

A Correlative Study of Duration of Diabetes Mellitus, Microalbuminuria, Hyperlipidaemia with the Severity of Diabetic Retinopathy

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ABSTRACT

AIM: The present study was carried out with an aim to study the concordance and correlation of microalbuminuria, dyslipidemia with the severity of Diabetic Retinopathy in type II diabetes mellitus patient and to provide a possible basis for explanation of mechanisms governing this relationship.

MATERIAL AND METHOD: The study was conducted in a tertiary care hospital in North India. The patients underwent thorough history and ocular evaluation. The patients included in the study were advised to undergo biochemical investigations for Blood sugar, Urinary albumin to creatinine ratio in a random spot collection of urine and Lipid profile. Patients with acute or chronic renal failure,

Opaque/hazy ocular media preventing fundus visualization, Co-existing ocular disorders likely to mask the findings of diabetic retinopathy, Patients with presence of any of the confounding factors, like fever, active systemic infections, exercise, high protein intake, accelerated hypertension, congestive heart failure, patients not willing to participate in the study were excluded from the study.

RESULTS: 444 subjects of either gender were included in our study, out of which 236 patients were females and the rest were males. Majority of the patients lied in the age group of 41-60 years (54.73%) followed by 61-80 years (29.28%) and 20-40 years (15.09%), while only 4(0.90%) patients were aged > 80 years. A statistically significant association with severity of retinopathy and the age of the patients was observed. Proportion of Group I (No retinopathy) was higher in younger patients i.e. 20- 40 (74.6%) and 41-60 (54.3%) as compared to elderly cases i.e. 61-80 (46.2%) and this difference was found to be statistically significant ($p < 0.001$). Statistically significant association was found between the severity of retinopathy and duration of diabetes ($p < 0.001$). Proportion of severe to very severe retinopathy and proliferative diabetic retinopathy were higher in higher grade of microalbuminuria (Grade II and Grade III). A statistically significant association between microalbuminuria grade and severity of retinopathy was observed ($p < 0.001$). Total cholesterol was found to be high (240 mg/dl) in 13.74% patients. Prevalence of retinopathy was 60.7%, in patients having high total cholesterol levels. Proportional difference in severity of retinopathy in patients with different total cholesterol levels was found to be statistically significant ($p = 0.002$). Trivariate analysis between severity of retinopathy, microalbuminuria and serum cholesterol levels, revealed that in microalbuminuria grade 0, difference in prevalence of retinopathy in patients with different serum cholesterol levels was not found to be statistically significant.

CONCLUSION: Duration of diabetes and microalbuminuria have been found to be the independent risk factors for diabetic retinopathy, but serum cholesterol levels did not show an independent role in our study. The findings in present study endorsed the view that microalbuminuria poses a risk for diabetic retinopathy which is affected by duration of diabetes, level of glycemic control and lipid levels.

Key words: Diabetes Mellitus; Diabetic Retinopathy; Microalbuminuria; Hyperlipidaemia

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INTRODUCTION

Diabetes is one of the most common metabolic disease globally and hence one of the most challenging health concerns in modern era^[1]. It is recognized as a group of heterogeneous disorders with the common elements of hyperglycemia and glucose intolerance, due to insulin deficiency or impaired effectiveness of insulin action, or both^[2,3].

Type 2 diabetes owes its rapid growth to cultural and social changes and urbanized lifestyle, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioral patterns.^[1]The direct and indirect effects on the human vascular tree are the major source of morbidity and mortality.

The effects of hyperglycemia are broadly classified into macrovascular complications and microvascular complications. Among the microvascular complication of diabetes, retinopathy is the most common^[4].

The retinal changes can be broadly divided into proliferative (PDR) and nonproliferative diabetic retinopathy (NPDR) groups according to ETDRS classification. Further NPDR can be classified into 1) very mild NPDR 2) mild NPDR 3) moderate NPDR 4) Severe NPDR and 5) very severe NPDR. PDR can be classified as mild to moderate PDR and high risk PDR^[5].

The other microvascular complication associated with diabetes is diabetic nephropathy which is preceded by lower degrees of proteinuria, or "microalbuminuria". Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. As many as 7% of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes^[6].

Apart from hyperglycemia and hypertension, hyperlipidemia is also a major risk factor for development of diabetes.

Thus, the present study was carried out with an aim to study the concordance and correlation of microalbuminuria, dyslipidemia and Diabetic Retinopathy in type II diabetes mellitus patient and to provide a possible basis for explanation of mechanisms governing this relationship.

MATERIAL AND METHOD

This is a Hospital based cross sectional study conducted in the Department of Ophthalmology. 600 cases of diabetes mellitus type II were referred from the Diabetic Clinic, out of which 124 cases were excluded as they did not match the study criteria. Further 32 patients

were also excluded as they did not give consent or did not come for follow up. Remaining 444 participants who fulfilled our study criteria were included in this study. Informed consent was obtained from all the patients in adherence to the tenets of Declaration of Helsinki.

For the study, type II DM is defined as a fasting plasma glucose of more than or equal to 126 mg/dl or 2-hour post glucose load plasma glucose of more than or equal to 200 mg/dl or a random plasma glucose of more than or equal to 200 mg/dl in the presence of symptoms of hyperglycemia. All the Patients with acute or chronic renal failure, Opaque/hazy ocular media preventing fundus visualization, Co-existing ocular disorders likely to mask the findings of diabetic retinopathy, Patients with presence of any of the confounding factors, like fever, active systemic infections, exercise, high protein intake, accelerated hypertension, congestive heart failure, patients not willing to participate in the study were excluded from the study.

The patients underwent thorough history and ocular evaluation which included demographic details and medical history, which was recorded on a preset proforma.

Thorough ocular evaluation was done on all selected patients both clinically as well as with the help of diagnostic instruments. Both Uncorrected and best corrected visual acuity was recorded using a Snellen's chart. Anterior segment evaluation was done using slit lamp examination to look for any other ocular disease or ocular surgery. Amsler Grid Examination was also performed. The intraocular pressure was measured using an applanation tonometer.

Fundus examination was performed by Direct Ophthalmoscopy, Indirect Ophthalmoscopy and +90D lenses. Optical coherence tomography was performed using Cirrus 500 machine manufactured by Carl-Zeiss, Germany to measure the macular thickness, and Fundus Fluorescein Angiography by using Carl Zeiss fundus camera. Diabetic retinopathy was graded as per the ETDRS guidelines.

The biochemical evaluation was done by obtaining 2 ml of blood sample from the patient in a sterile vial and sent to the Department of Biochemistry. All the biochemical assessments were done using an Auto analyzer. All the patients were advised to undergo biochemical investigations for Blood sugar (fasting/pp), Hb_{A1c} taken as Hb_{A1c}. Good Control: = 7.0%: grade1, Fair control: 7.1-8.5%: grade 2; poor control: > 8.5%: grade3^[7]. Urinary albumin to creatinine ratio in a random spot collection of urine and Lipid profile.

Table 1 Sex and Age distribution.

Sex	No. of Cases	Percentage
Sex		
Male	208	46.85
Female	236	53.15
Age group (years)		
Age Group (In Years)	No. of Cases	Percentage
20-40	67	15.09
41-60	243	54.73
61-80	130	29.28
>80	4	0.9

Table 2 Correlation of severity of retinopathy with age.

Age Group (In Years)	Group I (No Retinopathy) (n = 246, 55.41%)		Group Iia (Very Mild to Moderate) (n = 116, 26.13%)		Group Iib (Severe to very Severe) (n = 58, 13.06%)		Group Iic (Proliferative Diabetic Retinopathy) (n = 24, 12.12%)	
	NO.	%	NO.	%	NO.	%	NO.	%
20-40 (n = 67)	50	74.6	10	14.9	7	10.4	0	0
41-60 (n = 243)	132	54.3	74	30.5	28	11.5	9	3.7
61-80 (n = 130)	60	46.2	32	24.6	23	17.7	15	11.5
>80 (n = 4)	4	100	0	0	0	0	0	0

Table 3 Correlation of severity of retinopathy and duration of diabetes mellitus

Duration Of Diabetes (Years)	Group I (No Retinopathy) (n = 246)		Group Iia (Very Mild to Moderate) (n = 116)		Group Iib (Severe to very Severe) (n = 58)		Group Iic (Proliferative Diabetic Retinopathy) (n = 24)	
	NO.	%	NO.	%	NO.	%	NO.	%
<10 years (n = 208)	162	77.9	30	14.4	11	5.3	5	2.4
10-20 years (n = 131)	71	54.2	20	15.3	23	17.6	17	13
21-40 years (n = 75)	7	9.3	42	56	24	32	2	2.7
>40 years (n = 30)	6	20	24	80	0	0	0	0

Table 4 Correlation of Retinopathy and Microalbuminuria.

Micro-Albuminuria Grade	Group I (No Retinopathy) (n = 246)		Group IIA (Very mild to moderate) (n = 116)		Group IIB (Severe To Very Severe) (n = 58)		Group IIC (Proliferative Diabetic Retinopathy) (n = 24)	
	No.	%	No.	%	No.	%	No.	%
Grade 0(n = 187)	167	89.3	18	9.6	2	1.1	0	0
Grade I(n = 154) (2.5-12.5 mg/mmoll)	73	47.4	68	44.2	13	8.4	0	0
Grade II (n = 77) (>12.5-25 mg/mmoll)	6	7.8	30	39	27	35.1	14	18.2
Grade III (n = 26) (>25 mg/mmoll)	0	0	0	0	16	61.5	10	38.5

Table 5 Correlation of Severity of Retinopathy and Total cholesterol

Total cholesterol Level	Group I (No Retinopathy) (n = 246)		Group IIA (Very mild to moderate) (n = 116)		Group IIB (severe to Very-severe) (n = 58)		Group IIC (Proliferative Diabetic Retinopathy) (n = 24)	
	NO	%	No	%	No	%	NO	%
Desirable (<200)(n = 168)	99	58.9	39	23.2	25	14.9	5	3
Borderline high (200-239) (n = 215)	123	57.2	62	28.8	19	8.8	11	5.1
High (>=240) (n = 61)	24	39.3	15	24.6	14	23	8	13.1

Table 6 Trivariate analysis of severity of Retinopathy, Microalbuminuria and S. Cholesterol.

S.Chol. level	No Retinopathy (N=246)		Very mild- moderate (N=116)		Severe-very severeNDPR (N=58)		Proliferative Diabetic Retinopathy (N=24)		Statistically significant	
	No	%	No	%	No	%	No	%	X2	P
Microalbuminuria Grade 0 (n = 187)										
Desirable (n = 77)	67	87.01	9	11.69	1	1.3	0	0	2.46	0.652
Borderline High (n = 93)	83	89.25	9	9.68	1	1.08	0	0		
High (n = 17)	17	100	0	0	0	0	0	0		
Microalbuminuria Grade 1 (n = 154)										
Desirable(n = 52)	31	59.62	16	30.77	5	9.62	0	0	13.858	0.008
Borderline High (n = 80)	35	43.75	42	52.5	3	3.75	0	0		
High (n = 22)	7	31.82	10	45.45	5	22.73	0	0		
Microalbuminuria Grade II (n = 77)										
Desirable(n = 32)	1	3.13	14	43.75	15	46.88	2	6.25	14.112	0.028
Borderline High (n = 30)	5	16.67	11	36.67	8	26.67	6	20		
High (n = 15)	0	0	5	33.33	4	26.67	6	40		
Microalbuminuria Grade III (n = 26)										
Desirable(n = 7)	0	0	0	0	4	57.14	3	42.86	0.399	0.819
Borderline High (n = 12)	0	0	0	0	7	58.33	5	41.67		
High (n = 7)	0	0	0	0	5	71.43	2	28.57		

Table 7 Multivariate analysis for retinopathy.

	B	S.E.	Wald	df	Sig.	Exp(B)
Duration of diabetes (> 20 years)	3.542	0.404	76.938	1	<0.001	34.541
Microalbuminuria	2.998	0.482	39.66	1	<0.001	20.05
HbA1c	2.26	0.324	48.628	1	<0.001	9.583
Total Cholesterol (High or Borderline high)	0.392	0.309	1.611	1	0.204	1.48
Constant	-2.821	0.345	66.972	1	<0.001	0.06

B: β constant, SE: standard error, df: Degree of Freedom.

For the purpose of this study microalbuminuria was further sub graded as-Grade 0: < 2.5mg/mmol; Grade I: 2.5-12.5mg/mmol; Grade II: > 12.5-25mg/mmol and Grade III: > 25mg/mmol for men and Grade 0: < 3.5mg/mmol; Grade I: 3.5-12.5mg/mmol; Grade II: > 12.5-25mg/mmol and Grade III: > 25mg/mmol for women^[8].

Lipid profile was also sub graded as- Desirable (< 200); Border line high (200-239); High (\geq 240)^[9].

The data was analyzed using SPSS software version 15.0. Categorical data chi-square test was used whereas continuous data was analyzed using ANOVA and student "t-test". Multivariate assessment was done using logistic regression. The confidence level of the study was kept at 95% and hence a "p" value of less than 0.05 indicated a statically significant association.

OBSERVATION AND RESULTS

A total of 444 subjects of either gender were included in our study, out of which 236 (53.15%) were females and rest were males (208; 46.85%). The male to female ratio was 0.88:1. Majority of the patients lied in the age group of 41-60 years (54.73%) followed by 61-80 years (29.28%) and 20-40 years (15.09%), while only 4(0.90%) patients were aged > 80 years (Table 1).

On ophthalmologic examination we found that only 198 out of 444 diabetics suffered from diabetic retinopathy and the rest 246 (55.41%) did not show any signs of diabetic changes in the fundus. Out of 198 patients in the retinopathic group, 116 (26.13%) of them suffered from very mild to moderate NPDR, 58 (13.06%) patients showed signs of severe to very severe NPDR and only 24 (12.12%) had proliferative diabetic retinopathy.

A statistically significant association with severity of retinopathy and the age of the patients was observed. None of the 4 patients aged > 80 was suffering from retinopathy. Proportion of Group I (No retinopathy) was higher in younger patients i.e. 20-40 (74.6%) and 41-60 (54.3%) as compared to elderly cases i.e. 61-80 (46.2%) and this difference was found to be statistically significant ($p < 0.001$). (Table 2).

Another statistically significant association was found between the severity of retinopathy and duration of diabetes ($p < 0.001$). It was found that proportion of Group I (non-retinopathy) patients was higher in patients with duration of diabetes < 10 years (77.9%) as compared to patients with duration 10-20 years (54.2%), 21-40 years (9.3%) and > 40 years (20.0%). Majority of patients with duration of diabetes 21-40 years and > 40 years belonged to Group IIA. (Very mild to moderate retinopathy) (Table 3).

Majority of patients (89.3%) of Grade 0 microalbuminuria (< 2.5 mg/mmol) had no Retinopathy. It was found that higher the level of microalbuminuria more is the severity of retinopathy. Proportion of Severe to very severe retinopathy and proliferative diabetic retinopathy were higher in higher grade of microalbuminuria (Grade II and Grade III). A statistically significant association between microalbuminuria grade and severity of retinopathy was observed ($p < 0.001$) (Table 4).

Out Of 444 patients of diabetes, total cholesterol was found to be desirable (< 200 mg/dl) in only 168 (37.84%) patients. Out of these 168 patients with desirable cholesterol majority (58.90%) had no retinopathy (Group I), 25.2% had very mild to moderate retinopathy (Group IIA), 14.90% had severe to very severe retinopathy (Group IIB) and 3.0% had proliferative diabetic retinopathy (Group IC).

A total of 215 (48.42%) patients had borderline total cholesterol level and of these 215 patients. 123 (57.2%) had no retinopathy (Group I), 62 (28.8%) had very mild to moderate retinopathy (Group

IIA). 19 (8.8%) had severe to very severe retinopathy and I I (5.1%) had proliferative retinopathy.

Total cholesterol was found to be high (240 mg/dl) in 61 (13.74%) patients. Prevalence of retinopathy was 60.7%, in patients having high total cholesterol levels. Proportional difference in severity of retinopathy in patients with different total cholesterol levels was found to be statistically significant ($p = 0.002$) (Table 5).

On doing a trivariate analysis between severity of retinopathy, microalbuminuria and serum cholesterol levels, it was observed that in microalbuminuria grade 0, difference in prevalence of retinopathy in patients with different serum cholesterol levels was not found to be statistically significant ($p = 0.652$). In microalbuminuria grade I, prevalence of retinopathy in patients having desirable cholesterol levels was lower as compared to those having borderline or high cholesterol levels and this difference was found to be statistically significant ($p = 0.008$).

In microalbuminuria grade II, proportional differences in grades of retinopathy and serum cholesterol levels were observed and these differences were found to be statistically significant ($p = 0.028$).

In microalbuminuria grade III, majority of patients were suffering from very mild-moderate retinopathy and no statistically significant association between retinopathy and serum cholesterol levels was found ($p = 0.819$) (Table 6).

Multivariate analysis revealed a statistically significant association of Diabetic retinopathy with HbA1c values. High grade Microalbuminuria (Grade II and III Duration of diabetes >20 years). Association between retinopathy and high total cholesterol levels (Borderline high and high) was not found ($p = 0.204$) (Table 7).

DISCUSSION

Diabetes has become a global epidemic affecting children, adolescents, and adults. According to the World Health Organization, approximately 150 million people worldwide currently have type 2 DM (formerly called adult-onset diabetes): The number of people with type 2 DM is estimated to double by 2030^[10]. Diabetes is a disease that is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes. Among different microvascular complications, diabetic retinopathy is the most common^[5].

Microalbuminuria is a nephrotic disorder which if remains untreated progresses to proteinuria and overt diabetic nephropathy. It has been reported that as many as 7% of patients with type 2 diabetes already have microalbuminuria at the time they are diagnosed with diabetes^[2]. Thus microalbuminuria is a microvascular complications that is often accompanied with the diagnosis of type 2 diabetes and in effect may have a crucial role in determining the future course of disease and per se complications associated with it.

A total of 444 diabetic patients with microalbuminuria were enrolled in this study. Majority of patients were females (53.16%) and aged between 41 and 60 years (54.730)^[28]. Contrary to the profile of patients in present series, Chung *et al*^[11] (2011) had majority of male patients (54%) with a mean age of 64.9 ± 10.8 years in the study population, thus, showing the patients in their series to be older than in present study. Similarly a study done on Indian population by us in 2016 showed that prevalence of diabetic retinopathy is significantly higher in men (68.5%) than in women and in those who were 50-70years of age (75.5%)^[27]. Manaviat *et al*^[12] (2004) had majority

of females (58.64%) and mean age of patients comparable to that in present study (54.9 +/- 10.2 years). He *et al*^[13] (2012) had majority of male patients (57%) with mean age of 59.69 +/- 12.28 years. These findings indicate that gender and age of patients with diabetes and microalbuminuria might vary and is a study characteristic rather than being a population characteristic.

Fundus examination findings positive for retinopathy were observed in 198 (44.59%) cases. Thus, prevalence of diabetic retinopathy in type II diabetic cases with microalbuminuria as observed in present study was 44.59%^[28].

In the present study, majority of diabetic retinopathy patients had very mild to moderate non-proliferative diabetic retinopathy (58.58%) followed by severe to very severe non-proliferative diabetic retinopathy (29.29%), Only 24 (12.12%) cases had proliferative diabetic retinopathy. In different cross- Sectional studies, prevalence of different grades of retinopathy have been shown to be of similar order with prevalence of lower grades of retinopathy being higher as compared to higher grades or proliferative retinopathy^[5,14,15,16,17,28].

Retinopathy, a progressive disorder, assumes greater severity if remains undiagnosed and untreated^[18,19] hence late stages (i.e. severe to very severe NPDR and proliferative diabetic retinopathy) are diagnosed at advanced stages of diabetes. The findings in most of the studies^[14,15,16,17], support the rate of proliferative diabetic retinopathy to be lower as compared to non-proliferative diabetic retinopathy.

We also investigated the role of duration of diabetes on causation of diabetic retinopathy among microalbuminuria patients and found that this logical relationship was working perfectly. It was observed that in general, prevalence as well as severity of diabetic retinopathy increased significantly with increasing duration of diabetes. This finding eventually correlates well with the observations of other clinical studies^[2,21,22,23] as well as population studies^[20] which have laid emphasis that early onset of diabetes (\approx longer duration of diabetes) poses increased risk for diabetic retinopathy in general and that in patients with microalbuminuria in particular. We also conducted a study in past in which we found that albuminuria was significantly higher in our patients with diabetic retinopathy than in those without retinopathy^[29]. Owing to sustained hyperglycemia in diabetic patients, longer duration of diabetes causes microvascular complications that include diabetic retinopathy. Hyperglycemia leads to no enzymatic formation of advanced glycosylated end products (AGEs). In experimental studies, AGEs have been found to be associated with formation of microaneurysms and pericyte loss^[4]. Longer duration of diabetes might have a role in promoting AGEs production and hence could result in increased risk of microvascular complications in general and diabetic retinopathy in particular.

Present study shows a significant association between total cholesterol levels and severity as well as prevalence of diabetic retinopathy ($p < 0.001$). Hyperlipidemia is regarded as one of the major factors responsible for diabetic retinopathy apart from hyperglycemia and hypertension^[10]. A significant association between retinal hard exudate secretion and elevated serum lipid levels has also been reported^[24,25]. However, some studies have rejected this relationship^[26] but they are limited in number. On multivariate analysis, we found that duration of diabetes, microalbuminuria and HbA1c levels were independent significant predictors of diabetic retinopathy, but serum cholesterol levels did not show an independent role. These findings suggest that hyperlipidemia has a limited role which is often confounded and that is the reason that in some studies, the role of lipid levels as predictor of diabetic retinopathy and its severity remains unexplained.

CONCLUSION

Duration of diabetes and microalbuminuria have been found to be the independent risk factors for diabetic retinopathy, but serum cholesterol levels did not show an independent role in our study.

Our study was limited by time and limited subjects; hence a better understanding of this relationship could be gathered with the help of longitudinal clinical trials among new onset type 2 diabetic patients. The findings in present study endorsed the view that microalbuminuria poses a risk for diabetic retinopathy which is affected by duration of diabetes, level of glycemic control and lipid levels. The findings in present study are interesting and need further substantiation in longitudinal studies.

REFERENCES

1. World Health Organisation. Prevention of diabetes mellitus. Technical Report Series of Geneva: World Health Organisation, 1994. [DOI: 10.1093/annhyg/9.2.91]
2. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes* 2008; **26**(2): 77-82. [DOI: 10.2337/diaclin.26.2.77]
3. International Diabetes Federation (IDF). IDF Diabetes Atlas, Sixth Edition, 2013. [DOI: 10.1016/j.diabres.2015.05.037]
4. Fong DS, Aiello LP, FL 3rd, Klein R: Diabetic Retinopathy. *Diabetes care* 2004; **27**: 2540-2553. [DOI: 10.2337/diacare.27.10.2540]
5. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33). *Lancet* 1998, **352**: 837-853. [DOI: 10.1016/S0140-6738(98)00090-7]
6. Nguyen TT, Wang JJ, Wong TY. Retinal vascular changes in Pre-Diabetes and Prehypertension: New findings and their research and clinical implications. *Diabetes care* 2007; **30**(10): 2708-2715.17595350. [DOI: 10.2337/dc07-732]
7. American Diabetes Association (ADA).Diagnosis and Classification of Diabetes Mellitus: Position Statement.*Diabetes Care* 2010; **33**(1): 562-569. [DOI: 10.2337/dc10-s062]
8. Rossing P, Hougaard P, ParvingH : Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic nephropathy in type 1 diabetic patients: A 10-Year prospective observational study. *Diabetes Care* 2002 **25**: 859-864. [DOI: 10.2337/diacare.25.5.859]
9. Reddy SC, Kihn YM, Ramil A. Retinopathy in type 2 diabetic patients with microalbuminuria. *Nepal J Ophthalmol.* 2013 Jan; **5**(9): 69-74.23584650. [DOI: 10.3126/nepjo.v5i1.7830]
10. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care.* 2003 Sep; **26**(9): 2653-64. [DOI: 10.2337/diacare.26.9.2653]
11. Chung M-S, Lee J-J, Lee C-T, Shen F-C, Kuo H-K, Huang S-T, Chiou TT-Y, Sun C-K, Yang KD, Liu R-T. Prevalence and risk factors of Taiwanese microalbuminuric type 2 diabetic mellitus with and without diabetic retinopathy. *Acta Nephrologica* 2011; **25**(2): 43-49. [DOI: 10.1156/1471-2458-13-318]
12. Manaviat MR, Afkhami A, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. *BMC Ophthalmology* 2004, **4**: 9 [DOI: 10.1186/1471-2415-4-9]
13. Singh DK, Winocour P, Farrington K. Mechanisms of disease: the hypoxic tubular hypothesis of diabetic nephropathy. *Nat Clin PractNephrol* 2008; **4**: 216-226. [DOI: 10.1038/ncpneph0757]
14. He B-B, Wei L, Gu Y-J, Han J-F, Han J-F, Li M, Liu Y-X, Bao Y-Q, Jia W-P. Factors Associated with Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes Mellitus. *International*

- Journal of Endocrinology* Volume 2012 (2012), Article ID 157940, 8 pages. [DOI: 10.1155/2012/157940]
15. Ichinose K, Kawasaki E., Eguchi K. Recent advancement of understanding pathogenesis of type 1 diabetes and potential relevance to diabetic nephropathy. *Am J Nephrol* 2007; **27**: 554-564. [DOI: 10.1159/000107758]
 16. Singh DK, Winocour P, Farrington K. Mechanisms of disease: the hypoxic tubular hypothesis of diabetic nephropathy. *Nat Clin Pract Nephrol* 2008; **4**: 216-226. [DOI: 10.1038/ncpneph0757]
 17. The Microalbuminuria Collaborative Study Group. Predictors of the development of microalbuminuria in patients with Type I diabetes mellitus: a seven-year prospective study. *Diabet Med.* 1999 Nov; **16**(11): 918-25. [DOI: 10.1046/j.1464-5491.1999.00182]
 18. Wong TY, Mwamburi M, Klein R, Larsen M, Flynn H, Hernandez-Medina M, Ranganathan G, Wirostko B, Pleil A, Mitchell P. Rates of Progression in Diabetic Retinopathy During Different Time Periods: A systematic review and meta-analysis. *Diabetes Care.* Dec 2009; **32**(12): 2307-2313. Keenan HA, Costacou T, Sun JK, Doria A, Cavallerano J, Coney J, Orchard TJ, Aiello LP, King GL: Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. *Diabetes Care* 2007; **30**: 1995-1997. [DOI: 102337/dc06-2222]
 19. Ellis JD, Zvandasara T, Leese G, McAlpine R, Macewen CJ, Baines PS, Crombie I, Morris AD.. Clues to duration of undiagnosed disease from retinopathy and maculopathy at diagnosis in type 2 diabetes: a cross-sectional study. *Br J Ophthalmol.* 2011 Sep; **95**(9): 1229-33. [DOI: 10.1136/bjo.2010.196204]
 20. Cruickshanks KJ, Klein, Ritter LL, Klein R, Moss SE. The association of microalbuminuria with Diabetic Retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology.* 1993 Jun; **100**(6): 862-7. [DOI: 10.1016/s0161-6420(93)31562-9]
 21. Singh DK, Winocour P, Farrington K. Mechanism of disease: the hypoxic tubular hypothesis of diabetic nephropathy. *Nat Clin Pract Nephrol* 2008; **4**: 216-226. [DOI: 10.1038/ncpneph0757]
 22. He B-B, Wei L, Gu Y-J, Han J-F, Li M, Liu Y-X, Bao Y-Q, Jia W-P. Factors Associated with Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes Mellitus. *International Journal of Endocrinology* Volume 2012 (2012), Article ID 157940. [DOI: 10.115/2012/157940]
 23. Chung M-S, Lee J-J, Lee C-T, Shen F-C, Kuo H-K, Huang S-T, Chiou TT-Y, Sun C-K, Yang KD, Liu R-T. Prevalence and risk factors of Taiwanese microalbuminuric type 2 diabetic mellitus with and without diabetic retinopathy. *Acta Nephrologica* 2011; **25**(2): 43-49. [DOI: 10.1111/j.1444-0938.2010.00574]
 24. Chew EY, Klein ML, Ferris FL 3rd, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Arch Ophthalmol.* 1996 Sept; **114**(9): 1079-84. [DOI: 10.1001/archophth.1996.01100140281004]
 25. Agroiya P, Philip R, Saran S, Gutch M, Tyagi R, Gupta KK. Association of serum lipids with diabetic retinopathy in type 2 diabetes. *Indian J EndocrMetab* 2013; **17**(Suppl S1): 335-7. [DOI: 10.4103/2230-8210.119637]
 26. Cetin EN, Bulgu Y, Ozdemir S, Topsakal S, Akin F, Aybek H, Yildrum C. Association of serum lipid levels with diabetic retinopathy. *Int. J. Ophthalmol.* 2013; **6**(3): 346-349. [DOI: 10.1530/endoabs.35.p452]
 27. Garg P, Ahmad L. Prevalence of various stages of Diabetic Retinopathy in patients of Diabetes Mellitus-2; *Journal of Medical Science and Clinical Research.* 2016 Dec; **4**(12): 14903-14908. [DOI: 10.18535/jmscr/v4i12.97]
 28. Garg P, Misra S, Yadav S, Singh L. Correlative Study of Diabetic Retinopathy with HbA1c and Microalbuminuria. *Int. J. Ophthalmic Res* 2018 August; **4**: 282-286. [DOI: 10.1055/b-0038]
 29. Karoli R, Fatima J, Shukla V, Garg P, Ali A. Predictors of Diabetic Retinopathy in Patients with Type 2 Diabetes Who Have Normoalbuminuria. *Annals of Medical and Health Sciences Research.* 2013; **3**(4): 536-540. [DOI: 10.4103/2141-9248.122087]