Dietary associations with diabetic retinopathy—A cohort study

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Purpose: To assess the role of dietary factors in the development of diabetic retinopathy (DR) in diabetics. **Methods:** This prospective study was carried out on patients attending the outpatient department of ophthalmology for a period of 1 year. An interview-based 24-hour diet recall was used to document average daily dietary nutrient intakes. Each patient was subjected to a comprehensive ocular examination to look for DR. **Results:** A total of 261 patients attending the outpatient department of ophthalmology were the participants for this study. The mean (±SD) age of the participants was 57.73 ± 11.29 years, and 67% were men. One hundred and six participants had DR. Univariate analysis revealed sex, duration, fish (times/week), egg (yes/no), rice lunch (yes/no), rice dinner, rice (boiled/white), and total calorie intake to be associated with DR ($P < 0.05$). Logistic regression multivariable analysis revealed males (OR: 3.20, 95% CI: 1.65–6.19), longer duration of diabetes (OR:1.05,95% CI:1.01-1.11), antioxidant intake (OR: 3.42, 95% CI: 1.65–7.05), and consumption of rice (OR: 3.19, 95% CI: 1.17–8.69) to have significant association with DR ($P < 0.05$), with the odds of developing DR increasing three times in these patients. The odds of developing DR were lesser with more frequent (>2 times/week) fish consumption (OR: 0.42, 95% CI: 0.18–0.94) and in patients on pharmacological treatment for diabetes mellitus (OR: 0.16, 95% CI: 0.04–0.58). Binary logistic regression revealed chapathi consumption (OR: 9.37, 95% CI: 1.64–53.68) to be associated with severe forms and fish consumption (OR: 0.06, 95% CI: 0.01–1.06) ($P < 0.05$) to be associated with less severe forms of DR. **Conclusion:** Males, longer duration of diabetes, antioxidant intake, fish consumption, and consumption of rice were associated with the occurrence of DR. Participants with diabetes who consumed fish more frequently and those who were on pharmacological treatment for diabetes mellitus had a significantly lower risk of DR and frequent fish consumption could reduce the risk of DR progression.

Key words: Diabetes mellitus, diabetic retinopathy, diet, fish

Diabetic retinopathy (DR) is one of the leading causes of blindness among the working-class individuals around the world.[1] Numerous risk factors that contribute to the progression of DR have been identified. Metabolic control and duration of diabetes were found to be strong risk factors.[2] It is regarded as a microvascular disease, but retinal neurodegeneration is also involved. Complex interrelated pathophysiological mechanisms triggered by hyperglycemia underlie the development of DR. These mechanisms include genetic and epigenetic factors, increased production of free radicals, advanced glycosylation end products, inflammatory factors, and vascular endothelial growth factor. Optimal control of blood glucose and blood pressure in individuals with diabetes remains the cornerstone for preventing the development and arresting the progression of DR.[3]

Control of blood glucose has been achieved either by diet control or medications. Although diet is an established factor in the development of diabetes, its role in the development and progression of DR needs further investigation.[4,5] While there may be several dietary guidelines for the management of diabetes in general, diet-specific guidelines for the prevention, retardation, and management of microvascular complications of diabetes such as DR are not available.[6]

Few studies have emphasized the role of certain micronutrients and food groups in the possible pathomechanism of DR.[7-9] Protective role of fish and fruits on DR onset and progression has been determined in some previous studies.[10,11] However, a more comprehensive study addressing the role of dietary pattern and various food groups is necessary to help fill the void in the existing information in the subject. Dietary patterns vary globally. In our coastal belt, people consume oily fish and rice, especially parboiled variety as the staple diet. We aimed at conducting a comprehensive assessment of the dietary associations with DR.

Methods

A one-year prospective institutional study was conducted on 261 patients attending the outpatient department of ophthalmology. Prior approval for conducting this study was obtained from the Institutional Review Board, and all study procedures were adhered to recommendations of the Declaration of Helsinki. Written informed consent was obtained from each participant.

The present study included all consenting patients aged 30 years and above who were diagnosed as diabetic at least

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1 year before the study. The presence of diabetes was defined as physician diagnosed diabetes, with the information retrieved from participant's case notes, and excluded all nondiabetic patients. Three hundred and twenty-six consenting participants were interviewed on 24-hour diet recall. Sixty-five participants with incomplete information, type 1 DM, and coexisting ocular disease were excluded ending up with 261 participants for analysis (Fig. 1 shows the consort flow diagram of selection of study participants).

Dietary variables in this study were obtained by structured interviews with participants on 24-h diet recall. It was administered twice nonconsecutively to each participant. Less frequently consumed food was further questioned and documented as weekly consumption. The average daily calorie intake was calculated based on calorific values of individual components.[12] Consumption of meat and fish were reported as times per week. Egg consumption was recorded as to whether or not consumed daily. Milk, tea, and coffee consumption were reported as the number of glasses per day and fruit consumption as the number of serves per day (a serve = 1 medium piece or 2 small pieces of fruit or 1 cup of diced pieces). Breakfast preference (depending on the items most commonly consumed by this population—idli, dosa, upma, jola roti) was also noted. Further, consumption of rice and preference for white rice or parboiled, chapathi and the predominant meal at dinner (rice or chapathi) were also taken into consideration. Additionally, we also enquired about the intake of antioxidants and the modality of treatment for diabetes—oral hypoglycemic agents, insulin therapy, combination therapy, or dietary modification alone. Glycated hemoglobin and fasting blood sugar were also recorded.

The following baseline variables were also documented in the present study: demographic factors like age, gender, family history of diabetes, diabetes duration, and lifestyle factors (smoking and alcohol drinking). The ocular examination included slit-lamp anterior segment examination, and a dilated fundus examination using slit-lamp biomicroscopy (90D), indirect ophthalmoscopy to look for DR, and fundus photography.

The primary outcome variable studied was DR and the secondary outcome studied was the severity of DR. The independent variables include demographic factors, treatment, and dietary factors. Demographic factors included age, sex, duration, smoking, alcohol consumption, and family history. Treatment included antioxidant intake and treatment with oral hypoglycemic agents, insulin, or dietary control. Dietary factors included breakfast meal, milk, coffee, tea intake, fruit, meat, rice, chapathi, egg, and fish.

Statistical analysis

The data were checked for its distribution by Anderson Darling test. Statistical analysis was performed using Minitab® 17.1.0.

All data will be presented as numerical or categorical data. Numerical data are presented with a mean (SD), median with IQR, and categorical data with proportions. Univariate analysis was attempted using Chi square or fisher exact test for categorical variables influencing the DR. Univariate analysis with P values <0.1 was considered for significance and those predictors were included in multivariate analysis.

Binary logistic regression analysis was used to find out the associations between DR and factors influencing it. The logit link function, the calculated odds ratio (OR), and a 95% confidence interval (CI) for the OR were considered to determine whether the association between the response events and the predictors is statistically significant with $P \leq 0.05$ (adjusted P, P/number of predictors in the model). Predictors included in the final model were age, sex, duration, antioxidants (yes/no), pharmacological treatment, egg (yes/no), fish (more frequent [>2 times/week]/ less frequent), chapathi (yes/no), and rice (yes/no). The model was assessed with R^2 values and the goodness-of-fit tests with Hosmer–Lemeshow P values. The variance inflation factor (VIF) was checked for multicollinearity. If VIF values were found high for any predictors, such predictor was excluded from the final model. A positive coefficient and an OR greater than 1 would indicate a high chance of DR, when correlated with a specific predictor.

A binary logistic regression analysis was used to find out the associations between severity of DR and predictors. The severity was described as presence (severe NPDR, PDR) of or absence (mild, moderate NPDR) of severe forms of DR. Predictors included in the model were age, duration, antioxidant (yes/no), fish (yes/no), chapathi (yes/no), and rice (yes/no). The final model fit was checked with log-likelihood values and goodness-of-fit P value (both Pearson and Deviance). The ability of predictability was checked using Somers' D values. A negative coefficient and an OR lesser than 1 would indicate protection against DR correlated with a specific predictor. All primary and secondary outcomes were compared using a conventional α level of 0.05.

Results

The mean (±SD) age of participants was 57.73 ± 11.29 years, and 67% were men. One hundred and six (40.6%) participants had DR. Fifty (47%) had mild nonproliferative DR (NPDR), 41 (38.6%) had moderate NPDR, 12 (12.2%) had severe NPDR, and 3 (2.8%) had PDR. Univariate analysis showing the association between each food group and DR is presented in Table 1. Sex, duration, HBA1c, antioxidant, meat (times/week), fish (times/week), egg (yes/no), rice lunch (yes/no), rice dinner (yes/no), rice (parboiled/white), and total calorie were significantly associated with DR ($P < 0.05$). No significant association was observed between occurrence of DR and any of the following variables: smoking, alcohol, hypertension, and family history, consumption of milk, coffee, tea, and breakfast meal.

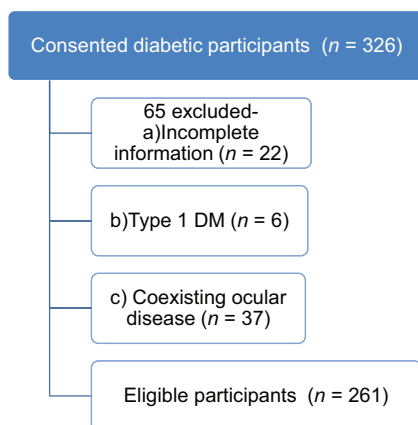**Figure 1:** Flow diagram showing the selection of study participants

Consented diabetic participants (n = 326)

65 excluded-
a)Incomplete information (n = 22)

b)Type 1 DM (n = 6)

c) Coexisting ocular disease (n = 37)

Eligible participants (n = 261)

Table 2 details the results of multivariate regression analysis of various predictors with DR. It shows no association between occurrence of any grade of DR with age ($P = 0.981$). After adjusting for other factors that were tested, increased risk of developing DR is associated with longer duration of DR (OR: 1.05, 95% CI: 1.01–1.11) ($P = 0.014$), males (OR: 3.20, 95% CI: 1.65–6.19) ($P < 0.001$), consumption of antioxidant (OR: 3.42, 95% CI: 1.65–7.05) ($P = 0.001$), and consumption of rice (OR: 3.19, 95% CI: 1.17–8.69) ($P = 0.018$). Diabetics on pharmacological treatment (insulin and oral hypoglycemic agents) (OR: 0.16, 95% CI: 0.04–0.58) compared to those on diet control and diabetics consuming fish more frequently (>2 times/ week) (OR: 0.42, 95% CI: 0.18–0.94) ($P = 0.030$) were at less risk of developing DR. Consumption of egg and *chapathi* were not associated with the occurrence of DR.

Table 1: Univariate associations between predictors and diabetic retinopathy

Predictors	Presence of DR (*n*=106)	Absence of DR (*n*=155)	*P*
Age			
<40 years	7 (6.6)	13 (8.4)	0.073
41-70 years	85 (80.2)	127 (81.9)	
>70 years	14 (13.2)	15 (9.7)	
Sex			
Female	25 (23.6)	61 (39.4)	0.008
Male	81 (76.4)	94 (60.6)	
Duration			
1-10 years	70 (66.0)	124 (80)	0.028
>10 years	36 (34.0)	31 (20)	
Smoking	7 (6.6)	16 (10.3)	0.298
Family history	17 (16.0)	30 (19.4)	0.493
Alcohol	23 (21.7)	31 (20)	0.739
Hypertension	36 (34.0)	54 (34.8)	0.884
Antioxidant	32 (30.2)	20 (12.9)	0.001
Treatment			
Pharmacological treatment	86 (81.1)	151 (97.4)	<0.001
Diet	20 (18.9)	4 (2.6)	
Milk (yes/no)	4 (3.8)	13 (8.4)	0.717
Tea (yes/no)	82 (77.4)	121 (78.1)	0.893
Coffee (yes/no)	12 (11.3)	12 (7.7)	0.326
Fruits (yes/no)	45 (42.5)	61 (39.4)	0.617
Meat (yes/no)	54 (50.9)	72 (46.5)	0.476
Fish (yes/no)	54 (50.9)	87 (56.1)	0.409
Egg (yes/no)	23 (21.7)	16 (10.3)	0.011
Chapathi (yes/no)	33 (31.1)	63 (40.6)	0.118
Rice lunch (yes/no)	98 (92.5)	121 (78.1)	0.002
Rice dinner (yes/no)	85 (80.2)	101 (65.2)	0.008
Rice boiled/white	82 (77.4)	93 (60.0)	0.025
Rice (yes/no)	98 (92.5)	121 (78.1)	0.002
Total calories			
<500	3 (2.8)	6 (3.9)	0.032
500-1000	47 (44.3)	79 (51.0)	
>1000	56 (52.8)	70 (45.2)	

Data are represented as number (percentage). *P* values were obtained using Fisher's exact test or Chi-square tests as appropriate

Table 3 summarizes the results of binary logistic regression analysis of various predictors with severity of DR. Participants consuming antioxidants (OR: 0.08, 95% CI: 0.01–0.95) ($P = 0.001$) were at less risk of progressing to severe forms of DR. More frequent consumption of fish (OR: 0.06, 95% CI: 0.01–1.06) ($P = 0.028$) was associated with less severe forms of DR and a protective effect on the eye. Chapathi (OR: 9.37, 95% CI: 1.64–53.68) consumption was significantly associated with severe forms of DR. This finding in our study needs to be interpreted with caution as there is a general tendency for diet switchover to chapathis with increased severity of the disease in our subset of population.

Discussion

Dietary modification is a simple and achievable measure in the holistic management of diabetes and its microvascular complications in diabetic patients. To the best of our knowledge, ours is the first study of its kind ventured in our country to provide a comprehensive analysis of the association of food groups with DR. The influence of various dietary components in the development of DR among a sizeable proportion of indigenous population living in the coastal belt of South India has been discussed in the current study. We report that participants with longer duration of diabetes, male gender, antioxidants supplementation, patients on pharmacological treatment, consumption of fish, and rice consumption had an association with DR. Consuming fish and antioxidant intake had a significantly lower risk of DR progression. Meanwhile, no direct association of consumption of fruits, meat, milk, tea, and breakfast type with DR could be ascertained from our observations.

Refined grains such as white rice and refined wheat have become staples of the modern Asian Indian diet. Shobhana *et al.*[13] in their study showed that as wheat based formulations yield lower glycemic indices than rice-based ones, wheat based formulations as a food supplement or a meal replacer in diabetic subjects were more suitable than rice- based formulations. However in our study chapathi (wheat based) intake was significantly associated with severe forms of DR. We speculate that this finding could be attributed to the fact that in India uncontrolled diabetics often take to consuming chapathis largely in their diet. Though the nutritional value and safety of consuming either rice or chapathi in diabetics have been debated for decades, parboiled rice, because of its increased fiber content, high nutrition value, and low glycemic index compared to white rice, has been claimed to be good for diabetic patients.[14] Parboiled rice is the preferred grain by South Indians. The majority of the participants in our study also consumed parboiled rice (67%). Odds of development and progression of DR increased significantly in the subjects consuming rice. Though parboiled rice has been considered to be superior to white rice, the quantity of consumption is often ignored. As the serving sizes of food preparation are not paid attention, individuals consume far more calories than they realize. Increased quantity of consumption of rice or chapathi can be detrimental for diabetics. High calorie intake was significantly associated with DR in our study. Wong *et al.* in a systematic review also suggested the possibility of association of high total caloric intake with greater DR risk.[15]

In the present study, we observed an inverse association between more frequent (>2 times/week) fish consumption and DR progression. Seafood is a very important constituent of the staple diet among the coastal population. In our

Table 2: Multivariate regression analysis for occurrence of diabetic retinopathy (of any severity) versus various risk factors (n=261)

Predictors	OR	95% CI		P
		Lower	Upper	
Age	0.98	0.95	1	0.179
Sex				
Male	3.2	1.65	6.19	<0.001
Female	1			
Duration	1.05	1.01	1.11	0.014
Antioxidant				
Yes	3.42	1.65	7.05	0.001
No	1			
Pharmacological treatment				
Yes	0.16	0.04	0.58	0.002
Diet	1			
Consumption of rice				
Yes	3.19	1.17	8.69	0.018
No	1			
Consumption of chapathi				
Yes	1.04	0.53	2.04	0.898
No	1			
Consumption of egg				
Yes	1.35	0.61	3.01	0.451
No	1			
Consumption of fish				
More frequent	0.422	0.18	0.94	0.03
Less frequent	1			

OR=Odds ratio, CI=Confidence intervals; adjusted *P* value was used for statistical significance

Table 3: Multivariate regression analysis for severity of diabetic retinopathy versus various risk factors (n=106)

Predictors	OR	95% CI		P
		Lower	Upper	
Age	0.81	0.71	0.93	<0.001
Duration	0.94	0.82	1.06	0.309
Antioxidant				
Yes	0.08	0.01	0.95	0.001
No	1			
Consumption of rice				
Yes	0.23	0.02	3.63	0.285
No	1			
Consumption of chapathi				
Yes	9.3	1.64	53.68	0.006
No	1			
Consumption of fish				
More frequent	0.06	0.01	1.06	0.028
Less frequent	1			

OR=Odds ratio, CI=Confidence intervals; adjusted *P* value was used for statistical significance

study, consumption of fatty fish such as mackerel, sardines, croaker fish, and silver fish showed a decreased likelihood of developing DR changes in the study participants. Fish intake had a significant protective effect on a diabetic eye. Recently two large studies,[10,16] one on Spanish adults and one on Asian population, showed that at least two servings of oily fish per week had a significantly lower risk of vision-threatening DR. Similarity of finding in two different ethnic groups may suggest a biological association between fish intake and DR as suggested by Chua *et al.*[10]

Fruits are known to be low-glycemic-index foods rich in dietary fiber, which can slow down the conversion of carbohydrates into glucose after ingestion. Mahoney *et al.* concluded that more frequent consumption of foods rich in flavonoid particularly fruits like citrus fruit, apples, berries, and dark green leafy vegetables was associated with reduced odds of having DR.[11] However, we failed to find any association of fruit with DR; this could be attributed to the smaller number of subjects consuming fruits in our study.

Even though egg consumption was reported as a risk factor for diabetes mellitus in previous studies, it was not associated with the risk of DR in this study. While there is little or no evidence of the role of eggs on the development of DR, many studies have tried to explain its association with diabetes. Djousse *et al.*[17] have demonstrated that daily consumption of at least one egg is associated with a greater risk of type 2 diabetes in both men and women, independently of traditional risk factors for type 2 diabetes. The observed relation between egg intake and diabetes may be partially explained by the cholesterol content of eggs. However, besides dietary cholesterol, eggs contain other important nutrients that have been shown to increase (i.e., saturated fat and cholesterol) or decrease (i.e., polyunsaturated fat) the risk of type 2 diabetes.[18-20] This explains why it could be difficult to assign a protective or deleterious label to the inclusion of eggs in the diet of diabetics.

A beneficial effect of key antioxidant nutrients was hypothesized based on the consideration that oxidative stress may contribute to microvascular pathology, thereby promoting DR.[21] Epidemiologic studies have reported that diets rich in antioxidants such as vitamin C, vitamin E, α-tocopherol, or β-carotene exhibit beneficial effects on glucose metabolism and diabetes prevention.[22] However, Davis *et al.* showed that while antioxidants like vitamin C, E, and β-carotene may be protective for other ophthalmic conditions like cataract and age-related macular degeneration, it had no beneficial effect on the prevalence and severity of DR.[23] As these antioxidant preparations contain a combination of many micronutrients, doses of which vary, increase or decrease of the dose of micronutrients can result in an inadequate result on DR. Odds of developing DR increased three times in patients on antioxidant supplementation in our study. This significant positive association between supplementation of antioxidants and DR can be attributed to the fact that antioxidant supplementation in our setup was often prescribed to patients who develop early retinal changes, considering the financial constraints and the socioeconomic status of the patient. Majority of our patients who received antioxidant preparation (β-carotene, copper, manganese, selenium, zinc, vitamin C, vitamin E, lutein) had mild-to-moderate grade of DR at baseline. However, antioxidant supplementation was associated inversely with DR progression after adjusting for other confounders in this study, indicating a protective effect on

diabetic retina. Further research is needed to better understand this beneficial effect of antioxidants in DR.

Yan *et al.* showed that consumption of red meat was not associated with the risk of progression of DR. They have also suggested that poultry intake may have a protective role.[24] The benefits of the intake of milk and other dairy products on retinal vasculature have been highlighted in a study conducted by Gopinath *et al.*,[25] which concluded that participants who consumed five serves or less per week (i.e., 0.75 serves/day) of total dairy products had wider retinal venular caliber. However, we did not find any significant benefit on the retina of diabetic patients conferred by consuming meat, milk, and milk products in our study; this may be due to the fact that <50% of the participants consumed these products.

Strength and limitations: Inclusion of multiple food groups and data collection on energy intake is the major strength of our study. Small sample size is the major limitation of our study. Other limitations, including recall bias regarding dietary consumption, lifestyle factors like physical activity, and body mass index that could be confounding factors in nutritional research, were also not considered. Finally, as there is variation in the dietary pattern globally; our results can be extrapolated only in an area with similar diet patterns.

Conclusion

In conclusion, males, longer duration of the disease, antioxidant supplementation, fish, and rice consumption had an association with DR. Consumption of fish had a significantly lower risk of DR, whereas rice consumption was a significant risk factor for DR. Antioxidant supplementation and fish consumption posed a significant lower risk of DR progression. Hence, a restricted balanced diet can substantially help in preventing DR changes. However, further studies are essential to derive a cause–effect relationship between food and DR. Formulating proper dietary guidelines should be the next direction of research in this field.

Conflicts of interest

There are no conflicts of interest.

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