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Research Article

The Association between Diabetic Retinopathy and Diabetic Nephropathy among Patients with Type 2 Diabetes Attending PSMMC Primary Health Care Center in Riyadh, Saudi Arabia

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Abstract

Background: Worldwide, type 2 Diabetes Mellitus (DM) is a public health concern and a major cause of morbidity and mortality. In general, most type 2 diabetic patients are managed in primary healthcare centers. Screening for Diabetic Retinopathy (DR) must not be neglected among patients, and studies suggest that DR is a predictive factor for Diabetic Nephropathy (DN). **Aim:** To evaluate the possible associations between retinopathy and nephropathy in Saudi patients with type 2 DM attending family medical centers. **Methodology:** A retrospective study included patients with type 2 diabetes reporting for fundus photography at the Retina Clinic at Al-Wazarat center, Prince Sultan Military Medical City (PSMMC) in Riyadh, Saudi Arabia between January 2019, and December 2021. The collected data included age, gender, clinical parameters including duration of current diabetic status, value of HbA1c, stage of DR, presence of macular edema, presence of hypertension (HTN), DM medication, and presence or absence of microalbuminuria or macro albuminuria. **Results:** The study sample included 364 patients with type 2 DM. The results showed that 50% of the patients had DR, and 37.6% of the patients had DN, that they were aged ≥ 55 years, the duration of DM (5 - < 10, 10 - < 15, 15 - < 20, ≥ 20 years), and HbA1C level (7.9%, 8%–8.9%, 9%–9.9%, ≥ 10%) associated with the significant risk of DR (OR = 1.59, $P = 0.042$), (OR = 2.60, 10.15, 18.33, and 12.99; $P = 0.015$, < 0.001, < 0.001, and < 0.001), and (OR = 6.26, 6.41, and 8.23, and $P < 0.001$), respectively. In addition, DM medication has associated risk factors with DR (OR = 10.90, 10.18, and $p < 0.001$) for insulin and oral and insulin, respectively. There was a significant association between DR and DN among type 2 diabetes patients ($p = 0.002$). Macro albuminuria > 300 mg\g and the GFR level at Stage 2 and Stage 3b are associated with a significant risk of DR (OR=6.07, $P < 0.001$) and (OR = 1.88, 5.40 $P = 0.007$, 0.004, respectively). Diabetic nephropathy was an associated significant risk factor for DR (OR = 1.99, $P = 0.002$). **Conclusion:** Our study extends these results by demonstrating that there is a correlation between DR and DN.

Background

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia. The underlying cause of diabetes varies by type. Type 1 diabetes mellitus (T1DM) is the result of an autoimmune response that triggers the destruction of insulin-producing β cells in the pancreas. Type 2 diabetes mellitus (T2DM) has a strong genetic component and lifestyle risk factors [1]. Globally, the prevalence of diabetes in adults has been increasing in recent decades. In 2015, it was estimated that there were 415 million people with diabetes aged 20-79 years, and

the number was predicted to rise to 642 million by 2040 [2]. The number of people with diabetes is increasing due to population growth, urbanization, obesity, and a sedentary lifestyle [3].

Type 2 diabetes is associated with multiple comorbidities, including but not exclusive to DR and DN. Diabetic retinopathy is a microvascular disorder that eventually leads to blindness in patients with DM. It is the most common cause of blindness among working-aged adults around the world [4]. The global estimate of the prevalence of DR is 93 million people with DR: 17 million with proliferative DR, 21 million with diabetic macular edema, and 28 million with Vision-Threatening Diabetic Retinopathy (VTDR) [5]. Nephropathy is a major cause of morbidity and a key determinant of mortality in patients with diabetes [6]. Diabetic nephropathy is a syndrome characterized by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, and a loss of the Glomerular Filtration Rate (GFR) in diabetics [6,7]. In most countries, it is the leading cause of End-Stage Renal Disease (ESRD) [8]. The prevalence of DN is still rising dramatically; the cumulative risk of developing ESRD in both T1DM and T2DM following five years of consistent proteinuria is estimated to be 40% [9].

Many studies have suggested that DR is a predictive factor for DN in type 2 patients with DM. Severe forms of DR are readily detectable in diabetic patients with proteinuria or those on dialysis; however, the correlation of DR with DN, especially in the early stages, is not fully understood [10]. A meta-analysis has suggested a potential role for DR in predicting DN in T2DM patients with renal disease and has proposed DR as useful in diagnosing or screening patients [11]. However, few studies have demonstrated an association between DN and DR in T2DM patients in Saudi Arabia. The goal of our study is to recognize associations between retinopathy and nephropathy in the Saudi Arabian population attending family medical centers, with the possibility of recognizing correlation and current trends of investigations to facilitate treatment and develop preventive measures in diabetic patients. To our knowledge, this is the first study of its kind in our center, Prince Sultan Military Medical City (PSMMC), in Riyadh, Saudi Arabia.

Methods

A retrospective study was approved by the institutional review board, and approval was obtained in advance by the ethics and research committee of PSMMC in Riyadh, Saudi Arabia, and was conducted in accordance with the guidelines of the Helsinki Declaration. All of the patients' data were extracted from their medical records. The criteria for inclusion in this study were all type 2 diabetic patients reporting to the Retina Clinic for fundus photography between January 2019 and December 2021. Patients with hazy ocular media, in which fundus assessment was not possible, and patients with other retina disorders, such as hypertensive retinopathy and retinal vein occlusion, were excluded from the study. The collected data were age, gender, clinical parameters, including duration of current diabetic status, value of HbA1c, stage of DR, presence of macular edema, presence of Hypertension (HTN), DM medication, and presence or absence of microalbuminuria or macro albuminuria.

The sample size was calculated by $n = \frac{Z\alpha/2^2}{\mathbb{E}^2} \times P(1-P)$, where P stands for the prevalence of DR in Riyadh from previous literature ($P = 31\%$) [12,13]. The estimated sample size was 362 individuals with a confidence of 95%, and confidence interval of 5%. Ten percent of the sample size was added to compensate for missing patients.

The data were analyzed using the Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, USA). Categorical variables were expressed as percentages. The chi-square test was used for categorical variables. Univariate logistic regression was used to assess the factors associated with DR among patients with type 2 diabetes, and a p-value < 0.05 was considered statistically significant.

Results

The study sample included 364 patients with type 2 DM, more than two-fold of them were aged 55 years and above, and the females represented the higher percentage with 205 (56.3%). More than half of the patients had had DM for 10 years or longer. More than 76% of the patients had HbA1C levels of 8% or more. Of the sample, 182 (50%) patients had DR, and 137 (37.6%) patients had DN. Sixty-six (36.7%) of the patients had mild Non-Proliferative Diabetic Retinopathy (NPDR), and 87 (23.9%) had macular edema. Almost two-fold of the patients had a normal range (< 30 mg\g) of albumin-creatinine ratio. Of the patients, 173 (47.5%) had Stage 1 GFR levels, 230 (63.2%) had HTN, and 223 (61.3%) took both oral and insulin medications (Table 1).

		Number	%
Age	25 - 34	7	1.9
	35- 44	30	8.2
	45- 54	77	21.2
	55- 64	157	43.1
	65 and above	93	25.5
Gender	Male	159	43.7
	Female	205	56.3
Duration of DM by years	<5	70	19.2
	5-< 10	95	26.1
	10-< 15	81	22.3
	15-< 20	53	14.6
	≥20	65	17.9
HbA1C level	7%-7.9%	86	23.6
	8%-8.9%	79	21.7
	9%-9.9%	73	20.1
	10% and above	126	34.6
Has Diabetic Retinopathy (DR)?	Yes	182	50.0
	No	182	50.0
If Yes, What type of DR?	Mild NPDR	66	36.7
	Moderate NPDR	59	32.8
	Sever NPDR	37	20.6
	PDR	18	10.0
Has Macular Edema?	Yes	87	23.9
	No	277	76.1
Albumin\ Creatinine Ratio	Normal < 30 mg\g	237	65.1
	Micro albuminuria 30 -299 mg\g	81	22.3
	Macro albuminuria >300 mg\g	46	12.6
GFR level	Stage 1=>90	173	47.5
	Stage 2=60-89	131	36.0
	Stage 3a=45-59	32	8.8
	Stage 3b=30-44	18	4.9
	Stage 4=15-29	9	2.5
	Stage 5=<15	1	.3
Has Diabetic Nephropathy (DN)?	Yes	137	37.6
	No	227	62.4
Has HTN	Yes	230	63.2
	No	134	36.8

DM Medication?	Oral	125	34.3
	Insulin	16	4.4
	Both	223	61.3

Table 1: Characteristics of the patients (n=364).

The association between DR and DN among patients with type 2 diabetes is shown in Table 2. There is a significant association between DR and DN among patients with type 2 diabetes (p-value = 0.002).

		Has Diabetic Nephropathy (DN)				P value
		Yes (n=137)		No(n=227)		
		Number	%	Number	%	
Has Diabetic Retinopathy (DR)	Yes (n=182)	83	60.58	99	43.61	0.002*
	No(n=182)	54	39.42	128	56.39	
*Significant p value						

Table 2: Association between Diabetic Retinopathy and Diabetic Nephropathy among Patients with Type 2 Diabetes.

The results showed a significant difference between patients with DR and patients without DR, according to the duration of DM, HbA1C levels, macular edema, albumin-creatinine ratio, GFR level, DN, and DM medication with p-values < 0.001, < 0.001, < 0.001, < 0.001, 0.001, 0.002, and < 0.001, respectively. Table 3 shows the characteristics of the patients by retinopathy state.

		DR(n=182)		Non- DR(n=182)		P value
		Number	%	Number	%	
Age	25-34	4	2.2	3	1.6	0.138
	35-44	9	4.9	21	11.5	
	45-54	35	19.2	42	23.1	
	55-64	83	45.6	74	40.7	
	65 and above	51	28.0	42	23.1	
Gender	Male	85	46.7	74	40.7	0.245
	Female	97	53.3	108	59.3	
Duration of DM by years	<5	11	6.0	59	32.4	<0.001*
	5-<10	31	17.0	64	35.2	
	10-<15	53	29.1	28	15.4	
	15-<20	41	22.5	12	6.6	
	≥20	46	25.3	19	10.4	
HbA1C level	7%-7.9%	15	8.2	71	39.0	<0.001*
	8%-8.9%	45	24.7	34	18.7	
	9%-9.9%	42	23.1	31	17.0	
	10% and above	80	44.0	46	25.3	
Has Macular Edema	Yes	82	45.1	5	2.7	<0.001*
	No	100	54.9	177	97.3	
Albumin\ Creatinine Ratio	Normal <30 mg\g	104	57.1	133	73.1	<0.001*
	Micro albuminuria 30 -299 mg\g	40	22.0	41	22.5	
	Macro albuminuria >300 mg\g	38	20.9	8	4.4	

GFR level	Stage 1=>90	68	37.4	105	57.7	0.001*
	Stage 2=60-89	72	39.6	59	32.4	
	Stage 3a=45-59	21	11.5	11	6.0	
	Stage 3b=30-44	14	7.7	4	2.2	
	Stage 4=15-29	6	3.3	3	1.6	
	Stage 5=<15	1	.5	0	0	
Has Diabetic Nephropathy (DN)	Yes	83	45.6	54	29.7	0.002*
	No	99	54.4	128	70.3	
Has HTN	Yes	124	68.1	106	58.2	0.050
	No	58	31.9	76	41.8	
DM Medication	Oral	21	11.5	104	57.1	<0.001*
	Insulin	11	6.0	5	2.7	
	Both	150	82.4	73	40.1	
*Significant p value						

Table 3: Characteristics of the patients by retinopathy state.

Table 4 presents the odds ratio and confidence interval (95% CI) for the factors associated with DR among patients with type 2 diabetes. It is clear that an old age ≥ 55 years is associated with a significant risk of DR (OR = 1.59, $P = 0.042$). The duration of DM (5 - < 10, 10 - <15, 15 - < 20, ≥ 20 years) had a significant odds ratio (OR = 2.60, 10.15, 18.33, 12.99 and $P = 0.015, < 0.001, < 0.001, < 0.001$, respectively). In addition, HbA1C levels (7.9%, 8% - 8.9%, 9% - 9.9%, ≥10%) had a significant odds ratio (OR = 6.26, 6.41, 8.23 and $P < 0.001$). Macular edema was associated with a significantly high risk of DR (OR = 29.03, $P < 0.001$), and macro albuminuria > 300 mg\g had a significant odds ratio (OR = 6.07, $P < 0.001$). According to the GFR level, Stages 2 and 3b were associated with a significant risk of DR (OR = 1.88, 5.40 and $P = 0.007, 0.004$, respectively). Diabetic nephropathy was associated as a significant risk factor for DR (OR = 1.99, $P = 0.002$). In addition, DM medication had associated risk factors with DR (OR = 10.90, 10.18, and $p < 0.001$) for insulin and oral and insulin, respectively.

		OR$	95% CI		P value
			Lower	Upper	
Age ≥ 55 years		1.59	1.02	2.48	0.042*
Gender	Male	1.28	0.84	1.94	0.245
	Female**	1.00			
Duration of DM by years	<5**	1.00			
	5-<10	2.60	1.20	5.63	0.015*
	10-<15	10.15	4.61	22.37	<0.001*
	15-<20	18.33	7.38	45.53	<0.001*
	≥20	12.99	5.62	29.98	<0.001*
HbA1C level	7%-7.9%**	1.00			
	8%-8.9 %	6.26	3.07	12.78	<0.001*
	9%-9.9%	6.41	3.11	13.24	<0.001*
	10% and above	8.23	4.24	16.00	<0.001*
Has Macular Edema	Yes	29.03	11.39	73.98	<0.001*
	No**	1.00			
Albumin\ Creatinine Ratio	Normal <30 mg\g	1.00			
	Micro albuminuria 30-299 mg\g	1.25	0.75	2.07	0.391
	Macro albuminuria >300 mg\g	6.07	2.72	13.58	<0.001*

GFR level	Stage 1=>90 **	1.00			
	Stage 2=60-89	1.88	1.19	2.98	0.007*
	Stage 3a=45-59	2.95	1.34	6.50	0.007
	Stage 3b=30-44	5.40	1.71	17.11	0.004*
	Stage 4=15-29	3.09	0.75	12.76	0.119
Has Diabetic Nephropathy (DN)	Yes	1.99	1.29	3.06	0.002*
	No**	1.00			
Has HTN	Yes	1.53	1.00	2.35	0.051
	No**	1.00			
DM Medication	Oral**	1.00			
	Insulin	10.90	3.43	34.63	<0.001*
	Both	10.18	5.89	17.57	<0.001*
*Significant p value; ** Used as a reference; $Odds ratio					

Table 4: Odds ratio and confidence interval (95% CI) for the associated factors of diabetic retinopathy among patients with type 2 diabetes.

The correlation between the type of DR and DN among patients with type 2 diabetes is shown in Table 5. It is clear that there is a significant correlation between the type of DR and DN among patients with type 2 diabetes ($p = 0.021$).

		Has Diabetic Nephropathy (DN)				**P value**
		Yes	**%**	**No**	**%**	
Type of DR	Mild NPDR	22	33.33	44	66.67	0.021*
	Moderate NPDR	27	45.76	32	54.24	
	Sever NPDR	24	64.86	13	35.14	
	PDR	9	50.00	9	50.00	
*Significant p value						

Table 5: Correlation between the type of Diabetic Retinopathy and Diabetic Nephropathy among Patients with Type 2 Diabetes.

The distribution of the type of DR is shown in Figure 1. Mild NPDR and moderate NPDR represent 70% of DR. Figure 2 shows the HbA1C levels among the patients with type 2 diabetes by DR state. It is clear that 44% of the patients with DR had an HbA1C level of 10% and above, and 39% of the patients without DR had a 7%-7.9% HbA1C level.
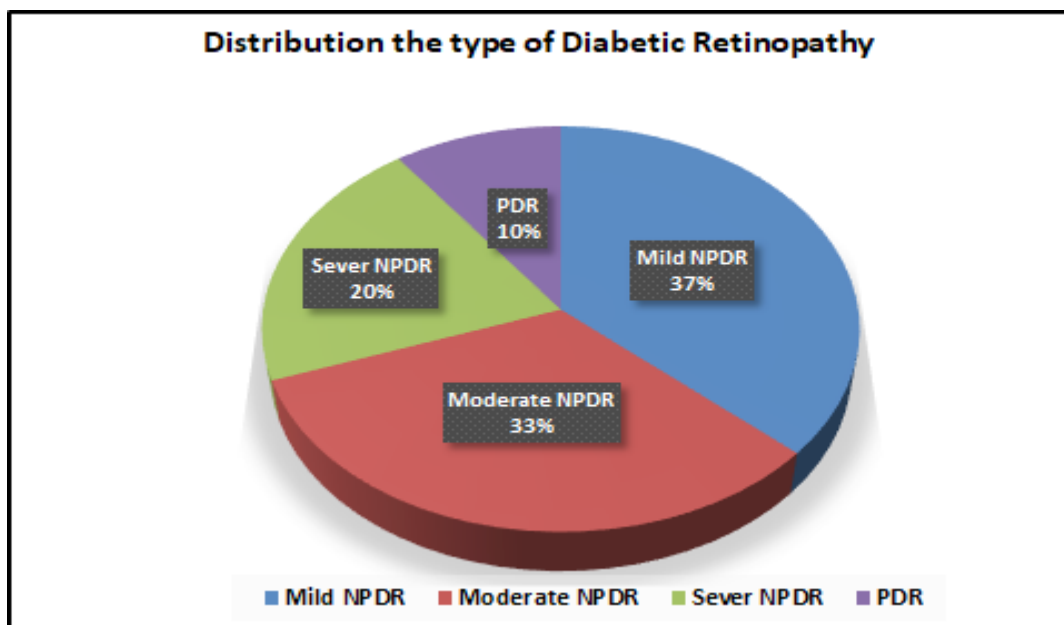
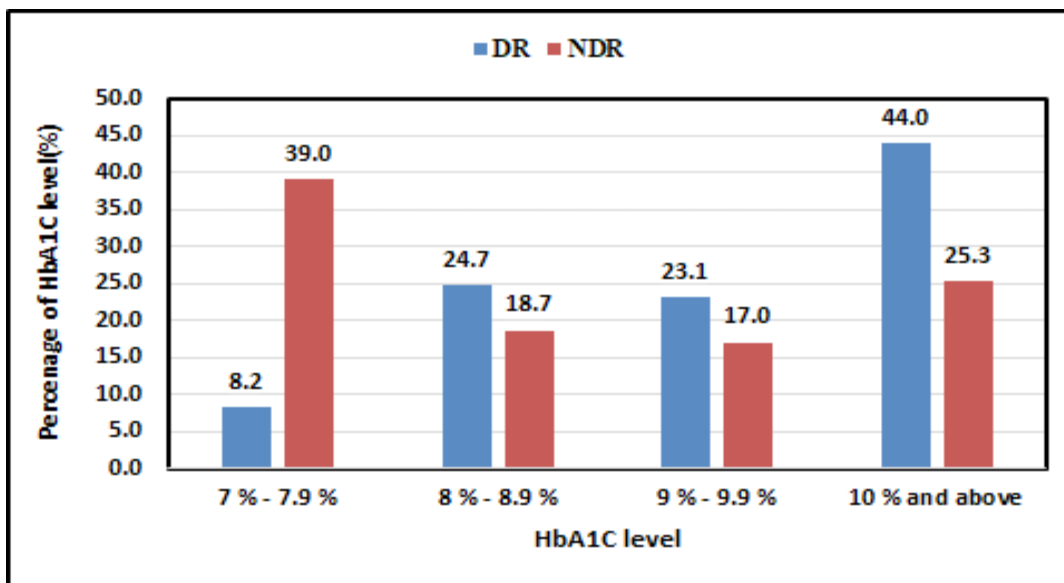**Figure 1:** Distribution the type of Diabetic Retinopathy.

Figure 2: HbA1C level for Among Patients with Type 2 Diabetes by Diabetic Retinopathy state.

Discussion

Limited studies in the literature have investigated the association between diabetic nephropathy and diabetic retinopathy in DM type 2 patients. Studies suggests a potential role for Diabetic retinopathy in predicting diabetic nephropathy in type 2 diabetes mellitus, however, the correlation of DR with of diabetic nephropathy especially in early stages is not fully understood [9,10]. To our knowledge, this is the first study in our center Prince Sultan Military Medical City (PSMMC) in Riyadh, Saudi Arabia, try to recognize associations between retinopathy and nephropathy. The study sample included 364 patients with type 2 DM, results show that 50% patients have Diabetic Retinopathy, and 37.6% patients have Diabetic Nephropathy. Regarding the type of retinopathy Mild NPDR and Moderate NPDR represent 70% and 23.9% have Macular Edema. A statistically significant association difference was found between patients with DR and patients without DR in the manner of the duration of DM, HbA1C level, Macular Edema, Albumin\ Creatinine Ratio, GFR

level, Diabetic Nephropathy, and DM Medication. More than 76% of the patients have HbA1C level of 8% in our study sample. Older patients and HbA1C level of (7.9%, 8% - 8.9%, 9% - 9.9%, ≥10%) associated with the significant higher risk of diabetic retinopathy. In addition, 44% from the patients with DR have 10% and above of HbA1C level. Macro albuminuria >300 mg\g and GFR level Stage 2 and Stage 3b associated with the significant risk of DR. A statistically significant association Between Diabetic Retinopathy and Diabetic Nephropathy among Patients with Type 2 Diabetes was found.

Diabetic retinopathy is the most common microvascular complication of diabetes. Almost 80% of insulin-treated T2DM patients and 50% of those not requiring insulin after two decades of disease will have some degree of retinopathy [14]. The overall prevalence of DR in Saudi Arabia ranges from 11%-36.8% [13,15-17]. However, a significant gap is known to exist in reliable population-based data from developing nations with regard to the prevalence of DR [18]. There are two types of DR, 1) NPDR the more common form, and 2) advanced DR, the Proliferative Diabetic Retinopathy (PDR). Severe vision loss usually occurs only in the advanced stages of the disease, such as Diabetic Macular Edema (DMO) and/or PDR, in addition to the socioeconomic status of the patient [14]. In our study, the results showed that 50% of the patients had DR. Mild NPDR and moderate NPDR represented 70%, and PDR represented 10%. The risk factors shown in various studies are age, duration of disease, presence of hypertension, uncontrolled diabetes, and HbA1C levels [19,20]. Regarding the HbA1c level, studies have shown that every 1% decrease in HbA1c will result in a 40% reduction of retinopathy, 25% need for retinal laser, and 15% of blindness [20]. In our study, older patients and HbA1C level of (7.9%-≥10%) was statistically significantly associated with a higher risk of DR.

Diabetic nephropathy is a major cause of ESRD and affects ~40% of type 1 and type 2 diabetic patients. It is categorized into stages based on the values of Urinary Albumin Excretion (UAE): microalbuminuria (UAE > 20 μg/min and ≤ 199 μg/min) and macro albuminuria (UAE ≥200 μg/min) [21]. Microalbuminuria has been considered a risk factor for macro albuminuria; however, not all patients progress to this stage, and some may regress to a normal level. The risk of developing DN was found to be 29 times greater in patients with type 2 diabetes with UAE values >10 μg/min during a duration of 10 years [22]. A variety of modifiable risk factors were identified, including high glucose levels, high blood pressure, obesity, and dyslipidemia. In addition, relatively new risk factors were identified (oxidative stress, genetic background, ethnicity, and GFR) [23]. The prevalence of DN in type 2 diabetic patients was found to be high in Arab countries [24]. In Saudi Arabia, the prevalence of DN is estimated to be 10.8%, and the rate of microalbuminuria ranges from 45.6%-54.3% among type 2 diabetic patients [24,25]. In our data, 37.6% of the patients had

DN. Almost two-fold of the patients had a normal range (<30 mg\g) of albumin-creatinine ratio, and 47.5% of the patients had stage 1 of GFR level.

In 1993, an epidemiological study established an association between microalbuminuria and the existence of proliferative disease. This study proposed that microalbuminuria could be a marker of the risk of developing proliferative retinopathy [26]. In 2001, Abu El-Asrar, et al.'s study showed that retinopathy significantly predicted the presence of nephropathy. Furthermore, the associations between retinopathy severity levels and the prevalence rate of nephropathy were significant. In patients with mild to moderate NPDR, nephropathy was present in 17.2% of patients with IDDM, and in 11.4% of patients with NIDDM. In patients with severe NPDR, nephropathy was present in 23.3% of patients with IDDM, and in 11.8% of patients with NIDDM. In patients with Proliferative Retinopathy (PDR), nephropathy was present in 50% of patients with IDDM, and in 45.5% of patients with NIDDM [27]. In a population-based cross-sectional study, every sixth person within the type 2 diabetes population had albuminuria. Patients with microalbuminuria were about twice as likely to have DR as those without micro albuminuria, and this risk was almost six times greater in the presence of macro albuminuria [28]. Throughout the years, multiple studies have found a link between nephropathy and progressive DR, and most agree that DR could be an indicator of the presence of DN [29-33]. In this study, a statistically significant association was found between DR and DN among patients with type 2 diabetes.

There are several limitations to this study: this study included data collected from only one clinic (Retina clinic in Al- Wazarat center) in tertiary hospital in Riyadh Saudi Arabia; however, as this center is the one of largest of the kingdom, it is likely that the patient group was representative. Ethnicity is not recorded in the medical files in our hospitals, however, as our center is relatively exclusive to Saudi military man and their family, we believe the error estimation to be minimal. The lack of control subjects is another limitation. Further prospective cohorts and interventional trials should be conducted to verify the outcomes we report. General practitioner and family medicine doctors have a higher responsibility for educating patients regarding the microvascular complications. As a study in Saudi showed that most of the DM patient were not followed for possible microvascular complications [34].

Conclusion

Few studies have demonstrated an association between DN and DR in type 2 DM patients in Saudi Arabia. Our study indicates that there is a correlation between DR and DN. General practitioners and family doctors have a greater responsibility to educate patients regarding microvascular complications.

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