Correlation of poor oral hygiene with diabetic retinopathy and its relation with altered ocular blood flow in middle aged type 2 diabetes patients residing in sub Himalayan West Bengal

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Abstract

Aim: To assess correlation of poor oral hygiene with diabetic retinopathy and its relation with altered ocular blood flow. **Method:** Observational cross sectional institution based study with 46 cases of diabetic retinopathy and 46 diabetes patients with no retinopathy as controls. Colour Doppler study of carotid artery, central retinal artery and ophthalmic artery; simplified oral hygiene index scoring was done. Main outcome measure was correlation of simplified oral hygiene index with resistivity index and pulsatality index of ophthalmic and central retinal artery. **Results:** Simplified oral hygiene index was significantly higher among the cases ($p < 0.001$). Those with simplified oral hygiene index value > 2.9 were 5 times more likely to develop retinopathy (OR 5.34, 95% CI: 2.1 – 13.5). There was no significant difference in OHI-S (p=0.761) between those with HbA1C d" 6.5 and >6.5, among the cases. Severity of retinopathy had a significant correlation with simplified oral hygiene index (Spearman's rho: 0.4, $p < 0.001$). No blood flow parameter showed a significant correlation with simplified oral hygiene index. **Conclusions:** Poor oral hygiene demonstrates a very strong correlation of with diabetic retinopathy although without any correlation with alteration in ocular blood flow.

Keywords: Diabetic retinopathy, oral hygiene, periodontitis, colour Doppler

Periodontal disease is defined as an inflammation of the soft tissues surrounding the teeth and destruction of the supporting structures of the teeth[1]. Prevalence of periodontal diseases is very high and can affect up to 90% of the population[2]. Diabetes and periodontal disease have bidirectional relationship. On one hand, more than two fold increase in prevalence of periodontitis has been reported in type 2 diabetes compared to non-diabetics[3], the severity of periodontitis being related to the glycaemic control[4]. On the other hand, periodontitis adversely affects glycaemic control in diabetes[5]. Recently studies have suggested association between diabetic retinopathy (DR) and periodontal diseases, as well[6,7,8].

Pathogenesis of DR is multifactorial and not yet fully understood. Vascular changes and subsequent disturbances of ocular circulation are critical events in the pathogenesis of DR. The role of hemodynamic in DR has not been clearly defined. Association of carotid atherosclerosis has been described both with diabetes and DR. The prevalence of carotid plaques was reported to be 34.2% in controls compared to 72.9% in established diabetic patients[9]. Severity of DR has also been associated with carotid artery intima-media wall thickness (odds ratio of 1.09 for each 0.1-mm thickness)[10].

There are strong epidemiologic evidences for association of periodontitis with increased risk for future cardio-vascular disease[11]. Association of periodontal diseases with atherosclerotic vascular disease exists independent of confounders[12]. Periodontal disease is reported to be associated with carotid atherosclerosis (Odds Ratio: 1.27)[13]. A significant association between periodontitis and carotid calcification has been demonstrated[14]. Mean carotid intima media thickness (CIMT) was found significantly higher in subjects with chronic periodontitis[15]. However there is no established causal relationship as yet.

Colour Doppler imaging (CDI) is colour-encoded velocity information which is one of the most widely used and well established techniques for assessing ocular blood flow velocities in the retro bulbar vessels[16]. Good

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Received on : 30/09/2018, Revision accepted on : 05/06/2019
Conflict of Interest : None, Financial Disclosure : None

reproducibility has been reported in the localization and hemodynamic measurement within the central retinal artery (CRA) and ophthalmic artery (OA)[17]. There is conflicting data regarding changes in blood flow velocity and resistivity index (RI) in diabetics. Numerous clinical studies have demonstrated increase in the resistivity index in the retro bulbar vessels with progression of diabetic retinopathy[18,19].

Although there are reports to suggest association between DR and periodontal diseases, a cause and effect relationship could not be established. In carotid atherosclerosis, there is theoretical possibility of resultant altered hemodynamic in orbital blood flow and thereby in ocular blood flow.

As DR[10] and periodontitis[12-15] both is associated with carotid atherosclerosis, there is a theoretical possibility that periodontal diseases may have relationship with DR through alteration of ocular blood flow due to carotid atherosclerosis. No study on orbital blood flow in DR has taken oral hygiene into consideration so far.

Our aim was to find association of oral hygiene index with diabetic retinopathy and its correlation with orbital blood flow in diabetes patients.

Material and method:

Institutional ethics committee permitted the study. The work described has been carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki) for experiments involving humans and informed consent was obtained from all participants.

Already diagnosed Type 2 diabetes patients between 45-64 years of age attending retina clinic of a tertiary care teaching institute in Eastern India were recruited in this cross sectional study between July 2014 and Dec 2016. Patients who had any retinopathy in both the eyes were included as cases (Group 1). Patients who had no retinopathy in either eye were included as control (Group2). Using the value of peak systolic velocity (PSV) in the ophthalmic artery(9.0 ± 3.1 cm/second) in a previous study[20], the sample size was calculated with 95% confidence level and 90% power as 46 patients in each group.

Patients with active ocular inflammation, glaucoma, significant media opacity, history of ocular surgery within last 6 months/ laser photocoagulation/ intravitreal injection/ significant trauma/non-diabetic vascular disease in any eye were excluded. Pregnant and lactating women were not included. Patients with diagnosed rheumatoid arthritis/ vasculitis were excluded. Patients with history of a major cardiovascular event were not included. All the consecutive patients satisfying the criteria were included till the sample size was reached.

Body mass index (BMI) and blood pressure were measured. Best corrected visual acuity (BCVA) was measured with Snellen's chart and converted to LogMAR value. Intraocular pressure (IOP) was measured by Goldmann applanation tonometer. DR was diagnosed and classified by one single ophthalmologist as per modified Early Treatment Diabetic Retinopathy Study (ETDRS) classification.

OHI-S (Oral Hygiene Index-Simplified)[21] was used to determine the status of oral hygiene. OHI-S refers to the summation of debris index (DI-S) and calculus index (CI-S). OHI –S was assessed by a single experienced dentist of our institute who was masked to the diagnosis of retinopathy.

Fasting blood sugar (FBS)and post-prandial blood sugar(PPBS), HbA1C,serum lipid profile, albumin, globulin, urea, and creatinine were measured (Transasia XL- 600 Auto-analyser) in the department of Biochemistry of our institute within one week of inclusion in the study.

Blood flow velocities were measured, within one week of inclusion in the study excluding the day of dilated examination, by orbital CDI (PHILIPS-HD-7 with 10MHz transducer) in the department of Radio-diagnosis of our institute by two experienced radiologists masked to the diagnosis of retinopathy. Peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured, in the central retinal artery (CRA), ophthalmic artery (OA), central retinal vein (CRV), common carotid artery(CCA) and internal carotid artery(ICA).Using the values of PSV and EDV, the following parameters were calculated for each vessel : resistivity index(RI) = (PSV-EDV)/PSV; pulsatility index(PI) = (PSV-EDV)/V mean (where V mean = 1/3 (PSV-EDV) + EDV). We measured these indices as they are independent of the Doppler angle, because any change in angle has a concomitant effect on both PSV and EDV[22].

Primary outcome measure was correlation of OHI-S with RI and PI of ophthalmic artery and central retinal artery in study population. Secondary outcome measure was correlation of OHI-S with duration of diabetes, BMI and biochemical parameters tested.

All mean values were compared using independent t-test and ANOVA. Analysis was done using SPSS V20 and graphs were prepared with Stata v 8.0.

Result:

In this study, 46 cases of diabetic retinopathy were compared with 46 controls, who had no diabetic retinopathy (no DR). Out of 46 cases, 3 had proliferative diabetic retinopathy (PDR). For purpose of analysis, PDR was clubbed with severe NPDR. Among the cases, 33% had mild and 45% had moderate NPDR.

Mean age among cases and control was 52.9 ± 6.4 years and 53.6 ± 6.0 years respectively (p=0.34). Among cases there were 23 (50%) male and 23 female. Among controls there were 29 (63.0%) male and 17 (37.0%) female. There was no significant difference in gender distribution among two groups (p=0.29). Various possible risk factors of retinopathy were assessed among cases and controls (Table-1).

As OHI-S was found to be not normally distributed, all statistical analysis involving OHI-S was carried out using non parametric tests. OHI-S was significantly higher among the cases (p < 0.001; Mann Whitney U test). Logistic regression analysis suggested that respondents who had OHI-S value greater than 2.9 were 5 times more likely to develop retinopathy (OR 5.34, 95% CI: 2.1 – 13.5).

The OHI-S was compared between those with HbA1C d" 6.5 and those with HbA1C >6.5 among the cases (patients with DR). The mean OHI-S levels were 4.1 ±0.29 and 3.99 ±0.25 respectively. The difference was not statistically significant (p=0.761).

PI and RI among cases and controls are shown in Table-2. PI of CCA and ICA of left side and RI in the left ICA were significantly higher among cases. As orbital colour Doppler ultrasonography was performed by two masked observers; inter observer variation was tested in initial nine cases. Good inter-observer agreement (mean kappa coefficient =0.64) was noted.

A hypothesis was tested whether the association between OHI-S and retinopathy was mediated through ocular blood flow. If it was so, then increasing OHI-S score would be associated with decreasing blood flow. However, no significant correlation could be found between OHI-S and RI and PI of CCA, CRA, ICA and OA. Spearman's correlation coefficient was calculated between OHI-S and all parameters of blood flow, but none showed a significant correlation. However, severity of retinopathy had a significant correlation with OHI-S (Spearman's rho: 0.4, p < 0.000). Similarly, no significant correlation between OHI-S and age, duration of diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL,

Table-1: Distribution of risk factors for diabetic retinopathy

Risk factors	Cases Mean ±S.E.	Control Mean ±S.E.	P value
Duration of diabetes (years)	6.92 ± 0.63	5.82 ± 0.77	0.275
Duration of hypertension (years)	3.32 ± 0.87	2.82 ± 0.46	0.648
BMI	23.54 ± 0.27	23.50 ± 0.28	0.912
OHI-S	4.0 ± 0.19	2.90 ± 0.20	0.001*
HbA_1C	8.25 ± 0.25	7.28 ± 0.29	0.013*
HDL	42.15 ± 1.3	41.75 ± 1.23	0.828
LDL	105.64 ± 5.97	101.29 ± 4.00	0.547
VLDL	29.18 ± 1.70	33.7 ± 1.60	0.026*
Total cholesterol	176.51 ± 6.33	176.98 ± 4.92	0.954
Total protein	7.30 ± 0.09	7.46 ±0.07	0.170

*Significance at 0.05 level (Mann Whitney U test), BMI=body mass index, OHI-S= simplified oral hygiene index, HbA_1C= glycosylated hemoglobin, HDL=high density lipoprotein, LDL= low density lipoprotein, VLDL= very low density lipoprotein.

Table-2: Pulsatility index and resistivity index among cases and controls

Parameters	Cases (N=46) Mean (±SE)	Controls (N=46) Mean (±SE)	P value
RI CCA Left	0.72 (0.01)	0.69 (0.01)	0.047*
RI CCA Right	0.72 (0.01)	0.72 (0.01)	0.676
PI CCA Left	1.43 (0.03)	1.31 (0.04)	0.034*
PI CCA Right	1.46 (0.04)	1.42 (0.03)	0.519
RI ICA Left	0.59 (0.01)	0.54 (0.01)	0.009*
RI ICA Right	0.59 (0.01)	0.58 (0.01)	0.740
PI ICA Left	1.03 (0.04)	0.87 (0.03)	0.005*
PI ICA Right	1.02 (0.04)	1.00 (0.04)	0.778
RI OA Left	0.70 (0.01)	0.69 (0.01)	0.914
RI OA Right	0.71 (0.01)	0.69 (0.01)	0.387
PI OA Left	1.35 (0.04)	1.34 (0.03)	0.794
PI OA Right	1.41 (0.05)	1.35 (0.04)	0.323
RI CRA Left	0.59 (0.01)	0.58 (0.01)	0.467
RI CRA Right	0.60 (0.02)	0.58 (0.02)	0.462
PI CRA Left	1.06 (0.06)	0.99 (0.05)	0.393
PI CRA Right	1.08 (0.06)	1.02 (0.06)	0.499

*Significance at 0.05 level, RI=Resistivity index, PI=Pulsatilty index, CCA= Common carotid artery, ICA=Internal carotid artery, OA= Ophthalmic artery, CRA= Central retinal artery

LDL, VLDL, TGL, albumin, globulin, urea and creatinine was found.

Based on extent of diabetic retinopathy, patients were classified as having no retinopathy (control group) and for NPDR, were given a score of 1, 2, 3 for mild, moderate and severe retinopathy respectively. Proliferative DR was considered along with severe NPDR as explained earlier. Table-3 shows relationship of parameters with severity of retinopathy.

One way ANOVA was used to compare the mean values of continuous variables with respect to severity of retinopathy. Statistically significant differences were observed with respect to OHI-S and systolic blood pressure. The variables that showed statistically significant differences among various categories of retinopathy were RI and PI in left internal carotid artery. RI was significantly different in left common carotid artery as well.

DR was proportionately distributed among patients with raised and normal HbA1C levels. Systolic blood pressure >140 mm of Hg was seen in 50% of NPDR and 33% of PDR patients and diastolic blood pressure >90 mm of Hg was seen in more than 50% of NPDR patients, but these differences between NPDR and PDR patients were not significant. Severity of NPDR was more in left eye compared to right, although the difference was not significant.

Severity of NPDR increased with duration of DM but Chi squared for trend analysis did not show any significant association between duration of DM and retinopathy in either eye. No correlation was observed between DR and serum globulin level, albumin-globulin ratio and pulse pressure.

As observed in Table-1, OHI-S showed significantly high value among cases, it became pertinent to examine the relationship of OHI-S with other predictors of retinopathy to explore the causal pathway. Table-3 also reveals that there is a linear trend in OHI-S score with respect to severity of DR.

In figure1, PI has been compared for different arteries between cases and controls. Using ordinal logistic

Table 3: Blood flow indicators across categories of retinopathy

Measures of blood flow	Retinopathy				P value
	No (control)	Mild	Moderate	Severe	
OHI-S	2.90 ±0.20	3.98±0.39	4.00±0.28	4.17±0.39	0.002*
RI CCA Right	0.72±0.01	0.72±0.02	0.73±0.02	0.73±0.02	0.962
RI CCA Left	0.69±0.01	0.69±0.02	0.74±0.01	0.74±0.01	0.031*
PI CCA Right	1.42±0.03	1.43±0.08	1.48±0.07	1.45±0.06	0.884
PI CCA Left	1.31±0.04	1.32±0.07	1.50±0.04	1.40±0.07	0.041*
RI ICA Right	0.58±0.01	0.54±0.02	0.60±0.01	0.63±0.03	0.137
RI ICA Left	0.54±0.01	0.53±0.02	0.60±0.02	0.59±0.03	0.001*
PI ICA Right	1.00±0.04	0.88±0.06	1.0±0.05	1.14±0.10	0.143
PI ICA Left	0.87±0.03	0.85±0.06	1.12±0.06	1.03±0.09	0.001*
RI OA Right	0.69±0.01	0.69±0.03	0.71±0.01	0.74±0.02	0.423
RI OA Left	0.69±0.01	0.67±0.02	0.71±0.02	0.71±0.03	0.593
PI OA Right	1.30±0.04	1.37±0.12	1.38±0.06	1.53±0.09	0.445
PI OA Left	1.34±0.03	1.26±0.09	1.37±0.06	1.42±0.10	0.577
RI CRA Right	0.58±0.01	0.60±0.03	0.61±0.01	0.59±0.03	0.894
RI CRA Left	0.58±0.01	0.58±0.03	0.60±0.02	0.61±0.04	0.811
PI CRA Right	1.02±0.01	1.08±0.04	1.10±0.09	1.04±0.11	0.905
PI CRA Left	0.99±0.04	1.00±0.08	1.05±0.07	1.15±0.19	0.645

*Significance at 0.05 level, RI=Resistivity index, PI=Pulsatilty index, CCA= Common carotid artery, ICA=Internal carotid artery, OA= Ophthalmic artery, CRA= Central retinal artery.

regression between OHI-S and retinopathy, after removing the control group, did not yield any significant relationship.

For resistivity index, retinopathy severity was tested for being a function of OHI-S. Absence of retinopathy had an OR of 5.2 for low OHI-S category but it was not statistically significant. For other grades of severity of retinopathy also, no significant association was seen with higher OHI-S levels. Distribution of RI across categories of retinopathy is shown in figure 2.

Discussion:

We included middle aged diabetes patients in this study and thereby excluded elderly patientsbecause age is a significant independent risk factor for carotid plaque[23] as well as periodontal diseases[24]. Global prevalence of type 2 DM is highest in the working age group[25] and the majority of type 2 DM in Indian population also is in the same age group[26].

The cases and controls were matched for age and gender with no significant difference. We observed significantly higher HbA1C in DR, as expected. Controls (NO DR) in our study had fairly good glycaemic control.

We used simplified oral hygiene index (OHI-S) by Green and Vermillion[21] to objectively categorize the level of dental plaque and calculus. OHI-S has been used extensively in epidemiological studies as well as longitudinal studies for the understanding of periodontal disease. The OHI-S has got objective criteria, is easy and quick to perform with high level of reproducibility and high inter-examiner agreement and; hence, can be used with a minimum of training sessions[27]. The other methods of assessment like periodontal screening and recording (PSR) or community periodontal index of treatment needs (CPITN) could also be used. However we opted for OHI-S considering its simplicity.

OHI-S was significantly higher among DR cases among our study population. This suggests that poor oral hygiene is associated with significantly higher risk of diabetic retinopathy. There was significant difference in HbA1C levels between cases and controls in our series, which may indicate that OHI-S in this study was related to diabetes control and not to DR. However when we compared OHI-S among the cases, there was no significant difference between those with HbA1C d" 6.5 and those with HbA1C >6.5; suggesting no influence of diabetes control on OHI-S in our series.

We also found diabetes patients with OHI-S value less than 2.9 were 50% less likely to develop retinopathy. This even emphasizes the possible protective role of oral hygiene in DR. In our study, severity of retinopathy had a significant correlation with OHI-S. These findings are similar to observation made by few recent studies in this field. The severity of periodontal disease was significantly correlated with the severity of DR in a group in Iranian diabetes patients of 30-65 years of age[6]. Significantly more retinopathy was observed in a small subset of Indian population with periodontal disease and diabetes mellitus[28]. An association between periodontal disease status and the occurrence of DR was reported in 100 type 2 diabetes patients[29]. On the other hand diabetic microangiopathic change has been considered as a risk factor for periodontitis[30]. In a multi-centre hospital-based cross-sectional study with 620 type 2 diabetes patients retinopathy was found to be a risk factor for severity of periodontitis[31].

We did not find any difference in the RI and PI of the central retinal artery and ophthalmic artery between cases (DR) and controls (no DR). This is in conformity with findings of Goebel W et al[32]. However some investigators have observed significant difference in the RI of the central retinal artery[20], RI of the ophthalmic artery[33], and PI of the ophthalmic artery[34] in DR cases compared to no DR. Interestingly we observed significantly higher PI and RI in the CCA of the left eye among DR patients. Severity of DR was also significantly correlated with RI and PI of left CCA and left ICA. There are reports of higher cross-sectional area of the left carotid artery intima-media complex thickness (CIMT) compared with the right between the ages of 35 and 65 years (p=0.01-0.05)[35]. We did not measure the CIMT. However the difference in RI and PI can probably be explained by possible difference in CIMT between two sides.

Analysis of English language primary research reports published since 1960on effects of periodontal infection on diabetes complications suggests periodontal infection having an adverse effect on incidence of diabetes complications[36]. The number of systemic micro vascular complications (including retinopathy) has been found to increase with the severity of periodontitis[31]. We tested hypothesis whether the association between poor oral hygiene and retinopathy was mediated through ocular blood flow. This study failed to demonstrate any significant alteration in ocular blood flow with change in oral hygiene status and thus failed to prove our proposed causal relationship between poor oral hygiene and retinopathy. Some researchers proposed that micro vascular morphological retinal changes in diabetes are reflective of systemic micro vascular changes which also include periodontal tissue. Streptozotocin-induced diabetes in rats has been found to cause morphological changes in the periodontal tissues which may in turn predispose to periodontal disease[37]. Primary diabetic micro-angiopathy has been proposed responsible for development of diabetic parodontopathy[38]. Thus both retinopathy and periodontal disease may be independent end organ changes of diabetes.

Limitations of our study were failure to include smoking history, tooth brushing report, CIMT value, CIPTN and also the cross sectional nature of study. OHI-S was assessed by a single observer. Two independent, masked observers were preferable for this qualitative assessment. Comparison of carotid plaques in DM patients with and without retinopathy could not be done in this study. Ocular blood flow was assessed by CDI and other methods like laser Doppler velocimetry/flowmetry, blue field entoptic technique were not employed.

This study clearly demonstrates a very strong correlation of oral hygiene with diabetic retinopathy in middle aged patients although without demonstrating any causal relationship through altered blood flow. This emphasizes the need of awareness regarding oral hygiene among diabetes patients.

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Cite this article as:
Sharma UR, Roy PK, Sharma AK, Kabiraj SP, Ghosh S. Correlation of poor oral hygiene with diabetic retinopathy and its relation with altered ocular blood flow in middle aged type 2 diabetes patients residing in sub Himalayan West Bengal. Current Indian Eye Research 2019;6:53-60.