ORIGINAL ARTICLE

Lipid Profile in Childhood-and Youth-Onset Type 2 Diabetes and their Association with Microvascular Complications

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Abstract

Aim: To assess the lipid profiles in childhood and youth onset type 2 diabetes (T2DM) and study their association with microvascular complications.

Methods: Clinical details of individuals with childhood and youth onset T2DM, age at diagnosis between 10 and 25 yrs (n=1340) were retrieved from electronic medical records. Lipid abnormalities were classified based on the NCEP (ATP III) guidelines and management of dyslipidemia in children and adolescents with diabetes. Retinopathy was assessed by retinal photography; nephropathy, if albumin excretion was ≥300 mg/g of creatinine or if the 24 hour protein excretion was >500 mg and neuropathy by elevated vibration perception threshold (≥20 V) on biothesiometry.

Results: Out of 1,340 individuals with childhood and youth with T2DM, 53.3% of them were male. The mean age and duration of diabetes were 28.4 ± 10.4 and 7.4 ± 9.5 years respectively. Overall, the prevalence of dyslipidemia was 82.1%. Prevalence of hypercholesterolemia, hypertriglyceridemia, low HDL-C and high LDL-C were 40.7%, 52.8%, 59.1 % and 64.5% respectively. In logistic regression, both in unadjusted and adjusted model, hypercholesterolemia, and hypertriglyceridemia were associated with diabetic retinopathy [OR:1.8, CI:1.4-2.4, p<0.001 and 1.7, 1.3-2.2, p<0.001] and nephropathy [OR:1.7, CI:1.1-2.5, p=0.015 and 1.8, 1.2-2.8, p=0.007]. Additionally, hypercholesterolemia was associated with neuropathy, even after adjusting for age at diagnosis of diabetes and glycated hemoglobin [OR1.6, 1.0-2.5, p=0.041].

Conclusions: Lipid abnormalities are common and associated with microvascular complications among these T2DM individuals. This underscores the need for effective control of lipids among childhood and youth onset T2DM.

Editorial Viewpoint

- Type 2 diabetes mellitus is increasingly found in children and adolescents.
- This study finds lipid abnormalities with microvascular complications in this group of patients emphasizing need for controlling dyslipidemia.

Introduction

Type 2 diabetes (T2DM) is increasing in children and adolescents and their increased risk for vascular disease is similar to that seen in adults with T2DM.[1,2] Evidences suggest that the rapid progression of T2DM in the young is associated with higher rates of dyslipidemia, hypertension and microalbuminuria.[3] T2DM is typically associated with low High Density Lipoprotein Cholesterol (HDL-C), high serum triglycerides and increased concentration of atherogenic Low Density Lipoprotein Cholesterol (LDL-C) particles[4-6] and these changes are seen even among children and adolescents with T2DM.[7]

Screening for lipid disorders during childhood has been recommended for more than 2 decades as a means of identifying children at increased risk for early atherosclerosis.[7] Identifying lipid disorders and treating aggressively with different interventions during childhood may intercept the

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outcome of early microvascular complications and distant clinical atherosclerotic disease later in life.[3,7] Lipid sub fractions and lipoprotein concentrations are related to both macrovascular and microvascular complications in diabetes individuals.[8,9] In this study we assessed the profile of lipid sub fractions and the proportion of lipid abnormalities and their association with micro vascular complications in childhood and youth onset type 2 diabetes in a south Indian clinic population.

Methods

Individuals diagnosed with type 2 diabetes between 10 and 25 years of age (n=1340) registered between 1992 and 2013 at a tertiary diabetes care centre in Chennai (formerly Madras), southern India, were selected for the study. Using diabetic electronic medical records (DEMR), individuals were tracked over time using a unique registration number given to them at the first visit to the centre.

The Institutional Ethics Committee (IEC) approval was obtained prior to the start of the study. Written informed consent was obtained according to the local IEC guidelines. In addition, assent was obtained from the study individuals less than 18 years of age in addition to obtaining parental consent.

After registration at the center, the individuals were first seen by the dietician/diabetes educator who obtained a detailed medical history which included presenting symptoms, past illness, dietary pattern, family history of diabetes, current medications, surgical procedures and hospitalization history if any. This was followed by a complete physical examination by a physician looking for signs of insulin resistance like acanthosis nigricans and/or skin tags.

Anthropometric measurements including weight, height, waist, and hip measurements were obtained using standardized techniques by dietitians. Body mass index (BMI) was calculated using the formula weight (kg)/ height squared (m^2). Waist circumference was measured using a measuring tape that measured the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration with the subject standing in the erect posture; two measurements were made, and the mean of the two was taken as the waist circumference. Blood pressure was recorded in the right arm in sitting posture to the nearest 2 mmHg using a mercury sphygmomanometer (Diamond Deluxe BP apparatus; Pune, India) by a physician (age specific cuffs were used to measure blood pressure). Two readings were taken 5 min apart, and the mean of the two was taken as the blood pressure. At each clinic visit, all the patients undergo all the assessments as per standard protocol followed at the centre.

After an overnight fast of at least 8 hours, fasting blood sample was obtained. A venous blood sample was drawn 90 min after a standard south Indian breakfast (containing around 60 g of carbohydrate) for estimating postprandial glucose values in individuals already known to have diabetes status.[10] Those without confirmed diagnosis of diabetes were given anhydrous glucose (75 g) with 300 ml water, and 2 hr later a venous sample was drawn for assessment of the post-load glucose values (2 h PG).

During earlier years, the biochemical parameters were evaluated by different methods and they were detailed elsewhere.[11] Currently, plasma glucose was measured by the hexokinase method on a Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany) in a laboratory certified by the College of American Pathologists (CAP), USA and the National Accreditation Board for Testing and Calibration of Laboratories (NABL), India,. Serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method), and HDL cholesterol (direct method-polyethylene glycol-pre-treated enzymes) were measured using a Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.[12] Glycated haemoglobin (HbA1c) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA., USA). The intra- and inter- assay co-efficient of variation for the biochemical assays ranged between 3.1% and 7.6%. Fasting and stimulated C-peptide estimations were done by the electrochemiluminescence method estimated on Elecsys 2010 (Hitachi, Mannheim, Germany). Glutamic acid decarboxylase (GAD) antibodies were measured on a Bio-Rad plate reader 680 (USA) using Elisa Euro Immun kit (Lubeck, Germany).

Definitions

Diabetes was diagnosed based on the WHO Consulting Group Criteria,[13] i.e. fasting plasma glucose ≥126 mg/dl (≥7.0 mmol/l) and/or 2 h post-load plasma glucose (2 h PG) ≥200 mg/dl (≥11.1 mmol/l) or a self-reported history of diabetes on treatment by a physician or on drug treatment for diabetes (insulin or oral hypoglycemic agents).

Type 2 diabetes (T2DM-Y) was diagnosed based on absence of ketosis, good beta cell reserve as shown by C-peptide assay ≥0.6 pmol/ml), absence of pancreatic calculi (by means of X-ray abdomen), and good response to oral hypoglycemic agents for more than 2 years.[14]

Hypertension was diagnosed if blood pressure was ≥140/90 mmHg[15] or based on self-reported

Table 1: Clinical and biochemical profile of childhood and youth onset T2DM

Variables	Childhood and youth-onset T2DM (n=1340)
Male*	714 (53.3)
Age (years)	28.4 ± 10.4
Age at diagnosis of diabetes (years)	20.9 ± 3.4
Duration of diabetes (years)	7.4 ± 9.5
BMI (kg/m^2)	25.7 ± 4.8
Waist circumference (cm)	89.4 ± 12.3
Systolic blood pressure (mmHg)	123 ± 17
Diastolic blood pressure (mmHg)	80 ± 9
Fasting plasma glucose (mg/dl)	193 ± 74
Glycated hemoglobin (%)	9.6 ± 2.4
Total cholesterol (mg/dl)	178 ± 40
Hypercholesterolemia*	546 (40.7)
Serum triglycerides (mg/dl)	151 ± 89
Hypertriglyceridemia*	708 (52.8)
HDL cholesterol (mg/dl)	41 ± 10
Low HDL cholesterol*	792 (59.1)
LDL cholesterol (mg/dl)	108 ± 34
High LDL cholesterol*	864 (64.5)
C peptide fasting (pmol/ml)	0.9 ± 0.3
C peptide stimulated (pmol/ml)	1.7 ± 0.9
GAD antibodies-positive*	20/386 (5.2)
Dyslipidemia*	1100 (82.1)
Hypertension*	600 (44.8)
Treatment*	
Insulin only	106 (7.9)
OHA only	695 (51.9)
Insulin and OHA	523 (39.0)
Diet and Exercise	16 (1.2)

Data are presented as Mean ± SD. *Data given as n%

history of hypertension on drug treatment. For adolescents, if systolic blood pressure or diastolic blood pressure is greater than or equal to 95th percentile for age, sex and height.[16]

Dyslipidemia: National Cholesterol Education Programme (NCEP) guidelines for adults[17] for children and adolescents[18] and American Diabetes Association guidelines[19,20] were used for definition of dyslipidemia among diabetic individuals as follows:

Hypercholesterolemia – serum cholesterol levels ≥200 mg/dl or drug treatment for hypercholesterolemia.

Hypertriglyceridemia – serum triglyceride levels ≥150 mg/dl or drug treatment for hypertriglyceridemia.

Low HDL cholesterol – HDL cholesterol levels <40 mg/dl for men and <50 mg/dl for women and for adolescents <35 mg/dl.

High LDL cholesterol – LDL cholesterol levels ≥100 mg/dl

Retinopathy: A comprehensive ocular examination was carried out in all study individuals. Visual acuity was recorded using an illuminated Snellen's chart. A detailed retinal (fundus) examination was done by both direct and indirect ophthalmoscope by a trained retinal specialist including grading of retinal lesions. An international grading system (Early Treatment of Diabetic Retinopathy Study) that was modified and standardized in other population-based studies was used for the diagnosis of diabetic retinopathy. The minimum requirement for diagnosis of diabetic retinopathy was the presence of at least one microaneurysm in any field photographed in either eye.[21,22]

Nephropathy: Macroalbuminuria/overt nephropathy, if albumin excretion was ≥300 mg/g of creatinine or if the 24 hour protein excretion was >500 mg.[23,24]

Neuropathy: Neuropathy was assessed using a digital biothesiometer (Biomedical Instrument Co., Newbury, OH). Vibratory perception threshold (VPT) of the great toes was measured in a standardized fashion by a single observer as reported earlier.[25,26] Neuropathy was diagnosed if the mean VPT was ≥20 V.

Statistical Analysis

All statistical analyses were performed using SPSS statistical package version 15.0. Continuous data are expressed as mean ± standard deviation while categorical data are presented as proportions. Student's t test was used to compare means of continuous and chi square test was used to compare proportions. Logistic regression analysis was done to find out the risk factors associated with lipid abnormalities and their association with microvascular complications. For all statistical tests, p value <0.05 was considered significant.

Results

Table 1 describes the clinical and biochemical profile of childhood and youth onset T2DM. Out of 1340 individuals with T2DM, 53.3% of them were male. The mean age and duration of diabetes were 28.4 ± 10.4 and 7.4 ± 9.5 years. Fasting plasma glucose and glycated hemoglobin were 193 ± 74 mg/dl and 9.6 ± 2.4%. GAD antibody positive was found in 5.2% of these T2DM individuals. Prevalence of dyslipidemia was 82.1% and hypertension was 44.8%. Prevalence of hypercholesterolemia, hypertriglyceridemia, low HDL-C and high LDL-C among T2DM were found in 40.7%, 52.8%, 59.1% and 64.5% respectively. Retinopathy, nephropathy and neuropathy were found in 342/913 (37.4%), 100/1088 (9.2%) and 90/745 (12.1%) respectively in these youth onset T2DM.

Logistic regression analysis (Table 2) was carried out to study the association between lipid sub fractions and various micro vascular complications. Microvascular complications were used as dependent variables and hypercholesterolemia and hypertriglyceridemia were used as independent variables adjusted for age at diagnosis of diabetes and glycated hemoglobin. Both in the unadjusted and adjusted model, hypercholesterolemia and hypertriglyceridemia were associated with retinopathy and nephropathy. Additionally, hypercholesterolemia was associated with neuropathy

Table 2: Multiple logistic regression analysis to find out the association of lipid abnormalities with microvascular complications among childhood and youth onset T2DM

Complications	Childhood and youth onset T2DM OR (CI) p value
Retinopathy	
Hypercholesterolemia	
Unadjusted	1.80 (1.37 – 2.37) 0.000
Adjusted for Age at Diagnosis of Diabetes and HbA1c	1.62 (1.21 – 2.17) 0.001
Hypertriglyceridemia	
Unadjusted	1.68 (1.28 – 2.21) 0.000
Adjusted for Age at Diagnosis of Diabetes and HbA1c	1.59 (1.19 – 2.13) 0.002
Nephropathy	
Hypercholesterolemia	
Unadjusted	1.68 (1.11 – 2.55) 0.015
Adjusted for Age at Diagnosis of Diabetes and HbA1c	1.60 (1.04 – 2.49) 0.034
Hypertriglyceridemia	
Unadjusted	1.80 (1.17 – 2.76) 0.007
Adjusted for Age at Diagnosis of Diabetes and HbA1c	1.63 (1.05 – 2.54) 0.031
Neuropathy	
Hypercholesterolemia	
Unadjusted	1.83 (1.18 – 2.86) 0.007
Adjusted for Age at Diagnosis of Diabetes and HbA1c	1.61 (1.02 – 2.55) 0.041
Hypertriglyceridemia	
Unadjusted	1.65 (1.04 – 2.61) 0.032
Adjusted for Age at Diagnosis of Diabetes and HbA1c	1.41(0.88 – 2.26) 0.147

Values presented as odds ratio OR (confidence interval CI). Glycated hemoglobin (HbA1c)

even after adjusting for age at diagnosis of diabetes and glycated hemoglobin.

Discussion

The role of dyslipidemia in causing atherosclerotic progression in adult onset diabetes has been reported by several studies such as the San Antonio study,[27] United Kingdom Prospective Diabetic Study[28] and Cardiovascular Health Study[29,30] The major lipid abnormalities in T2DM are an increase in serum triglycerides and reduced HDL-C. However, there are only a few studies in childhood and youth onset T2DM on the association of dyslipidemia with microvascular complications of diabetes. In this study we report on the association of abnormal levels of lipid sub fractions with microvascular complications among childhood and youth onset T2DM.

The prevalence of dyslipidemia reported varies from 18 to 61% at the time of diagnosis in youth with type 2 diabetes[31] In our study, dyslipidemia prevalence was 82% which was found to be higher when compared to a UK based study[32] (76.4%), but the diabetes duration was found to be shorter (2.7 ± 1.2 years) than our study subjects (7.4 ± 9.5 years). Screening and treatment of dyslipidemia in this high risk group is of utmost importance at present.

The prevalence of lipid abnormalities appears to be higher among Asian Indians with childhood and youth onset T2DM. The prevalence of hypercholesterolemia in our study (40.7%) is higher when compared to the prevalence reported in SEARCH for Diabetes in Youth Study.[33] Similarly, the prevalence of hypertriglyceridemia is also higher (52.8%) when compared to SEARCH study (38.5%)[33] and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study (18.2%).[34] These results reveal the aggressive nature of dyslipidemia and the need for effective control among Indians with youth onset T2DM.

The mechanisms by which lipids are assessed with worsening retinopathy are due to elevation of blood viscosity and variations in the fibrinolytic system, change in the fluidity of cellular membrane by incorporating triglycerides, accumulation of basal linear deposits in Bruch's membrane due to high cholesterol levels and damage to endothelial cells and pericytes by oxidized LDL cholesterol.[35] When adjusted for age at diagnosis of diabetes we found that hypercholesterolemia and hypertriglyceridemia were associated with diabetic retinopathy among youth onset T2DM. While Mayer-Davis et al[36] noted that high LDL-C concentrations were the strongest correlates of diabetic retinopathy among youth onset type 2 diabetes. In an earlier study, Rema et al[37] reported that, total cholesterol and triglycerides were significantly associated with diabetic retinopathy in adults with T2DM, even after adjusting for age, gender and duration of diabetes.

High triglyceride concentrations have been shown to be independently associated with elevated albumin creatinine ratio (ACR) among youth with T2DM aged <20 years.[38] However, in this study, we found that hypercholesterolemia, and hypertriglyceridemia were associated with diabetic nephropathy among youth onset T2DM. Agrawal et al[39] reported LDL-C to be associated with nephropathy. Recently, a global case-control study[40] reported that diabetic kidney disease is associated with higher levels of plasma triglycerides and low HDL-C whereas the association with retinopathy was less prominent. Several studies have reported that dyslipidemia worsens renal damage, but the exact mechanism is unclear. Interestingly, binding of LDL causes mesangial cell proliferation and causes damage on the arterial smooth muscle cells.

Further, atherosclerotic damage to renal arteries due to dyslipidemia may reduce renal blood flow leading to renal dysfunction.[35]

The known risk factors for neuropathy in adults include severe hyperglycemia, duration of diabetes, dyslipidemia, hypertension and smoking. Even though the pathogenesis of neuropathy is poorly understood, it is known that it develops due to prolonged glycemic exposure and its associated metabolic disorders like accumulation of advanced glycosylation end products, lipid derangements and oxidative stress.[41] In the present study, hypercholesterolemia and hypertriglyceridemia was identified as a independent risk factor for neuropathy among childhood and youth onset T2DM. Earlier studies[42-44] have also stated that hypertriglyceridemia significantly increases the risk of peripheral neuropathy in adults.

Some of the limitations in our study were specific lipoprotein fractions could not be studied due to cost constraints. Secondly, since our centre is a referral centre, there could be referral bias of patients attending the centre. Since this is a cross sectional study, the results should be viewed in caution.

To conclude, nearly 20 to 60% of the youth onset T2DM have lipid abnormalities. More importantly, lipid abnormalities were associated with microvascular complications like retinopathy, nephropathy and neuropathy. This underscores the need for aggressive control of lipids and both pharmacologic and behavioral interventions to reduce these risk factors among youth onset T2DM.[45]

Conflict of interest statement

The authors have no conflict of interest to declare.

Author contributions

VM conceived the study and revised all drafts of the article. AA, RP and KSC checked the integrity and accuracy of data and analyzed the data. AA wrote the first draft of the article and carried out the corrections in consecutive drafts. RU and RMA gave valuable suggestions and helped in revising the manuscript.

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References

1. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. *Lancet* 2007; 369:1823-31.
2. Liese AD, D'Agostino RB Jr, Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics* 2006; 118:1510-1518.
3. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. *Nat Clin Pract Endocrinol Metab* 2000; 5:150-159.
4. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003; 46:733-749.
5. Chahil TJ, Ginsberg HN. Diabetic dyslipidemia. *Endocrinol Metab Clin North Am* 2006; 35:491-510.
6. Rodriguez BL, Fujimoto WY, Mayer-Davis EJ, et al. Prevalence of cardiovascular disease risk factors in U.S. children and adolescents with diabetes: the SEARCH for diabetes in youth study. *Diabetes Care* 2006; 29:1891-1896.
7. de Ferranti SD. Childhood cholesterol disorders: the iceberg base or non disease?. *Med Clin North Am* 2012; 96:141-54.
8. Vijayaraghavan K. Treatment of dyslipidemia in patients with type 2 diabetes. *Lipids Health Dis* 2010; 9:144.
9. Chaturvedi N, Fuller JH, Taskinen MR; EURODIAB PCS Group. Differing associations of lipid and lipoprotein disturbances with the macrovascular and microvascular complications of type 1 diabetes. *Diabetes Care* 2001; 24:2071-7.
10. Viswanathan M, Snehalatha C, Ramachandran A, et al. Glycaemic and insulin responses to some breakfast items in diabetic subjects. *Nutrition Reports International* 1988; 37:409-418.
11. Amutha A, Datta M, Unnikrishnan IR, et al. Clinical profile of diabetes in the young seen between 1992 and 2009 at a specialist diabetes centre in south India. *Prim Care Diabetes* 2011; 5:223-9.
12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18:499-502.
13. K.G. Alberti, P. Zimmet, Definition diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabet Med* 1998; 15:539–553.
14. Amutha A, Datta M, Unnikrishnan R, et al. Clinical profile and complications of childhood- and adolescent-onset type 2 diabetes seen at a diabetes center in south India. *Diabetes Technol Ther* 2012; 14:497-504.
15. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–2572.
16. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; 114:555-76.
17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143-421.
18. National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992; 89:495-501.
19. American Diabetes Association. Management of dyslipidemia in children and adolescents with diabetes. *Diabetes Care* 2003; 26:2194-7.
20. Le PT, Huisingh CE, Ashraf AP. Glycemic control and diabetic dyslipidemia in adolescents with type 2 diabetes. *Endocr Pract* 2013; 19:972-9.
21. Rema M, Deepa R, Mohan V. Prevalence of retinopathy at diagnosis among type 2 diabetic patients attending a diabetic centre in South India. *Br J Ophthalmol* 2000; 84:1058-60.
22. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification: ETDRS report number 10. Early Treatment of Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991; 98:786–806.

23. Unnikrishnan RI, Rema M, Pradeepa R, Deepa M, Shanthirani CS, Deepa R, MohanV. Prevalence and risk factors of diabetic nephropathy in an urban South Indian population: the Chennai Urban Rural Epidemiology Study (CURES 45). *Diabetes Care* 2007; 30:2019–2024.
24. Mohan V, Meera R, Premalatha G, Deepa R, Miranda P, Rema M: Frequency of proteinuria in type 2 diabetes mellitus seen at a diabetes centre in southern India. *Post Grad Med J* 2000; 76:569 –573.
25. Ashok S, Ramu M, Deepa R, Mohan V. Prevalence of neuropathy in Type 2 diabetic patients attending diabetes centre in south India. *J Assoc Phys India* 2002; 50:546–550.
26. Deepa M, Pradeepa R, Rema M, et al. The Chennai Urban Rural EpidemiologyStudy (CURES)—study design and methodology (urbancomponent) (CURES-I). *J Assoc Phys India* 2003; 51:863–870.
27. Mahaney MC, Blangero J, Comuzzie AG, et al. Plasma HDL cholesterol, triglycerides and adiposity. A quantitative genetic test of the conjoint trait hypothesis in the San Antonio Family Heart Study. *Circulation* 1995; 92:3240-3248.
28. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:837-853.
29. Psaty BM, Furbert CD, Kuller LH, et al. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults: The Cardiovascular Health Study. *Arch Intern Med* 1999; 159:1339-1347.
30. Kuller L, Borhani N, Furbert C, et al. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol* 1994; 139:1164-1179.
31. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. *Lancet* 2007; 369:1823–1831.
32. Song SH. Complication characteristics between young-onset type 2 versus type 1 diabetes in a UK population. *BMJ Open Diabetes Research and Care* 2015; 3:e000044. doi:10.1136/bmjdrc-2014-000044.
33. Petitti DB, Imperatore G, Palla SL, et al. SEARCH for Diabetes in Youth Study Group. Serum lipids and glucose control: the SEARCH for Diabetes in Youth study. *Arch Pediatr Adolesc Med* 2007; 161:159-65.
34. TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care* 2013; 36:1758-64.
35. Misra A, Kumar S, Kishore Vikram N, Kumar A. The role of lipids in the development of diabetic microvascular complications: implications for therapy. *Am J Cardiovasc Drugs* 2003; 3:325-38.
36. Mayer-Davis EJ, Davis C, Saadine J, et al. SEARCH for Diabetes in Youth Study Group. Diabetic retinopathy in the SEARCH for Diabetes in Youth Cohort: a pilot study. *Diabet Med* 2012; 29:1148-52.
37. Rema M, Srivastava BK, Anitha B, et al. Association of serum lipids with diabetic retinopathy in urban South Indians-the Chennai Urban Rural Epidemiology Study (CURES) Eye Study-2. *Diabet Med* 2006; 23:1029-1036.
38. Maahs DM, Snively BM, Bell RA, et al. Higher prevalence of elevated albumin excretion in youth with type 2 than type 1diabetes: the SEARCH for Diabetes in Youth study. *Diabetes Care* 2007; 30:2593-8.
39. Agrawal RP, Sharma P, Pal M, et al. Magnitude of dyslipidemia and its association with micro and macro vascular complications in type 2diabetes: a hospital based study from Bikaner (Northwest India). *Diabetes Res Clin Pract* 2006; 73:211-4.
40. Sacks FM, Hermans MP, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. *Circulation* 2014; 129:999-1008.
41. Tesfaye S, Boulton AJ, Dyck PJ, et al. Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33:2285-93.
42. Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. J Diabetes Complications. 2013; 27:436-42.
43. Katulanda P, Ranasinghe P, Jayawardena R, et al. The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. *Diabetol Metab Syndr* 2012; 4:21.
44. Cardoso CR, Salles GF. Predictors of development and progression of microvascular complications in a cohort of Brazilian type 2 diabetic patients. *J Diabetes Complications* 2008; 22:164–170.
45. TODAY Study Group, Zeitler P, Hirst K, Pyle L, Linder B, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012; 366:2247-56.