Relationship Between Retinal-Renal Complications Among Type 2 Diabetic Subjects in India

Research Article

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Abstract

Aim: The aim of this study was to determine the relationship between retinal-renal complications among type 2 diabetic subjects in India.

Subjects and Methods: A total of 502 subjects with type 2 diabetes who underwent Fundus Photography and Fundus Fluorescein Angiography (FFA) for diabetic retinopathy (DR) and 24hr urinary creatinine clearance (Crcl) test for diabetic nephropathy (DN) on the same day were included in this analysis. They were divided into groups based on the severity of retinopathy and Crcl values. Out of 502 subjects, 272 subjects had subsequent follow-up details spanning 22 months. Anthropometric, haemodynamic and biochemical details at baseline and follow-up and mortality details were recorded.

Results: The mean Crcl values decreased significantly with increasing severity of DR (p<0.001). The percentage of subjects with non-proliferative diabetic retinopathy also decreased with decreasing Crcl. In the follow-up data, severity of DR increased compared to baseline as per stages of Crcl. There was a decline in survival when both the complications are present. Number of subjects who died was high at severe stages of these complications. Crcl was significantly associated with declining status of both the complications.

Conclusions: The degree of diabetic retinopathy and severity of diabetic nephropathy showed significant asso-ciation among type2 diabetic subjects

Keywords: Diabetic Nephropathy; Diabetic Retinopathy; Type2 Diabetes; India

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Introduction

The prevalence of type 2 diabetes shows a significant rise world wide [1]. Diabetic Retinopathy (DR) and Nephropathy (DN) are the most common microvas-cular complications of diabetes [2]. They share com-mon pathogenic mechanisms even though common pathways of capillary damage may lead to different structure and functions of the organs involved. High prevalence of proteinuria in patients with prolifera-tive retinopathy has been reported earlier [3] and some studies reported that DR is more severe in patients with severe DN and those with advanced DN have far more lesions of DR than those without DN [2,4]. These studies lay evidence that DR and DN coexist and there is a close

relationship between the develop-ment and progression of these two complications.

There are few similarities in the coexistence of DR and DN be-ing both as microvascular disease and mi-croscopically both have capillary basement membrane thickening. However, capillary clo-sure is apparent in the retina and kidney after sufficient exposure to dis-ease with duration. The pathophysiology of DN and DR is more or less similar, which commences with in-crease in vascu-lar permeability. The selective increase in permeability to albumin in early DN is caused by loss of polarity across the glomerular basement mem-brane [5] and the disease mechanism in the eye is prob-ably a breakdown of tight junctions between cells. The onset of proteinuria and proliferative retinopathy are both related to previous poor glycemic control, dura-tion of diabetes and hy-pertension [6-8].

It has been suggested that 25-50% of type 2 diabetic patients may have kidney alterations [9]. From the re-cent studies, it is evident that the presence of retinopa-thy itself may reveal patients at risk for nephropathy [10-12]. In a cross sectional study of patients with type 1 and type 2 diabetes to determine the predictive value of DR, univariate analysis indicated that patients with DR were 5.68, 13.39 and 3.51 times as likely to have DN compared with those without DR in the whole study population and in type 1 and type 2 diabetes re-spectively [10].

The association between DR and DN has been dem-onstrated in other populations. However, there is lack of evidence that deter-mine the association of retinal-renal complications among sub-jects with type 2 diabe-tes in India. Hence the aim was to evaluate the impact of retinopathy as assessed by Fundus Photography and Fundus Fluorescein Angiography (FFA) on the rate of pro-

gression of nephropathy as assessed by creatinine clearance (Crcl) in 24hr urine collection. We also aimed to evaluate the associated risk factors and its outcome in the coexistence of these two complications.

Materials and Methods

Subjects with type 2 diabetes who underwent retinal and renal examination on the same day from June 2006 to June 2007 in a tertiary care hospital in India were included in this study. All the subjects underwent Fun-dus Photography and FFA for DR and 24 hour urinary Crcl test for DN. Those who had presence of DR (any grade) attributable to type 2 diabetes and with persis-tent proteinuria were included and subjects with type 1 diabetes, gesta-tional diabetes and subjects with incom-plete laboratory data were excluded from this analysis. A total of 502 (M:F 351:151) subjects with mean age of 55.8 years and mean duration of diabetes of 13.8 years were selected for this analysis. Out of 502 sub-jects, 272 (M:F 191:81) subjects who had subsequent follow-up details of both the complications spanning a median follow-up period of 22 months were further analysed for their outcome. All the follow-up bio-chemical, anthropometric and haemodynamic de-tails were obtained from the medical records of the sub-jects. All the subjects were known diabetic patients and were on treatment with oral hypoglycemic agents and known hypertensives were on antihypertensive medi-cation. The study was approved by the In-stitutional Ethics committee.

Retinal examination was performed in all the subjects by a trained ophthalmologist. Fundus Photography was taken to document DR followed by FFA to con-firm findings, to look for macular ischaemia and to rule out subtle neovascularization. DR was clas-sified based on International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [13].

This international clinical classification system is based on an evidence-based approach of ETDRS and WESDR studies. Retin-opathy was classified as non-prolifer-ative (microaneurysms, in-tra-retinal hemorrhages, hard exudates without new vessels) or proliferative (newly formed blood vessels and/or growth of fi-brous tissue into the vitreous cavity or scars of photocoagulation). Subjects were divided into groups based on the sever-ity of DR [Group1 had Non-Proliferative Diabetic Retinopathy (NPDR) (n=231), group2 had clinically significant macular edema (NPDR with maculopathy) (n=231) and group3 subjects had Proliferative Dia-betic Retinopathy (PDR) (n=40)]. They were further divid-ed into groups based on the Crcl values as per KDOQI guide-lines from stage 1 to stage 4. Stage1 (group1) (Crcl ≥90ml/min) (n=219), stage2 (Crcl 60-89ml/min) (group 2) (n=181), stage3, (group 3) (Crcl 30-59ml/min) (n=64) and stage4 (group 4) (Crcl <30ml/min) (n=38).

Demographic, anthropometric and hemodynamic de-tails like age, gender, systolic blood pressure (SBP), di-astolic blood pres-sure (DBP), family history and dura-tion of diabetes were re-corded. BMI was calculated. Biochemical details like fasting and postprandial plasma glucose, HbA1c, lipid profile, urea, creatinine and 24hr proteinuria values were recorded. All the biochemical estimations were done by using standard enzymatic procedures using Hitachi auto analyzer 912. Plasma glucose was estimated by glucose oxidase peroxidase method. HbA1c was measured by HPLC (Bio-Rad) method. Renal parameters like urea were esti-mated by kinetic enzymatic UV assay. Serum or urine creatinine was estimated by Jaffe's kinetic method. Urinary pro-tein was

determined by turbidimetric procedure using trichloroacetic acid reagent. Fasting serum samples were used to estimate total cho-lesterol by using spe-cific enzymatic reagents which react with cholesterol oxidase-PAP. Triglyceride by GPO-PAP method, low density lipoprotein cholesterol by direct method and high density lipoprotein cholesterol enzymatically by cholesterol esterase and cholesterol oxidase coupled with polyethylene glycol to the amino groups. Very low density lipoprotein cholesterol was calculated by divid-ing triglyceride by 5 (TG/5).

Presence of other diabetic complications like diabetic neuropa-thy, peripheral vascular disease and coronary artery disease (CAD) occurred during the follow-up visits was noted. Neuropathy was diagnosed as Vibra-tion Perception Threshold >25V by bioth-esiometer [14]. Peripheral vascular disease was diagnosed if the ankle brachial index was <0.8. The presence of CAD was defined by any history of CAD, hospital records of confirmed myocardial infarction and definite histo-ry of angina or coronary revascu-larization procedure. Out of 502 subjects, 272 subjects who had follow-up details were again divided as per KDOQI guidelines and DR status. Outcome of the subjects was deter-mined from their current status of DR and DN com-pared to their baseline status. Subjects who died were recorded and the cause of death was obtained and not-ed from the hospital mortality register. Car-diovascular death was defined as death caused by ischaemic heart disease, definite history of angina, stroke or sudden death.

During follow-up visits, subjects were coded as im-proved if they showed improvement in their renal sta-tus as per KDOQI stages and decrease in the severity of their retinopathy status. Subjects were considered as retaining same status if during their follow-up they were found to be in the same stage of renal and DR status; however they were considered as deteriorated if they showed de-terioration in DR and DN status com-pared to baseline status. Latest status available for the subjects who died was noted.

Statistical Methods

The analysis was performed using SPSS (version 16.0, Illinois, USA) software. Mean and SD and proportions are reported as relevant. Unpaired student's t-test was used to compare continu-ous variables and chisquare test was used to evaluate proportions between groups.

Cox's proportional hazard model (Forward stepwise addition method) was used to examine the predictive factors for the occur-rence of the two complications. The model included age, gender, BMI, hypertension, family history of diabetes, duration of diabe-tes, smok-ing habit, HbA1c and presence of other complications like diabetic neuropathy and cardiovascular disease, to-tal choles-terol, triglycerides and Crcl as independent variables. All the sub-jects having the follow-up data and showing decline in any of the two complications were included as dependent variable. Subjects who at-tained mortality were excluded from the analysis.

Kaplan Meier survival analysis was performed for 253 subjects who had follow-up details available to deter-mine their survival time.

Results

A total of 502 subjects at baseline were categorized according to their DR and Crcl status. Table 1 summa-rizes the baseline demo-graphic, hemodynamic, anthro-pometric and biochemical details

of the study groups as per grades of DR. There was no significant differ-ence observed in age, BMI, family history and duration of diabetes, presence of hypertension and smoking habit among the groups. SBP was significantly higher in subjects with PDR. HbA1c% was similar among the groups. Subjects with PDR had significantly higher urea levels than subjects with NPDR. The mean Crcl values decreased significantly with increasing severity of DR (p<0.001).

Table 2 shows baseline demographic, anthropomet-ric, haemo-dynamic, biochemical and DR status of the groups as per stages of Crcl. Age, BMI, presence of positive family history and dura-tion of diabetes, smok-ing habit were similar among the groups. Presence of hypertension was significantly higher among group3 and group4 (p=0.001). Blood pressure values were sig-nificantly higher among group4 than groups 1 and 2. There was no sig-nificant difference noted among the four groups with respect to their glucose levels. Urea and creatinine levels were higher among groups 3 and 4. At baseline, among group1, NPDR was found in 102 (44.2%), 102 (44.2%) subjects had NPDR with Maculopa-thy and 15 (37.5%) had PDR. Similarly, in group2, 90 (39%) had NPDR, 79 (34.2%) had NPDR with maculopathy and 12 (30%) had PDR. In Group3, it was 22 (9.5%), 33 (14.3%) and 9 (22.5%) respectively whereas it was 17 (7.4%), 17 (7.4%) and 4 (10%) of subjects in group 4. The percentage of subjects with NPDR de-creased drastically with decreasing Crcl.

Table 3 shows the comparison of baseline and follow-up details, retinopathy status and mortality as per stages of Crcl in a sub-group of 272 subjects who had follow-up details out of 502 sub-jects. There was no significant difference in age, BMI and SBP in the baseline and follow-up data. DBP was higher in group4 with Crcl<30ml/min compared to groups 1 and 2 at baseline whereas DBP values were similar at follow-up. There was no statistically significant difference noted in lipid profile both in the baseline and follow-up data except triglycerides at follow-up.

At follow-up, in group1, 12.5% had no DR, 38.8% had NPDR, 31.3% had NPDR and Maculopathy, and 17.5% had PDR. In group2, the percentage of subjects with no NPDR was 4.3%, 31.4% had NPDR, 50% had NPDR and Maculopathy, 14.3% of subjects had PDR. Similarly, in group3, the percentages were 3.7 vs 31.5 vs 44.5 vs 20.4% respectively. None of the sub-jects were without retinopathy in group4, while 18.4% had NPDR, 55.1% had NPDR with Maculopathy and 26.5% had PDR. Table 3 also shows the number of cases died during follow-up.

In the baseline data, group 1 subjects with Crcl ≥90 ml/min, 15.2% of subjects were treated with ACE in-hibitors (ACEI), 7.1% with Angiotensin II Receptor Blocker antagonist (ARB), 27.7% with combination of ACEI and ARB, 2.7% with beta blockers (BB) and 47.3% of subjects were treated with a combi-nation of any two or three drugs. In Group 2 subjects with Crcl 60-89 ml/min, about 3.5% were treated with ACEI, 21.2% with ARB, 7% with a combination of ACEI and ARB, 11.8% with BB and 56.5% with combina-tion of any two or three drugs. In Group 3 subjects (Crcl of 30-59 ml/min), none of them were treated with ACEI or BB, whereas 7.1% were treated with ARB and 92.8% were treated with a combination of drugs. In Group 4 (Crcl <30 ml/min), none of the subjects were treated with ACEI or BB, 14.3% were treated with ARB and 85.7% with a combina-tion of drugs. At follow-up, it was 10.1 vs 8.9 vs 20.2 vs 7.9 vs 52.8% respectively in Group 1. In Group 2, 3.0% were treated with ACEI, 7.6% with ARB, 25.8% with ACEI plus ARB, none of them were treated with BB and

63.6% with a combination of drugs. In Group 3, none of them were treated with ACEI and BB, 25% were treated with ARB, 8.3% were treated with a combina-tion of ACEI and ARB and 66.7% with a combination of any two or three drugs. In group 4, none of them were treated with BB, 5% with ACEI, 20% with ARB, 10% with ACEI and ARB and 65% were treated with a combination of drugs.

Table 1: Baseline demographic, anthropometric, hemodynamic and biochemical details of the study groups as per grades of diabetic retinopathy Dur-DM; duration of diabetes, FH-DM; family history of diabetes, HTN; Hypertension

Variables	Group 1 NPDR n = 231	Group 2 NPDR + Maculopathy n = 231	Group 3 PDR n = 40	P value
M:F	154:77	172:59:00	25:15:00	
Values are mean ± SD				
Age (years)	56 ± 7.7	56.2 ± 7.8	56.5 ± 8.1	0.945
Dur-DM (years)	12.8 ± 6	13.4 ± 6.1	14.5 ± 6.7	0.233
BMI (kg/m2)	26.8 ± 4.7	26.1 ± 4.5	26.1 ± 4.1	0.239
Blood Pressure (mmHg) Systolic Diastolic	136.6 ± 16.3 82.6 ±7.6	139.8 ± 18.6 84.5 ± 9.1	143.1 ± 21.4* 83.5 ± 11.9	0.038 0.073
HbA1c (%)	9.5 ± 1.8	9.6 ± 1.9	9.9 ± 2.6	0.431
Urea (mmol/L)	5.7 ± 3.2	5.8 ± 3.2	7.5 ± 5.7*,#	0.008
Creatinine (µmol/L)	97.2 ± 79.5	106.0 ± 70.7	132.6 ± 123.7	0.105
Creatinine clearance (ml/min)	87.1 ± 32.6	78.8 ± 30.8*	66.7 ± 30.2*	<0.0001
Values are n (%)				
FH- DM	144 (62.3)	154 (66.7)	27 (67.5)	0.579
Presence of HTN	172 (74.5)	177 (76.6)	30 (75)	0.861
Smoking	30 (13)	34 (14.7)	5 (12.5)	0.84

p<0.05; * Vs NPDR; # Vs NPDR+Maculopathy

Table 2: Clinical characteristics of the study groups as per stages of Creatinine clearance (Crcl)

Dur-DM; Duration of diabetes, FH-DM; family history of diabetes

Variables	Group 1 Crcl ≥90ml/min n = 219	Group 2 Crcl 60-89ml/min n = 181	Group 3 Crcl 30-9ml/min = 64	Group 4 Crcl <30ml/min n = 38	P Value
M:F	158:61	113:68	51:13:00	29:09:00	--
Values are mean ± SD					
Age (years)	55.5 ± 7.9	56.9 ± 7.5	56.6 ± 6.8	55.5 ± 9.3	0.24
Dur-DM (Years)	12.9 ± 6.3	13.8 ± 5.9	13.9 ± 5.7	13.8 ± 6.7	0.246
BMI (Kg/m2)	26.6 ± 4.2	26.7 ± 4.9	25.3 ± 4.7	25.4 ± 3.6	0.066
Blood Pressure (mmHg) Systolic Diastolic	137.6 ± 17.8 83.2 ± 8.6	137.5 ± 16.8 82.6 ± 7.9	143.1 ± 17.2 84.4 ± 17.2	146.1 ± 22.2*,** 88.8 ± 11.1*,**	0.021 0.001
Plasma Glucose (mmol/L) Fasting Post prandial	9.6 ± 4.2 13.6 ± 4.7	10.1 ± 4.1 13.6 ± 4.9	10.4 ± 5.8 13.1 ± 4.9	8.2 ± 3.6 11.5 ± 3.4	0.102 0.067
Urea (mmol/L)	4.8 ± 2.7	5.3 ± 1.9	7.5 ± 2.9*,**	12.4 ± 6.6*,**,#	<0.0001
Creatinine (µmol/L)	79.6 ± 44.2	88.4 ± 26.5	141.4 ± 61.9*,**	282.9 ± 168.0*,**,#	<0.0001
Values are n (%)					
FH- DM	151 (68.9)	110 (60.8)	40 (62.5)	24 (63.2)	0.372
Presence of HTN	148 (67.6)	142 (78.5)	56 (87.5)	33 (86.8)	0.001
Smoking	32 (14.6)	23 (12.7)	8 (12.5)	6 (15.8)	0.915
DR status NPDR	102 (44.2)	90 (39)	22 (9.5)	17 (7.4)	<0.0001
NPDR + Maculopathy	102 (44.2)	79 (34.2)	33 (14.3)	17 (7.4)	<0.0001
PDR	15 (37.5)	12 (30)	9 (22.5)	4 (10)	0.041

* Vs Crcl ≥90ml/min; ** Vs Crcl 60-89ml/min; # Vs Crcl 30-59ml/min

Table 3: Comparison of biochemical details and retinopathy status at baseline and during follow-up in a subgroup of subjects as per stages of Creatinine clearance

Variables	Baseline details (n = 272)					Follow-up Details (n = 253)				
	Group 1 Crcl ≥90ml/min n = 126	Group 2 Crcl 60-89ml/min n = 88	Group 3 Crcl 30-59ml/min n = 35	Group 4 Crcl <30ml/ min n = 23	P Value	Group 1 Crcl ≥90ml/min n = 80	Group 2 Crcl 60-89ml/min n = 70	Group 3 Crcl 30-59ml/min n = 54	Group 4 Crcl <30ml/min n = 49	P Value
Values are mean ± SD										
Age (years)	55.6 ± 8.3	57.1 ± 7.4	57.9 ± 7.3	55.4 ± 8	0.282	58±8.2	58.9±7	59.3±8	59.3±7.6	0.05
BMI (kg/m2)	26.6 ± 4.3	27.6 ± 5.2	25.8 ± 4.6	25.6 ± 3.3	0.115	28.4±4.8	28.1±3.9	27.2±4.9	26.5±4.2	0.119
Blood Pressure (mmHg) Systolic Diastolic	137.3±15.9 82.5±8.6	137.6±17.6 82.4±8.2	140.6±18 84.9±8.2	146.7±20.3 88.9±10.4*,**	0.09 0.005	137.2±16.9 82.2±5.9	137.6±17 83.1±7.5	136.6±16.4 83.4±6.7	144.9±21.2 83.7±9.5	0.073 0.71
Plasma Glucose (mmol/L) Fasting Post Prandial	9.7±4.1 13.6± 4.9	10.1±3.9 13.2±4.7	9.7±5.3 12.6±4.6	7.7±2.9 10.4±2.8*	0.092 0.02	8.9±3.3 13.4±3.7	8.7±3.4 12.9±4.4	8.6±3.1 13.1±3.7	7.7±3.5 11.9±3.8	0.351 0.267
T-Chol (mmol/L)	4.8±1.3	4.83±1.33	4.87±1.4	4.76±1.45	0.968	4.3±1.19	4.4±1.4	4.39±1.48	4.29±1.5	0.989
Triglycerides (mmol/L)	1.9±0.91	2.1±1.1	2.18±1.1	2.07±1.0	0.374	1.73±0.87	1.67±0.75	2.3±1.1**	1.9±1.0	0.024
HDL (mmol/L)	1.14±0.32	1.1± 0.29	1.13±0.22	1.22±0.36	0.278	1.1±0.28	1.08±0.26	1.06±0.35	0.99±0.23	0.565
LDL (mmol/L)	2.87±0.96	2.86±1.08	2.89±1.18	2.67±1.1	0.852	2.57±0.92	2.68±0.97	2.56±1.03	2.53±1.16	0.903
VLDL (mmol/L)	0.7±0.43	0.89±0.46	0.86±0.5	0.87±0.48	0.119	0.69±0.43	0.66±0.43	0.86±0.45	0.76±0.46	0.229
Crcl (ml/min)	109.3±18.8	74.4±9.5*	43.7±8.5*,**	19.3±6.8*,**,#	<0.001	102.6±20.7	79.5±15.9*	51.5±12.9*,**	23±17.3*,**,#	<0.001

Values are n (%)										
No DR	No DR	No DR	No DR	No DR	No DR	No DR	No DR	No DR	No DR	
NPDR	NPDR	NPDR	NPDR	NPDR	NPDR	NPDR	NPDR	NPDR	NPDR	
NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	NPDR + Maculopathy	
PDR	PDR	PDR	PDR	PDR	PDR	PDR	PDR	PDR	PDR	
Mortality	Mortality	Mortality	Mortality	Mortality	Mortality	Mortality	Mortality	Mortality	Mortality	

* Vs Crcl ≥90ml/min; ** Vs Crcl 60-89ml/min; # Vs Crcl 30-59ml/min

Table 4 Panel A: Conversion of the study subjects from baseline till median follow-up of 22 months as per Creatinine clearance stages

	Crcl stages		Improved	Same Status	Deterio-rated	Mortality
Groups	Baseline/ Follow-up	n	37	80	136	19
Group 1	Crcl ≥90ml/min	126	--	51 (40.5)	69 (54.8)	6 (4.8)
Group 2	Crcl 60-89ml/min	88	28 (31.8)	13 (14.8)	45 (51.1)	2 (2.3)
Group 3	Crcl 30-59ml/min	35	6 (17.1)	3 (8.6)	22 (62.8)	4 (11.4)
Group 4	Crcl <30ml/min	23	3 (13.04)	13 (56.5)	--	7 (30.4)

Values are n (%)

Table 4 Panel B: Conversion of the study subjects from baseline till median follow-up of 22 months as per Diabetic Retinopathy (DR) stages

DR stages		Improved	Same Status	Deteriorated	Mortality
Baseline/ Follow-up	N	55	93	105	19
NPDR	131	19(14.5)	28(21.4)	77 (58.8)	7 (5.3)
NPDR + Maculopathy	119	29 (24.4)	51 (42.8)	28 (23.5)	11 (9.2)
PDR	22	7 (31.8)	14 (63.6)	--	1 (4.5)

Values are n (%)

Figure 1. shows the Kaplan Meier survival analysis of the individuals who had follow up details

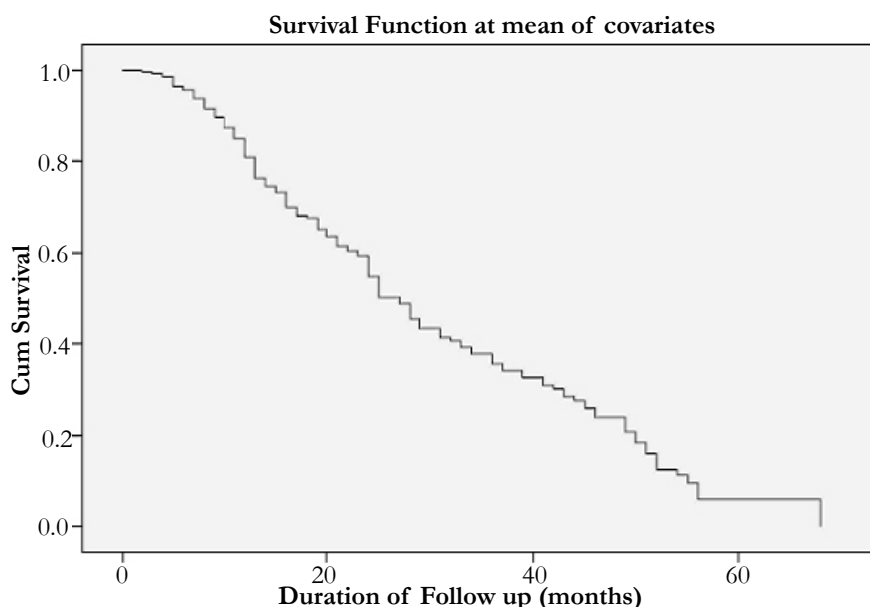

Survival Function at mean of covariates

Table 4 shows the conversion of 272 subjects from baseline till median follow-up of 22 months as per Crcl and DR stages. Considering Crcl stages, among group1, none of the subjects showed improvement in renal status, 40.5% remained similar as baseline, 54.8% showed deteriorated renal status from baseline. Among group2, 31.8% improved, 14.8% remained same and 51.1% had deteriorated renal status. In group3, im-provement was seen in 17.1%, 8.6% remained same and 62.9% had worsened renal sta-tus. In group4, 13% showed improvement, 56.5% remained same and none of them showed deterioration in the renal status. The percentages of subjects who died were 4.8, 2.3, 11.4 and 30.4 % in the four groups respectively (Table 4, Panel A).

Conversion of study subjects from baseline till medi-an follow-up of 22 months as per DR stages showed that among NPDR group, 14.5% had improved retinal status, 21.4% remained same as base-

line, 58.8% had deteriorated retinal status and 5.3% of subjects died.

Among NPDR with maculopathy, 24.4% improved, 42.8% remained same, 23.5% had deteriorated retinal status and the percentage of subjects who died was 9.2%. In PDR, 31.8% improved, 63.6% remained same, none of the subjects deteriorated while 4.5% died (Table 4, Panel B). The cause of death was either due to renal failure or cardiovascular events.

As per the Cox's proportional hazard model, consider-ing all the subjects who had follow-up data and had showed deterioration in any of the two complications over a median follow-up of 22 months as dependent variable, total cholesterol with Hazard Ratio (HR) of 1.004, 95% confidence interval (CI) (1.001-1.007),(P=0.007) and Crcl with HR of 0.995, 95% CI (0.990-1.000), (P=0.041) emerged as significant determinants of declining status in the subjects having both the complications as compared to baseline. Subjects who died were not included in this analysis.

Figure 1 shows the survival rate of subjects with both complications with respect to duration of follow-up in months. It was observed that there is a continuous decline in the survival rate once both the complica-tions are attained. Nearly, 60% deteriorated at about 22 months. It was also found that the survival will be for a maximum of 68 months with the presence of both the complications.

Discussion

It is a well known fact that subjects with diabetes are at high risk of developing complications such as nephropathy, retinopathy and neuropathy than subjects without diabetes [15]. DR is characterized by micro-vascular abnormalities, proliferation of retinal vessels and increased retinal vascular permeability leading to the development of non proliferative and proliferative DR and macular edema [16]. DN is a life threatening complication which predisposes to excess morbidity and mortality resulting from renal failure and cardio-vascular disease[17,18]. Our hypothesis was that to see whether the severity of DR had any relationship with the presence and severity of DN in people with type2 diabetes. Studies in other populations documented a well known association between advanced DR stages and macroalbuminuria in type2 diabetic patients [19,20]. Data from developing countries show-ing the rela-tionship between these two diabetic complications are sparse but the current study supports the close rela-tionship between presence of DR and severity of DN among type 2 diabetic patients in India.

It was reported that atleast one fifth of the diabetic individuals are affected by multiple complications and the frequency increases with increasing age and dura-tion of diabetes [21]. Our study sub-jects were also old-er and had longer duration of diabetes which evidently proved that increased age and duration of diabetes were responsible for the development of both the complications. In the baseline data, the groups were matched with respect to age, BMI, presence of posi-tive family history of diabetes, glucose lev-els, smoking habit and duration of diabetes both as per grades of DR and stages of Crcl.

A study from Jordan showed that nephropathy, which is assumed to result from other microvascular compli-cations of diabetes, was found to be significantly as-sociated with DR [22]. In WES-

DR, there was a strong correlation between DN and severity of DR in all age groups [23,24]. Our study results also complied with similar findings of worsening of DN with increasing severity of DR. In our study, the mean Crcl was found to be decreased sig-nificantly with increasing severity of DR. The percentage of sub-jects with NPDR also de-creased with decreasing Crcl.

In contrast to the well known 3 major risk factors for the de-velopment of microvascular disease, such as gly-cemic status, hypertension and duration of diabetes, our study revealed total cholesterol and Crcl to be sig-nificantly associated with the declin-ing status of both the complications by Cox's proportional hazard model. When comparing basal and follow-up mean lipid lev-els, there was no significant difference noted except triglycerides at follow-up, but total cholesterol showed significant association in this analysis.

Findings from our study also highlighted that the mor-tality rate will be high when both DR and DN co-occur. Continuous de-cline of renal function was also found to be correlating with the advanced stages of DR. In the follow-up data, severity of DR increased compared to baseline as per stages of Crcl. More num-ber of sub-jects died who had Crcl <30 ml/min at follow-up. The cause of death was either renal failure or cardiovas-cular event. Similar to our findings Trevisan et.al also revealed that there was a drastic reduction in kidney function and higher death rate among type 2 diabetes in the presence of both the complications [25].

Since the mortality rate of the patients in our study was high, it was also observed that once both the com-plications occur, the improvement was seen in much lesser percentage of subjects in a median follow-up pe-riod of 22 months. Approximately 60% of subjects re-mained in the same status of severe Crcl or DR stages. Majority of the patients remained in the same status as that of baseline. This could be because the follow-up period considered is too short to observe probable changes. This is one of the limi-tations of our study. A decline in survival was noted when both the com-plications are present and about 60% of the cases de-teriorated at about a median follow-up of 22 months. The maxi-mum survival rate was less than 65 months. A similar declining pattern was observed in another study stating only 22.2% survival rate in 10 years follow-up of type 1 diabetic patients [26].

Another limitation was that it was not a prospectively planned randomized study. The analysis was done with the available hospi-tal based data, so the effect of other potential confounders needs to be studied in future. There was a lack of systematic examina-tion of both the complications during follow-up. The data was col-lected retrospectively and survival analysis was done only for the subjects whose follow-up details were available. However, ut-most care has been taken while collecting the data of subjects who had follow-up of both the complications.

The present study highlights the need for screening the patients periodically to look for diabetic compli-cations. Modification of risk factors with appropriate treatment strategies may delay the progression of these diabetic complications. In conclusion, a pos-itive asso-ciation was found between the degree of DR and DN in type2 diabetes. Patients with DR should undergo an evaluation of renal function and vice-versa.

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