Original Research Paper

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Diabetology

TO STUDY THE FREQUENCY OF DIABETIC RETINOPATHY IN PRE-DIABETICS AND ITS CORRELATION WITH ASSOCIATED RISK FACTORS

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INTRODUCTION:

Diabetes is a global epidemic and already showing its devastating human, social and economic consequences. The disease claims as many lives per year as HIV/AIDS and a real cause for our health expenditure[1]. It is estimated that in 2012, the number of people with diabetes worldwide was approximately 366 million. India, China, and the United States have the highest numbers of people with diabetes in the world. It has also been estimated by 2030, the number of people with diabetes in the world will increase by 552 million. [2] According to the International Diabetes Federation, 61.3 million people in India had diabetes in 2011. That figure is projected to rise to 101.2 million by 2030.[3]

Pre-diabetes refers to a state of impaired glucose tolerance (IGT), impaired fasting glucose (IFG) either singly or in combination, and is an intermediary step between normoglycemia and hyperglycemia. 50-60% of pre-diabetics develop diabetes, and others may revert back to normal by proper preventive measures.[4] Hepatic insulin resistance with normal muscle insulin-sensitivity is the basis of IFG, whereas in isolated IGT, moderate-to-severe muscle insulin-resistance is the predominant feature. IFG has a defect in early phase insulin secretion with an almost normal late phase insulin secretion. Severe deficit in late-phase insulin secretion is reported in IGT subjects.[5] Diabetic retinopathy (DR) is a microvascular complication seen in pre-diabetes, type 1 and type 2 diabetes. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. The earliest signs are microaneurysms (10-100 µm sized saccular capillary extensions due to pericyte loss) in the retinal capillaries and retinal haemorrhages. Microaneurysms have been shown to be important predictive lesions for the progression of diabetic retinopathy.[6] Diabetic retinopathy is the most common microvascular complication of diabetes. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes.[7]

The present study was aimed at seeing the frequency of retinopathy in pre-diabetic patients, type of retinopathy and its correlation with risk factors.

MATERIAL AND METHODS:

The present study was conducted in the Department of Ophthalmology, Indira Gandhi Medical College, Shimla. It was a prospective study of patients with impaired fasting glucose (IFG) i.e. FPG between 100-125 mg% or impaired glucose tolerance(IGT) i.e. 2 hr plasma glucose between 140-199 mg% or Hb1Ac level between 5.7–6.4%; attending the general medicine OPD/ward and eye OPD/ward of Indira Gandhi Medical College, Shimla from July 2013 to June 2014. They were taken as a sample population.

Inclusion Criteria:

All patients of pre-diabetes (Defined as per ADA criteria).[8]

Exclusion Criteria:

All patients of known diabetes.
Others.

1. Fundus photographs/FFA taken on fundus camera not clearly visible for making a diagnosis.
2. Patients presenting with opaque ocular media.
3. Not willing for study

METHOD:

All patients attending medicine OPD/ward meeting the criteria were examined and detail of demography, BMI, BP, etc. was recorded. The patients were subjected to various biochemical investigations and detailed ophthalmological examination as per Performa enclosed.

The informed consent was taken from all patients to be taken up for study.

INVESTIGATIONS:

Blood sugar level, renal function test (RFT), lipid profile was done by Konelab Prime-30 clinical chemistry analyzer of Thermo Fisher Scientific Company, United States of America.Hb_1AC was done by Nyco card readermethod, Axis-Shield Company, Norway.

All patients referred from medicine OPD with IFG, IGT or Hb_1AC between 5.7-6.4% were subjected to detailed fundus examination.

Defining Criteria

1.Pre-diabetes:- Fasting plasma glucose is between 100mg/dL-125mg/dL (5.6 mmol/L -6.9 mmol/L) OR
2-hours plasma glucose in the 75-g OGTT is between 140mg/dL – 199mg/dL (7.8 mmol/L-11.0 mmol/L) OR
HbA1C between 5.7–6.4 %(ADA criteria)[8]
2.Hypertension:- BP values of ≥140/90 mm of Hg (JNC-VII criteria)
3.Obesity:- BMI of ≥25(JAPI criteria)
4.Retinopathy:-ETDRS(modified Airlie House) criteria[9]
5.Dyslipidemia:- According to NCEP - ATP III guidelines, hypercholesterolemia is defined as TC >200mg/dl, LDL-C as >100mg/dl, hypertriglyceridemia as TG >150mg/dl and HDL-C <40mg/dl. Dyslipidaemia is defined by presence of one or more than one abnormal serum lipid concentration.[10]

Initial Assessment:

In all the subjects, ophthalmological examination was performed under the following headings and the findings documented.

1. Visual acuity - It was measured by using Snellen's chart, kept at a distance of six meters.
2. Fundus examination was done by using the direct and indirect ophthalmoscope after dilating pupil by instilling one to two drops of 5% Phenylephrine Hydrochloride with 0.8% Tropicamide (TROPAC-P of Optho pharma).

3. Clinical evaluation of fundus was done by using Haag Streit slit lamp biomicroscope with +90D lens
4. Fundus Photography:
   a) Anterior Segment Evaluation
b) Posterior Segment Evaluation: Retina, macula, optic nerve head, vitreous humour.
5. Fundus Fluorescein Angiography (wherever indicated).
6. CAMERA PHOTOGRAPHICS:

The photographs were taken on the fundus camera (KOWA'S FUNDUS CAMERA VX-10, KOWA Company Ltd,4-14, Nihonbashi-honcho 3-chome, Chuo-ku, Tokyo 103-8433 Japan). This equipment is capable of mydriatic and non-mydriatic photography with two angles of view: 50 degree and 25 degree (45 degree and 22 degree for non-mydriatic photography). Preferably the photographs were taken on mydriatic mode. The software used is the Kowa Ophthalmic Medical Imaging Software VK-27E; version 5.13 for windows XP, windows vista.

PHOTOGRAPHY (METHOD):-

The pupil was dilated by instilling one to two drops of 5% Phenylephrine Hydrochloride with 0.8% Tropicamide (TROPAC-P of Optho pharma). After 45 minutes when the pupil is fully dilated, the patient was examined. The subjects were instructed to be seated in front of the fundus camera. Height of the optical bench was adjusted to let the chin on the chin rest and forehead on the forehead rest in a natural posture. The chin rest height was adjusted by chin rest handle. The examined eyes were at the eye level mark. The fixation lamp was selected with help of fixation lamp switch to take photograph of central optic disk. Examined eye's dioptre was compensated by inserting dioptre lens by dioptre lens switch.

Fundus camera was positioned such that the luminous spots for alignment can come in the centre and the luminous spot is smallest and sharpest. By this, examined eye position is set. Focusing was adjusted by adjusting the position of luminous lines by turning the focusing knob such that they are arranged in a straight line. Then by pressing the shutter button for photographing the images were taken. The same procedure was repeated in the other eye.

Statistical Analysis: Data collected was managed on an excel spreadsheet. Significance was determined by using appropriate statistical methods.

RESULTS:

The present study was conducted in the Department of Ophthalmology, Indira Gandhi Medical College, Shimla. It was a prospective study of patients with impaired fasting glucose (IFG) i.e. FBG between 100-125 mg% or impaired glucose tolerance(IGT) i.e. 2 hr plasma glucose between 140-199 mg% or Hb1Ac level between 5.7–6.4%; attending the general medicine OPD/ward and eye OPD/ward of Indira Gandhi Medical College, Shimla from July 2013 to June 2014. In total 103 subjects were examined. The following observations were made during the course of the study:

Age Wise Distribution:-

Table 1: Age (years) Wise Distribution Of Patients

Age	No Retinopathy	Retinopathy present	Total	Retinopathy Percentage	Percentage of Subjects
20-35	15	0	15	0%	14.6%
35-50	30	0	30	0	29.1%
50-65	35	4(50.0%)	39	10.3%	37.9%
65-80	14	4(50.0%)	18	22.2%	17.5%
>80	1	0	1	0%	0.01%
Total	95	8	103		
P value-0.04					

The age range of patients was from 20 years to 83 years with a mean age of 53 years. 15 patients (14.6%) were in 20-35 years, 30 patients (29.1%) were in 35-50years, 39 patients (37.9%) were in 50-65 years, 18 patients (17.5%) were in 65-80 years and 1 patient (0.01%) was >80 years.

In the age groups 20-35 years, 35-50 years and above 80 years no retinopathy (0%) was found whereas in the age groups 50-65 years and 65-80 years retinopathy was found in 4 persons each. So retinopathy percentage in the age groups 50-65 was 10.3% and in the age groups 65-80 was 22.2%. This shows significant association of age between 50-80 years (p value <0.04) with retinopathy in pre-diabetic persons.

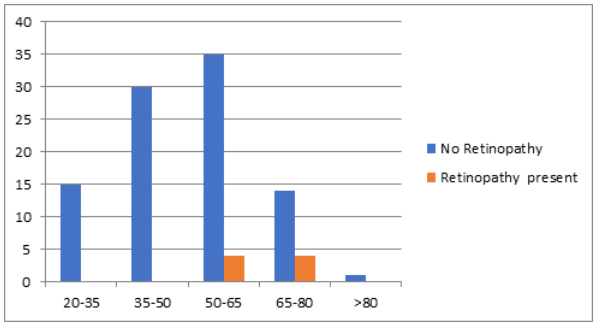

Figure2:Distribution Of Retinopathy In Patients With Respect To Age:

Gender Wise Distribution:-

Table 2: Gender Wise Distribution Of Patients.

Gender	No Retinopathy	Retinopathy present	Total	Retinopathy Percentage	Percentage of subjects
Male	60	6	66	9.0%	64.1
Female	35	2	37	5.4%	35.9
Total	95	8	103		
P value- 0.54					

In the present study out of the 103 patients 64.1% were male patients while 35.9% were female patients.

In the study out of 66 male patients 6 (9.0%) had retinopathy and out of 37 female patients only 2(5.4%) had diabetic retinopathy which was of mild non-proliferative diabetic retinopathy type. The findings were not statistically significant(p value 0.54)

In the Patients studied 13.6% had BMI in underweight category,54.4% had BMI in normal range,22.3% in Pre-obese range and 9.7% in obese range.

Out of 103 patients studied retinopathy was found in 1(7.1%) person in underweight category, retinopathy was found in 4(7.1%) persons in normal BMI range, in 1(4.3%)person in pre-obese range and in 2(20.0%) persons in obese range. There was no statistically significant association (p value 0.47)

Table 4: Distribution Of Patients With Hypertension:

In our study 33.0% patients had blood pressure in normal range, 33.0% patients had BP in pre-hypertension range, 25.2% had grade I hypertension and 8.8% had grade II hypertension. Figure 7

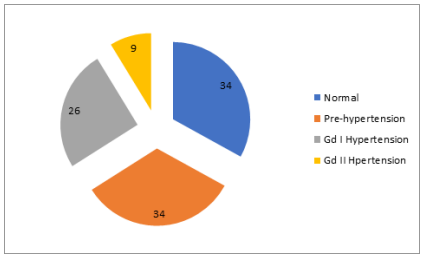

Figure 7: Distribution Of Patients With Hypertension:

In the normal blood pressure category among 34 persons no retinopathy (0.0%) was found, retinopathy was found in 4(11.8%) persons out of 34 in pre-hypertension group, in 3(11.5%) persons out of 26 with grade (Gd) I hypertension and in 1(11.1%) person out of 9 with Gd II hypertension. It was not statistically significant (p value 0.23)

Out of 77 persons who were non-smokers retinopathy was found in 6(7.8%) persons and out of 26 persons who were smokers retinopathy was found in 2(7.6%) persons. This was found to be statistically non-significant (p value 0.97).

In the study 15.5% of the patients had a family history of diabetes whereas 84.5% patients had no such family history.

Retinopathy was found in 1(6.6%) person out of 16 in patients with

family history of diabetes and in 7(7.9%) persons out of 87 persons without family history of diabetes. This was found to be statistically non-significant (p value 0.94).

Retinopathy was found in 6(6.5%) persons out of 93 persons who had normal renal functions and in 2(20.0%) persons out of 10 persons with deranged renal function. This was found to be statistically significant (p value <0.001).

Retinopathy was found in 3(3.5%) persons out of 84 persons who had normal total cholesterol level and in 5(26.3%) persons out of 19 persons with deranged total cholesterol level. This was found to be statistically significant (p value 0.005). Retinopathy was found in 4(5.7%) persons out of 70 persons who had normal triglyceride level and in 4(12.1%) persons out of 33 persons with deranged triglyceride level. This was found to be statistically non-significant (p value 0.29). Retinopathy was found in 2(2.6%) persons out of 76 persons who had normal LDL cholesterol level and in 6(22.2%) persons out of 27 persons with deranged LDL cholesterol level. This was found to be statistically significant (p value 0.004). Retinopathy was found in 4(4.4%) persons out of 90 persons who had normal HDL cholesterol level and in 4(30.8%) persons out of 13 persons with deranged HDL cholesterol level. This was found to be statistically significant (p value 0.009).

DISCUSSION:

Pre-diabetes refers to a state of impaired glucose tolerance (IGT), impaired fasting glucose (IFG) either singly or in combination, and is an intermediary step between normoglycemia and hyperglycaemia. So, pre-diabetes is a major risk factor for the development of diabetes. This metabolic state keeps company with major risk factors for athero-vascular disease, e.g. metabolic syndrome and insulin resistance.50-60% of pre-diabetics develop diabetes, and others may revert back to normal by proper preventive measures.

In our study out of 103 pre-diabetic patients mild non-proliferative diabetic retinopathy was found in 8 (7.77 %) persons .

Tyrberg M, Melander A, Lövestam-Adrian M et al [11](2008) studied retinopathy in subjects with impaired fasting glucose in 90 men and 64 women. . These persons with IFG were fundus photographed. Of these, 16 subjects (10%) had mild or very mild retinopathy.[11] Our study was comparable to this study in terms of frequency of diabetic retinopathy in the patients.

Nagi, D.K., et al[12] (1997) assessed diabetic retinopathy by fundus photography in American native Indians with impaired glucose tolerance and NIDDM. In a population-based epidemiological study, 991 native Indians with non-insulin-dependent (Type 2) diabetes mellitus (NIDDM) and 288 without diabetes aged ≥15 years were examined for retinopathy by fundus photography with a 45 degrees fundus camera after mydriasis.. Non-proliferative retinopathy was present in 11.2 % (19/169) subjects who were diagnosed as diabetics for the first time without any previous records and in 8.3% (4/48) in newly diagnosed subjects who had a documented non-diabetic oral glucose tolerance test within 4 years prior to diagnosis of diabetes. The prevalence of retinopathy in subjects with impaired glucose tolerance was 12% (8/68).[12]Our study was in concordance with this study.

The Diabetes Prevention Program (DPP) Research Group (2007) recruited persons with elevated fasting glucose (5.6–6.9 mmol/l) and impaired glucose tolerance, and with no history of diagnosed diabetes. Seven-field, stereoscopic fundus photography was completed in a mean of 3.1 years after the development of diabetes in 594 of 878 participants who had developed diabetes during the DPP, and in a random sample of 302 participants who remained non-diabetic and found that retinopathy consistent with diabetic retinopathy was detected in 12.6 and 7.9% of the diabetic and pre-diabetic participants, respectively (P = 0.03), comparing prevalence in the two groups.[13] The results in this study were comparable to our study in which 7.7% persons had retinop athy in pre-diabetic subjects.

Gabir MM, Hanson RL, Dabelea D et al(2000) studied the prevalence of retinopathy and nephropathy at baseline and during the subsequent 10 years and mortality rates were examined in relation to baseline fasting plasma glucose (FPG) and 2-h post load plasma glucose (2-h PG) among 5,023 native Indian adults and in relation to the cut points defined by the ADA and WHO criteria. The frequencies of retinopathy and nephropathy were directly related to baseline FPG and 2-h PG with approximate thresholds near or below the current diagnostic criteria for diabetes (FPG > or =7.0 and 2-h PG ≥ 11.1 mmol/l). The rates of retinopathy were 4.7% in impaired fasting glucose (IFG) and 20.9% in diabetes by ADA criteria; 1.6% for impaired glucose tolerance (IGT) and 19.7% for diabetes by 1985 WHO criteria.[14]

Age-wise Distribution:

In our study the mean age of pre-diabetic persons was 53 years, with the age range 20-83 years. The average age for males was 55.85±7.85 years while average age of females was 51.41±7.41 years. The age group50-65 years had the maximum number of patients. The patients who had retinopathy were in the 50-65 year (4 in no.) and 65-80(4 in no.). So 50-80 years age group showed significant association of age (p value 0.04) with retinopathy in pre-diabetic persons.

Age and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian groups was studied by Qiao Q., Hu G., Tuomilehto J. et al (2003). They performed 11 studies in 4 countries, comprising 24,335 subjects (10,851 men and 13,484 women) aged 30-89 years who attended the 2-h oral glucose tolerance test and met the inclusion criteria for data analysis and concluded that Indians had the highest prevalence of diabetes among Asian countries. Indian subjects also had a higher prevalence of (impaired glucose regulation) IGR in the younger age-groups (30-49 years) compared with that for Chinese and Japanese subjects (40-59 years).The age at which the peak prevalence of diabetes was reached was approximately 10 years younger in Indians compared with Chinese and Japanese subjects.[15]

S Cugati, L Cikamatana, J J Wang, A Kifley, G Liew and P Mitchell (2006) examined 3654 persons with impaired glucose tolerance aged 49+ years (82.4% response rate) during 1992–1994, and re-examined 2335 (75.1% of survivors) during 1997–1999. Retinopathy lesions (microaneurysms, haemorrhages, hard or soft exudates) were assessed from 6-field retinal photographs in persons with impaired glucose tolerance. Retinopathy was assessed in persons who were at risk .It was found that in over 5 years, retinopathy developed in 10% of people without diabetes. Age more than 55 years was significantly associated with the development of these lesions.[33]In our study also the maximum number of the patients were in the age group (50-80yrs).[16]

X Chen, Y Zhao , Z Zhou et al(2007) studied prevalence and risk factors of diabetic retinopathy in pre-diabetes patients of Chongqing province. A total of 750 participants were recruited in this study. All participants underwent a complete physical examination and an oral glucose-tolerance test. In all, 110 of the 125 newly diagnosed pre-diabetics and their healthy spouses as controls were examined with fluorescence fundus angiographies, and their blood with biochemical analyses. All the pre-diabetics with DR (23 subjects), 23 normal controls and 23 pre-diabetics without DR were compared for serum concentrations of the chemokine (C-C motif) ligand 5 (also CCL5); a protein which in humans is encoded by the *CCL5* gene; also called regulated upon activation, normal T-expressed and secreted (RANTES). There was a statistically significant difference in serum concentrations of RANTES between pre-diabetics with and without DR (P<0.01), and also between pre-diabetics with DR and normal controls (P<0.01). However age seemed to have no reliable relationship with DR in pre-diabetics (P>0.05).[17]

Peng XY, Wang FH, Liang YB (2010) studied Retinopathy in persons without diabetes in the Handan Eye Study in a population-based cross-sectional study of 6830 Han Chinese aged ≥ 30 years from 13 villages of Yongnian County, Handan City, Hebei Province, China. All participants underwent extensive examinations including retinal photography, measurement of blood pressure (BP) and fasting plasma glucose (FPG). Diabetes mellitus was defined as either FPG ≥ 7.0 mmol/l, use of diabetic medication or a physician diagnosis of diabetes. Photographic grading of retinopathy followed the modified Early Treatment Diabetic Retinopathy Study classification system. Logistic regression models were used to assess associations of retinopathy. They found that prevalence of retinopathy among participants without diabetes was 13.6%. Age was found to be an independent risk factors associated with retinopathy.[18]This study was in tune with our study in which we also found significant association of age (p value <0.04) with retinopathy in pre-diabetic persons.

Gender Wise Distribution:

In the present study out of the 103 patients 66 persons (64.1%) were

male patients while 37(35.9%) were female patients. In the study out of 66 male patients 6 had retinopathy and out of 37 female patients only 2 had diabetic retinopathy which was of mild non-proliferative diabetic retinopathy type. The findings were not statistically significant(p value 0.54)

Buckley CM, Madden J, Balanda K et al (2007) studied 1132 participants ≥ 45 years and determination of pre-diabetes was based on American Diabetes Association HbA_{1c} cut points of 39-46 mmol/L (5.7-6.4%).It was found that prevalence estimate of pre-diabetes in participants ≥ 45 years was 19.8%.[19] There was no significant difference between gender-specific prevalence rates as was in our study.

Jennifer R. Chao, Mei-Ying Lai, Stanley P. Azen (2007) studied retinopathy in persons without Diabetes in The Los Angeles Latino Eye Study.This was a population-based, cross-sectional study comprising 6357 Latinos, 40 years of age and older, from six census tracts in La Puente, Los Angeles, California. An interviewer-administered questionnaire assessed sociodemographic factors and medical history. Color fundus photographs were taken and graded according to Early Treatment of Diabetic Retinopathy Study. Participants underwent a physical examination that included height, weight, blood pressure, random serum glucose, and glycosylated hemoglobin measurements. Univariate and multivariate logistic regression analyses were used to assess associations between sociodemographic and clinical characteristics and retinopathy in persons without diabetes. The prevalence of retinopathy among individuals without diabetes in the Los Angeles Latino Eye Study (LALES) population was 6.6%. Stepwise logistic regression indicated that stage II hypertension (World Health Organization 2003 Guidelines), male gender, current smoking status, and obesity (body mass index ≥ 30 kg/m^2) were associated with retinopathy. The data suggest that the prevalence of retinopathy in nondiabetic individuals among Latinos of primarily Mexican ancestry is significant. Male gender was found to be an independent risk indicator for retinopathy in the study population.[20]

A study conducted by Peng XY, Wang FH, Liang YB (2010) in a population-based cross-sectional study of 6830 Han Chinese aged > or =30 years from 13 villages of Yongnian County, Handan City, Hebei Province, China (Already quoted). The age and gender standardized prevalence of retinopathy in the Chinese adult population (aged 30+ years) without diabetes was estimated to be 12.1%. Male gender was found to be independent risk factors associated with retinopathy.[18]

BMI Wise Distribution:

In our study 14 subjects (13.6%) had BMI in underweight category, 56 subjects (54.4%) had BMI in normal range,23 subjects (22.3%) in Pre-obese range and 10 subjects (9.7%) in obese range. Out of 103 patients studied retinopathy was found in 1 person in underweight category, retinopathy was found in 4 persons in normal BMI range, in 1person in pre-obese range and in 2 persons in obese range. There was no statistically significant association (p value 0.47) retinopathy and BMI in pre-diabetic persons in our study.

In a study conducted by Buckley CM, Madden J, Balanda K et al (2007) 1132 participants were studied who were ≥ 45 years and determination of pre-diabetes was based on American Diabetes Association HbA_{1c} cut points of 39-46 mmol/L (5.7-6.4%).It was found that prevalence estimate of pre-diabetes in participants ≥ 45 years was 19.8%. Obesity, physical inactivity and poor diet were significantly associated with pre-diabetes.[19]

In a population-based study which included 2,484 Caucasians persons of age group 50 to 74 years old; Hendrik A. van Leiden, Jacqueline M. Dekker, Annette C. Moll, MD (2002) et al studied the association of blood Pressure, Lipids, and Obesity and retinopathy. The prevalence of retinopathy was positively associated with BMI.[21] This study was in contrast to the study conducted by us in which there was no significant association with BMI was found.

In the Shanghai diabetic complications study; Pang C, Jia L, Jiang S et al (2012) studied the determination of diabetic retinopathy prevalence and associated risk factors in Chinese diabetic and pre-diabetic subjects. They investigated the prevalence of and risk factors associated with retinopathy in diabetic and pre-diabetic subjects from Chinese communities. A total of 3736 Chinese subjects were recruited from urban communities in Shanghai. The prevalence of diabetic retinopathy in patients with diabetes and impaired glucose tolerance was 9.4% and 2.5%, respectively. In subjects with impaired glucose regulation (IGR) obesity was significantly associated with diabetic retinopathy.[22]

Hypertension Wise Distribution:

In our study 34 (33.0%) patients had blood pressure in normal range, 34 (33.0%) patients had BP in pre-hypertension range,26(25.2%) had grade I hypertension and 9(8.8%) had grade II hypertension. In the normal blood pressure category among 34 persons no retinopathy was found, retinopathy was found in 4 persons out of 34 in pre-hypertension group, in 3 persons out of 26 with Gd I hypertension and in 1 person out of 9 with Gd II hypertension. It was not statistically significant (p value 0.23) .

A population-based study was conducted by Hendrik A. van Leiden, Jacqueline M. Dekker, Annette C. Moll, MD (2002) which included 2,484 50- to 74-year-old Caucasians. This study revealed that prevalence of retinopathy was positively associated with hypertension (p value <0.05).[21] It was in contrast to our study in which no significant association with hypertension was found.

A study was conducted by Tyrberg M, Melander A, Lövestam-Adrian M et al (2008) in 90 men and 64 women with impaired fasting glucose. These persons with IFG were fundus photographed. Of these, 16 subjects (10%) had mild or very mild retinopathy. There was no difference in occurrence of retinopathy between subjects with known diagnosis of hypertension or not. However, subjects with retinopathy had significantly higher systolic (154 vs. 141 mmHg, p = 0.013) and diastolic (86 vs. 81 mmHg, p = 0.008) blood pressure levels.[11]

In a study conducted by Peng XY, Wang FH, Liang YB (2010) of persons without diabetes in a population-based cross-sectional study of 6830 Han Chinese aged ≥ 30 years. All participants underwent a standardized interview and extensive examinations including retinal photography, measurement of blood pressure (BP) and fasting plasma glucose (FPG). They concluded that retinopathy was common among rural Chinese adults without diabetes. Its association with FPG and BP suggests that early microvascular damage is occurring at high normal levels of blood glucose and BP.[18]

In the year 2012; Pang C, Jia L, Jiang S et al conducted a study in which diabetic retinopathy prevalence and associated risk factors were studied in 3736 Chinese diabetic and pre-diabetic subjects. It was found that in subjects with IGR, hypertension, including elevated systolic and diastolic blood pressure was significantly associated with diabetic retinopathy .[22]

Smoking Habit Wise Distribution:

In our study 26 (25.2%) patients were smokers and 77(74.8%) were non-smokers. Out of 77 persons who were non-smokers retinopathy was found in 6 persons and out of 26 persons who were smokers retinopathy was found in 2 persons. This was found to be statistically non-significant (p value 0.97).

Sakai Y, Yamaji T, Tabata S et al (2006) studied relation of alcohol use and smoking to glucose tolerance status in Japanese men. They performed a cross-sectional study of 3038 male officials aged 46-59 years in the Self-Defense Forces. Glucose tolerance status was determined by a 75-g oral glucose tolerance test. A self-administered questionnaire was used to ascertain alcohol use, smoking habits, and other lifestyle characteristics. Statistical adjustment was made for parental history of diabetes, body mass index, and leisure-time physical activity. Cigarette smoking was not related to any categories of glucose intolerance.[23]

Jennifer R. Chao ,Mei-Ying Lai,Stanley P. Azen et al (2007) studied 6357 Latinos persons without Diabetes in The Los Angeles Latino Eye Study.This was a population-based, cross-sectional study of persons 40 years of age and older, from six census tracts in La Puente, Los Angeles, California. The prevalence of retinopathy among individuals with pre-diabetes in the Los Angeles Latino Eye Study (LALES) population was 6.6% and stepwise logistic regression indicated that smoking was associated with retinopathy.[20]

Distribution With Family History Of Diabetes:

In our study 16 (15.5%) of the patients had a family history of diabetes whereas 87 (84.5%) patients had no such family history. Retinopathy

was found in 1 person out of 16 in patients with respect to family history of diabetes and in 7 persons out of 87 persons without family history of diabetes. This was found to be statistically non-significant (p value 0.94).

Wagner R, Thorand B, Osterhoff MA (2013) studied a population of 8,106 non-diabetic individuals of European origin collected from four study centres (normal glucose tolerance, NGT n = 5,482, IFG and/or IGT n = 2,624). They analysed that having at least one first degree relative with diabetes is associated with pre-diabetes. The analyses were performed using the same models in each population separately. Afterwards, a meta-analysis was performed and found that family history of diabetes was significantly associated with the risk for pre-diabetes.[24] However this was in contrast to our study.

Distribution With Renal Function:
In our study 93 (90.2%) patients had normal renal functions and 10(9.8%) had deranged renal function. Retinopathy was found in 6persons out of 93 persons who had normal renal functions and in 2 persons out of 10 persons with deranged renal function. This was found to be statistically significant (p value <0.001).

Gabir MM, Hanson RL, Dabelea D et al(2000) studied the prevalence of retinopathy and nephropathy at baseline and during the subsequent 10 years and mortality rates were examined in relation to baseline fasting plasma glucose (FPG) and 2-h postload plasma glucose (2-h PG) among 5,023 native Indian adults and in relation to the cut points defined by the ADA and WHO criteria.The frequencies of retinopathy and nephropathy were directly related to baseline FPG and 2-h PG with approximate thresholds near or below the current diagnostic criteria for diabetes. Mortality rates from cardiovascular-renal-related diseases were higher in diabetic individuals (FPG ≥ 7.0 or 2-h PG > 11.1 mmol/l) than in those with normal FPG and 2-h PG but were not elevated in those with IFG or IGT. [25]It was in tune with our study in which there was a statistically significant association with deranged renal function.

Similarly in another study X Chen, Y Zhao , Z Zhou et al(2007) studied prevalence and risk factors of diabetic retinopathy in pre-diabetes patients of Chongqing province. A total of 750 participants were recruited in this cross-sectional study. There was a statistically significant difference in serum concentrations of RANTES between pre-diabetics with and without DR (P<0.01), and also between pre-diabetics with DR and normal controls (P<0.01). However blood urea nitrogen, blood creatinine seemed to have no reliable relationship with DR in pre-diabetics (P>0.05).[26] It was not in concordance with our study in which there was a statistically significant association with deranged renal function.

Distribution Of Patients According To The Total Cholesterol Level (table 8, Figure 15,16):
In our study 81.6% patients had normal total cholesterol and 9.8% had deranged total cholesterol values. Retinopathy was found in 3 persons out of 84 persons who had normal total cholesterol level and in 5 persons out of 19 persons with deranged total cholesterol level. This was found to be statistically significant (p value 0.005).

Hendrik A. van Leiden, Jacqueline M. Dekker, Annette C. Moll, MD (2002) et al studied that blood pressure, lipids, and obesity are associated with retinopathy in the The Hoorn Study. It was a population-based study including 2,484; 50 to 74-year-old Caucasians. The prevalence of retinopathy was positively associated with elevated total cholesterol level in the persons studied.[21] This was similar to the findings found in our study.

X Chen, Y Zhao , Z Zhou et al(2007) studied the prevalence and risk factors of diabetic retinopathy in pre-diabetes patients. A total of 750 participants of Chongqing province were included in this cross-sectional study. All participants underwent a complete physical examination and an oral glucose-tolerance test. There was a statistically significant difference in serum concentrations of RANTES between pre-diabetics with and without DR (P<0.01), and also between pre-diabetics with DR and normal controls (P<0.01). However total cholesterol (TC) seemed to have no reliable relationship with DR in pre-diabetics (P>0.05).[26]

Distribution with Triglyceride level:
In our study 70 (68.0%) patients had normal Triglyceride level and 33 (32.0%) had deranged triglyceride values. Retinopathy was found in 4 persons out of 70(5.7%) persons who had normal triglyceride level and in 4 persons out of 33 (12.1%) persons with deranged triglyceride level. This was found to be statistically non-significant (p value 0.29).

In a population-based study which included 2,484 Caucasians persons of age group 50 to 74 years old; Hendrik A. van Leiden, Jacqueline M. Dekker, Annette C. Moll, MD (2002) et al studied the association of blood pressure, lipids and obesity with retinopathy. This study came to the conclusion that prevalence of retinopathy was positively associated with increased triglyceride serum levels in all glucose categories which was in contrast to our study.[21]

However in a study conducted by X Chen, Y Zhao , Z Zhou et al(2007) already quoted) revealed that raised triglyceride levels seemed to have no reliable relationship with DR in pre-diabetics (P>0.05). [26]

Distribution With LDL Cholesterol Level:
In our study 76 (73.8%) patients had normal LDL cholesterol level and 27(32.0%) had deranged LDL cholesterol values. Retinopathy was found in 2 persons out of 76 persons who had normal LDL cholesterol level and in 6 persons out of 27 persons with deranged LDL cholesterol level. This was found to be statistically significant (p value 0.004).

Our findings were similar to what a study conducted in 2484 Caucasians by Hendrik A. van Leiden, Jacqueline M. Dekker, Annette C. Moll, MD (2002) et al that studied the various risk factors associated with retinopathy across the various glucose tolerance cohorts. It was of the opinion that the prevalence of retinopathy was positively associated with increased LDL cholesterol serum levels in all glucose categories.[21]

In a similar study conducted by X Chen, Y Zhao , Z Zhou et al(2007) who studied prevalence and risk factors of diabetic retinopathy in 750 pre-diabetes patients; raised low density lipoprotein cholesterol level seemed to have no reliable relationship with DR in pre-diabetics (P>0.05).[26] This was in contrast to the findings of our study.

Distribution with HDL cholesterol level:
In our study 90 (87.4%) patients had normal HDL cholesterol level and 13(12.6%) had deranged HDL cholesterol values.Retinopathy was found in 4 persons out of 90 (4.4%) persons who had normal HDL cholesterol level and in 4 persons out of 13 (30.8%)persons with deranged HDL cholesterol level. This was found to be statistically significant (p value 0.009).

Our findings were corroborated by Hendrik A. van Leiden, Jacqueline M. Dekker, Annette C. Moll, MD (2002) et al (already quoted) who studied that blood pressure, lipids, and obesity are associated with retinopathy. The prevalence of retinopathy was positively associated with decreased HDL cholesterol serum levels in all glucose categories.[21]

Our study was in contrast to a study conducted by X Chen, Y Zhao , Z Zhou et al(2007) who studied prevalence and risk factors of diabetic retinopathy in 750 participants of Chongqing province which concluded that decreased high-density lipoprotein cholesterol seemed to have no reliable relationship with DR in pre-diabetics (P>0.05).[26]

CONCLUSION:
We conclude that retinopathic changes consistent with diabetic retinopathy are also found in pre-diabetic persons which are accentuated by the associated risk factors. Hence people/population should be screened for pre-diabetes and fundus examination of all pre-diabetic persons should be done so that timely intervention could be initiated.

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