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Association of serum lipids with diabetic retinopathy in urban South Indians—the Chennai Urban Rural Epidemiology Study (CURES) Eye Study—2

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Abstract

Aims To study the association of serum lipids with diabetic retinopathy (DR) in Type 2 diabetic subjects.

Methods Type 2 diabetic subjects (n = 1736) were randomly selected from the Chennai Urban Rural Epidemiology Study (CURES), which was carried out on a representative population of Chennai in South India. DR was diagnosed by retinal colour photography and classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system. Classification of lipid abnormalities was done according to the National Cholesterol Education Programme–Adult Treatment Panel III (NCEP–ATP III) Guidelines.

Results The mean serum cholesterol (P = 0.024), serum triglycerides (P = 0.017) and non-high-density lipoprotein (HDL)-cholesterol (P = 0.025) concentrations were higher in subjects with DR compared with those without DR. Multiple logistic regression analysis revealed that after adjusting for age, gender, duration of diabetes, total cholesterol Standardised regression estimate (SRE) = 1.178, 95% confidence interval (CI) 1.042, 1.331, P = 0.014), non-HDL-cholesterol (SRE = 1.169, 95% CI 1.040, 1.313, P = 0.012) and serum triglycerides (SRE = 1.292, 95% CI 1.136, 1.467, P = 0.001) were associated with DR and non-HDL-cholesterol (SRE = 1.264, 95% CI 1.000, 1.592, P = 0.045) and low-density lipoprotein (LDL)-cholesterol (SRE = 1.453, 95% CI 1.107, 1.896, P = 0.005) with diabetic macular oedema (DME). After adjusting for HbA_{1c} and body mass index, only triglycerides maintained a significant association with DR (SRE = 1.137, 95% CI 1.000, 1.291, P = 0.007) and LDL-cholesterol with macular oedema (SRE = 1.358, 95% CI 1.034, 1.774, P = 0.026).

Conclusions There is a significant association of serum triglycerides with DR and LDL-cholesterol with DME.

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Keywords diabetic retinopathy, lipids, non-HDL-cholesterol, South Indians, triglycerides

Abbreviations BMI, Body Mass index; CURES, Chennai Urban Rural Epidemiology Study; DME, diabetic macular oedema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; KD, known diabetic subjects; LDL, low-density lipoprotein; NPDR, non-proliferative diabetic retinopathy; OGTT, oral glucose tolerance test; PDR, proliferative diabetic retinopathy

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Introduction

Marked variations in the prevalence of diabetic retinopathy (DR) have been reported in different populations [1–3]. While this could be due to differences in sample size and diagnostic methods used, true ethnic differences may also occur. We have recently shown that the overall prevalence of DR as well as the prevalence of DR at diagnosis of diabetes is remarkably lower [4,5] in our population compared with Europeans [6]. Previous studies have shown that the risk factors for DR are degree of glycaemic and blood pressure control, duration of diabetes, presence of nephropathy and raised serum lipids [7,8]. It is possible that some of the differences noted in the prevalence of DR are related to the levels of these risk factors. The association between serum lipids and DR has been widely studied but has produced conflicting results [9–21] due to differences in the methodology and ethnicity. Elevated lipid concentrations may be an additional risk factor for diabetic macular oedema, particularly the deposition of hard exudates in the retina. In a clinic-based report several years ago, we showed an association between low-density lipoprotein (LDL)-cholesterol and diabetic maculopathy [13]. To study whether there is any true relationship of conventional lipid parameters with DR we undertook this population-based study in an urban South Indian Type 2 diabetic population.

Methods

The study subjects were recruited from the Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiological study conducted on a representative population of Chennai (formerly Madras), in southern India. The city of Chennai with a population of 4.2 million is divided into 155 corporation wards representing socio-economically diverse groups. The methodology of the study has been published elsewhere [22]. Briefly, in Phase 1, in the urban component of CURES, individuals were selected by a systematic sampling technique from 46 randomly selected corporation wards and 26 001 individuals aged ≥ 20 years were screened for diabetes. Fasting capillary blood glucose was determined using a glucose meter (One Touch Basic; LifeScan Johnson & Johnson, Milpitas, CA, USA) in all subjects. Subjects with self-reported Type 2 diabetes who were on diet alone/drug treatment for their diabetes were classified as 'known diabetic subjects' (KD).

In Phase 2 of CURES, all the known Type 2 diabetic subjects (n = 1529) were invited to the centre for detailed retinal screening. In addition, subjects with fasting blood glucose concentrations in the diabetic range based on the American Diabetes Association fasting criterion [23] underwent an oral glucose tolerance test (OGTT) using a 75-g oral glucose load dissolved in 250 ml of water. Subjects who had fasting plasma glucose < 6.1 mmol/l and 2 h plasma glucose value < 7.8 mmol/l were categorized as having normal glucose tolerance. Those confirmed by OGTT to have 2-h plasma glucose value ≥ 11.1 mmol/l based on World Health Organization consulting group criteria [24] were categorized as 'newly detected Type 2 diabetic subjects'. Of the total 1529 KD, 1382 participated in the study (response rate 90.4%) in addition to 354 newly detected diabetic subjects.

The institutional ethics committee approved the study and informed consent was obtained from all study subjects.

Anthropometric measurements including weight, height and waist circumference were obtained. The BMI was calculated using the formula, weight (kg)/height (m^2). The blood pressure was recorded in the right arm while seated [22].

A fasting blood sample was taken for estimation of biochemical parameters. All biochemical assays were carried out using a Hitachi 912 Autoanalyser (Hitachi, Berlin, Germany) using kits supplied by Boehringer Mannheim (Mannheim, Germany). Fasting plasma glucose (GOD–POD method), serum cholesterol (CHOD-PAP method), serum triglycerides (GPO-PAP method) and high-density lipoprotein (HDL)-cholesterol (direct method, polyethylene glycol-pretreated enzymes) were measured. LDL-cholesterol was calculated using the Friedewald formula [25]. Non-HDL-cholesterol was calculated by subtracting the HDL-cholesterol from the total cholesterol. Glycated haemoglobin (HbA_{1c}) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA, USA).

Classification of lipid abnormalities was done according to the National Cholesterol Education Programme–Adult Treatment Panel III (NCEP–ATP III) Guidelines [26].

Ocular studies

Visual acuity

Visual acuity was recorded by trained optometrists using an illuminated Snellen's chart. The best-corrected visual acuity of each eye was documented. Slit lamp examination of the anterior segment was done and the intra-ocular pressure was recorded using a shiotz tonometer. The pupils were then dilated using one drop each of phenylepherine 10% and tropicamide 1% into both eyes and the drops were repeated until the best possible mydriasis was obtained.

Retinal photography

Four-field colour retinal photography was carried out by trained photographers with a Zeiss FF 450 plus Fundus camera using 35-mm colour transparenices. The four fields taken were stereoscopic pictures of the macula, disc, superior temporal and inferior temporal quadrants [27]. The photographs were coded using an identification number and assessed in a masked manner in order to minimize any possible bias. They were graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system [28]. The photographs were assessed in comparison with the ETDRS standard photographs for severity of retinopathy [28]. The minimum criterion for diagnosis of DR was the presence of at least one definite microaneurysm in any field of the eye. Photographs were assessed and assigned a retinopathy level and the final diagnosis for each patient was determined from the grading of the worse eye using ETDRS final retinopathy scale for individual eyes. Briefly, level 10 represents no retinopathy (no DR), level 20 to level 53E non-proliferative diabetic retinopathy (NPDR) and level ≥ 61 proliferative diabetic retinopathy (PDR) [28].

Diabetic macular oedema was defined as retinal thickening at or within one disc diameter of the centre of the macula or the presence of definite hard exudates [29]. DME may be present in both NPDR and PDR stages.

Two independent graders graded the photographs for DR. A subset of photographs of 100 patients was assessed for interobserver variation. Unweighted κ for agreement was 0.97, indicating good agreement. When there was disagreement between the two graders, a third grader graded the photographs and this was taken as the final diagnosis.

Definitions

Diabetes

Patients diagnosed by physician diagnosis and on diet/drug treatment for diabetes (insulin or oral hypoglycaemic agents) were termed KD, those diagnosed for the first time by 2 h post glucose value ≥ 11.1 mmol/l as newly detected Type 2 diabetic subjects [24].

Hypertension

Hypertension was diagnosed if there was a self-reported history of physician diagnosis or if subjects were on drug treatment for hypertension or had a systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg [30].

Statistical analysis

Values were expressed as mean ± SD. One-way ANOVA (with *post hoc* Tukey analysis) or Student's *t*-test, as appropriate, was used to compare groups for continuous variables and χ^2 test was used to compare proportions among groups. Ten subjects did not have lipid values and were excluded from the analysis. The associations of lipid parameters with either DR or DME were analysed using logistic regression analysis. Standardised regression effects for lipids were calculated by multiplying the beta estimate from logistic regression models by the standard deviation of that variable. $P < 0.05$ was considered significant. All analysis was done using the Windows-based SPSS statistical package (Version 10.0; SPSS Inc., Chicago, IL, USA).

Results

Of the 1736 diabetic subjects recruited, fundus photographs could not be taken in 21 subjects for various reasons, which included opacities in the ocular media and inability or refusal to cooperate. Thus, a total of 1715 subjects were photographed. Since lipid subfraction values were not available for 10 subjects, a total of 1705 subjects were included in the study of association of DR with serum lipids. Opacities in the ocular media also prevented photography of the right eye of 36 subjects and left eye of another 36 subjects. In these cases, the eye which could be photographed was taken for analysis.

Table 1 presents the clinical and biochemical characteristics of the diabetic subjects with and without retinopathy. Subjects with DR were older ($P < 0.0001$), had longer duration of diabetes ($P < 0.0001$), lower body mass index (BMI) ($P < 0.0001$), higher fasting plasma glucose ($P < 0.0001$) and higher HbA_{1c} ($P < 0.001$) concentrations compared with those without DR. Serum cholesterol ($P = 0.024$), serum triglycerides ($P = 0.017$) and non-HDL cholesterol ($P = 0.025$) concentrations were higher in subjects with DR, while LDL- and HDL-cholesterol concentrations were similar in the two groups.

Table 2 presents the prevalence of different grades of DR in relation to age, gender and clinical characteristics. Severity of retinopathy significantly increased with increase in age ($P = 0.002$) and duration of diabetes ($P < 0.0001$). Prevalence of all grades of DR was higher among men compared with women ($P = 0.001$). Visual acuity decreased with increase in severity of retinopathy ($P < 0.001$). There was no significant

Table 1 Clinical and biochemical characteristics of the study groups with and without retinopathy

Variables	Subjects without DR ($n = 1406$)	Subjects with DR ($n = 299$)	*P*-value
Age (years)	50 ± 11	53 ± 10	< 0.0001
Male, *n* (%)	605 (43%)	164 (54%)	< 0.0001
Body mass index (kg/m^2)	25.5 ± 4.3	24.0 ± 4.1	< 0.0001
Waist circumference (cm)	90.8 ± 9.9	88.9 ± 10.4	0.003
Systolic blood pressure (mmHg)	129 ± 21	131 ± 22	0.137
Diastolic blood pressure (mmHg)	78 ± 12	76 ± 11	0.076
Duration of diabetes (years)	5.0 ± 5.0	8.0 ± 6.0	< 0.0001
Fasting plasma glucose (mmol/l)	7.7 ± 3.3	9.6 ± 3.9	< 0.0001
HbA_{1c} (%)	8.5 ± 2.2	9.8 ± 2.3	< 0.0001
Creatinine (μmol/l)	74.3 ± 28.3	76.9 ± 19.4	0.148
Serum cholesterol (mmol/l)	5.0 ± 1.0	5.1 ± 1.2	0.024
HDL-cholesterol (mmol/l)	1.1 ± 0.2	1.1 ± 0.3	0.515
LDL-cholesterol (mmol/l)	3.1 ± 0.9	3.2 ± 0.9	0.632
Serum triglycerides (mmol/l)	1.7 ± 1.1	2.0 ± 1.8	0.017
Total cholesterol/HDL ratio	4.9 ± 1.2	5.0 ± 1.3	0.105
Non-HDL-cholesterol (mmol/l)	4.0 ± 1.0	4.1 ± 1.1	0.025

Values presented as mean ± SD.

Table 2 Prevalence of diabetic retinopathy in different groups

	Mild NPDR (n = 159)	Moderate NPDR (n = 118)	Severe NPDR (n = 6)	PDR (n = 16)	DME (n = 98)
Age (years)*					
< 40 (n = 274)	14 (5.1)	9 (3.3)	1 (0.4)	1 (0.4)	8 (2.9)
40–59 (n = 1033)	105 (10.2)	83 (8.0)	1 (0.1)	9 (0.9)	62 (6.0)
≥ 60 (n = 408)	40 (29.8)	26 (6.4)	4 (1.0)	6 (1.5)	20 (4.9)
Gender*					
Males (n = 946)	90 (57.0)	62 (53.0)	1 (17.0)	10 (63.0)	39 (40.0)
Females (n = 769)	69 (43.0)	56 (47.0)	5 (83.0)	6 (37.0)	51 (60.0)
Duration of diabetes (years)**					
< 1 (n = 420)	23 (5.5)	8 (1.9)	2 (0.5)	2 (0.5)	8 (1.9)
1–5 (n = 592)	55 (9.3)	37 (6.3)	1 (0.2)	4 (0.7)	28 (4.7)
6–10 (n = 337)	49 (14.5)	38 (11.3)	2 (0.6)	4 (1.2)	29 (8.6)
> 10 (n = 172)	27 (15.7)	34 (19.8)	1 (0.6)	6 (3.5)	24 (14)
Hypertension					
Normotensive (n = 1004)	96 (9.6)	63 (6.3)	1 (0.1)	6 (0.6)	45 (4.5)
Hypertensive without medication (n = 338)	32 (9.5)	25 (7.4)	2 (0.6)	2 (0.6)	19 (5.6)
Hypertensive on medication (n = 373)	31 (8.3)	30 (8.0)	3 (0.8)	8 (2.1)	26 (7)
Visual acuity**					
6/6 (n = 1037)	99 (9.5)	68 (6.5)	1 (0.1)	3 (0.3)	48 (4.6)
6/9–6/12 (n = 391)	42 (10.7)	30 (7.7)	2 (0.5)	5 (1.3)	26 (6.6)
6/18–6/36 (n = 111)	8 (7.2)	9 (1.1)	1 (0.9)	2 (1.8)	4 (3.6)
≤ 6/60 (n = 78)	7 (9.0)	6 (7.7)	1 (1.3)	6 (7.7)	6 (7.7)

Linear trend for the severity of retinopathy excluding DME, *P < 0.05; **P < 0.001.
All values are expressed as n (%).
NPDR, Non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DME, diabetic macular oedema.

Table 3 Mean values of the lipid subfractions in subjects categorized according to severity of diabetic retinopathy (DR)

Lipid parameters	Type 2 diabetic subjects without DR (n = 1406)	Mild NPDR (n = 159)	Moderate NPDR (n = 118)	Severe NPDR (n = 6)	PDR (n = 16)
Serum cholesterol (mmol/l)	5.2 ± 1.0	5.2 ± 1.1	5.5 ± 1.4*	5.4 ± 1.7	5.6 ± 1.4
Serum triglycerides (mmol/l)	1.7 ± 1.1	2.1 ± 1.9*	2.0 ± 1.7	1.6 ± 0.9	1.5 ± 0.7
LDL-cholesterol (mmol/l)	3.3 ± 0.9	3.1 ± 0.9	3.4 ± 0.9	3.5 ± 1.6	3.6 ± 1.0
HDL-cholesterol (mmol/l)	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	1.2 ± 0.3
Total cholesterol/HDL ratio	4.9 ± 1.2	4.9 ± 1.1	5.1 ± 1.6	5.5 ± 1.9	4.8 ± 1.3
Non-HDL-cholesterol (mmol/l)	4.1 ± 1.0	4.1 ± 1.1	4.4 ± 1.2*	4.4 ± 1.7	4.4 ± 1.3

Values presented as mean ± SD.
*P < 0.05 when compared with subjects with Type 2 diabetes without DR.
NPDR, Non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

difference in the prevalence of different grades of DR with hypertension and those on antihypertensive medication.

Table 3 shows the serum lipid concentrations in different grades of DR compared with those without DR. Serum total cholesterol concentrations were higher in subjects with moderate NPDR compared with subjects without DR (P < 0.05). Triglyceride concentrations were higher in those with mild NPDR compared with those without DR (P < 0.05). Except for these two parameters, there were no significant differences in the lipid concentrations with the severity of DR. Table 4 shows the concentrations of serum lipids with different levels of visual acuity. There were no significant differences in lipid concentrations with different grades of vision.

Table 5 presents the lipid subfractions in DR subjects with and without DME. Serum cholesterol (P = 0.023), serum LDL-cholesterol (P = 0.001) and non-HDL-cholesterol (P = 0.015) concentrations were significantly higher in the retinopathy subjects with DME compared with those without DME.

Table 6 shows the results of regression analysis using DR as the dependent variable. Even after adjusting for age, gender and duration of diabetes, total cholesterol [SRE = 1.178, 95% confidence interval (CI) 1.042, 1.331, P = 0.014], serum non-HDL cholesterol (SRE = 1.169, 95% CI 1.040, 1.313,

Table 4 Visual acuity and serum lipid levels

Lipid parameters	Visual acuity			
	6/6 (n = 1037)	6/9–6/12 (n = 391)	6/18–6/36 (n = 111)	≤ 6/60 (n = 78)
Serum cholesterol (mmol/l)	5.2 ± 1.1	5.2 ± 1.0	5.1 ± 1.2	5.4 ± 1.3
Serum triglycerides (mmol/l)	2.1 ± 1.6	1.9 ± 1.0	1.9 ± 1.0	1.8 ± 0.9
LDL-cholesterol (mmol/l)	3.2 ± 0.9	3.2 ± 1.0	3.2 ± 1.0	3.4 ± 1.0
HDL-cholesterol (mmol/l)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.3	1.2 ± 0.3
Total cholesterol/HDL ratio	4.9 ± 1.2	4.9 ± 1.2	4.9 ± 1.7	4.8 ± 1.1
Non-HDL-cholesterol (mmol/l)	4.1 ± 1.0	4.1 ± 0.9	4.1 ± 1.2	4.2 ± 1.1

Values presented as mean ± SD.
No significant association between the grades of vision and lipid parameters.

Table 5 Mean values of the lipid subfractions in the diabetic retinopathy (DR) subjects with and without DME

Variables	DR subjects without DME (n = 201)	DR subjects with DME (n = 98)	P-value
Serum cholesterol (mmol/l)	5.2 ± 1.1	5.6 ± 1.5	0.023
HDL-cholesterol (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	0.379
LDL-cholesterol (mmol/l)	3.1 ± 0.8	3.5 ± 1.0	0.001
Serum triglycerides (mmol/l)	2.4 ± 2.3	2.0 ± 1.1	0.128
Total cholesterol/HDL ratio	5.0 ± 1.4	5.1 ± 1.2	0.387
Non-HDL-cholesterol (mmol/l)	4.1 ± 1.1	4.5 ± 1.3	0.015

Values presented as mean ± SD.
DME, Diabetic macular oedema.

P = 0.012) and serum triglycerides (SRE = 1.292, 95% CI 1.136, 1.467, P = 0.001) were associated with DR. However, when HbA_{1c} and BMI were introduced into the model, the association of cholesterol and non-HDL-cholesterol with DR lost its significance, whereas triglycerides still showed a significant association with DR (SRE = 1.137, 95% CI 1.000, 1.291, P = 0.007).

Table 7 presents the results of regression analysis using DME as the dependent variable. Even after adjusting for age, gender and duration of diabetes, serum non-HDL-cholesterol (SRE = 1.264, 95% CI 1.000, 1.592, P = 0.045) and serum LDL-cholesterol (SRE = 1.453, 95% CI 1.107, 1.896, P = 0.005) showed an association with DME. On introducing age and gender into the model, the association with serum cholesterol was lost. When HbA_{1c} and BMI were introduced into the model, only LDL-cholesterol (SRE = 1.358, 95% CI 1.034, 1.774, P = 0.026) was significantly associated with DME.

Table 6 Association of serum lipids with diabetic retinopathy

Parameters	SRE	95% CI	P-value
Total cholesterol			
Unadjusted	1.131	1.000, 1.278	0.025
Adjusted for age and gender	1.178	1.042, 1.331	0.007
Adjusted for age, gender and duration of diabetes	1.178	1.042, 1.331	0.014
Adjusted for age, gender, duration of diabetes and HbA_{1c}	1.085	0.921, 1.227	0.357
Adjusted for age, gender, duration of diabetes, HbA_{1c} and BMI	1.085	0.921, 1.227	0.303
LDL-cholesterol			
Unadjusted	1.035	0.903, 1.185	0.745
Non-HDL-cholesterol			
Unadjusted	1.169	1.000, 1.313	0.025
Adjusted for age and gender	1.169	1.040, 1.313	0.010
Adjusted for age, gender and duration of diabetes	1.169	1.040, 1.313	0.012
Adjusted for age, gender, duration of diabetes and HbA_{1c}	1.081	0.925, 1.215	0.295
Adjusted for age, gender, duration of diabetes, HbA_{1c} and BMI	1.081	0.962, 1.263	0.219
Triglycerides			
Unadjusted	1.137	1.000, 1.291	0.002
Adjusted for age and gender	1.137	1.000, 1.291	0.002
Adjusted for age, gender and duration of diabetes	1.292	1.136, 1.467	0.001
Adjusted for age, gender, duration of diabetes and HbA_{1c}	1.137	1.000, 1.291	0.011
Adjusted for age, gender, duration of diabetes, HbA_{1c} and BMI	1.137	1.000, 1.291	0.007

BMI, Body mass index.

Table 7 Association of serum lipids with diabetic macular oedema

Parameters	SRE	95% CI	*P*-value
Total cholesterol			
Unadjusted	1.279	1.042, 1.631	0.016
Adjusted for age and gender	1.227	1.000, 1.504	0.059
Adjusted for age, gender and duration of diabetes	1.227	1.000, 1.504	0.057
Adjusted for age, gender, duration of diabetes and HbA_{1c}	1.131	0.921, 1.444	0.272
Adjusted for age, gender, duration of diabetes, HbA_{1c} and BMI	1.131	0.921, 1.444	0.247
LDL-cholesterol			
Unadjusted	1.504	1.185, 1.961	0.001
Adjusted for age and gender	1.453	1.107, 1.896	0.005
Adjusted for age, gender and duration of diabetes	1.453	1.107, 1.896	0.005
Adjusted for age, gender, duration of diabetes and HbA_{1c}	1.358	1.034, 1.774	0.032
Adjusted for age, gender, duration of diabetes, HbA_{1c} and BMI	1.358	1.034, 1.774	0.026
Non-HDL-cholesterol			
Unadjusted	1.314	1.040, 1.592	0.018
Adjusted for age and gender	1.264	1.000, 1.532	0.052
Adjusted for age, gender and duration of diabetes	1.264	1.000, 1.592	0.045
Adjusted for age, gender, duration of diabetes and HbA_{1c}	1.169	0.925, 1.474	0.199
Adjusted for age, gender, duration of diabetes, HbA_{1c} and BMI	1.169	0.925, 1.474	0.158
Triglycerides			
Unadjusted	0.880	0.681, 1.136	0.195

BMI, Body mass index.

Discussion

Numerous studies have shown an association of lipid fractions with macrovascular complications of diabetes (e.g. coronary artery disease), while relatively few have looked at the association of serum lipids with microvascular complications such as DR and the available results are conflicting [9–21]. This could possibly be due to heterogeneity in subject selection with variable inclusion criteria, such as age range, gender, diabetes duration, ethnicity and differences in the methodology of assessment and classification of DR.

Dornan *et al.* [9] first showed in a landmark study the association of LDL-cholesterol in subjects with DR. In the Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR), Klein *et al.* [10] reported an association of unadjusted serum cholesterol with severity of hard exudates in the macula. In an earlier clinic-based study [13], we reported an association between LDL-cholesterol and DME. Data from the ETDRS have also demonstrated the association of total cholesterol and LDL-cholesterol with the onset as well as severity of retinal hard exudates [12]. In another interesting study, van Leiden *et al.* [31] showed that the hard exudates in DR are related to elevated serum LDL-cholesterol concentrations. This is consistent with our findings of an association between total cholesterol, LDL-cholesterol and non-HDL-cholesterol with DME in subjects with Type 2 diabetes. However, the association of total cholesterol was lost after adjusting for age and gender, whereas with non-HDL-cholesterol it was attenuated when adjusted for HbA_{1c} and BMI. LDL-cholesterol was significantly associated with DME even after adjusting for HbA_{1c} and BMI.

Additionally, we report an association between serum triglyceride concentrations and DR in subjects with Type 2 diabetes; this association was present even after adjusting for age, gender and duration of diabetes, HbA_{1c} and BMI. This is consistent with the study by van Leiden *et al.* [31], who showed an association between unadjusted triglyceride levels and DR in subjects with Type 2 diabetes. The report by the DCCT/EDIC group has also shown that the severity of retinopathy was associated with serum triglycerides after adjusting for gender in subjects with Type 1 diabetes [32]. However, Larsson *et al.* [21] reported no association between serum triglycerides and degree of retinopathy in subjects with Type 1 diabetes. Hove *et al.* [33] found no association between DR and triglycerides, total cholesterol and HDL-cholesterol in an unselected population of Type 2 diabetic patients from Denmark. Also, Sinav *et al.* [17] reported that while total serum cholesterol, LDL-cholesterol and HDL-cholesterol were related to PDR, serum triglycerides showed no association. In our study there was an overall association of DR with triglycerides but this did not correlate with the severity of DR, except in subjects with mild NPDR.

Non-HDL-cholesterol represents cholesterol carried on all of the potentially pro-atherogenic apo B-containing particles (primarily VLDL, IDL, LDL, as well as chylomicron remnants and lipoprotein a) [34]. Many cross-sectional and prospective studies have demonstrated the value of non-HDL-cholesterol as an index of coronary heart disease risk across different populations [35–37], similar to LDL-cholesterol. Recently, the Strong Heart Study has shown non-HDL-cholesterol to be a predictor of cardiovascular disease in subjects with Type 2 diabetes [38]. We report an association between

non-HDL-cholesterol and total cholesterol with DR in our South Indian subjects with Type 2 diabetes. Moreover, even among those with DR, subjects with DME had higher levels of non-HDL-cholesterol and total cholesterol in comparison with subjects without DME. This relationship is found to be unaffected by age, gender and duration of diabetes, but on adjusting for HbA_{1c}, the association disappears, suggesting that the relationship is mediated through glycaemic control.

The mechanisms by which high serum lipids cause the development and progression of DR are not fully understood. It has been postulated that an increase in blood viscosity and alterations in the fibrinolytic system occur in hyperlipidaemia and lead to the formation of hard exudates [39]. Also, incorporation of triglycerides into the cell membrane may lead to changes in membrane fluidity and leakage of plasma constituents in the retina [40]. This results in haemorrhage and oedema in the retina. Also, high lipid levels are known to cause endothelial dysfunction [41,42] through a local inflammatory response, with subsequent release of cytokines and growth factors, hypoxia, increase in LDL oxidation, etc. In animal models it has been shown that endothelial dysfunction in the diabetic vasculature results in blood–retinal barrier breakdown [42–44].

The strengths of our study are that it is population based, conducted on a large population of urban South Indians; as the demographics of Chennai are similar to the rest of the Indian urban population, the results can be generalized to the whole of the urban population in India. However, the study results probably cannot be generalized to rural areas of India or other populations. The drawback of the study is that, because it is cross-sectional, one cannot speculate about causality and the relationship between lipid subfractions and retinopathy, as this would need a prospective follow-up study.

Competing interests

None declared.

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