Diabetes & Metabolic Syndrome: Clinical Research & Reviews 12 (2018) 715–719

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Low-density lipoprotein cholesterol and risk of type 2 diabetes: The Isfahan diabetes prevention study

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ARTICLE INFO

Keywords:
LDL cholesterol
Diabetes
Incidence

ABSTRACT

Background: Studies reported that lipid-lowering treatment may increase the risk of diabetes, support the hypothesis that low-density lipoprotein cholesterol (LDLC) may be associated with type 2 diabetes (T2D).
Objective: The aim of this study was to assess the association between the LDLC levels and the incidence of T2D in an Iranian high-risk population not treated with lipid-lowering medications.
Methods: Mean 10-year follow-up data (1819) in non-diabetic first-degree relatives (FDR) of consecutive patients with T2D 30–70 years old, who were not treated with lipid-lowering drugs at baseline were examined. The diagnosis of T2D based on serial oral glucose tolerance test was the primary outcome. Cox proportional hazard model was used to estimate the hazard ratio (HR) for the incidence of T2D within tertiles of LDLC.
Results: A higher LDLC concentration was significantly associated with higher risk of T2D. Compared with the first tertile, the adjusted risk of T2D increased for the second (HR 1.20, 95% CI: 1.07, 1.35, $P < 0.01$) and third (HR 1.22, 95% CI: 1.08, 1.37, $P < 0.01$), tertiles of LDLC.
Conclusions: While these results await confirmation, a higher LDLC level was significantly associated with higher risk of T2D, independent of age, gender, fasting plasma glucose, waist circumference or blood pressure, in high-risk individuals in Iran.

1. Introduction

High low-density lipoprotein cholesterol (LDLC) is a well-known risk factor for cardiovascular disease [1] and lipid-lowering drugs such as statin and niacin decrease circulating LDLC [2–5]. Randomized controlled trials stated that lipid-lowering treatment may increase the risk of type 2 diabetes (T2D) [6–9]. These statements could propose that low LDLC levels may be associated with an increased risk of T2D.

While there are not many maintaining data for the association between low LDLC levels and risk of T2D [10–14], the role of LDLC as a risk factor for T2D remains disputable. Framingham Heart Study, the only longitudinal study of the association between LDLC levels and T2D risk, revealed that low LDLC levels was associated with incident T2D [10] and assume that the relationship between LDLC and T2D could be attributable to lipid-lowering treatment that increases the risk of T2D. However, while this study referred to LDLC as a possible risk factor of T2D, it is likely that genetic factors also play a part as well. Recently a few studies proposed that the risk of T2D observed with statin treatment could be attributable to genetically predisposed to higher levels of LDLC have a lower incidence of T2D [15–17]. As first-degree relatives (FDR) of people with T2D have a common genetic basis and are at high risk of T2D, they are suitable for testing the relationship between LDLC levels with T2D incidence. Therefore, the purpose of this longitudinal study was to assess the relationship between the LDLC and the incidence of T2D in an Iranian high-risk population who were not on any lipid-lowering treatment and who were free from diabetes at baseline. We hypothesized that lower LDLC concentrations may be associated with the incident T2D in non-diabetic FDR of people with T2D who are not on any lipid lowering treatment.

2. Subjects and methods

2.1. Study population and data collection

Data were drawn from the Isfahan Diabetes Prevention Study (IDPS), details of which have been presented elsewhere [18]. In

Abbreviations: BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; FPG, fasting plasma glucose; FDR, first-degree relatives; HbA1c, glycosylated hemoglobin; HDLC, high density lipoprotein cholesterol; HC, hip circumference; HR, hazard ratio; IDPS, Isfahan diabetes prevention study; LDLC, low-density lipoprotein cholesterol; T2D, type 2 diabetes; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic curve; SD, standard deviation; WC, waist circumference; WHR, waist-hip ratio.

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https://doi.org/10.1016/j.dsx.2018.04.019
1871-4021/

brief, the IDPS started between the years 2003 and 2005, is a continuing longitudinal study carried out in a cohort of FDRs of people with T2D in central Iran to assess the various possible risk factors for diabetes in individuals with a family history of T2D. Our study sample at baseline consists of 3483 (919 men and 2564 women) FDR of consecutive patients with T2D. All contributors were attenders at the Isfahan Endocrine and Metabolism Research Center, which is part of the Isfahan University of Medical Sciences, Iran. At the time of each evaluation, subjects submitted to anthropometric measurements and completed laboratory tests, including a standard 75 g 2-h oral glucose tolerance test (OGTT), and a questionnaire on their health condition and various possible risk factors for diabetes. The participants were followed up according to the standard of medical care for diabetes [19], to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes. If OGTT was normal at baseline, then repeat testing was accomplished at least at 3-year intervals. Otherwise, repeat testing was usually accomplished annually.

2.2. Ethics statement

The Isfahan University of Medical Sciences ethical committee approved the protocols for the IDPS. All participants provided written informed consent.

2.3. Procedures

Data on age, gender, body size, glycosylated hemoglobin (HbA1c), total cholesterol (TC), LDLC, high-density lipoprotein cholesterol (HDLC), triglyceride (TG), and blood pressure (BP), family and personal medical history was collected at baseline and at follow-ups. The same methodology was used at baseline and at follow-ups. The participants were siblings and children of patients with T2D. They were asked to abstain from forceful exercise in the evening before and in the morning of their visit when they reported to the clinic after an overnight fast. Smokers were stimulated to abstain from smoking in the morning of the investigations. Firstly, after arriving at the clinic, the information provided by the participants in the questionnaire on family history was checked. Then, with the individuals in light clothing and without shoes, weight, height, waist circumference (WC) and hip circumference (HC) were measured using standard apparatus and recorded to the nearest 0.1 kg and 0.5 cm. The WC was measured midway between the lower rib margin and the iliac-crest at the end of gentle expiration in the upright position. HC was measured over the greater trochanters directly over the underwear. Body mass index (BMI) (kg/m^2) was considered as weight (kg) divided by the squared of height (m^2). Resting systolic (phase I) and diastolic (phase V) BP was measured at each examination by a clinician with the participants in a sitting position, upon resting in this position for at least 10 min, using a mercury column sphygmomanometer and appropriately sized cuffs. A blood sample was drawn between 7.00 and 9.00 AM. FPG was measured using the glucose oxidase method. Those with FPG $<$ 126 mg/dl experienced a standard OGTT (75 g of glucose, 2 h) at baseline and follow-ups. Venous blood was sampled 0, 30, 60, and 120 min after oral glucose administration.

HbA1c, TC, TG, HDLC, LDLC was recorded. LDLC levels were calculated by using the Friedewald equation [20], provided total TG did not exceed 400 mg/dl. As a sensitivity analysis, we used directly measured TC levels to further ensure that any observed association was not due to the inaccurate calculation of LDLC levels by the Friedewald formula [10]. All blood sampling procedures were achieved in the central laboratory of the Isfahan Endocrine and Metabolism Research Center on the day of blood collection using an enzyme-linked method.

Abdominal obesity was defined by waist circumference ($\geq$102 cm in men and $\geq$ 88 cm in women).

2.4. Follow-up and diagnosis of T2D

Of the 3483 individuals who participated at baseline, 319 were excluded because of prevalent T2D or with history of taking lipid-lowering agents, and 1126 did not join follow-ups; a further 219 individuals who participated in follow-up, but had missing data on key covariates at baseline were also excluded, resulting in 1819 participants who completed the study. The mean (standard deviation [SD]) age of participants was 43.0 (6.5) (range 30–70) years, and all of them had at least one subsequent examination during a mean (SD) follow-up period of 10.1 (2.3) (range, 4-13) years. Pregnant women were excluded.

Participants with fasting plasma glucose (FPG) $\geq$ 200 mg/dl or pharmacological treatment were considered as persons with diabetes. If FPG was $>$125 mg/dl and $<$200 mg/dl, a second FPG was measured on another day. If the second FPG was also $>$ 125 mg/dl, participants were considered as persons with diabetes [21]. Those with FPG $<$ 126 mg/dl submitted to a standard OGTT (75 g glucose 2-h) at baseline and the follow-ups.

Most of the baseline characteristics of individuals who did not return for the follow-up visit (non-respondents), such as age, height, weight, BMI, WC, HC, waist-to-hip ratio (WHR), LDLC, TC, TG, FPG, and obesity were similar to those who joined the follow-up visits. However, non-respondents had slightly lower plasma glucose (PG) at 30 min. (140.0 mg/dl vs. 143.7, $P < 0.01$), 60 min. (141.2 mg/dl vs. 149.1, ($P < 0.001$), and 120 min. (111.2 mg/dl vs. 118.7, $P < 0.001$), levels of HbA1c (5.0% vs. 5.1%, $P < 0.05$), systolic BP (113.0 mm Hg vs. 115.7, $P < 0.001$), diastolic BP (73.1 mmHg vs. 75.7, $P < 0.001$), and higher HDLC (46.9 mg/dl vs. 44.9, $P < 0.001$) than respondents.

2.5. Analysis

Participants were followed until the occurrence of T2D, the date of the last completed follow-up, death, or end of follow-up on September 30, 2016, whichever event occurred first. We used the date of the examination in which a new case of T2D was recognized as the date of diagnosis.

The following statistical methods were included in the data analysis: Student *t*-test; one-way analysis of variance (ANOVA) for continuous variables; chi-square test, and Cox proportional hazard model. Differences between more than two groups were evaluated using one-way ANOVA with the Bonferroni post hoc test. To test the significance of LDLC concentration as a predictor of incident T2D, the incidence of T2D was calculated for each tertile of LDLC level, and the risk in each tertile was compared with the lowest tertile (reference group). Univariate and multivariate Cox proportional hazard equations were fitted to calculate the hazard ratios for new-onset T2D in relation to LDLC tertiles using the SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). We adjusted for the following covariate: age, gender, BMI or WC, systolic BP, and FPG. Diastolic BP was not included in the multivariate analysis to avoid co-linearity between systolic and diastolic BP. TC, HDLC, and TG were not included simultaneously in regression analysis to avoid co-linearity between these independent variables and LDLC calculated by Friedwald equation. As sensitivity analyses, all models were repeated using directly measured TC levels instead of estimated LDLC. A general linear model was used to examine the significance of trends in potential predictors of T2D across LDLC tertiles and compared age-adjusted means. The reported *P* values are 2-tailed, and *P* values $<$ 0.05 were considered to indicate statistical significance.

3. Results

Over 18,234 person-years of follow-up, 321 (17.6%) incident cases of T2D occurred. The mean (SD) level of LDLC was 119.7 (34.9). Participants on average were overweight with a mean (SD) BMI of 28.9 kg/m^2 (4.2). Table 1 shows the baseline characteristics of those participants who did and who did not progress to T2D. As expected, those who progressed to T2D were older and had higher age-adjusted mean BMI, WC, HC, WHR, FPG, PG at 30, 60, and 120 min, HbA1c, TG, and TC, and lower HDLC at baseline, and a higher proportion of obesity. The average (SD) age was 44.4 (6.6) years for those move on to T2D and 42.7 (6.4) years for those who did not move on to T2D. The mean (SD) LDLC was 120.4 mg/dl (34.3) for those progressing to T2D and 119.6 (33.4) for those who did not progress to T2D.

The characteristics of the study participants at baseline by LDLC tertile are shown in Table 2. In comparisons of variables at baseline, age, BMI, WC, FPG, and PG at 60 min, TC, HDL, diastolic BP, and obesity were more likely to increase across all three subject groups.

The incidence of T2D was 17.7 per 1000 person-years (95% CI: 14.5, 21.0) for individuals in the bottom tertile, 15.5 per 1000 person-years (95% CI: 12.4, 18.7) for second tertile, and 19.5 per 1000 person-years (95% CI: 16.0, 23.1) for the top tertile of LDLC. Compared with individuals in the bottom tertile, the risk of T2D was 27% higher in those in the top tertile at baseline (hazard ratio (HR) 1.27; 95% CI: 1.13, 1.42) and 19% higher in those in the second tertile (HR 1.19; 95% CI: 1.07, 1.33) in unadjusted models. Controlling for gender, age, WC or BMI, systolic BP, and FPG did not appreciably alter the HR compared to the unadjusted model (Table 3). Compared with participants in the lowest tertile, the risk of T2D was 22% higher for those in the highest tertile (HR 1.22; 95% CI: 1.08, 1.37, $P < 0.01$), and 20% higher for those in the second tertile (HR 1.20; 95% CI: 1.07, 1.35, $P < 0.01$) at baseline in the multivariable-adjusted models. Therefore, we performed additional analyses using LDLC concentration as continues variable. In multivariate adjusted model, a higher LDLC level was associated with a higher risk of T2D (HR 1.002; 95% CI: 1.001, 1.003). We did additional analyses comparing those below the first tertile with those above. In the multivariate adjusted model, the risk of T2D was 22% higher for those in the above tertiles (HR 1.22; 95% CI: 1.09, 1.36).

Analyses based on direct measurement of total cholesterol levels yielded results consistent with those observed for LDLC levels (Table 3).

4. Discussion

The current study revealed that high LDLC levels were significantly associated with higher risk of T2D independent of age, gender, FPG, WC, or blood pressure, in a cohort of high-risk individuals who were not using lipid-lowering drugs in Iran. This suggests that high LDLC levels may be recognized as a risk factor for T2D. Recently, Andersson et al. [10], in the Framingham Heart Study, the only longitudinal study of the relationship between LDLC levels and T2D risk, reported that low LDLC level was associated with incident T2D in the fully adjusted model. The Framingham Heart Study revealed that the lowest tertile of LDLC levels led to a 42% increased risk of new-onset T2D, which is contrary to 22% increase found in the highest tertile of LDLC level in the present study. In a large community-based cross-sectional analysis in the Netherlands, Besseling et al. [11] compared the prevalence of T2D between patients with familial hypercholesterolemia and their unaffected relatives and reported that individuals with familial hypercholesterolemia had a substantially lower prevalence of T2D than unaffected relatives. This finding is interesting but is not in agreement with our observation where higher LDLC concentrations were associated with higher incident T2D when adjusted for age, gender, WC, BP, or FPG. Our findings did not support the hypothesis that lower LDLC concentrations play a role in the development of T2D. Clearly, more studies are required to assess the relationship between LDLC concentration and increase risk of T2D.

Our study has several strengths and limitations. The strengths include accomplishment of standard OGTT and information on contributing factors of T2D. At follow-up, non-attendees in the entire population did not differ from attendees, according to major risk factors for progression to T2D, although a difference too small to explain the high progression rate to T2D in our study was seen in the mean levels of PG. Our databank is one of the few that followed FDR of patients with T2D, so permitting us to concurrently control the genetic factors that may predict T2D. Our study was limited to a cohort of

Table 1
Age and age-adjusted means (SD) and percentages of selected baseline characteristics in 321 first-degree relatives of patients with and 1498 without type 2 diabetes.

Variables	Developed diabetes Mean (SD)	Not developed Diabetes Mean (SD)	P value
Age (yr.)	44.4 (6.6)	42.7 (6.4)	0.000
Body mass index (kg/m^2)	30.1 (4.2)	28.6 (4.1)	0.000
Waist circumference (cm)	91.7 (8.9)	88.8 (9.5)	0.000
Waist-to-hip ratio	0.84 (0.06)	0.83 (0.07)	0.017
Hip circumferences (cm)	109.4 (9.0)	106.8 (8.7)	0.000
Systolic BP (mmHg)	116.9 (16.5)	115.5 (16.0)	0.105
Diastolic BP (mmHg)	76.6 (12.4)	75.6 (11.7)	0.123
Baseline fasting glucose (mg/dl)	103.3 (12.1)	93.7 (10.9)	0.000
Plasma glucose 30 min (mg/dl)	162.3 (33.4)	139.3 (28.7)	0.000
Plasma glucose 60 min (mg/dl)	183.8 (42.0)	141.0 (38.3)	0.000
Plasma glucose 120 min (mg/dl)	142.9 (33.5)	113.1 (30.4)	0.000
HbA1c (%)	5.3 (0.8)	5.0 (0.8)	0.000
Triglyceride (mg/dl)	194.5 (133.1)	158.6 (88.5)	0.000
Cholesterol (mg/dl)	200.6 (43.2)	195.6 (39.9)	0.033
HDL cholesterol (mg/dl)	43.5 (11.5)	45.3 (11.7)	0.010
LDL cholesterol (mg/dl)	120.4 (38.5)	119.6 (34.1)	0.713
	No. (%)	**No. (%)**	
Men	104 (28.1)	421 (26.1)	0.434
Obese (BMI $\geq$ 30)	166 (45.7)	539(33.8)	0.000
Abdominal obesity	180 (50.0)	571 (36.3)	0.000

Differences in the mean or percentage values of variables between participants who developed and not developed type 2 diabetes. CI = confidence interval.

Table 2
Age, age-adjusted mean (SD) and percentage characteristics of first-degree relatives of patients with type 2 diabetes by baseline low-density lipoprotein cholesterol (LDLC) tertile, The Isfahan Diabetes Prevention Study.

Characteristic	Tertile of LDLC			P value
	1st (≤104.4)	2nd (104.5–132.3)	3rd (>132.3)	
Participants no. (%)	608 (33.4)	605 (33.3)	606 (33.3)	–
Age (yr.)	41.7 (6.1)	42.6 (6.3)	44.7 (6.3)	0.000
Waist circumference (cm)	88.5 (9.7)	88.8 (9.9)	89.9 (8.9)	0.037
Hip circumference (cm)	107.1 (8.9)	107.1 (9.0)	107.9 (8.3)	0.159
Waist-to-hip ratio	0.83 (0.07)	0.83 (0.07)	0.83 (0.07)	0.312
Body mass index (kg/m^2)	28.6 (4.3)	28.8 (4.3)	29.3 (3.9)	0.026
FPG (mg/dl)	94.2 (12.2)	95.1 (11.4)	96.8 (11.6)	0.001
PG 30 min (mg/dl)	141.9 (30.5)	142.4 (30.7)	144.9 (30.9)	0.216
PG 60 min (mg/dl)	146.5 (42.6)	145.8 (42.0)	153.5 (41.7)	0.003
PG 120 min (mg/dl)	118.1 (32.8)	117.3 (32.3)	119.9 (33.5)	0.384
HbA1c (%)	5.1 (0.9)	5.1 (0.7)	5.1 (0.8)	0.432
Cholesterol (mg/dl)	160.6 (23.4)	192.6 (17.2)	234.3 (32.4)	0.000
HDL (mg/dl)	44.1 (12.7)	45.0 (10.1)	46.5 (11.8)	0.002
Triglyceride (mg/dl)	158.7 (83.3)	147.7 (67.5)	155.7 (62.2)	0.021
Systolic BP (mm Hg)	114.5 (15.4)	115.2 (14.9)	116.6 (17.4)	0.071
Diastolic BP (mm Hg)	74.5 (12.0)	75.8 (11.5)	76.5 (11.8)	0.015
Diabetes, no. (%)	113 (18.6)	93 (15.4)	115 (19.0)	0.196
Obesity (BMI ≥ 30), no. (%)	227 (38.4)	238 (40.1)	274 (46.1)	0.003
Men, no. (%)	159 (26.2)	162 (26.8)	147 (24.3)	0.576

Data are expressed as mean (SD) or number (%). Comparison across all three groups.

Table 3
Hazard ratio (HR) and incidence rates of type 2 diabetes by baseline low-density lipoprotein cholesterol (LDLC) and total cholesterol terrtiles, The Isfahan Diabetes Prevention Study.

	Tertiles of LDLC		
	1st (≤104.4)	2nd (104.5–132.3)	3rd ((>132.3)
Number of cases (%.)	113 (18.6)	93 (15.4)	115 (19.0)
Person year	6368	5981	5885
Incidence/1000 person-year (95% CI)	17.7 (14.5, 21.0)	15.5 (12.4, 18.7)	19.5 (16.0, 23.1)
LDLC level			
Hazard ratio (95% CI)			
Unadjusted	1.00	1.19 (1.07, 1.33)**	1.27 (1.13, 1.42)*
Gender adjusted	1.00	1.19 (1.07, 1.34)**	1.27 (1.14, 1.43)*
Age and gender adjusted	1.00	1.19 (1.06, 1.33)**	1.22 (1.09, 1.38)**
Age, gender, and WC adjusted	1.00	1.19 (1.06, 1.34)**	1.24 (1.10, 1.39)*
Age, gender, WC, and systolic BP adjusted	1.00	1.20 (1.07, 1.35)**	1.25 (1.11, 1.41)*
Age, gender, WC, systolic BP, and FPG adjusted	1.00	1.20 (1.07, 1.35)**	1.22 (1.08, 1.37)**
	tertiles of total cholesterol		
	1st (≤178.0)	2nd (178.1–210.0)	3rd (>210.0)
Total cholesterol level			
Unadjusted	1.00	1.16 (1.04, 1.29)**	1.28 (1.15, 1.43)*
Gender adjusted	1.00	1.15 (1.04, 1.29)**	1.29 (1.15, 1.43)*
Age and gender adjusted	1.00	1.14 (1.02, 1.28)***	1.24 (1.11, 1.39)*
Age, gender and WC adjusted	1.00	1.14 (1.02, 1.27)***	1.25 (1.11, 1.40)*
Age, gender, WC, and triglyceride adjusted	1.00	1.12 (1.01, 1.26)***	1.23 (1.09,1.38)**
Age, gender, WC, triglyceride, and HDLC adjusted	1.00	1.13 (1.01, 1.27)***	1.24 (1.09, 1.40)**
Age, gender, WC, triglyceride, HDLC, and systolic BP adjusted	1.00	1.15 (1.02, 1.29)***	1.25 (1.10, 1.41)**
Age, gender, WC, triglyceride, HDLC, systolic BP, and FPG adjusted	1.00	1.13 (1.01, 1.28)***	1.22 (1.08, 1.39)**

CI = Confidence interval. *P < 0.001, **P < 0.01, ***P < 0.05.

individuals who are at increased risk of developing T2D because they had an FDR with the patients with T2D, thus, the selection bias may lead to an underestimation of associations and generalizability to other populations is unknown.

In term of our definition of incident T2D, some selection bias may be present as participants who attend for screening may have been more likely to be tested and consequently diagnosed as having T2D. Therefore, people with T2D who had lower risk may have been ignored through lack of testing. Residual confounders could not be eliminated so may increase the possibility that uncontrolled or inadequately measured confounders affected our results. However, it is necessary to validate the association of LDLC and T2D in other populations.

In conclusion, high LDLC levels are a predictor of T2D, independent of age, gender, FPG, WC or BP, in high-risk individuals in Iran. More cohort study is warranted to confirm our observations and to elucidate the mechanism underlying the observed relationship.

Informed consent

Informed consent was taken from all contributors for being included in the study.

Statement of human and animal rights

This article does not enclose any studies with human or animal subjects carried out by the any of the authors.

Authors' contributions

Janghorbani M develops the original idea for the study, conceived and designed the study, analyzed the data and wrote the manuscript, Amini M, recruited samples and contributed to the discussion and revision of the manuscript and obtained funding for the IDPS. Aminorroaya A and Soltanian N contributed to the discussion and revision of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors state that they have no conflicts of interest.

Acknowledgments

We are grateful to M. Abyar for technical computer assistance. This study was supported by the Elite Researcher Grant Committee under award number 958697 from the National Institutes of Medical Research Development (NIMAD), Tehran, Iran.

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