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The impact of dyslipidaemia on cardiovascular mortality in individuals without a prior history of diabetes in the DECODE Study

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ABSTRACT

Objective: To evaluate the impact of dyslipidaemia on cardiovascular disease (CVD) mortality in relation to fasting (FPG) and 2-h (2hPG) plasma glucose levels in individuals without a prior history of diabetes.
Methods: Data from 14 European population-based prospective studies of 9132 men and 8631 women aged 25–89 years were jointly analysed. A total of 871 CVD deaths occurred during the average 10 years of follow-up. Subjects were classified into normoglycaemia, isolated fasting hyperglycaemia (IFH, FPG ≥ 6.10 mmol/l and 2hPG < 7.80 mmol/l), isolated post-load hyperglycaemia (IPH, FPG < 6.10 mmol/l and 2hPG ≥ 7.80 mmol/l) and combined fasting and post-load hyperglycaemia (CH, FPG ≥ 6.10 mmol/l and 2hPG ≥ 7.80 mmol/l). Multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD mortality were estimated using Cox proportional hazard analysis.
Results: Multivariate-adjusted HRs (95% CIs) for high-density lipoprotein cholesterol (HDL-C) were 0.84 (0.75–0.94), 0.66 (0.48–0.92), 1.03 (0.84–1.27) and 0.67 (0.51–0.89) in individuals with normoglycaemia, IFH, IPH and CH, respectively. For total cholesterol (TC) to HDL-C ratio they were 1.14 (1.03–1.27), 1.44 (1.13–1.84), 0.94 (0.77–1.15) and 1.26 (1.05–1.50), respectively. HRs for TC and triglycerides (TG) were not significant in most of the glucose categories except for TG in those with CH [HR 1.12 (1.00–1.27)].
Conclusions: Low HDL-C and high TC/HDL-C increase CVD mortality in either diabetic or non-diabetic individuals defined based on the fasting glucose criteria, but not the 2-h criteria. TG is a significant CVD risk predictor only in the presence of combined hyperglycaemia or diabetes. The difference between fasting and post-load hyperglycaemia with regard to the lipid-CVD relation may suggest a different pathophysiology underlying these two prediabetic states.

1. Introduction

The risk of mortality from cardiovascular disease (CVD) is increased in subjects with diabetes or impaired glucose tolerance (IGT) [1–5]. It is well known that type 2 diabetes is associated with a high prevalence of dyslipidaemia including reduced high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG) and very-low-density lipoprotein (VLDL) and increased small dense LDL particles [6]. Among the numerous studies of lipid components

Abbreviations: CH, combined fasting and post-load hyperglycaemia; CI, confidence interval; CVD, cardiovascular disease; DECODE, diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; 2hPG, plasma glucose 2 h after 75-g glucose load; IFG, impaired fasting glucose; IFH, impaired fasting hyperglycaemia; IGT, impaired glucose tolerance; IPH, impaired post-load hyperglycaemia; NFG, normal fasting glucose; NGT, normal glucose tolerance; Non-HDL-C, non-HDL cholesterol; TC, total cholesterol; TG, triglycerides.

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in general or diabetic populations, HDL-C is well documented as an independent predictor of CVD events [7]. In contrast, the role of plasma TG as an independent risk factor for CVD is more controversial [8–13]. Recently, the use of total cholesterol to HDL ratio (TC/HDL-C) [11,14] and non-HDL cholesterol (non-HDL-C) for assessment of CVD risk has increased and as a CVD risk predictor the non-HDL-C has been considered to be superior to LDL-C [14–18].

Studies among non-diabetic subjects [19–21] have also demonstrated that impaired fasting glucose (IFG) and IGT are associated with abnormal lipid levels. But little is known with regard to the role of these lipid parameters for the risk of CVD mortality in different glucose categories of non-diabetic range. This was investigated in the DECODE (diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe) study.

2. Subjects and methods

2.1. Study populations

The study populations and the recruitment of the participants have been described in detail in previous DECODE publications [3,18,22–24]. Briefly, researchers who had carried out population-based or large occupational epidemiological studies on diabetes in Europe, using a standard 2-h 75-g oral glucose tolerance test, were invited to participate. Individual data on fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) concentrations as well as on blood TC, HDL-C and TG and a number of other variables were sent to the Diabetes Epidemiology Unit of the National Public Health Institute in Helsinki, Finland for collaborative data analysis. Information on measures of lipids and lipoproteins in each study was given in Appendix 1. Non-HDL-C levels were calculated by subtracting HDL-C from TC levels. In the current analyses, cohorts with data on cause-specific mortality and required variables (baseline measurement of lipid components, blood glucose, blood pressure, hypertension and smoking status) were included. A total of 14 cohorts including 9132 men and 8631 women aged 25–89 years provided data on cause-specific mortality and covariates required for this collaborative data analysis.

2.2. Classification of hyperglycaemia

According to the WHO 1999 criteria [25], a person with a prior history of diabetes was classified as previously diagnosed diabetes and was not included in the current data analysis, and those without prior history of diabetes were classified based on either FPG or 2hPG levels. Classification of newly diagnosed diabetes, IGT and normal glucose tolerance (NGT) was made according to the 2hPG concentrations of ≥11.10, 7.8–11.09, and <7.80 mmol/l. FPG levels of ≥7.00, 6.10–6.99, and <6.10 mmol/l classified subjects into newly diagnosed diabetes, IFG, and normal fasting glucose (NFG), respectively. According to the both criteria combined, subjects were further classified into normoglycaemia (NFG and NGT), isolated fasting hyperglycaemia (IFH, FPG ≥ 6.10 mmol/l and 2hPG < 7.80 mmol/l), isolated post-load hyperglycaemia (IPH, FPG < 6.10 mmol/l and 2hPG ≥ 7.80 mmol/l) and combined fasting and post-load hyperglycaemia (CH, FPG ≥ 6.10 mmol/l and 2hPG ≥ 7.80 mmol/l).

2.3. Definition of fatal events

Vital status and the date and the cause of death for those deceased were recorded for each subject attending the baseline examination. Subjects who had emigrated and for whom the vital status could not be confirmed were treated as censored at the time of emigration. The International Classification of Diseases (ICD) was used for coding the causes of death. CVD deaths were defined using ICD codes 401–448 for the eighth or ninth revision and codes I10–I79 for the tenth revision. Participants who died, but for whom information on the causes of death was not available, were considered as missing and were excluded in the calculation of CVD mortality.

2.4. Statistical analysis

Data were analyzed using SPSS for Windows (version 15.0). Baseline characteristic of each lipid variable was shown as mean and the lower 25th and the upper 75th percentile of the distribution by sex and study cohort (Appendix 2). Hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD mortality in relation

Table 1
Baseline characteristics of subjects and number of deaths from cardiovascular disease during follow-up.

Countries and studies	No. (male/female)	Mean age in years (range)	IFG (%)	IGT (%)	Diabetes (%)	Hypertension (%)	Current smoking (%)	Follow-up year (Max)	No. of CVD deaths (male/female)
Finland									
East-West[a]	354/–	76 (69–89)	15.8	27.1	12.7	81.9	14.1	17.1	137/–
Finrisk 1992	841/1007	54 (44–64)	13.6	11.1	5.1	64.5	20.6	15.0	54/18
Finrisk 2002	1640/1934	57 (45–74)	20.3	16.8	8.7	64.6	28.3	4.9	22/5
Oulu Study	304/401	55 (55–55)	30.6	28.7	17.6	71.3	23.3	15.0	13/7
Vantaa Study	240/308	65 (64–66)	10.8	27.9	6.6	80.7	16.6	13.9	29/10
Italy									
Cremona Study	731/927	57 (40–88)	4.4	8.7	3.4	58.7	22.7	15.7	76/65
Poland									
MONICA	163/181	57 (43–73)	13.7	22.7	7.3	47.4	25.6	6.6	13/2
Sweden									
MONICA	993/1077	46 (25–74)	5.5	7.2	2.5	32.1	21.6	20.6	36/19
ULSAM[a]	1095/-	70 (69–73)	9.3	28.4	11.1	73.9	20.8	12.4	119/-
The Netherlands									
Hoorn Study	1081/1269	61 (49–77)	10.9	9.5	6.9	49.4	33.7	10.2	66/32
Zutphen Study[a]	442/–	75 (69–89)	17.9	10.0	10.6	67.4	22.6	4.8	46/-
U.K.									
ELY	425/599	54 (40–69)	22.7	15.4	6.6	32.5	16.8	15.7	22/6
Newcastle Heart Project	375/360	54 (30–76)	21.2	13.3	7.2	34.6	28.0	10.6	25/8
The Goodinge Study	448/568	54 (39–76)	31.9	9.3	8.9	21.9	37.7	9.7	28/13
Total	9132/8631	57 (25–89)	15.1	14.4	7.2	54.1	25.3	20.6	686/185

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CVD, cardiovascular disease.
[a] Study of male gender only.