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ORIGINAL ARTICLE

Hyperglycemia and duration of diabetes as risk factors for abnormal lipids: a cross sectional survey of 19,757 patients with type 2 diabetes in China

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Abstract
Purpose Type 2 diabetes (T2D) increases the risk of cardiovascular disease (CVD). Achieving glycated hemoglobin (HbA1c) below 7.0 % in newly diagnosed T2D reduced CVD risk. It is uncertain whether HbA1c below 7.0 % in T2D with varying duration of diabetes also reduced CVD risk. This study investigated the associations between hyperglycemia and abnormal lipid metabolism in patients with T2D.
Methods We conducted a survey of 19,757 outpatients with T2D who were 18 years of age or more and treated with oral antidiabetes drugs (OADs) alone or OADs combined with other drugs. The coverage rates of the 3A hospitals were 74.4 % for Beijing ($n = 32$), 76 % for Shanghai ($n = 22$), 55 % for Tianjin ($n = 11$) and 29.3 % for Guangzhou ($n = 12$). Abnormal lipids were defined as $\geq$2.6 mmol/L for low-density lipoprotein (LDL) cholesterol, $\leq$1.0 mmol/L in men and $\leq$1.3 mmol/L in women for high-density lipoprotein (HDL) cholesterol; $\geq$1.7 mmol/L for triglyceride. Logistic regression stratified on city and hospital was used to obtain odds ratio (OR) of hyperglycemia for abnormal lipids.
Results The patients had 4.0 (interquartile range 1.7–8.8) years of duration of diabetes. HbA1c $\geq$7.0 % was associated with increased risk of high LDL cholesterol (multivariable OR of $\geq$7.0 vs. <6.0 %:1.37, 95 % confidence interval 1.19–1.57). HbA1c $\geq$6.5 % was associated increased risk of high triglyceride. HbA1c was associated with low HDL cholesterol in a J-shaped manner, whereby

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HbA1c levels of <6.0 % as well as ≥6.5 % being associated with increased risk of low HDL cholesterol.
Conclusions Hyperglycemia defined as HbA1c ≥7.0 % increased risk of high LDL cholesterol in T2D.

Keywords Hyperglycemia · LDL cholesterol · Triglyceride · Type 2 diabetes · Chinese

Introduction

Diabetes is prevalent in the world, especially in Asian countries [1–3]. A more recent survey reported that the prevalence of diabetes in Chinese adults in mainland China was up to 11.6 % in 2010 [4]. It is well established that diabetes predisposes to increased risk of coronary heart disease (CHD) [5]. In this regard, the diabetes control and complications trial (DCCT) and its further long-term follow up study [6, 7] demonstrated that tight hyperglycemia control was able to reduce the risk of micro- and macrovascular diseases in type 1 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) and its follow-up study showed that maintaining glycated hemoglobin (HbA1c) around 7 % by intensive blood-glucose control versus 7.9 % in the conventional group was able to achieve a 25 % risk reduction in microvascular endpoints over a 10-year period [8] and a 24 % risk reduction in the microvascular endpoint and a 15 % risk reduction in myocardial infarction over further 10 years of follow-up [9].

However, three recent large randomized trials of further tight control of hyperglycemia reported negative findings [10–13]. The action to control cardiovascular risk in diabetes (ACCORD) trial found that tight control of HbA1c below 6.0 % increased CVD death [10], and both the ACCORD trial and the veterans affairs diabetes trial (VADT) did not find that tight control of HbA1c below 6.0 % led to an additional reduction in the risk of cardiovascular disease [10, 11]. Although the action in diabetes and vascular disease preterax and diamicron modified release controlled evaluation (ADVANCE) [12, 13] found that achievement of HbA1c below 6.5 % was able to further reduce nephropathy by about 20 %, it failed to observe a further reduction in the risk of macrovascular disease in T2D. It is noted that the subjects enrolled in the UKPDS were patients with newly diagnosed T2D, but the three recent trials enrolled subjects with much longer durations of diabetes. For example, the subjects of the ADVANCE had a median duration of diabetes of 10 years at the time enrollment into the trial. Da Qing Diabetes and Impaired Glucose Tolerance Study from China [14] and the UKPDS from the United Kingdom [8, 9] all suggest that CHD takes a long time to be manifested as a clinical outcome, e.g., 20 years. Thus, it remains uncertain whether the negative findings by the three recent trials were due to short durations of these trials or cardiovascular benefits of tight hyperglycemia control reported by the UKPDS were only applicable to patients with newly diagnosed T2D [15].

Abnormal lipid levels are established risk factors for CVD in general and diabetic patients [16]. In T2D, typical abnormal lipids are increased levels of triglyceride, decreased levels of high-density lipoprotein (HDL) cholesterol and increased levels of small dense low-density lipoprotein (LDL) particles, due to increased free fatty acid flux subsequent to insulin resistance [17]. The American Diabetes Association (ADA) recommends that the treatment goals for lipids among patients at low CVD risk were LDL cholesterol <2.6 mmol/L, triglyceride <1.7 and HDL cholesterol ≥1.0 mmol/L in men and ≥1.3 mmol/L in women [16]. Nevertheless, it is uncertain whether hyperglycemia itself increased abnormal lipids, especially LDL cholesterol. Thus, the research question was whether hyperglycemia increased abnormal lipids and how high is high enough for hyperglycemia to increase abnormal lipids.

Methods

Patients

The Chinese Diabetes Society launched an HbA1c surveillance system among patients with T2D in the mainland China in 2009. A total of 400 hospitals from 75 cities in 20 provinces, 3 autonomous regions and 4 municipalities (Beijing, Shanghai, Tianjin and Chongqing) directly under the central government agreed and participated in the surveillance system. The number of participating hospitals was increased to 414, with 81 cities in 30 provincial administrative regions of China in 2011, from all the provincial administrative regions in China except for Tibet. The ethics approval was obtained from People's Liberation Army (PLA) General Hospital and informed consent was obtained before collecting data from the patients. The survey in 2011 was conducted from March to June 2011. The inclusion criteria were (1) being an outpatient with T2D being treated with OADs alone, OADs combined with insulin, or OADs combined with Glucagon-like peptide

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(GLP)-1 receptor agonists; aged 18 years and more; (2) with at least one previous outpatient medical record pertaining to diabetes; being a local resident for at least six consecutive months prior to participation in the study. The exclusion criteria included: (1) diabetes secondary to other diseases; (2) on insulin monotherapy; (3) not on OAD monotherapy, OADs combined with insulin, or OADs in combination with GLP-1 receptor agonists; (4) type 1 diabetes; (5) inpatients; (6) on diet and other lifestyle therapy only or on Chinese herbal medicine; (7) being pregnant or breast feeding an infant; (8) being unable to complete the survey due to mental diseases; and (9) unconsciousness or being unable to communicate.

During the recruitment period, fieldworkers sequentially screened patients with T2D for their eligibility. Those who met the inclusion criteria and did not have any of the exclusion criteria were invited to participate in the survey. The process continued until 7 patients were successfully recruited in a consecutive way in each day and until 400 patients were recruited in the pre-specified period. The fieldworker/s (either a research nurse or a postgraduate medical student) used a short questionnaire to collect demographic information and to record clinical profile and the results of laboratory essays.

The collected data included gender, height, and weight, blood pressure, and lipid profile. Laboratory data on HbA1c, fasting plasma glucose [18], and postprandial plasma glucose (PPG) levels were collected. Specific information about the treatments used for the management of their T2D were identified, including the use of OADs [including dipeptidyl peptidase (DPP)-4 inhibitors], GLP-1 receptor agonists, and different types of insulin, as well as combinations of OADs and insulin and the combination of OADs and a GLP-1 receptor agonist. Prior history of diabetes complications and the date of their diagnosis were retrieved from medical records, including hypertension, coronary heart disease, dyslipidemia, cerebrovascular disease, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, diabetes-related foot ulcers, and others. All laboratory evaluations were performed in the local hospitals where the interviews were conducted.

This current study analyzed data on subjects from the accredited 3A hospitals in four major cities in China: Beijing, Shanghai, Tianjin and Guangzhou because of the high coverage rates in these major cities of the surveillance system. The coverage rates of the 3A hospitals were 74.4 % for Beijing ($n = 32$), 76 % for Shanghai ($n = 22$), 55 % for Tianjin ($n = 11$) and 29.3 % for Guangzhou ($n = 12$) after excluding those 3A hospitals that recruited less than 30 patients during the pre-specified recruitment period. The recruitment goal was 400 patients by each hospital. The selected 3A hospitals in four cities were assumed to represent the population of patients with T2D cared by the top hospitals in China.

Essays of LDL cholesterol, total cholesterol and triglyceride were conducted in individual hospitals. HDL cholesterol was calculated using the Friedewald's equation [19]. A total of 29,442 patients were recruited in 77 tertiary hospitals in China were successfully recruited. We further excluded 58 patients with missing LDL-C, HDL-C or triglyceride, and 9,627 patients who had history of coronary heart disease, prior stroke or hyperlipidemia were further excluded. The remaining 19,757 patients with T2D were included in the analysis.

Statistical analysis

The statistical analysis system (SAS) release 9.3 (SAS Institute Inc., Cary, NC, USA) was used in all the data analysis. Data were expressed as mean (standard deviation, SD) or median (interquartile range) were appropriate. Chi-square test or Fisher's exact test where appropriate was used to compare categorical variables and Student *t* test or Wilcoxon Two Sample test where appropriate was used to compare continuous variables between patients with and without abnormal individual lipids of interest. Duration of diabetes was calculated as the period from the date of diagnosis of diabetes to that of measurement of HbA1c. Body mass index (BMI) was calculated as body weight in kilograms divided by squared body height in meters. Abnormal lipids were defined using the criteria recommended by the American Diabetes Association [20], i.e., LDL cholesterol $\geq$2.6 mmol/L, HDL cholesterol $\leq$1.0 mmol/L in men and $\leq$1.3 mmol/L in women, and triglyceride $\geq$1.7 mmol/L. Logistic regression was used to obtain odds ratio of hyperglycemia and duration of diabetes for the risk of abnormal lipids. Stratified logistic models on cities and hospitals were to obtain the ORs. HbA1c was stratified into 4 levels: <42 mmol/mol (6.0 %), 42–46 mmol/mol (6.0–6.4 %), 48–52 mmol/mol (6.5–6.9 %) and $\geq$53 mmol/mol (7.0 %). Firstly, we obtained ORs of HbA1c groups, and duration of diabetes. Then, we adjusted for age, gender, body height, BMI. Systolic blood pressure (SBP), treatment schemes for hyperglycemia and self monitoring of blood glucose (SMBG). A p value below 0.05 for two-sided tests was considered as statistically significant.

To specifically address whether the results applicable to patients with longer duration of diabetes, we repeated the analysis after exclusion of 5,510 patients with T2D diagnosed for <2 years. Additional sensitivity analysis was performed with re-inclusion of 9,627 patients who had history of coronary heart disease, prior stroke or hyperlipidemia to observe whether potential use of lipid-lowering drugs among high risk patients might bias the findings from the main analysis.

Table 1 Clinical and biochemical characteristics of study patients by LDL cholesterol

Variables	LDL-C <2.6 mmol/L (n = 7,587) Mean/number (SD or %)	LDL-C ≥2.6 mmol/L (n = 12,170) Mean/number (SD or %)	P value
Age (year)	59.0 (11.7)	59.4 (10.9)	0.0074
Male gender	3908 (51.5 %)	6612 (54.3 %)	0.0001
Body height (cm)	165.7 (8.2)	166.2 (7.8)	0.0003
BMI (kg/m^2)	24.3 (3.2)	24.3 (3.1)	0.2627
Duration of diabetes (year)*	3.93 (1.50–8.28)	4.11 (1.89–9.11)	<0.0001
Systolic blood pressure (SBP), mmHg	130 (13.7)	132 (13.0)	<0.0001
Diastolic blood pressure (DBP), mmHg	80 (9.4)	81 (12.0)	0.0004
HbA1c (mmol/mol)	58 (12)	61 (13)	<0.0001
HbA1c (%)	7.5 (1.5)	7.7 (1.6)	<0.0001
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	604 (8.0 %)	1,212 (8.3 %)	
42–46 (6.0–6.4)	823 (10.9 %)	1,236 (10.2 %)	
48–52 (6.5–6.9)	1,466 (19.3 %)	1,606 (13.2 %)	
≥53 (7.0)	4,694 (61.9 %)	8,316 (68.3 %)	
High density lipoprotein cholesterol (mmol/L)	1.65 (1.18)	0.92 (1.61)	<0.0001
Triglyceride (mmol/L)*	1.45 (1.05–2.01)	1.60 (1.12–2.19)	<0.0001
Use of antidiabetes drugs			
Alpha-glucosidase inhibitors	3,060 (40.3 %)	4,518 (37.1 %)	<0.0001
Sensitizers			
Metformin	3,894 (51.3 %)	5,171 (42.5 %)	<0.0001
Thiazolidinedione	667 (8.8 %)	1,240 (10.2 %)	0.0012
Secretagogues			
Sulphonylurea	3,043 (40.1 %)	5,462 (44.9 %)	<0.0001
Mitiglinide/nateglinide/repaglinide	1,594 (21.0 %)	2,665 (21.9 %)	0.1397
Dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 agonists	46 (0.6 %)	133 (1.1 %)	0.0004
Insulin	1,789 (23.6 %)	2,724 (22.4 %)	0.0513
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Location			<0.0001
Beijing	3,495 (46.1 %)	5,310 (43.6 %)	
Tianjin	838 (11.1 %)	1,984 (16.3 %)	
Shanghai	1,763 (23.2 %)	2,882 (23.7 %)	
Guangzhou	1,491 (19.7 %)	1,994 (16.4 %)	

LDL-C/HDL-C low/high-density lipoprotein cholesterol

* Median (interquartile range) and their P values were derived from two sample Wilcoxon's test

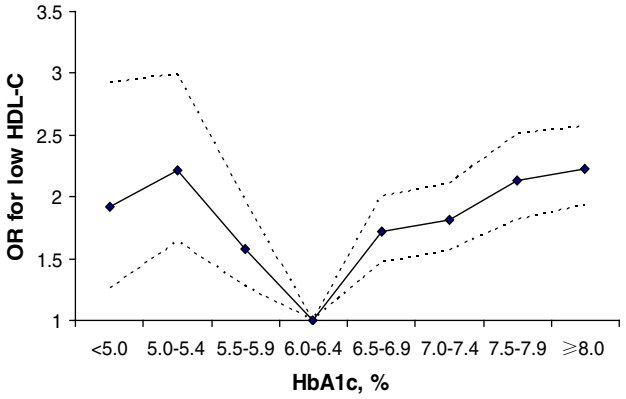

Fig. 1 Odds ratio of HbA1c for low HDL cholesterol in patients with type 2 diabetes. *OR* odds ratio, *HDL-C* high-density lipoprotein cholesterol, *HbA1c* glycated haemoglobin. The curve was obtained in univariable logistic regression analysis; The *solid line* stands for OR and the *dotted lines* for 95 % confidence intervals

Results

The patients with T2D included in the analysis had a mean age of 59 (SD 11.2) years and a median of 4.0 (interquartile range 1.7–8.8) years of duration of diabetes. Male accounted for 53.3 % of the patients. Patients with LDL cholesterol ≥2.6 mmol/L were older, more likely to be male, higher body height, longer duration of diabetes, higher systolic blood pressure/diastolic blood pressure (SBP/DBP), higher HbA1c, and higher triglyceride but lower HDL cholesterol than those patients with LDL cholesterol <2.6 mmol/L (Table 1). Patients with low HDL cholesterol were younger, less likely to be male, higher body height, longer duration of diabetes, higher DBP, lower HbA1c, and higher triglyceride and LDL cholesterol (Appendix Table 1). Patients with low HDL cholesterol were younger, less likely to be male, higher body height, higher BMI, longer duration of diabetes, higher SBP/DBP, lower HbA1c, and higher LDL cholesterol but lower HDL cholesterol than their counterparts with triglyceride <1.7 mmol/L (Appendix Table 2).

After adjusting for duration of diabetes and other co-variables, HbA1c ≥53 mmol/mol (7.0 %) was associated with more likelihood of high LDL cholesterol (OR 1.39, 95 % CI 1.21–1.59). HbA1c was associated with low HDL cholesterol in a J-shaped manner, whereby both HbA1c levels of <42 mmol/mol (6.0 %) as well as ≥48 mmol/mol (6.5 %) were all associated with increased risk of low HDL cholesterol before (Fig. 1) and after adjusting for duration of diabetes and other covariables when compared with patients with HbA1c at 42–46 mmol/mol (6.0–6.4 %) [OR of HbA1c <42 mmol/mol (6.0 %) vs. 42–46 mmol/mol (6.0–6.4 %) 1.75, 95 % CI 1.45–2.11; OR of HbA1c at 48–52 mmol/mol (6.5–6.9 %) vs. at 42–46 mmol/mol

Table 2 Hyperglycemia and duration of diabetes as risk factors for abnormal lipids in patients with type 2 diabetes

Variables	Number (%)	OR (95 % CI)	*P* value
LDL-C ≥2.6 mmol/L as the outcome			
HbA1c groups (%)			<0.0001
<6.0	1,012 (62.6 %)	Reference	
6.0–6.4	1,236 (60.0 %)	0.97 (0.82–1.14)	
6.5–6.9	1,606 (52.3 %)	1.02 (0.88–1.19)	
≥7.0	8,316 (63.9 %)	1.37 (1.19–1.57)	
Duration of diabetes, per 5 years		1.08 (1.05–1.12)	<0.0001
Drug use			0.3915
Insulin sensitizers only	3,063 (57.3 %)	Reference	
Insulin secretagogues only	4,619 (66.4 %)	0.93 (0.84–1.02)	
Neither of them	1,533 (61.8 %)	0.94 (0.83–1.06)	
Both of them	2,955 (59.4 %)	0.98 (0.89–1.08)	
HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women as the outcome			
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	788 (48.8 %)	1.75 (1.45–2.11)	
42–46 (6.0–6.4)	526 (22.6 %)	Reference	
48–52 (6.5–6.9)	970 (31.6 %)	1.71 (1.46–1.99)	
≥53 (7.0)	5,031 (38.7 %)	2.14 (1.86–2.45)	
Duration of diabetes, per 5 years		0.94 (0.90–0.98)	<0.0001
Drug use			<0.0001
Insulin sensitizers only	2,085 (39.0 %)	Reference	
Insulin secretagogues only	2956 (52.5 %)	0.87 (0.78–0.96)	
Neither of them	735 (29.6 %)	0.61 (0.53–0.70)	
Both of them	1,539 (31.0 %)	0.80 (0.72–0.89)	
Triglyceride ≥ 1.70 mmol/L as the outcome			
HbA1c groups, mmol/mol (%)			
<42 (6.0)	648 (40.1 %)	Reference	
42–46 (6.0–6.4)	620 (30.1 %)	0.89 (0.74–1.06)	
48–52 (6.5–6.9)	1,087 (35.4 %)	1.55 (1.31–1.83)	
≥53 (7.0)	5,574 (42.8 %)	1.97 (1.69–2.29)	
Duration of diabetes, per 5 years		0.94 (0.90–0.97)	<0.0001
Drug use			<0.0001
Insulin sensitizers only	2270 (42.5 %)	Reference	
Insulin secretagogues only	2601 (37.4 %)	0.99 (0.90–1.09)	
Neither of them	873 (35.2 %)	0.74 (0.66–0.84)	

Table 2 continued

Variables	Number (%)	OR (95 % CI)	*P* value
Both of them	2185 (27.6 %)	0.97 (0.87–1.07)	

Variables adjusted for in the analysis included age, gender, body mass index, body height, self monitoring of blood glucose and use of alpha-glucosidase inhibitors and insulin

LDL-C/HDL-C low/high-density lipoprotein cholesterol

(6.0–6.4 %) 1.71, 95 % CI 1.46–1.99). On the other hand, HbA1c ≥48 mmol/mol (6.5 %) and higher was associated increased risk of high triglyceride after adjusting for duration of diabetes and further adjusting for other convariables [OR of HbA1c at 48–52 mmol/mol (6.5–6.9 %) vs. <42 mmol/mol (6.0 %) 1.55, 95 % CI 1.31–1.83; OR of HbA1c at ≥53 mmol/mol (7.0 %) vs. 42 mmol/mol (6.0 %) 1.97, 95 % CI 1.69–2.29) (Table 2).

Longer duration of diabetes was associated with increased risk of high LDL cholesterol. However, longer duration of diabetes was associated with decreased risk of low HDL cholesterol and high triglyceride after adjusting for HbA1c and other covariables (Table 2). Use of insulin secretagogues was associated with higher risk of low HDL cholesterol but not for high LDL cholesterol and high triglyceride when compared with use of insulin sensitizers.

After further exclusion of 5,510 patients with T2D diagnosed for <2 years, the results were the same except that the OR of duration of diabetes for low HDL cholesterol was no longer significant in multivariable analysis (Table 3).

After re-inclusion of patients with prior CHD, stroke or hyperlipidemia, the OR of HbA1c at 48–52 mmol/mol (6.5–6.9 %) vs. at <42 mmol/mol (6.0 %) for high LDL cholesterol became statistical significance after adjusting for duration of diabetes and after further adjusting for other covariables (Table 4). All the other ORs of HbA1c levels for high LDL cholesterol and low HDL cholesterol and high triglyceride remained statistically significant. Long duration of diabetes was still associated with high risk of high LDL cholesterol and low risk of low HDL cholesterol but not with high triglyceride.

Discussion

In a large survey of Chinese T2D patients, we found that hyperglycemia defined as HbA1c ≥53 mmol/mol (7.0 %) was associated with high LDL cholesterol and HbA1c ≥48 mmol/mol (6.5 %) was associated with high triglyceride. On the other hand, HbA1c was associated with low HDL cholesterol in a J-shaped relation and both

Table 3 Hyperglycemia and duration of diabetes as risk factors for abnormal lipids in 14,247 patients with type 2 diabetes diagnosed for 2 years and more

Variables	Number (%)	OR (95 % CI)	*P* value
LDL-C ≥2.6 mmol/L as the outcome			
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	562 (59.2 %)	Reference	
42–46 (6.0–6.4)	833 (59.9 %)	1.14 (0.94–1.39)	
48–52 (6.5–6.9)	1,077 (53.6 %)	1.20 (0.99–1.44)	
≥53 (7.0)	6,521 (65.9 %)	1.53 (1.32–1.85)	
Duration of diabetes, per 5 years		1.14 (1.09–1.18)	<0.0001
Drug use			0.8696
Insulin sensitizers only	1,998 (56.6 %)	Reference	
Insulin secretagogues only	3,565 (69.5 %)	1.04 (0.93–1.17)	
Neither of them	1,131 (62.0 %)	1.01 (0.87–1.17)	
Both of them	2,299 (61.1 %)	1.00 (0.89–1.12)	
HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women as the outcome			
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	377 (39.7 %)	1.76 (1.38–2.23)	
42–46 (6.0–6.4)	304 (21.9 %)	Reference	
48–52 (6.5–6.9)	682 (31.2 %)	1.93 (1.60–2.34)	
≥53 (7.0)	3,918 (39.6 %)	2.29 (1.93–2.71)	
Duration of diabetes, per 5 years		0.99 (0.95–1.04)	0.7346
Drug use			0.0036
Insulin sensitizers only	1,228 (34.8 %)	Reference	
Insulin secretagogues only	2,330 (45.4 %)	0.97 (0.85–1.11)	
Neither of them	515 (28.3 %)	0.79 (0.67–0.93)	
Both of them	1,154 (30.6 %)	0.86 (0.76–0.98)	
Triglyceride ≥1.70 mmol/L as the outcome			
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	314 (33.1 %)	Reference	
42–46 (6.0–6.4)	375 (27.0 %)	0.85 (0.68–1.06)	
48–52 (6.5–6.9)	705 (35.1 %)	1.63 (1.33–2.00)	
≥53 (7.0)	4,391 (44.4 %)	2.31 (1.91–2.78)	

Table 3 continued

Variables	Number (%)	OR (95 % CI)	*P* value
Duration of diabetes, per 5 years		0.88 (0.84–0.92)	<0.0001
Drug use			<0.0001
Insulin sensitizers only	1,539 (43.6 %)	Reference	
Insulin secretagogues only	1,926 (37.6 %)	0.96 (0.86–1.09)	
Neither of them	625 (34.3 %)	0.63 (0.54–0.73)	
Both of them	1,695 (45.0 %)	0.97 (0.86–1.10)	

Variables adjusted for in the analysis included age, gender, body mass index, body height, self monitoring of blood glucose and use of alpha-glucosidase inhibitors and insulin

LDL-C/HDL-C low/high-density lipoprotein cholesterol

<42 mmol/mol (6.0 %) and ≥48 mmol/mol (6.5 %) were all associated with higher risks of low HDL cholesterol.

These lipid cutoff points, i.e., LDL cholesterol ≥2.6 mmol/L, HDL cholesterol <1.0 mmol/L in men and <1.3 mmol/L in women, and triglyceride ≥1.7 mmol/L, were established as lipid control goals for clinical management of T2D as there is strong evidence that being above (or below) these cutoff points are associated with increased risk of CHD in T2D [20]. The UKPDS established that hyperglycemia defined as HbA1c levels of more than 7.0 % plays a causal role in development of cardiovascular disease in newly diagnosed T2D [9, 21]. However, recent megatrials did not generate evidence that further lowering HbA1c could lead to further reduction of CVD risk among patients with varying duration of diabetes [10–13]. One of the possible reasons was that these megatrials had short observation periods for CVD to develop and manifest [22]. Our study supports that hyperglycemia defined as HbA1c ≥53 mmol/mol (7.0 %) increased CVD risk mediated by increased LDL cholesterol. In this study, we also observed that longer duration of diabetes increased LDL cholesterol, probably due to worsened hyperglycemia control and albuminuria. In this regard, the Hong Kong Diabetes Registry demonstrated that albuminuria preceded or promoted occurrence of high LDL cholesterol [23] and high total cholesterol increased CHD risk among T2D patients with albuminuria but the risk association between total cholesterol and CHD disappeared among those T2D patients without albuminuria [24]. Consistently with findings in type 1 diabetes, a large part of reduction in CVD with hyperglycemia control was mediated via albuminuria though not all [6, 7]. Thus, our data support that HbA1c ≥53 mmol/mol (7.0 %) increased CVD risk via albuminuria and then high LDL cholesterol. Similar with findings

Table 4 Sensitivity analysis of hyperglycemia and duration of diabetes as risk factors for abnormal lipids with re-inclusion of 9,627 patients who had history of coronary heart disease, prior stroke or hyperlipidemia

Variables	Number (%)	OR (95 % CI)	*P* value
LDL-C ≥2.6 mmol/L as the outcome			
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	1,352 (62.3 %)	Reference	
42–46 (6.0–6.4)	1,765 (59.9 %)	1.05 (0.92–1.19)	
48–52 (6.5–6.9)	2,602 (56.8 %)	1.21 (1.07–1.36)	
≥53 (7.0)	12,927 (65.8 %)	1.48 (1.32–1.66)	
Duration of diabetes, per 5 years		1.05 (1.03–1.08)	0.0001
Drug use			0.0111
Insulin sensitizers only	5,000 (60.7 %)	Reference	
Insulin secretagogues only	6,269 (66.7 %)	0.89 (0.82–0.96)	
Neither of them	2,473 (62.7 %)	0.94 (0.85–1.03)	
Both of them	4,904 (62.8 %)	0.99 (0.92–1.07)	
HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women as the outcome			
HbA1c groups, mmol/mol (%)			
<42 (6.0)	989 (44.9 %)	1.61 (1.37–1.88)	
42–46 (6.0–6.4)	734 (24.9 %)	Reference	
48–52 (6.5–6.9)	1326 (29.0 %)	1.51 (1.33–1.71)	
≥53 (7.0)	7089 (36.1 %)	1.90 (1.70–2.13)	
Duration of diabetes, per 5 years		0.92 (0.89–0.95)	<0.0001
Drug use			<0.0001
Insulin sensitizers only	2,834 (34.4 %)	Reference	
Insulin secretagogues only	3,850 (41.0 %)	0.90 (0.82–0.98)	
Neither of them	1,089 (27.6 %)	0.68 (0.61–0.76)	
Both of them	2,365 (30.3 %)	0.85 (0.78–0.92)	
Triglyceride ≥1.70 mmol/L as the outcome			
HbA1c groups, mmol/mol (%)			<0.0001
<42 (6.0)	903 (41.0 %)	Reference	
42–46 (6.0–6.4)	1,002 (34.0 %)	1.00 (0.87–1.15)	
48–52 (6.5–6.9)	1,918 (41.9 %)	1.58 (1.39–1.80)	

Table 4 continued

Variables	Number (%)	OR (95 % CI)	*P* value
≥53 (7.0)	9,853 (50.1 %)	2.06 (1.83–2.32)	
Duration of diabetes, per 5 years		0.99 (0.96–1.02)	0.4183
Drug use			<0.0001
Insulin sensitizers only	3,977 (48.3 %)	Reference	
Insulin secretagogues only	4,110 (43.7 %)	1.03 (0.96–1.12)	
Neither of them	1,547 (39.2 %)	0.72 (0.66–0.79)	
Both of them	4,042 (29.6 %)	1.07 (0.99–1.15)	

Variables adjusted for in the analysis included age, gender, body mass index, body height, self monitoring of blood glucose and use of alpha-glucosidase inhibitors and insulin

LDL-C/HDL-C low/high-density lipoprotein cholesterol

from the ADVANCE [12, 13], we did not find that HbA1c at 48–52 mmol/mol (6.5–6.9 %) increased LDL cholesterol among patients at low CVD risk but did not deny that HbA1c at 42–46 mmol/mol (6.0–6.4 %) might increase LDL cholesterol among patients at high CVD risk. In this regard, HbA1c ≥44 mmol/mol (6.2 %) enhanced the effect of albuminuria on the development of ischemic stroke in T2D [25].

In T2D, typical abnormal lipids are high triglyceride and low HDL cholesterol [17] and both high triglyceride and low HDL cholesterol are related with metabolic syndrome and insulin resistance [26]. This study also found that HbA1c at 48–52 mmol/mol (6.5–6.9 %) or higher was associated with higher likelihoods of high triglyceride and low HDL cholesterol. Differently from what was expected, longer duration of diabetes was associated with reduced likelihood of high triglyceride and low HDL cholesterol. It is noted that insulin increases free fatty acid synthesis by selectively activating sterol regulatory element binding protein-1c [27]. Given that insulin secretion capacity worsens over time, it is plausible that decreased insulin secretion capacity over time may contribute to the controversial finding that longer duration of diabetes was associated with "better" profile of triglyceride and HDL-C. The main lipoprotein of HDL cholesterol, apolipoprotein A-I, can stimulate the phosphorylation of AMP-activated protein kinas and acetyl-coenzyme A carboxylase to increase glucose uptake in muscle and insulin sensitivity [28]. Thus, the detected associations between hyperglycemia and triglyceride and between hyperglycemia and HDL cholesterol are more likely to be reverse ones, not causal relationships. We also observed that users of insulin secretagogues were more likely to have lower risk of low HDL cholesterol than users of insulin sensitizers but not for high LDL cholesterol and high triglyceride. The data should be interpreted with caution as prevalent user bias could not be removed in cross sectional studies [29].

This study also observed that HbA1c at <42 mmol/mol (6.0 %) increased the likelihood of low HDL cholesterol. In this regard, data from the Hong Kong Diabetes Registry showed that albuminuria predicted high LDL cholesterol while chronic kidney disease (CKD) predicted low HDL cholesterol [23] and modified the risk association between HDL cholesterol and CHD in T2D [24], i.e., among patients with CKD, low HDL cholesterol being no longer predictive of increased risk of CHD. These paradoxical observations highlight complex interplays of risk factors including insulin resistance, hyperglycemia, albuminuria, CKD, inflammation and lipids towards increased risk of CVD in T2D. Further investigations are warranted to understand biological links for hyperglycemia and CVD in T2D.

Our study has strong clinical implications. Hyperglycemia defined as HbA1c ≥53 mmol/mol (7.0 %) in low risk patients with T2D and varying durations of diabetes may increase CVD risk via increasing LDL cholesterol and probably other abnormal lipids. Thus, the data support that achieving hyperglycemia control goal of <53 mmol/mol (7.0 %) may decrease the CVD risk via improving lipid profile including LDL cholesterol among patients with non-newly diagnosed T2D.

This study has several limitations. Firstly, the study was a cross-sectional survey and cannot establish a causal relationship between hyperglycemia and lipid profile. Secondly, laboratory essays of LDL cholesterol, total cholesterol and triglyceride were not standardized before the survey in the laboratories of participating hospitals. Thirdly, lipid-lowering drugs were not documented in the survey. Use of lipid lowering drugs was not collected. We cannot adjust for use of lipid lowering drugs in the analysis. Patients with CVD or hyperlipidemia are more likely to use this class of drugs. However, the sensitivity analysis showed that inclusion of patients with CVD or hyperlipidemia did not decrease but increase the OR numerically, i.e., from 1.37 (1.19–1.57) to 1.48 (1.32–1.66). In the Hong Kong Diabetes Registry, <15 % of the patients were using lipid lowering drugs at baseline [30]. In contrast, a large survey in China showed that only 1.9 % of Chinese with diabetes in the urban areas used lipid lowering drugs, including that 1.7 % used statins [31]. The users of lipid lowering drugs without CVD and hyperlipidemia in this study might only account for a small proportion of the total sample. Given that up to 62 % of the patients had LDL-C ≥2.6 mmol/L, the impact of further adjustment for use of

lipid lowering drugs on the ORs should be small. Fourthly, the survey patients were under care of top tertiary hospitals and the findings may not be readily extrapolated to patients under care of other tertiary and secondary care hospitals and community health centres.

Conclusions

The study found that hyperglycemia defined as HbA1c ≥53 mmol/mol (7.0 %) increased the likelihood of high LDL cholesterol while HbA1c ≥48–52 mmol/mol (6.5–6.9 %) and higher increased the likelihood of high triglyceride and low HDL cholesterol. The findings suggest that hyperglycemia may increase CVD risk via abnormal lipid metabolism and control of hyperglycemia to HbA1c below 53 mmol/mol (7.0 %) among patients with varying durations of diabetes may contribute to decreased risk of CVD.

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