement.

In addition , presence of HbA1C>6.5 mg/dl was an exclusion criteria for group 1 (No DM)

.

# Methodology

Participants who consented to take part in the study were divided into 3 sub-groups based on their clinical presentation: No diabetes (No DM group) , Diabetics with no retinopathy (DM with no DR group), Diabetics with retinopathy (DM with DR group). For each patient, the right eye was chosen by default unless the right eye had a contraindication for the same.

Patients without Diabetes (No DM) were mostly in-patients who were planned on being operated for cataract surgery the following day. For all patients without Diabetes, blood was sent for serum HbA1C levels on the same day, irrespective of whether an AC/PC was done in the recent past. Blood samples were taken in the ward for the admitted patients by trained nursing staff or by the primary investigator. For the few patients who were selected with consent from the outpatient department, blood was withdrawn at the laboratory in the Eye Hospital, CMC Vellore. All the blood samples were tested in the Biochemistry Laboratory under the Department of Biochemistry, CMC Hospital Vellore.

Funding for the blood test was by the research fund. A/c no 22X873 (appendix) Patients who were found to have HbA1C levels above 6.5 were discontinued from the study.

Patients with Diabetes, with or without retinopathy were approached through the out-patient department in the Eye Hospital, CMC Vellore.

Diabetic patients (with or without Diabetic retinopathy) were identified by doctors in the outpatient department and referred to the principal investigator for further evaluation after orienting each patient briefly on what the study involved.

The patients were then explained in detail about what the study involved, the minimal risks involved, and the possible benefits from the study. If they were willing for the same, they were recruited.

Having given consent for participation in the study, the participants again underwent a dilated fundus examination by the principle investigator using a 90 D condensing lens assisted by a Haag Streit slit lamp in order to confirm absence of exclusion criteria. This also enabled uniformity in the protocol in checking ocular pulse amplitudes after dilatation, as there are possible effects of mydriatics on the autonomic regulation of blood flow within the eye.

Patients with Diabetic retinopathy were classified based on the modified Airlee staging standard photographs into mild , moderate, severe and very severe non proliferative diabetic retinopathy and proliferative diabetic retinopathy.

Based on the clinical findings, patients underwent OCT and FFA where indicated based on the protocol followed in the department of Ophthalmology, CMC Vellore.

Once all the exclusion criteria were eliminated, the patients underwent blood pressure measurements by trained staff in the department of Ophthalmology. Blood pressures were checked in the sitting position, after 10 minutes of waiting, in the right arm, except in those who had a contraindication for the same. The BP cuff and the sphygmomanometer were placed approximately at the level of the heart.

If the blood pressures were recorded to be more than equal to 140/90 mm Hg, they were rechecked after an hour. If the blood pressures were still more than 140/90 mm Hg , the patients were either referred to department of Medicine, CMC Vellore (if affordable) or the Low Cost Effective Care Unit CMC Vellore, for further management.

Once all the exclusion criteria were eliminated, patients underwent Ocular Pulse Amplitude measurements using the PASCAL Dynamic Contour Tonometer after entering preliminary information about the patient on the proforma sheet.(appendix2)

Once the PASCAL DCT unit was attached to the Haag Streit slit lamp, a drop of topical paracaine 1% was instilled. Having confirmed that the patient was comfortably seated and not straining to place his or her chin on the chin rest, the head was kept leaning on the head rest. The sensor tip of the DCT unit was then brought close to the cornea, with the patient fixing on a target straight ahead with the left eye. A darkened area in the centre of the sensor tip cover (approximately half of the diameter of the visualised sensor tip area) represented the area in contact with the eye. Visualisation was with the left eye piece, using the right eye of the observer.

3 values of either quality score 1 or 2 were taken and entered in the proforma (appendix 2). Intraocular pressures (which were automatically displayed on the screen along with the Ocular Pulse Amplitude values) were also noted down to confirm absence of ocular

hypertension, which has been hypothesised to affect the pulse ocular blood flow and therefore the ocular pulse amplitude.

The measured data was then transferred to a devoted computer via a blue tooth device.
All the ocular pulse amplitude readings were taken by the principal investigator.

Contact details were not obtained for all patients as they did not require follow up visits. As all the patients examined had a CMC hospital number, the Patients who were found to be Diabetic based on HbA1C levels were advised to get an OPD check up in the Low Care Effective Care Unit/ department of general medicine or Endocrinology, Christian Medical College Hospital Vellore.

Each proforma was stored in a file for future reference with date. Age and sex were documented along with the date of testing. History of Hypertension and whether on medications was also noted. The details of medications which the patients was on was also noted as some antihypertensives had a intraocular pressure lowering effect and therefore may have had an effect on the ocular pulse amplitude.

**Sample size calculation**:

Based on results of Orna- Geyer et al,(35) on ocular blood flow and ocular pulse amplitude using pneumotonometry, there was a significant difference in ocular pulse amplitudes

between diabetics with no retinopathy and normals. Non proliferative and proliferative retinopathy did not show to have any significant difference from the normal mean. They found a mean difference of 1.0 between the normal (2.8 mm Hg; SD=1.0) and diabetics with no retinopathy (NDR= 1.8 mm Hg; SD 0.7).

Taking this data, with alpha error of 5% and power of 80%, we calculated the sample size required in each subgroup and found it to be 12. We then decided to club all diabetic patients that showed some features of Diabetic retinopathy into one group, diabetics with no retinopathy into another and lastly having the normal as the third group.

50 participants in each group would be adequate to get accurate inferences while doing univariate analysis. Also, this would ensure that atleast 12 patients with mild, moderate, severe non proliferative and proliferative retinopathy were in the Diabetics-with-retinopathy arm. We thought that these numbers (three times the required sample size in each arm) would be sufficient to analyse any new subgroups which we may observe during the course of the study.

The sample size was calculated based on **hypothesis testing for 2 means**, using the formula:

$$n = 2sp^2[Z_{1-alpha/2} + Z_{1-beta}]^2 / u_d^2$$

**Where** $s_p^2 = (s_1^2 + s_2^2) / 2$

$\mathbf{S_1^2}$ : standard deviation in the first group

$\mathbf{S_2^2}$ : standard deviation in the second group

$\mathbf{U_d^2}$ : mean difference between the samples

**Alpha**: significance level

**1-beta**: power

In the analysis, all data was analysed using SPSS software version 20.0, along with Microsoft Excel 2010. To assess the clinical significance of each statistical question asked, t-test for equality of means was used.

# Results

The total number of participants included in the study was 172. 3 Patients, who were screened to be selected in the No DM arm, who were found to have raised HbA1c (>6.5 mg/dl) were taken out of the study and referred to Department of Medicine, CMC Vellore.

4 patients enrolled were not able to sit by the slit lamp for the period of time required and therefore the quality index was not 1 or 2 in these participants. Therefore, they were taken out of the study.

One of the patients had a neck ailment and mechanically found it difficult to place her chin on the chin rest on the slit lamp. Though not mentioned in the criteria, she was not selected in the study for obvious reasons.

3 patients refused to undergo blood tests to confirm absence of Diabetes. All three were women. Two of them felt that they were too anaemic for blood tests and the third did not want to be poked repeatedly after the trained nursing staff failed to get a vein in two attempts. Therefore, these 3 women were not included in the study.

**Mean OPA among patients with no Diabetes or Hypertension:**

The total number of patients with no Diabetes group was 53. The mean ocular pulse amplitudes in this group was 2.83± 0.94 . This represents the ocular pulse amplitudes among the "normal" population, with no systemic illnesses.

**Gender-wise number of patients:**

Out of these 172, the number of males were 83 and the number of females were 89. All the patients were from South India. One patient was originally from West Bengal but was living in Vellore during examination.

**Figure No.1 Gender distribution**

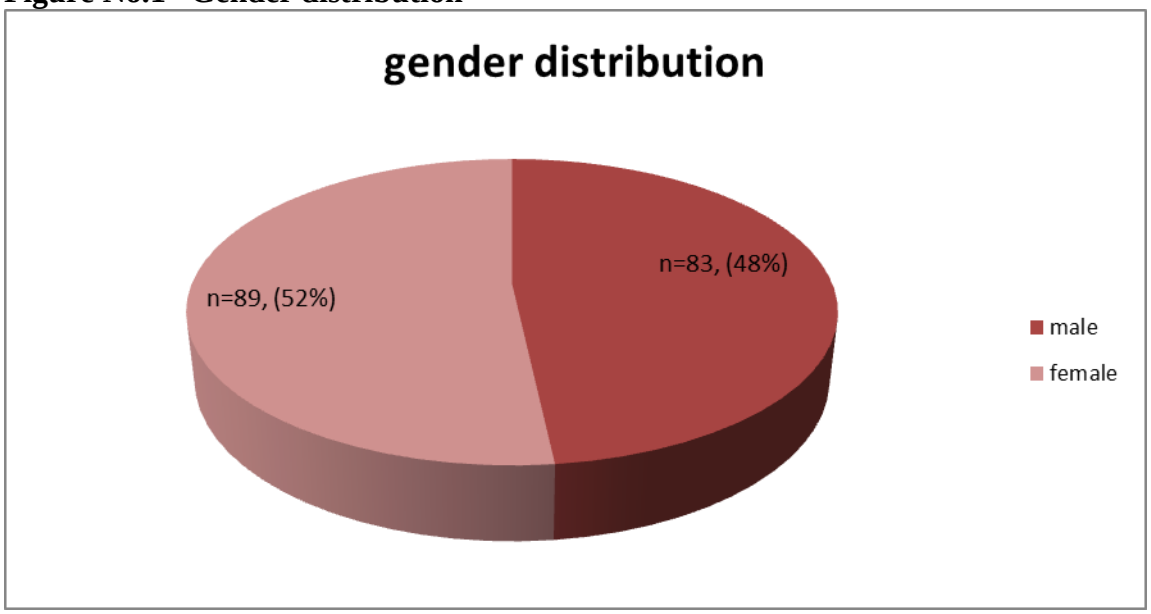


**Table No.1: Comparison between OPA of males and females**

| sex | N | Mean OPA ± SD |
|---|---|---|
| Male | 83 | **2.65 ± 0.96** |
| Female | 89 | **2.60 ± 0.95** |

**OPA in mm Hg.**

The mean OPA of men was 2.647 and for women was 2.60. It failed to show a significant difference in OPA with **p=0.769** .

Subgroup analysis was done comparing significance of difference between mean OPA among men and women. None of the 3 sub-group analysis had any significant difference. (Table No.2)

**Table No.2: Comparison of males and females in various subgroups**

| **No DM** | **number** | **Mean OPA± SD** | **T-test significance (comparing males and females)** |
|---|---|---|---|
| males | 29 | 2.63±0.90 | |
| females | 24 | 3.05±0.94 | 0.12 |
| **DM NO DR (n=66)** | | | |
| Males | 22 | 2.68±0.96 | 0.15 |
| females | 44 | 2.46±0.73 | |
| **DM +DR (n=53)** | | | |
| Males | 32 | 2.31±0.88 | |
| Females | 21 | 2.87±1.34 | 0.069 |

**Age wise distribution:**

The age of patients enrolled in the study ranged from 40 to 79 years. The decade wise distribution of participants is shown in Figure 2. Majority of the patients were in the $5^{th}$ decade with almost similar number s in the $4^{th}$ and $6^{th}$ decade. There were only 5% of participants in the 71- 80 year age group. The graph below shows the distribution of the number (in absolute numbers) of participants in each group.

**FigureNo.1b. age wise distribution of patients**

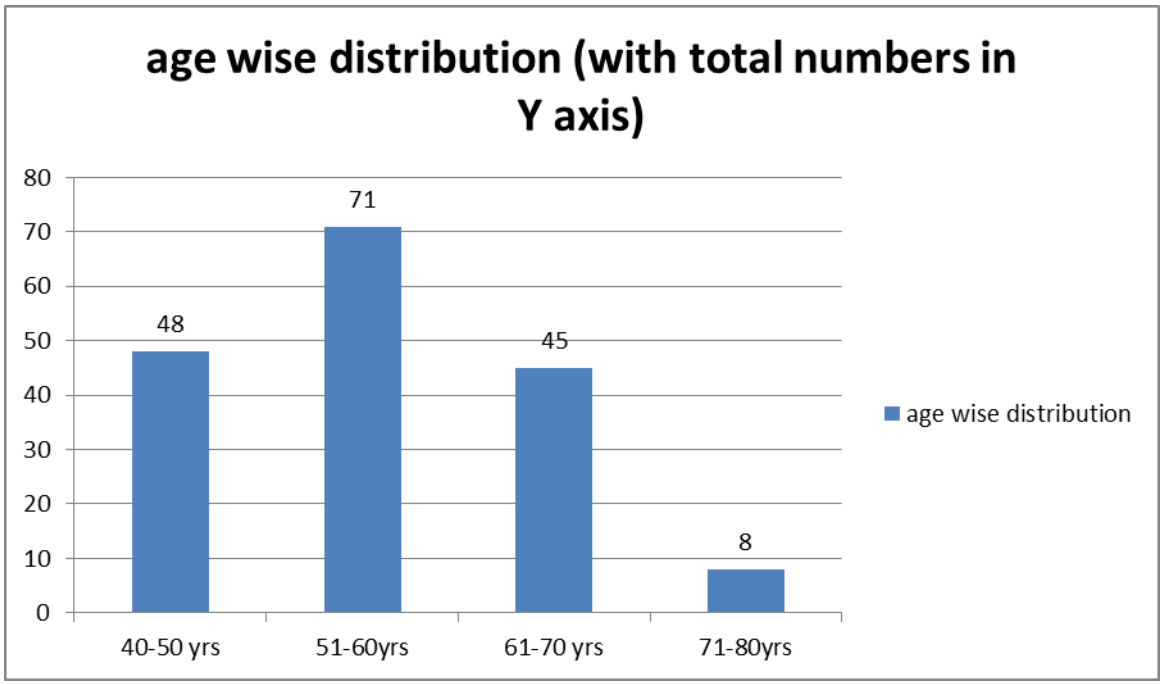



**Table No. 3: Mean OPAs among patients grouped by decade**

| Age yrs | number | Mean PA ± SD |
|---|---|---|
| 40-50 | 48 | 2.63±1.07 |
| 51-60 | 71 | 2.60±0.89 |
| 62-70 | 45 | 2.62±0.90 |
| 71-80 | 8 | 2.84±1.19 |
| mean | 172 | 2.63±0.95 |

OPA in mm Hg.

The mean OPA was almost the same in all the groups being considered. The mean OPA among the 172 population considered was 2.625. We took the subgroup 71-80 and cross tabulated with the mean OPA to see if the difference was significant. There was no significant difference seen ; **p= 0.54.**

**Table No. 4: Significance of difference in OPA between groups based on age**

| | Sum of Squares | Df | Mean Square | F | Sig. |
|---|---|---|---|---|---|
| Between Groups | .405 | 3 | .135 | .146 | .932 |
| Within Groups | 155.413 | 168 | .925 | | |
| Total | 155.817 | 171 | | | |

ANOVA was done to see if there was any significant difference between any of the sub groups. The table above shows the same. The test failed to show any significant difference between the four groups. P=0.932

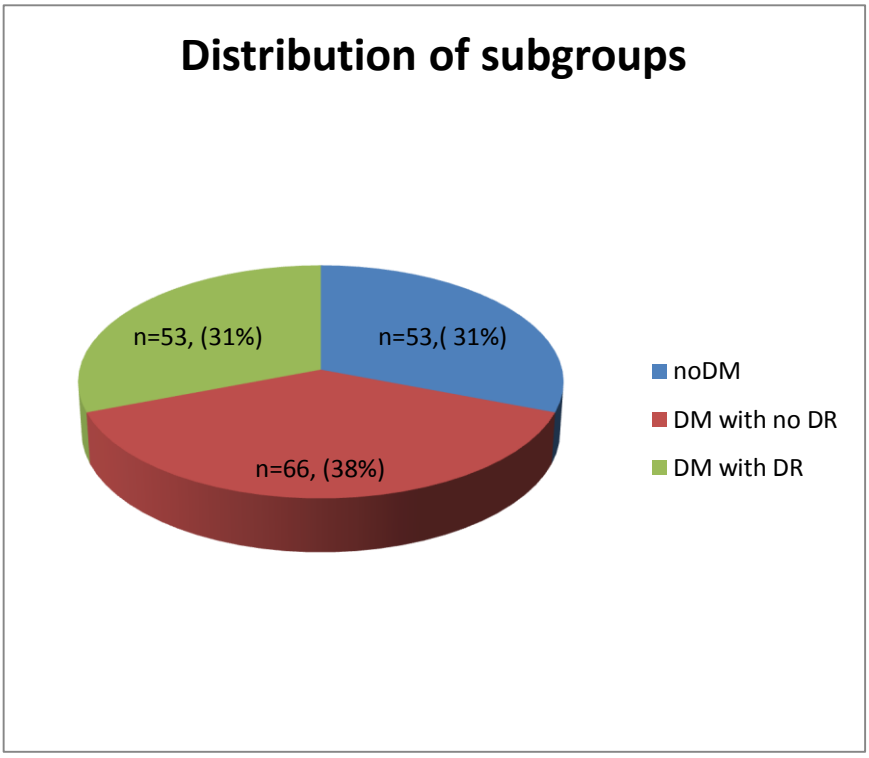
## SUB GROUP ANALYSIS:

**Analysis between the 3 major sub groups:**

As described in the methodology, there were 3 subgroups that we had selected. Group 1 was No DM, group2 DM with no DR, and Group 3, DM with DR. Given below is the distribution of these 3 subgroups.

The No DM group had 53, the group with DM and No DR had 66 and the DM with DR group had 53. The study criteria was to select a minimum of 50 participants per sub group, which was achieved. These groups formed 31%, 31% and 38% respectively.

**Figure No. 2 Percentage of patients without DM, with DM and no DR, with DM and DR**




In the DM with DR subgroup, Diabetics were further divided into 3 groups based on the severity of the retinopathy: mild diabetic retinopathy, moderate retinopathy and severe non proliferative retinopathy and proliferative retinopathy.

**Table No.5: Analysis between the 3 major subgroups**

| | **number** | **Mean OPA ± SD** | **t-test (compared to controls)** |
|---|---|---|---|
| No DM | 53 | 2.83 ± 0.94 | |
| DM no DR | 66 | 2.54 ± 0.81 | 0.068 |
| DM and DR | 53 | 2.53 ± 1.11 | 0.13 |

**OPA in mm Hg.**

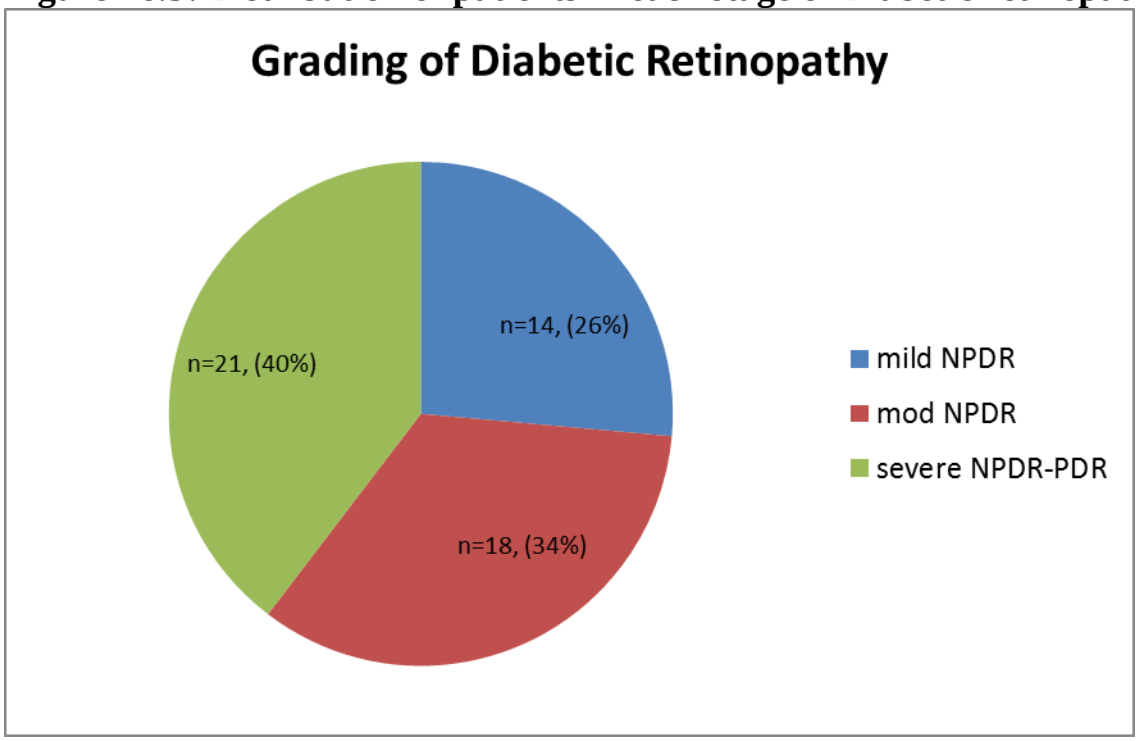
**Comparison of the groups DMnoDR with DM+DR:**

There was no significant difference between the two groups. P= 0.972 .

**Distribution of patients in each stage of Diabetic retinopathy:**

Out of the 53 in the Diabetics with retinopathy arm, 14 were with mild non proliferative diabetic retinopathy, 18 with moderate retinopathy and 21 with severe non proliferative and proliferative diabetic retinopathy.

**Figure no.3: Distribution of patients in each stage of Diabetic retinopathy**




The average Ocular pulse amplitude among the 3 groups are as shown:

**Table No.6: Mean OPA of patients in various stages of retinopathy**

| **Group** | **number** | **Mean OPA± SD** | **t-test (compared to controls)** |
|---|---|---|---|
| No diabetes (controls) | 53 | 2.83 ± 0.94 | |
| Diabetes with no retinopathy | 66 | 2.54± 0.81 | |
| Mild NPDR | 14 | 2.70± 1.51 | 0.69 |
| Moderate NPDR | 18 | 2.66± 0.93 | 0.50 |
| Severe NPDR , PDR | 21 | 2.31± 0.95 | 0.034 |

OPA in mm Hg.

There was a significant decrease in mean OPA in those with severe pre-proliferative and proliferative diabetic retinopathy.

**Comparison of LASER therapy on values of OPA among severe NPDR- PDR groups:**

Out of the 21 patients with severe non proliferative + proliferative diabetic retinopathy subgroup, 11 had had no LASER therapy and the rest of the patients had LASER .

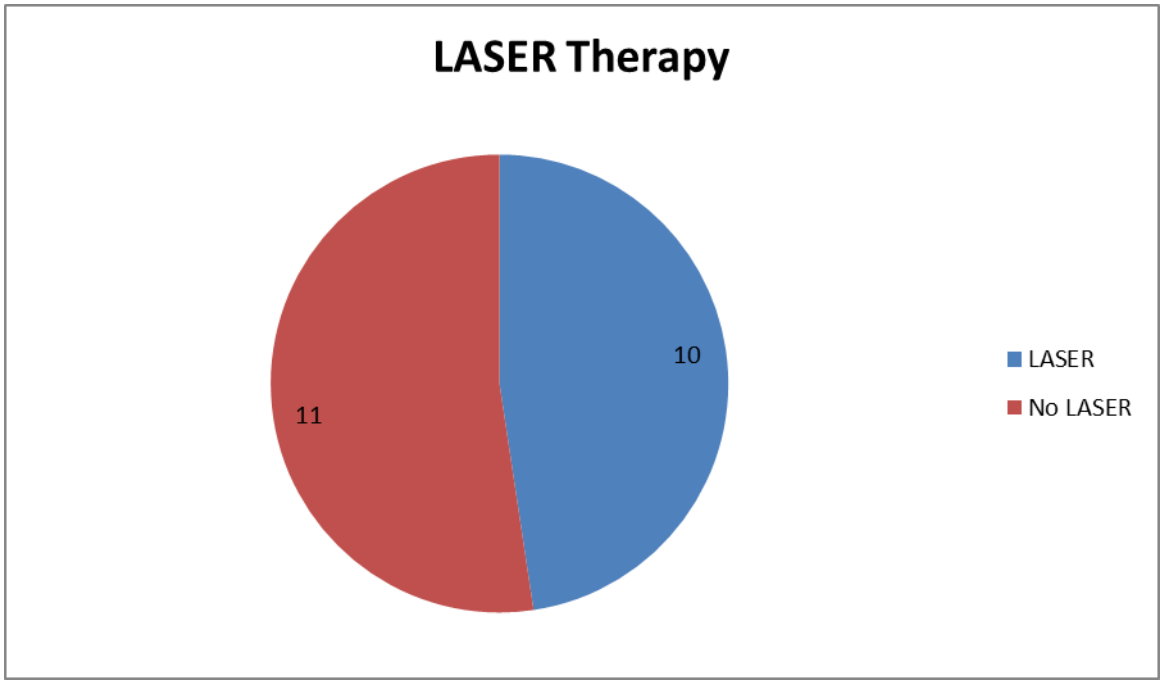



Figure NO.3b Subgroup severe NPDR, PDR – history of LASER therapy

**Table No.7: Comparison of patients with and without LASER in patietns with severe NPDR/** PDR

| Severe NPDR/PDR | n | Mean OPA* ± SD |
|---|---|---|
| No LASER | 11 | 2.33 ± 0.86 |
| LASER | 10 | 2.28 ± 1.09 |

*OPA in mm Hg

## Hypertension among Non-Diabetics and Diabetics:

Though Hypertension was not an exclusion criteria for selection of participants with no Diabetes, it was found that patients with Hypertension without Diabetes were very few. Also, there were 2 patients in whom Diabetes was found on doing HbA1c , both of whom claimed that they had Hypertension but no Diabetes.

The pie chart illustrates the point that the total percentage of patients with Hypertension but no diabetes was rare.

Out of the 53 non diabetics, only 5 were Hypertensives with documented absence of Diabetes. This formed only 8% of the total Hypertensives in this subgroup.

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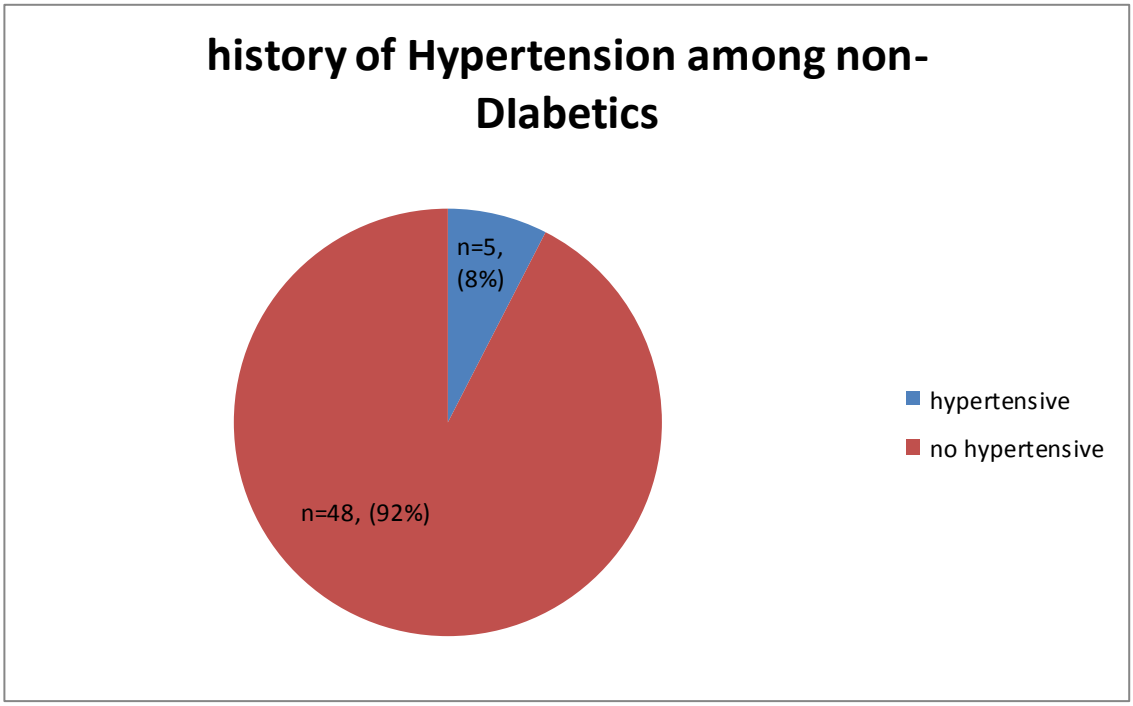
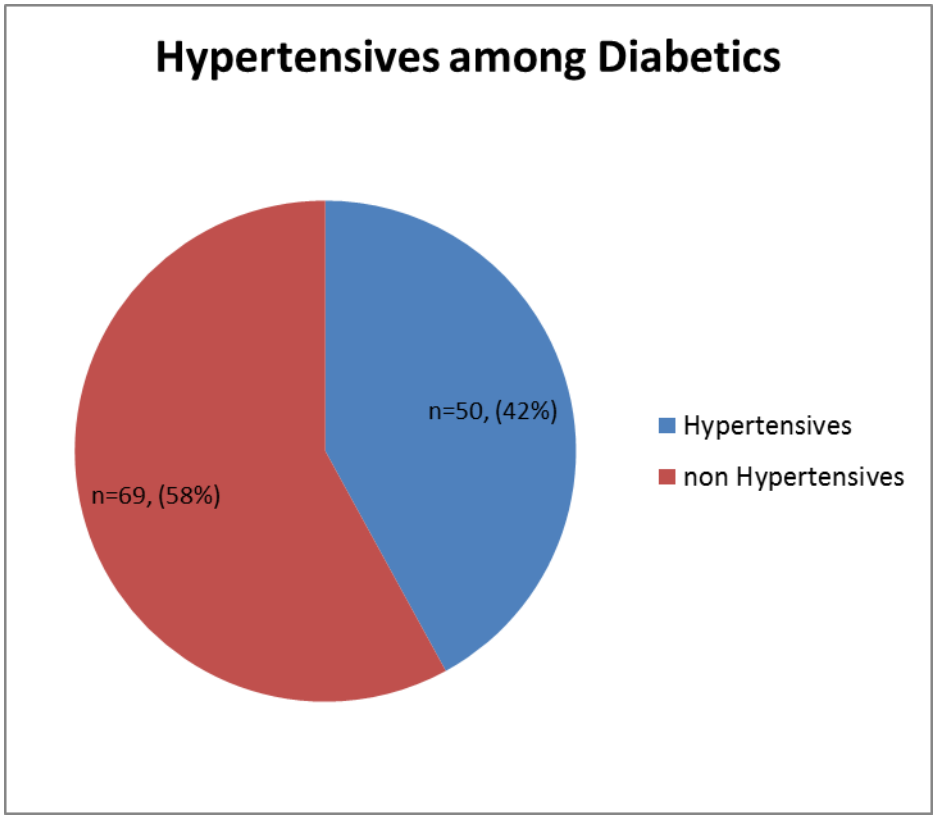
**Figure no.4 Percentage of non diabetics with Hypertension**



On the other hand, out of the patients with Diabetes, 42% had Hypertension, all of them were on medications. The rest of them underwent blood pressure checks and were found not to be Hypertensives. The method of blood pressure measurement has been described under methodology.

**Figure no. 5 Percentage of Hypertensives among Diabetics**



Among the diabetic patients who had retinopathy, lower OPA was found in those patients who had no hypertension as compared to those who were hypertensive. (p= 0.05). It was significantly lower OPA as compared to controls as well. (p=0.02 )

The OPA in the various categories of patients in the presence and absence of hypertension is depicted in table 8

**Table No.8: Comparison of Hypertension among various subgroups:**

| | **N(number in each category)** | **Mean OPA`± SD** | **t-test analysis** |
|---|---|---|---|
| No DM , No HTN | 48 | 2.80 ± 0.91 | |
| No DM, HTN + | 5 | 3.14 ± 1.18 | 0.44 |
| DM , No HTN | 69 | 2.40 ± 0.93 | |
| DM , HTN + | 50 | 2.73 ± 0.96 | 0.06 |
| DM , no DR, HTN+ | 30 | 2.61 ± 0.67 | |
| DM, no DR, no HTN | 36 | 2.48 ± 0.91 | 0.53 |
| DM, DR+, no HTN | 33 | 2.30 ± 0.95 | |
| DM, DR+, HTN+ | 20 | 2.90 ± 1.28 | 0.056 |

**OPA in mm Hg.**

## Type of anti Hypertensives taken by those with Hypertension:

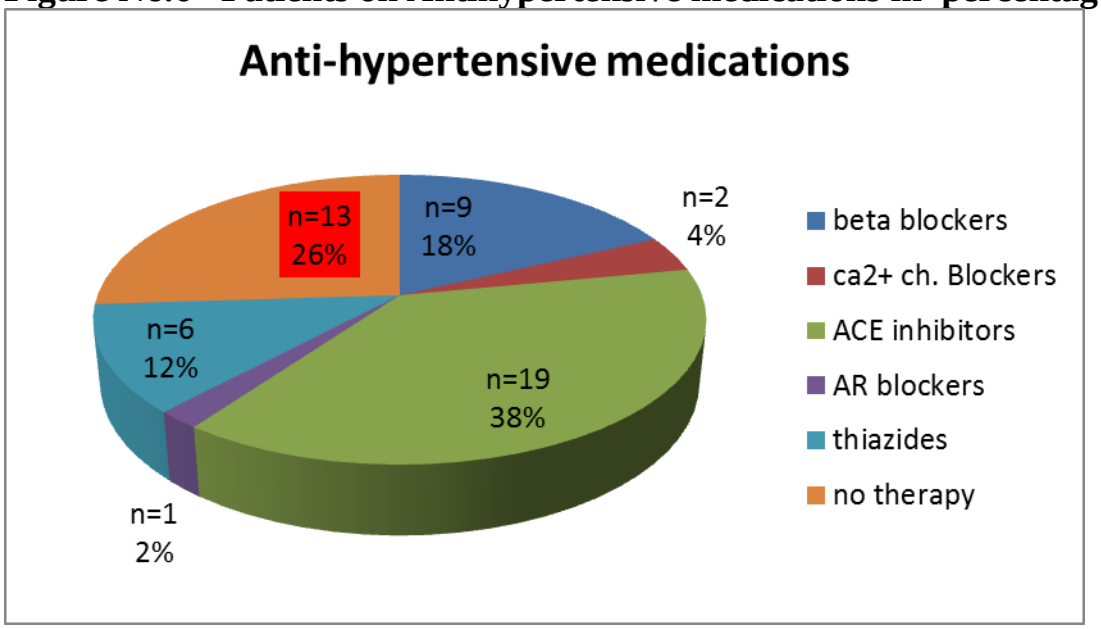
Anti-Hypertensive medications taken by these patients were also documented. All the patients were only on one antihypertensive. The results are as follows:

## Table No. 9: Antihypertensive medications

| **Antihypertensive Medications** | **Number** | **Percentage among Hypertensives (%)** |
|---|---|---|
| Beta Blockers | 9 | 18 |
| Calcium channel blockers | 2 | 4 |
| ACE inhibitors | 19 | 38 |
| Angiotensin Receptor blockers | 1 | 2 |
| thiazides | 6 | 12 |
| No documented Rx | 13 | 26 |

The above table shows a significant percentage of patients who were not on treatment despite being on medications for Diabetes and knowing that they had Hypertension. It was beyond the scope of the study to determine why these participants were not on antihypertensives despite knowing they had Hypertension.

**Figure No.6 Patients on Antihypertensive medications in percentages**




The numbers were not adequate to compare between Hypertensives with various antihypertensives. ANOVA done with the above data showed a significance of only 0.159.

**Table No.10: Mean OPA among Hypertensives on antihypertensives**

| **Antihypertensive used** | **N** | **Mean OPA ±SD** |
|---|---|---|
| Beta blockers | 9 | 2.31±0.46 |
| Calcium channel blockers | 4 | 2.16±0.99 |
| ACE inhibitors | 19 | 3.10±0.75 |
| Angiotensin receptor blockers | 1 | 3.57 |
| Thiazides | 6 | 2.60±0.88 |
| No documented therapy | 11 | 2.59±0.39 |

ACE inhibitors trended to show increased ocular pulse amplitudes as compared to the other antihypertensives used.

# DISCUSSION

Various ocular perfusion abnormalities at micro and macrovascular levels as well as defects in autoregulation occur in diabetics. Changes in the retinal capillary endothelium and pericytes, causing various manifestations of diabetic retinopathy have been well established. Choroidal changes have also been documented in diabetics(26,4)

Different studies on ocular blood flow and OPA have shown varying results. The varied results could be due to

1) the different methods used to study the ocular blood flow. It is possible that some methods measure the flow in the smaller choroidal vessels and some probably measure the flow in the larger choroidal vessels.

2) The fact that the POBF could vary with the duration of diabetes, with diabetics of shorter duration having higher POBF as compared to those with longer duration of diabetes.

This could explain the varied results of POBF in the category of patients with DM but no DR with some studies showing no change (49)and other studies showing decreased blood flow (32,35). 3) Acute changes in the blood sugar levels can lead to varied ocular blood flow. **Bursell et al** found that acute hyperglycemia resulted in increased retinal blood flow in diabetics with no retinopathy.(57) 4)

Most studies of ocular blood flow and OPA in diabetics have not looked at the confounding effect of co-existing hypertension. Hypertension causes increased retinal perfusion pressure

as well as altered choroidal perfusion. Whether this will result in increased OBF will depend on the extent of change in the intraocular vessels, both choroidal and retinal, as well as the state of the general circulation. Simple extrapolation of haemodynamic principles make it possible to theorise that increased blood pressure could result in increased tissue blood supply or, paradoxically, a decreased blood supply when the vessels are grossly narrowed. Thus, the effect of hypertension on ocular blood flow can be highly variable and dependant on individual factors in the local circulation which may not be possible to measure and assess.

In our study, the mean OPA in the control group (non-diabetic, non-hypertensive , n= 48) was 2.80 ± 0.91 mm Hg which is comparable to the OPA as measured by DCT in other studies- **Kaufmann et al**(53) found a median value of **3.0mmHg,** ***Hoffmann et al*** (55) **3.08± 0.92 mmHg among normals.**

Though some studies have shown a gender difference in OPA (39,40) , in our study the mean OPA was similar in males( n= 83; **2.65 ± 0.96 mmHg)** and females (n= 89; **2.60 ± 0.95 mmHg) [ p=0.77]** . Notwithstanding this, we looked for any difference in the distribution of males and females in the three subgroups (No DM, DM without DR, and DM with DR) since it could have a confounding effect on the results. There was no statistically significant difference in any of the three subgroups($p > .05$ in all three subgroups). (Table no. 2)

The age of patients included in our study ranged from 40 to 79 years with fewer patients (5%) in the $7^{th}$ decade(fig. 2 ). This was because many patients in this age group had dense cataract

which precluded a clear view to the fundus, and hence were excluded or because some of them could not cooperate for examination.

The OPA was similar in the three subgroups Group1: no DM ( 2.83 ± 0.94mmHg), Group 2: DM no DR( 2.54 ± 0.81 mmHg) , Group 3: DM + DR ( 2.53 ± 1.11 mHg).

Some studies (32,35) have shown a decrease in POBF and OPA in patients with diabetes without retinopathy as compared to controls whereas few other studies(29) (49) have shown no difference. Our study did not show any difference in the OPA between these two groups ( p=0.07).

There was no difference in OPA between controls vs those with retinopathy (p= 0.13). However, on further comparing the OPA of the subcategories of mild NPDR, moderate NPDR, severe NPDR + PDR with the control group (no DR), there was a statistically significant difference (p=**0.034** ) in the OPA between the severe NPDR+PDR group of patients compared to the controls. The OPA was lower (2.31**± 0.95 mmHg)** in the advanced stages of retinopathy compared to the controls (2.83 **± 0.94 mm Hg)** indicating compromised perfusion in this category of patients.

A few studies (21,32) have reported similar results whereas other studies have reported no difference(11,49). Confusingly, a few other studies have shown increased retinal blood flow, POBF and OPA (20,22,30,35) in patients with PDR not treated with laser and decrease in retinal blood flow, POBF and OPA in PDR patients treated with laser .(20,21,29,37)

In our study in patients with severe NPDR or PDR (n= 21), 10 had received laser. We analyzed the OPA in the laser group (n=10) vs the no laser group (n=11) and found no difference in the OPA (p= 0.913 ). Both the laser group (2.28 ± 1.09 mmHg ; p= 0.13) and the no laser group (2.33 ± 0.86 mmHg; p= 0.12 ) had lower OPA compared to the control group (2.80±0.91 mmHg ). However the number in each category was small reducing the power of the study.

Since hypertension can cause changes in ocular perfusion, we looked at the OPA in patients with and without hypertension. In the group of patients (n= 53) with no diabetes, only 8% (n=5) were hypertensives. Due to this uneven distribution of hypertensives and non-hypertensives, the evaluation of the effect of hypertension on OPA in non-diabetics was not possible.

On the other hand, among the diabetics, 42% were hypertensives. Presence of hypertension did not show any statistically significant difference in OPA in diabetic patients with no retinopathy. However in diabetics with retinopathy, absence of hypertension was associated with lower OPA (**2.30 ± 0.95mm Hg )** as compared to those had hypertension (**2.90 ± 1.28mm Hg )** which trended towards statistical significance (p=0.056). **Esgin et al**. (43) reported similar findings of reduced POBF and OPA in diabetics without hypertension as compared to controls.

It would have been ideal to evaluate the difference in OPA in hypertensives and non-hypertensives under each category of retinopathy. However this would have required much larger number of patients under each category of retinopathy. The small sample size under each category was a limitation of our study. Similarly, a much larger sample size would be required to evaluate the possible effects of various anti-hypertensives on the choroidal blood flow as evaluated by the OPA.

It is, however, interesting to speculate that the large numbers of hypertensives in our study population with the unpredictable effect of HT on OPA as discussed earlier may have contributed to the different results we obtained compared to the quoted literature. Ideally, we need to perform this study on persons without HT, but this is not logistically feasible owing to the high association of DM and HT.

In our study we found the OPA is reduced ($p=0.03$) in the severe NPDR and PDR group indicating significant reduction of choroidal perfusion occurring in the advanced stages of retinopathy. The no DR, mild and moderate NPDR categories showed mean ocular pulse amplitudes less than the normals, though not statistically significant. This indicates probable progressive decrease in choroidal blood flow with increasing severity of retinopathy which is in keeping with the progressive pathology.

Studies have noted initial decrease (32,35) in POBF in the diabetics with no retinopathy and subsequent increase in POBF in PDR(30,35) .Increased blood flow has been attributed to increased bulk blood flow demands induced by tissue hypoxia (11,13). On the other hand,

Geyer etal (35) attributed the increased POBF in patients with severe diabetic retinopathy to proliferative choroidopathy (4) , analogous to proliferative retinopathy occurring as a response to ischemia . However the occurrence of this proliferative choroidopathy as well as its temporal relationship with proliferative retinopathy has not been well studied. It is possible that in our study, the patients with severe NPDR and PDR had not yet developed proliferative choroidopathy and hence the choroidal Blood flow / OPA was low, thus indicating a diseased choroid where proliferation has not yet begun.

Choroidal vessels has been studied by ICG (58) and by histopathology (59). ICG study of choroidal vessels would probably give an idea of the presence or absence of proliferative choroidopathy in our patients. However this was not a part of the present study. It would be interesting to see if these patients have progressively increasing POBF/ OPA as the severity of disease advances and titrate the OPA with serial ICG studies to document proliferative choroidopathy. But as patients with proliferative retinopathy have a definite indication for pan retinal photocoagulation, it is unethical to delay treatment and inevitably worsen prognosis for these patients.

Decreased OPA noted in our study and in other studies in patients who had received laser treatment , could probably be explained by the closure of these proliferative choroidal vessels.

The POBF and OPA in hypertensives without any other systemic illnesses like diabetes has not been studied. Greishaber etal (41) , Pourjahan (42) noted no changes in OPA with

variation in systolic or diastolic blood pressures amongst normals. Our study also found that presence or absence of hypertension did not make a difference in the OPA in diabetic patients without retinopathy. The number of Hypertensives among non diabetics was too low to analyze, hence the effect of Hypertension in these patients cannot be commented upon.

However, we did note reduced OPA in diabetics without hypertension as compared to diabetics with hypertension. Retinal capillary perfusion depends on systemic blood pressure and IOP and is given by the equation :

| Ocular perfusion pressure= MAP – IOP. |
|---|

[where MAP (mean arterial pressure) = diastolic BP + $1/3^{rd}$ (Systolic- Diastolic BP). ]

This would explain the reduced perfusion pressure and, in turn, the reduced OPA in diabetics with retinopathy without hypertension. However it is not discernible why similar reduced OPA is not seen in the category of diabetics with no retinopathy and no hypertension. This could be due to the complex interaction of local retinal vasoregulation as well as choroidal autoregulation. Hypertension affects the perfusion in the choroidal, ophthalmic artery as well as posterior ciliary arteries where autoregulatory mechanisms operate .

Although choroidal vesels are innervated by autonomic system, the effect of Diabetic autoimmune dysfunction on choroidal blood flow has been examined in only a few studies and is unclear. It is likely that normal autoregulatory mechanisms are affected in diabetics

(51). This makes it difficult to estimate the effect of hypertension on the ocular blood flow in diabetics with abnormal autoregulation.

As reduction in blood pressures reduces the ocular perfusion pressures in patients with diabetic retinopathy who already have abnormal autoregulation, antihypertensive medications must be carefully titrated as very stringent reduction of blood pressures would in turn lead to further reduction of choroidal blood flow and possible worsening of retinopathy.

From the above discussion, we see that there are a number of coexisting factors such as duration of Diabetes, extent of control of blood Sugars and blood pressures, presence of Hypertension, which have a complex interaction on the ocular perfusion. This along with the variation in methods used for measuring ocular perfusion would account for the varying results which have been reported in choroidal blood flow studies.

# Conclusions

OPA is reduced in diabetics with severe NPDR and PDR as compared to normals and patients with milder grades of retinopathy

Reduced OPA is seen in non- hypertensive patients with diabetic retinopathy as compared to normals and hypertensives with diabetic retinopathy

Further studies with larger sample sizes in each grade of diabetic retinopathy is needed to evaluate the exact effect of hypertension in these patients

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# APPENDIX 1 : INSTITUTIONAL REVIEW BOARD CERTIFICATE

OFFICE OF THE VICE PRINCIPAL (RESEARCH)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002

Ref: 11/2011

June 20, 2012

OFFICE OF THE TREASURER
21 JUN 2012
487743
VELLORE 632 004

The Treasurer
CMC

Dear Mr. Denzil,

Sub: **FLUID Research grant project NEW PROPOSAL:**
Ocular pulse amplitudes in Diabetics in South India
Dr. Ashish George Kuruvilla, Registrar, Ophthalmology, Dr. Andrew Braganza, Ophthalmology, Dr. Arathi Simha, Ophthalmology.

Ref: IRB Min. No. 7665 dated 18.11.2011

The Institutional Review Board at its meeting held on November 18,2011 vide IRB Min No: ***7665*** accepted the project for ***12 months*** at a total sanction of sum of ₹ 40,000/- (Rupees Forty thousand only). Kindly arrange to transfer the sanctioned amount to a separate account to be operated by ***Drs. Ashish George Kuruvilla and Andrew Braganza.***

Thank you.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr Ashish George Kuruvilla, Registrar, Department of Ophthalmology, CMC
Dr. Andrew Braganza, Professor, Department of Ophthalmology, CMC
File

22x873. RF: Dr. Ashish George Kuruvilla - Ophthalmology (7665)

# APPENDIX 2: PROFORMA

## Ocular pulse amplitudes in Diabetics

**DATE OF TEST:**

**NAME :** **OPA examination number:**

**HOSPITAL NUMBER:**

**AGE IN YEARS (circle): 40-50 51-60 61-70 71-80**

**GENDER: male / female**

**PHONE NUMBER:**

**ADDRESS:**

**HISTORY OF MEDICATIONS FOR HYPERTENSION: YES / NO**

**IF YES, MEDICATIONS: beta blockers / thiazides / calcium ch. Blockers / ACE inhibitors / angiotensin receptor blocker**

**HISTORY OF DIABETES: YES / NO**

**If no, fasting plasma glucose levels (mg/dl) : AC:**

**Blood pressure levels: 1. 2.**

**EXAMINATION PARAMETERS:**

**Eye examined**: RIGHT / LEFT

**GRADE OF DIABETIC RETINOPATHY**: (based on modified Airlee staging system)

**NDR-** no diabetic retinopathy

**NPDR-** mild to moderate non proliferative diabetic retinopathy

**SNPDR-** severe to very severe non proliferative diabetic retinopathy

**PDR-** proliferative retinopathy

**CSME:** YES/NO

**PRESENCE OF HYPERTENSIVE RETINOPATHY CHANGES**: YES / NO

**EVIDENCE OF RETINAL PHOTOCOAGULATION ON FUNDUS PICTURE:** YES / NO

Fundus fluorescein angiography required: YES / NO

| **PRIMARY EYE (DEFAULT- RIGHT EYE)** | **OCULAR PULSE AMPLITUDE (of quality score 1 or 2)** |
|---|---|
| **1** | |
| **2** | |
| **3** | |
| **Average** | |

| **SECONDARY EYE (IF NO CONTRAIND.)** | **OCULAR PULSE AMPLITUDE (of quality score 1 or 2)** |
|---|---|
| **1** | |
| **2** | |
| **3** | |
| **Average** | |

# APPENDIX 3: INFORMED CONSENT

## INFORMED CONSENT

**Study number:** **date:**
**Name of participant:**
**Hospital number:**

I confirm that I have been explained that I have been given the option of undergoing testing to determine ocular pulse amplitudes by dynamic contour tonometry. I have understood the risks and complications of this study and have had the opportunity to ask the investigators any questions I may have had. I understand that my participation in the study is voluntary and that I can leave the study at any given time, without having my medical care or legal rights being affected. I agree that the investigators and their team have the access to all the data that I may provide them. I accept to share the data obtained during analysis in the faith that it will be used only for scientific purposes. I accept that my identity will not be revealed if the data be published or sent to a third party. I agree not to restrict the scientific use of any of the data or results that may arise from this study.

Understanding all the above, I give my consent for taking part in the above mentioned study.

Patient's/ Legally acceptable representative signature( or thumb impression) with date

Signature of a witness with date

Signature of the investigator with date

# INFORMED CONSENT

**தகவல் ஒப்புதல் படிவம் : தென் இந்தியாவில் நீரிழிவு / சர்க்கரை நோயின் விழி துடிப்பு வீச்சுகள் பற்றிய ஆய்வு**

ஆய்வு எண் : ..... தேதி : .....

பங்கேற்பாளரின் பெயர் : .....

மருத்துவ விவர அட்டை எண் : .....

என்னுடைய கண்ணின் விழித் துடிப்பு வீச்சுகளை அறிந்து கொள்வது எப்படி என்ற ஆய்வைக் குறித்து விளக்கிக் கூறினார்கள். எனவே இந்த ஆய்வில் பங்கு கொள்கிறேன்.

மேலும், இந்த ஆய்வைப் பற்றிய சந்தேகங்களை நான் கேட்டு அறிந்து கொள்ள எனக்கு வாய்ப்பளிக்கப்படுகிறது. மேலும் இந்த ஆய்வில் நான் மனமுவந்து பங்கேற்கிறேன் என்றும், எந்த நேரத்திலும் நான் இந்த ஆய்விலிருந்து விலகிக் கொள்ளலாம் என்றும், இதனால் எனக்குக் கொடுக்கப்படும் மருத்துவ பராமரிப்பு மற்றும் சட்ட உரிமைகள் பாதிக்கப்படாது என்று அறிந்திருக்கிறேன்.

இந்த ஆய்வில் பெறப்பட்ட தகவல்களை ஆய்வாளரும், அவருடைய குழு உறுப்பினர்கள் மட்டுமே பயன்படுத்திக் கொள்வார்கள் என்றும், மருத்துவ ஆராய்ச்சிக்காக பயன்படுத்தி கொள்ளலாம் என்றும் அனுமதி அளிக்கிறேன். என்னுடைய அடையாளங்கள் யாருக்கும் வெளிப்படுத்த / தெரிவிக்க மாட்டாது என்றும் அறிகிறேன்.

மேலே கூறப்பட்டுள்ள எல்லா விவரங்களையும் முழுமையாக அறிந்து கொண்டு இதில் பங்கேற்க ஒப்புதல் அளிக்கிறேன்.

நோயாளி
(அ)
பங்கேற்பாளர்

சட்டபூர்வமான பிரதிநிதியின்
கையொப்பம் / கைரேகை பதிவு

.....

தேதி : .....

சாட்சியின் கையொப்பம் மற்றும் தேதி : .....

ஆய்வாளரின் கையொப்பம் மற்றும் தேதி : .....

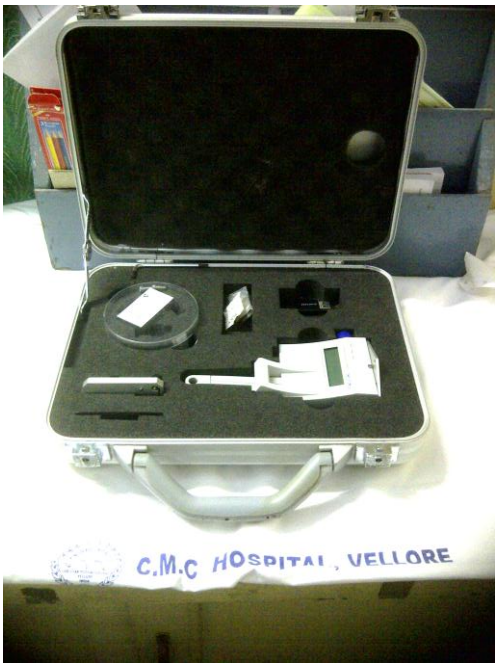



**Photo1**: Ocular Pulse amplitudes measurement
**Photo2**: The DCT instrument after mounting on a Haag Streit slit lamp
**Photo 3:** The PASCAL DCT instrument with case

**TITLE OF THE ABSTRACT : Ocular pulse amplitudes in diabetics in south India**

DEPARTMENT : Ophthalmology

NAME OF THE CANDIDATE : Ashish George Kuruvilla

DEGREE AND SUBJECT : MS Ophthalmology

NAME OF THE GUIDE : Andrew Braganza

OBJECTIVES: Describe the objectives of your study (maximum 30 words)

1. To document any difference in Ocular Pulse Amplitudes with increasing severity of Diabetic retinopathy
2. To document any difference in Ocular Pulse Amplitudes between Diabetics with and without systemic Hypertension

METHODS: Explain the clinical and statistical methods used (maximum 100 words)

This study was a prospective non randomised observational study to look at the ocular pulse amplitudes using dynamic contour tonometry in various stages of diabetic retinopathy and also in patients with Hypertension.

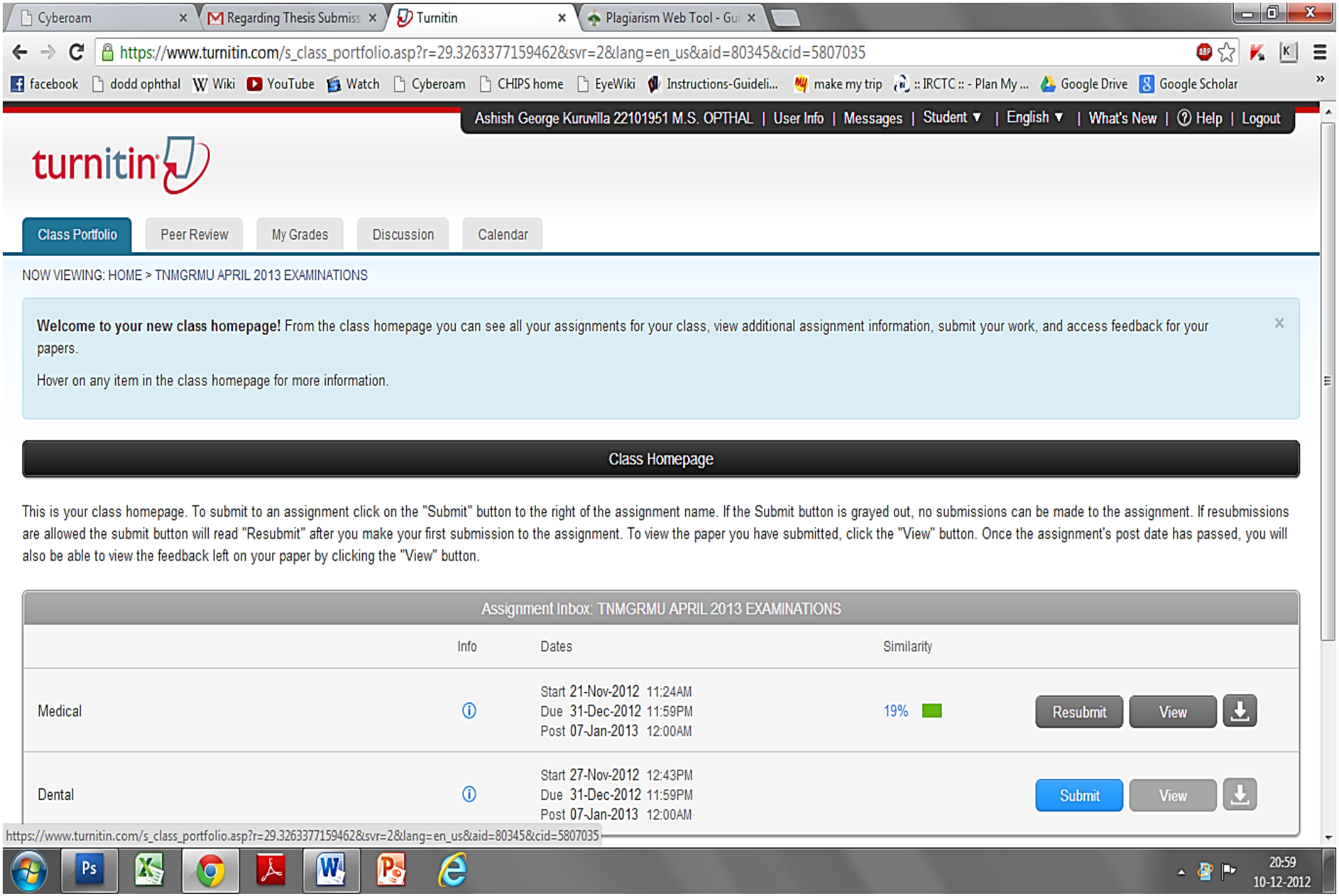
Participants were divided into groups based on the presence or absence of Diabetes. There were 3 groups, 50 in each group, namely: 1. No diabetes, 2. Diabetes with no diabetic retinopathy and 3. Diabetes with retinopathy. Participants with retinopathy were further divided into 3 sub groups: mild diabetic retinopathy, moderate diabetic retinopathy and severe non proliferative diabetic retinopathy and proliferative diabetic retinopathy being clumped into the last group

Statistical analysis was done mostly with hypothesis testing for 2 means, from which the sample size was calculated. ANOVA was also used.

RESULTS: Summarise the findings and conclusions of your study (maximum 90 words)

Conclusions:

1. OPA is reduced in diabetics with severe NPDR and PDR as compared to normals and patients with milder grades of retinopathy
2. Reduced OPA is seen in non- hypertensive patients with diabetic retinopathy as compared to normals and hypertensives with diabetic retinopathy
3. Further studies with larger sample sizes in each grade of diabetic retinopathy is needed to evaluate the exact effect of hypertension in these patients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