

Association of Diabetic Retinopathy and Maculopathy with Elevated HbA1c, Blood Pressure, Serum Creatinine, Microalbuminuria, Spot Urine Protein, Nephropathy and Diabetic Kidney Disease. An Experience from Data Analysis of 10,580 Diabetic Patients

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Abstract

Background: Diabetic kidney disease and retinopathy are the most important complications which usually co-exist together with high economic cost, morbidity, and mortality. Current research was designed to study these two complications and their associations with impaired glycemic control, elevated blood pressure, serum creatinine and proteinuria.

Methods: 10,580 patients were selected for this study. Retinopathy was graded as: within normal limits (WNL), non-proliferative diabetic retinopathy (npdr mild, moderate or severe), or proliferative diabetic retinopathy (PDR). For detection of diabetic kidney disease (DKD), patients were screened for elevated serum creatinine, microalbuminuria, and spot urine protein. Serum creatinine ≥ 1.5 mg/dl was labeled as "DKD".

Results: Severity (grading) of retinopathy increases with the advancement of duration of diabetes, HbA1c, serum creatinine, microalbuminuria, spot urine protein, and blood pressure (systolic and diastolic). ANOVA model P-values were significant for all tested variables ($p < 0.0001$ for all). Group of patients with maculopathy have higher levels of HbA1c, duration of diabetes, serum creatinine, microalbuminuria, spot urine protein and creatinine and their ratio (PCR), systolic and diastolic blood pressure with significant p-values. Significant χ^2 associations were observed for retinopathy with hypertension, and nephropathy with DKD (odds ratio 2.29 and 2.1, respectively; $p < 0.0001$ for all). For the development of retinopathy, ROC curve demonstrated cutoff point of 8.9 % (g/dl) for HbA1c, with 67% sensitivity and 50% specificity; 129 mmhg for systolic BP with 70% sensitivity and 55% specificity; and 79 mmhg for diastolic BP with 63% sensitivity and 51% specificity.

Conclusion: We concluded that all diabetic patients should be screened early for the detection of retinopathy, nephropathy, elevated serum creatinine, HbA1c and hypertension to prevent further diabetes complications.

Introduction

There is sufficient research evidence that diabetic retinopathy is associated with diabetic kidney disease (DKD) or chronic kidney disease (CKD) among diabetic subjects. There is also association of type-2 diabetic proteinuria with retinopathy and the kidney function usually deteriorate with the presence of retinopathy. In other words, if both of these complications (retinopathy and nephropathy or DKD) coexists, the prognosis is poor and may lead to end stage renal disease (ESRD) [1-12].

Diabetic retinal disease and pathology is the commonest cause of visual impairment in patients with diabetes. Poor glycemic control, raised blood pressure (BP), duration of diabetes, and microalbuminuria or proteinuria are the main risk factors which initiates and then complicates this pathology [13,14].

The likelihood of developing diabetic retinopathy is related

to the duration of the disease. The rate of onset is variable, but after twenty years after the diagnosis of diabetes, 80% of type-2 diabetics and nearly all type-1 diabetics show some signs of retinopathy [15,16].

The damaged retinal capillaries due to hyperglycemia are weak and possess out-pouchings of the vessel lumens (micro aneurysms), which eventually rupture to form hemorrhages within the retina, confined by the internal limiting membrane (ILM); they appear like dots and are called "dot-and-blot" hemorrhages. These fragile capillaries may leak fluid into the retina. When fluid is deposited under the macula (called "macular edema"), this interferes with the fine vision and common cause of vision loss with diabetic retinopathy (DR). Resolution/reabsorption of this fluid leaves behind the sediment, composed lipid byproducts which appears waxy and yellow (called "hard exudates"). As DR progresses, the blood vessels may also become

obstructed causing oxygen supply compromise and resulting in infarction of the nerve fiber layer, which appears as fluffy, white patches (called "cotton wool spots, CWS") [17].

Although different classification or grading systems are available (such as Early Treatment Diabetic, ETDRS), conventionally, involvement of retina in diabetic state has been classified into three categories; background, preproliferative retinopathy and proliferative retinopathy. Macula may be involved pathologically (called maculopathy/diabetic maculopathy) with any of these forms of retinopathy. Hence, retinopathy which affects the macula is separately described as diabetic maculopathy

For simplicity, retinopathy has also been classified as:

1- No visible retinopathy (within normal limits WNL) or normal fundus

2- Non proliferative diabetic retinopathy, NPDR (i.e., without neovascularization or abnormal blood vessel growth). This is further classified as early or mild non-proliferative retinopathy (micro-aneurysms only); moderate NPDR (characterized by multiple micro aneurysms, dot-and-blot hemorrhages, venous beading, and/or cotton wool spots); severe NPDR (hemorrhages/micro aneurysms, cotton wool spots, venous beading, and severe intra retinal micro vascular abnormalities, IRMA). Within one year, 52-75% of patients falling into this category will progress to PDR [18].

3- Proliferative diabetic retinopathy, PDR (presence of neovascularization on the disc or elsewhere, NVE) and has a potential of serious visual consequences, such as vision loss, and poor prognosis. The retina has a high metabolic requirement; hence with continued ischemia, retinal cells respond by releasing angiogenic chemicals, factors and modulators such as vascular endothelial growth factor (VEGF), which stimulate growth of new retinal blood vessels to maintain the retinal blood supply and leading to the neovascularization. New vessels are leaky, fragile, and often misdirected and these may even grow off the retina and into the vitreous. As the vitreous shrinks with age, it pulls on these fragile vessels, causing rupture of new vessels resulting in a vitreous hemorrhage and sudden vision loss (called separately as "high risk PDR"). The new vessels are also the cause scar formation (with the time) and this result in strong anchors between the retina and vitreous causing tractional retinal detachment with extensive vitreous hemorrhage (defined separately as "advanced PDR") causing sudden vision loss. If not treated urgently (especially with maculopathy), permanent vision loss may result. Involvement of the macula with exudative or ischemic changes has a potential to involve the fovea, thus threatening vision. Exudative maculopathy may be amenable to treatment, but ischemic changes are not (diagnosed ideally by fluorescein angiography). [19-21].

In the past association of nephropathy (and its markers) and blood pressure with retinopathy have not been studied. Under this literature review and research background, our objective was to investigate association of diabetic retinopathy (and maculopathy) with impaired glycemic control, elevated blood pressure and with diabetic kidney disease markers (creatinine,

microalbuminuria, and spot urine protein); and to study the association of diabetic retinopathy and diabetic kidney disease.

Methods

This is a prospective cross sectional analytical and cohort study, conducted at the diabetology clinic of Aseer Diabetes Center of Aseer Central Hospital, Ministry of Health Saudi Arabia. Study duration was more than 12 years, from August 2005 until September 2017. The study recruited 10,580 diabetic patients (after exclusion criteria) who, were followed up in this clinic. Study included both type-1 and type-2 diabetic patients. Children (less than 13 years of age), patients with severe liver or hepatic disorders, patients demonstrating urinary tract infection, known cases of nephrotic syndrome or retinopathy before the onset of diabetes, patients with end stage renal disease (ESRD) or dialysis and pregnant women were excluded from the study.

Systolic and diastolic blood pressure (BP, in mmHg) were measured by standardized methodology in resting position. Retinopathy was graded as: Within Normal Limits (WNL), Non-Proliferative Diabetic Retinopathy (NPDR either mild, moderate or severe), or Proliferative Diabetic Retinopathy (PDR), according to International Clinical Diabetic Retinopathy (DR) Disease Severity Scale [22]. Fundus or retina was examined by using computerized digital fundus photography camera (NIDEK Corporation, USA; approved by FDA for fundus photography). The data were reviewed by electronic file system and hospital information system (details given below).

Laboratory Methods

All samples were collected in fasting state of 12 hours, early in the morning. Both serum creatinine (mg/dl) and urine creatinine (mg/dl) were quantitatively measured by CREA methodology by Dimension® clinical chemistry system and device (Siemens Healthcare Diagnostics Inc. Newark, DE 19714, USA). The technique for the measurement of creatinine in plasma and urine involved picrate which, in the presence of a strong base NaOH, chemically reacts with creatinine to form a red chromophore. The rate of increasing absorbance at 510nm due to the formation of this chromophore is directly proportional to the creatinine concentration in the sample of blood or urine and which, is measured using by a bichromatic (510,600nm) rate methodology. Hence, creatinine in the plasma was determined quantitatively [23-25].

Spot urine protein was measured by UCFP (Urinary/Cerebrospinal Fluid Protein) method on Dimension® clinical chemistry system (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A). This is in vitro diagnostic test intended for the direct quantitative determination of total protein in human urine and cerebrospinal fluid, which is an adaptation of pyrogallol red molybdenum method by Y. Fujita, I. Mori and S. Kitano [26]. In the reaction sequence, pyrogallol red combined with sodium molybdate to form a red complex with maximum absorbance at 470 nm. The protein in the sample reacted with this complex in acid solution to form a bluish-purple colored complex, which absorbs at 600 nm. The absorbance at 600 nm was directly proportional to the concentration of protein in the sample. The

analyte concentration was determined by calculation using a logit curve fit on a previously stored calibration curve. PCR (protein to creatinine ratio) was measured by spot urine protein / spot urine creatinine.

HbA1c was measured by A1c Flex® Reagent by the Dimension® clinical chemistry system, in vitro diagnostic assay for the quantitative determination of both percent hemoglobin A1c and total hemoglobin, based on a turbid metric inhibition immunoassay (TINIA) principle, and the measurement of total hemoglobin is based on a modification of the alkaline hematin reaction, an NGSP certified methodology (Siemens healthcare diagnostics Inc. Newark, DE 19714, USA). The percentage of total hemoglobin that is glycated was calculated and reported as %HbA1c (in g/dL), and final result has been standardized to the results obtained in DCCT.

For the detection of nephropathy and presence of albumin or protein in urine, fasting urine samples were examined for the presence of microalbuminuria, macro albuminuria or proteinuria. All urine samples were first examined for the presence of gross proteinuria by Quick Check™ urinalysis reagent strips (ACON biotech, Co., Ltd.) to rule out macro albumin in urine. This technique is based on the phenomenon of pH indicators which releases hydrogen ions to the protein. Samples which demonstrated macro albuminuria (in mg/dl) or gross proteinuria by the color indicator of the reagent strips (ranging from 1+ to 4+) were defined/labeled as “nephropathy”. Samples with negative albumin were further examined for the presence of micro albumin in urine by MALB method used by Dimension® clinical chemistry system and device, in vitro diagnostic test for quantitative measurement of albumin (mg/L) in human urine by particle-enhanced turbid metric inhibition immunoassay (PETINIA) methodology (Siemens Healthcare Diagnostics Inc. Newark, DE 19714, USA). Samples demonstrating microalbuminuria (albumin excretion in urine in the range of 30-300 mg/L) were also labeled and defined as nephropathy.

Patients demonstrating levels of serum creatinine > 1.5 were defined as chronic renal/kidney disease (CRD/CKD) and these diabetic subjects were also considered “diabetic kidney disease” (DKD). Furthermore, patients demonstrating microalbuminuria or gross proteinuria were labeled as “nephropathy”.

All laboratory sample requests were entered in a computer software and results retrieved by Natcom Hospital Information System (NATCOM HIS; National Computer System Co. Ltd [27].

Statistical Methods

Patients’ data were analyzed by IBM® SPSS® statistics, version 20, for Microsoft windows. All statistical tests were applied according to the available standard medical statistical methods. Data were summarized as percentages with mean ± SD and 95%CI for the variables.

ANOVA methodology was utilized to measure significant associations between the retinopathy groups and continuous variables, while assuring that all participants/data and their groups were independent. Post-hoc tests, least significant difference LSD and Bonferroni were also performed to assess

the significant difference between the means of the groups of the graded retinopathy.

χ² test (chi-square test for independence and association / Pearson’s chi-square test) was utilized for significant analysis of diabetic retinopathy with nephropathy and DKD associations. Logistic Regression, Odds Ratio and Protective Odds Ratio were used to measure associations of retinopathy with hypertension, nephropathy and DKD. Statistical power of 90% was built for detection of significance and p-values (two-sided) of less than 0.05 were considered significant. This study was reviewed and approved by the research committee of Aseer Diabetes Center, and all methodologies on subjects reported in current study were in accordance with the Helsinki Declaration of 1975 (revised in 2008).

Results

Demographic data for the patients are presented in Table-1. Hypertension was observed in 43% of patients and 37% demonstrated nephropathy; while 13% demonstrated DKD/CKD.

Regarding retinopathy, the data are shown in table-2. Overall, 56% demonstrated normal fundus, while 44% demonstrated retinopathy during fundus examination. Retinopathy and fundus screening status is presented in table-2. Descriptive statistics for variables are shown in table-3.

Table-4 demonstrates the ANOVA statistics between variables and different stages of retinopathy. It is evident from the table that severity of retinopathy (and its grading) increases with the advancement of duration of diabetes, HbA1c, serum creatinine, microalbuminuria, spot urine protein, and blood pressure (systolic and diastolic). It can be observed that p-values for ANOVA model are significant for all tested variables (< 0.0001 for all; 0.002 for urine creatinine).

Patients with maculopathy were analyzed separately (regardless of stages of retinopathy). The data for the patients with maculopathy is shown in table-5. This table demonstrates levels of HbA1c, duration of diabetes, serum creatinine, microalbuminuria, spot urine protein and creatinine and their ratio (PCR), systolic and diastolic blood pressure. It is evident that there is a significant difference between the group of patients with or without maculopathy, with significant p-values.

Parameters	Description with N (%) ; Totals = 10,580	
	Male	Female
Gender	6242 (59%)	4338 (41%)
Type of Diabetes	Type-1 1587 (15%)	Type-2 8993 (85%)
Nephropathy	Positive 3914 (37%)	Negative 6666 (63%)
Hypertension (HTN)	Positive 4549 (43%)	Negative 6031 (57%)
Diabetic Kidney Disease (DKD) status	Positive 1481 (14%)	Negative 9099 (86%)

Table-2: Fundus photography / retinopathy screening status

Diabetic Retinopathy Status (N;%)	
Normal (no diabetic retinopathy)	56 %
Patients with diabetic retinopathy (total numbers)	44 %
Mild NPDR	24 %
Moderate NPDR	11 %
Severe NPDR	4 %
Proliferative DRP	5 %
Overall patients with Maculopathy	14 %

Table-3: Descriptive statistics for the variables with mean \pm SD

Variables	Mean \pm SD
Age (years)	53 \pm 13.5
Diabetes duration (years)	17 \pm 8.7
Serum creatinine (mg/dl)	0.967 \pm 0.593
HbA1c % (g/dl)	7.88 \pm 1.51
Micro albumin in urine (mg/L)	67 \pm 103
Spot Urine protein	52.8 \pm 28.9
Urine creatinine mg/dl	119.6 \pm 71.87
Protein to creatinine ratio (PCR)	.6025 \pm 2.06
Systolic BP	128.7 \pm 16.4
Diastolic BP	79.23 \pm 9

Table-4: ANOVA statistics between variables and the the graded retinopathy

Type of DiabeticRetinopahty (grading) with mean \pm SD 95% CI ; p-values							
Variables and indicators	Within Normal Limits	Mild NPDR	Moderate NPDR	Severe NPDR	Proliferative diabetic retinopathy (PDR)	ANOVA statistics ; Post-hoc tests	ANOVA model p-values
HbA1c % (g/dl)	7.62 \pm 1.51 7.49 to 7.75	8 \pm 1.31 7.8 to 8.3	8.1 \pm 1.47 7.9 to 8.4	8.22 \pm 1.29 7.7 to 8.3	8.36 \pm 1.3 8 to 8.7	F = 7.23; LSD and Bonferroni p-values < 0.05	< 0.0001
Duration of diabetes	14.8 \pm 7.8 14.3 to 15.4	22.5 \pm 8.4 21.6 to 23.5	25 \pm 7.24 23.7 to 26.1	27.2 \pm 7.25 24.4 to 30	28.77 \pm 7.78 27 to 30.4	F=128; LSD and Bonferroni p-values < 0.05	< 0.0001
Serum creatinine (mg/dl)	0.87 \pm 0.475 0.836 to 0.903	0.976 \pm 0.636 0.904 to 1	1.1 \pm 0.943 0.956 to 1.26	1.13 \pm 0.568 0.908 to 1.35	1.5 \pm 1.31 1.2 to 1.78	F = 19; LSD and Bonferroni p-values < 0.05	< 0.0001
Micro albu-min in urine (mg/L)	35 \pm 18 28.3 to 39	70 \pm 65.5 55 to 84.9	141 \pm 101 92 to 160	180 \pm 115 102 to 183	193 \pm 131 133 to 198	F = 13.8; LSD and Bonferroni p-values < 0.05	< 0.0001
Spot Urine protein (mg/dl)	31.9 \pm 28.7 22.6 to 41	58.46 \pm 40.8 36 to 90.5	70 \pm 69.3 55.6 to 120	152 \pm 138 130 to 239	209 \pm 196 189 to 396	F = 12.4; LSD and Bonferroni p-values < 0.05	< 0.0001
Urine creatinie mg/dl	126 \pm 65 120 to 135	112.3 \pm 55.5 107 to 130	108 \pm 54.53 97 to 116	103 \pm 48.8 90 to 134	88.78 \pm 39.7 77.6 to 100	F = 4.5; LSD and Bonferroni p-values < 0.05	0.002

PCR	0.2 ± 0.13 0.12 to 0.21	0.61 ± 1.58 0.4 to 0.85	1.07 ± 2.7 0.58 to 1.65	1.79 ± 3.22 0.89 to 2.7	2.6 ± 7 0.99 to 5.7239	F = 13.2; LSD and Bonferroni p-values < 0.05	< 0.0001
Systolic BP	124 ± 15 123 to 126	132.5 ± 15.6 130.5 to 134.4	135.5 ± 15.6 133 to 137	136.5 ± 12.4 132 to 143	141 ± 19.5 139 to 148.5	F = 33; LSD and Bonferroni p-values < 0.05	< 0.0001
Diastolic BP	78 ± 8.5 77 to 78.6	79.9 ± 8.9 78.7 to 80.75	82.3 ± 9.2 78.9 to 82.84	83.54 ± 9.4 79 to 84.12	85.49 ± 9.56 81.5 to 85.5	F = 11; LSD and Bonferroni p-values < 0.05	< 0.0001

Table 5: T-test for the variables with and without maculopathy

Variables	Mean ± SD ; 95% CI		T-statistics		
	With Maculopathy	Without Maculopathy	F-value	T-value	P-value
HbA1c % (g/dl)	8.3 ± 1.5 ; 8 to 8.6	7.7 ± 1.46; 7.6 to 7.9	2.1	3.7	0.001
Duration of diabetes	27.2 ± 7.8 ; 26 to 28.5	17.7 ± 8.86; 17.2 to 18.3	2.5	13.1	<0.0001
Serum creatinine (mg/dl)	1.3 ± 1.17 ; 1.13 to 1.5	0.91 ± 0.56; 0.883 to 0.947	75.4	7	<0.0001
Micro albu-min in urine (mg/L)	99.3 ± 138; 69.9 to 128.5	64.4 ± 109; 56.3 to 72.4	10.5	2.74	0.001
Spot Urine protein (mg/dl)	82.7 ± 143; 53.6 to 112.7	50.4 ± 119; 38.3 to 62.5	5.6	2.1	0.02
Urine creatin mg/dl	97.5±46.9; 87.9 to 106.9	122.7±117.4 to 128.4	6.6	3.1	0.001
PCR	1.1±2.1 ; 0.68 to 1.52	0.55 ± 1.9; 0.398 to 0.6	8.9	2.4	0.03
Systolic BP	137±17; 135 to 140	127± 15; 126 to 129	3.2	5.6	<0.0001
Diastolic BP	83.6± 8.8; 80.5 to 83.4	78±7.9; 77.4 to 79.2	2.7	4.3	<0.0001

Table-6 demonstrates significant associations between retinopathy and HTN, nephropathy and DKD.

It can be observed from the table that χ^2 value and odds ratio for retinopathy with HTN, nephropathy and DKD are 55.2 and 2.29 (95% CI 1.84 to 2.86), 42.6 and 2.1 (95% CI 1.7 to 2.63), 21.2 and 2.7 (95% CI 1.74 to 4.1) respectively with significant p-values (< 0.0001 for all).

To explore the cutoff values for HbA1c and blood pressures, receiver operating curve (ROC) was used. Table-7 demonstrates the cut off value for HbA1c for the development of diabetic retinopathy; HbA1c 8.9 % (g/dl) was found to be cutoff point for the development of retinopathy with 67% sensitivity and 50% specificity (AUC = 0.61; 95% CI 0.58 to 0.64; p<0.0001). Graphically, this is presented in figure-1.

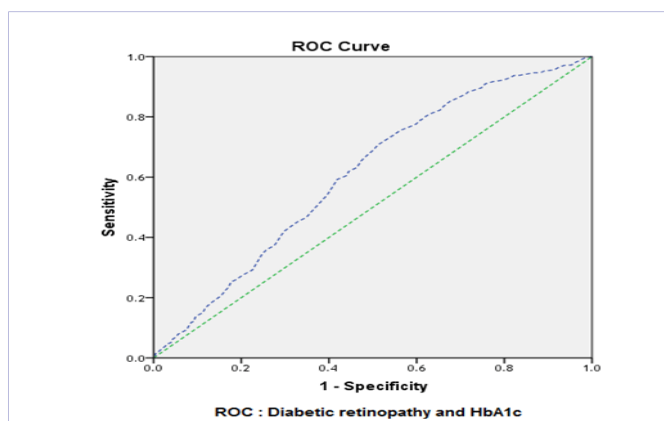


Figure 1: ROC curve for retinopathy and HbA1c

ROC curve values and statistics for diabetic retinopathy and cutoff values for systolic and diastolic BP are demonstrated in table-8. The cutoff point for the systolic BP and development of retinopathy was observed to be 129 mmHg with 70% sensitivity and 55% specificity (AUC = 0.662 ; 95% CI 0.633 to 0.691; p<0.0001). The cutoff point for the diastolic BP and development of retinopathy was found to be 79 mmHg with 63% sensitivity and 51% specificity (AUC = 0.585; 95% CI 0.555 to 0.616; p< 0.0001). This relationship is demonstrated graphically in figure 2 and 3, respectively.

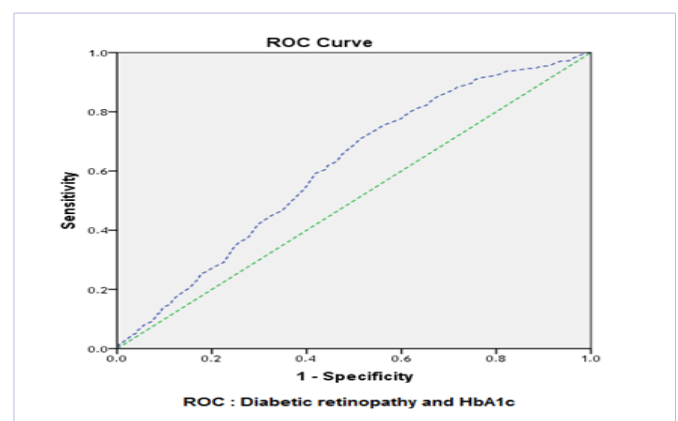


Figure 2: ROC curve for diabetic retinopathy and systolic BP

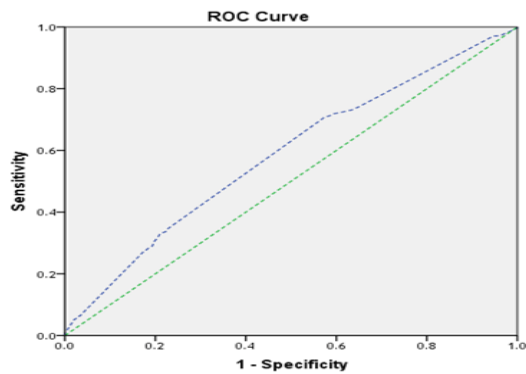


Figure 3: ROC curve for diabetic retinopathy and diastolic BP

Discussion

Present study was initiated to investigate the associations of elevated HbA1c and blood pressure with the development of retinopathy and Diabetic kidney disease; our aim was also to find cutoff values for HbA1c, systolic and diastolic blood pressures; our data has demonstrated significant associations with the conclusion that all diabetic patients should be screened early for the diabetes complications.

The complications of diabetes usually co-exist and progress together, if diabetes state is uncontrolled. Diabetic nephropathy (DN) and retinopathy also usually progress together. Type-2 diabetic subjects with proteinuria and retinopathy usually have a glomerulopathy or renal pathology. Furthermore, presence of retinopathy suggests that diabetic proteinuria or albuminuria

Table 6: Chi square test (χ^2) with logistic regression and odds ratio for retinopathy, nephropathy and DKD.

Variables tested for χ^2	Chi-square statistics with odds ratio and 95% CI				
	χ^2 Value	Fisher's exact test p-value	Linear-by-linear Association p-value	χ^2 p-value	Logistic Regression and Odds Ratio (95% CI)
Retinopathy and HTN	55.2	< 0.0001	< 0.0001	< 0.0001	2.29 ; 95 % CI 1.84 to 2.86
Retinopathy and nephropathy	42.6	< 0.0001	< 0.0001	< 0.0001	2.1 ; 95% CI 1.7 to 2.63
Retinopathy and DKD/CKD	21.2	< 0.0001	< 0.0001	< 0.0001	2.7 ; 95% CI 1.74 to 4.1

Table-7: Results of ROC with AUC, 95%CI, p-values and HbA1c cut off points

Test variables	Area under the curve (AUC)	Standard error	95% CI	P-Value	Coordinate HbA1c cutoff points for the development of diabetic retinopathy
Diabetic retinopathy and HbA1c	0.61	0.015	0.580 to 0.640	< 0.0001	8.9 % (g/dl) (67% sensitivity and 50% specificity)

Table 8: Results of ROC with AUC, 95% CI, p-values and triglyceride cutoff points

Test variables	Area under the curve (AUC)	Standard error	95% CI	P-Value	Coordinate blood pressure cutoff points for the development of diabetic retinopathy
Diabetic retinopathy and systolic BP	0.662	0.015	0.633 to 0.691	< 0.0001	129 mmHg (70% sensitivity and 55% specificity)
Diabetic retinopathy and diastolic BP	0.585	0.016	0.555 to 0.616	< 0.0001	79 mmHg (63% sensitivity and 51% specificity)

is due to diabetic glomerulopathy or glomerulosclerosis (DKD). Association of diabetic glomerulosclerosis (or DKD) with retinopathy has been found in the research literature [28-36].

Retinopathy can be considered a risk marker and not a risk factor for the development of diabetic kidney disease since these micro vascular complications (diabetic nephropathy and diabetic retinopathy) share common determinants, such as poor glycemic,

elevated blood pressure, and elevated lipids [37-39]. Diabetic retinopathy is one of the most common reasons for visual loss or blindness for the age group between 20 to 74 year-old adults [40,41].

Microalbuminuria, a phenotype and marker of early diabetic nephropathy/DKD, is one of the risk factors of gross proteinuria or macro albuminuria in the progression of disease. Additionally,

macro albuminuria itself is a risk factor for the development of decline in renal function and DKD [42-45].

Recently, it has been demonstrated that DR a risk factor for all-cause mortality, atherosclerosis, myocardial infarction or cardiovascular disease [22]. Co-existence of retinopathy with nephropathy usually indicates that nephropathy is due to diabetes and termed as diabetic kidney disease (DKD) or diabetic proteinuria. However, especially in type-1 diabetics, the presence of proteinuria in association with short diabetes duration and/or rapid decline of renal function, especially in the absence of diabetic retinopathy, warrants the need for renal biopsy [46-55].

Furthermore, research have demonstrated that both microalbuminuria and DR predict decline in renal function and development of CKD/DKD [56-62]. One of the common risk factor for the development of nephropathy and retinopathy is elevated blood pressure. Hypertension (HTN) usually aggravates nephropathy (or DKD) and retinopathy, and HTN must be controlled as it usually aggravates and complicates nephropathy and retinopathy [63-67].

While the effects of neovascularization in proliferative diabetic retinopathy (PDR) can be destructive with poor prognosis, the most common cause of vision loss among diabetic patients is macular edema or maculopathy. Macular edema may occur in NPDR, however it is more common in more severe cases of PDR due to leakage within neovascularization regions [68]. Furthermore, neovascularization can grow into the angle of the anterior chamber, causing obstruct outflow of aqueous fluid and ultimately resulting in acute glaucoma. Patient with DR usually do not have symptoms, which further delays the treatment. Hence, early retinopathy screening is essential to prevent complications of the diabetic eye disease or blindness [69-71].

Additionally, screening for nephropathy is as important as retinopathy screening. This can be achieved by routine urinalysis to detect presence of proteinuria. Early or incipient nephropathy can be detected by micro albumin in urine. Currently, spot urine protein and its ratio with urine creatinine, termed as protein to creatinine ration (PCR), is also recommended as this technique is easy and simple to perform. PCR ratio of up to 0.2 mg/mg is considered normal. Spot urine protein/creatinine relation can be interpreted as follows: normal ratio < 0.2g protein per gram creatinine (which correlates with 0.2g protein/day); nephrotic range ratio > 3.5 (which correlates with 3.5g protein). 300mg/day or higher is obviously abnormal and this higher value correlates to an approximate PCR of 0.2mg/mg (200mg/g) [72-81].

Several conditions, including marked hyperglycemia and hypertension, may cause transient elevations of urinary albumin or proteinuria. Hence, control of blood pressure and hyperglycemia is essential to prevent development and progression of nephropathy [82-85]

Current study was designed to investigate the associations of retinopathy with the development of diabetic kidney disease under the influence of high HbA1c, blood pressure and proteinuria, which, to our best knowledge, has not been investigated in the past medical history.

Our data analysis has demonstrated that 43% were diagnosed with HTN, 37% with nephropathy, 14% with DKD while 44% demonstrated diabetic retinopathy. We analyzed the data for maculopathy separately and its associations with other variables. Overall, 14% of patients demonstrated maculopathy.

Table-3 demonstrates levels or grading of diabetic retinopathy with levels of HbA1c, duration of diabetes, serum creatinine, micro albumin in urine, spot urine protein, spot urine creatinine, PCR, systolic and diastolic blood pressures. It is evident from the table that all variable values increase with increasing levels of retinopathy. ANOVA model demonstrates significant p-values (< 0.0001 for all variables).

We analyzed data for maculopathy separately as it can be present at any stage of retinopathy. It is evident from table-4 that patients with maculopathy have long duration of diabetes, higher levels of HbA1c, serum creatinine, microalbuminuria, spot urine protein and creatinine with PCR, and elevated systolic and diastolic blood pressures with significant p-values. All this data signifies the importance of good glycemic control, and blood pressure control to prevent development and progression of nephropathy and retinopathy. Best possible efforts should be done to control elevated blood glucose levels by oral agents or insulin. Under these circumstances, control of hyperlipidemia will be essential also to prevent further complications diabetes. Additionally, patients with diabetic foot or low ankle brachial index (ABI), with nephropathy and/or retinopathy should be given special attention as these subjects have poor prognosis. Furthermore, patients with hypothyroidism should be screened also for elevated blood pressure, elevated lipids and presence of proteinuria as this endocrine condition predisposes for the diabetes complications [86-96]

Regarding patients with diabetes and advanced renal disease or DKD, physicians must also screen for the presence of anemia. It should be noted that, anemia may occur even before the onset of advanced kidney failure or DKD (serum creatinine < 1.8mg/dl); this is due to erythropoietin deficiency. Furthermore, anemia is considered a risk factor for the progression of kidney disease and retinopathy. Such patients must be referred to nephrology specialist care units and it is recommended starting erythropoietin treatment when hemoglobin levels are less than 11 g/dl, with the targets of 12-13 g/dl. HTN should be monitored with erythropoietin therapy as this may increase blood pressure [97,98]. Hence, management of DKD or CKD may be challenging and needs diabetologist and nephrologist, and other specialties consultation for proper workup. All efforts should be done to screen diabetic patients for HTN, dyslipidemia, nephropathy and retinopathy; multidisciplinary approach is also required at tertiary care diabetes centers. Further research at multicenter level is required to confirm findings and reports of the current study.

Conclusion

In tertiary care diabetes centers, early screening for nephropathy, retinopathy and dyslipidemia is recommended; to avoid diabetes related renal and ophthalmic complications. Blood glucose and blood pressure control should be on the targets as

these conditions aggravate diabetes related complications. Best available guidelines and medications should be used according to the evidence based medicine and recent clinical trials [87,99-106]

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