International Journal of Cardiology 173 (2014) 295–299

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Time dependent changes in high density lipoprotein cholesterol and cardiovascular risk

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ARTICLE INFO

Article history:
Received 11 December 2013
Received in revised form 18 February 2014
Accepted 9 March 2014
Available online 15 March 2014

Keywords:
HDL cholesterol
Time dependent changes
Cardiovascular risk

ABSTRACT

Background: High-density lipoprotein cholesterol (HDL-C) is a strong inverse predictor of cardiovascular events. The aim of the current study was to evaluate the correlation between changes in HDL-C and subsequent cardiovascular events.

Methods: Study population comprised 13,037 subjects free of cardiovascular disease with a mean follow up of 6 ± 3 years. Low HDL-C was defined as <40 mg/dl for men and <50 mg/dl for women. Participants were divided into three groups based on HDL-C levels at the first and second baseline visits: persistently-low HDL-C (LL); persistently-high HDL-C (HH); and those with high HDL-C in a one visit only: intermittently high HDL-C (LH/HL). The primary endpoint was the first occurrence of a cardiovascular event.

Results: A total of 529 (4.1%) incident events occurred during follow-up. HDL-C levels increased significantly between the two landmark visits (47.5 ± 12.6 vs. 48.1 ± 12.2, $p < 0.001$). Kaplan–Meier survival analysis showed that the cumulative probability of cardiovascular events at 6 years was highest among subjects in the LL group (7.6%), and similar among LH/HL and HH groups (3.3% and 4%, respectively; log-rank $p = 0.001$). Multivariate Cox regression analysis, with HDL-C as time-dependent covariate, showed that subjects with persistently low HDL-C during follow up experienced a 51% increased cardiovascular risk compared with subjects with persistently high HDL-C ($p = 0.026$). Subjects with intermittently high HDL-C during follow up experienced similar risk to those with persistently high HDL-C (HR = 1.02; $p = 0.89$).

Conclusions: Variations in HDL-C levels during follow-up are associated with subsequent cardiovascular risk. Patients who retain low HDL-C levels are at the cardiovascular highest risk.

1. Introduction

High-density lipoprotein cholesterol (HDL-c) is a strong and independent inverse predictor of cardiovascular disease (CVD). Low HDL-C levels are correlated with increased cardiovascular risk among different populations including healthy adults, subjects suffering from dyslipidemia or the metabolic syndrome, and patients with established coronary artery disease [1–7]. Accordingly, the National Cholesterol Education Program—Adult Treatment Panel III (NCEPATP III) guidelines indicate that a low HDL-C level should be regarded as a major risk factor for CVD [8].

While multiple clinical trials focused on strategies aiming to increase HDL-C levels among high risk populations, little is known about how changes in HDL-C among apparently healthy individuals correlate with subsequent cardiovascular risk.

Therefore, the aim of the current study was to investigate the correlation between changes in HDL-C and subsequent cardiovascular events among large cohort of middle-aged apparently healthy adults.

2. Methods

2.1. Study population

The Chaim Sheba Medical Center Institute for Medical Screening performs approximately 9000 annual examinations. The center population comprise mainly of apparently healthy men and women who undergo annual health screening survey examinations. Study population was described previously [9–11]. In brief, all participants are interviewed at the time of each annual examination using standard questionnaires that gather information regarding demographic characteristics, medical history, and health-

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[1] All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2014.03.022
0167-5273/

related habits (including current smoking status, and regular physical activity). Thereafter, blood samples are drawn after a 12 h fast and analyzed immediately. A physician at the center performs a complete physical examination, including blood pressure measurement. All subjects undergo exercise stress testing according to the Bruce protocol in each annual visit. A computerized database of all the annual visits in this center was established in the year 2000 and is the source of data for this study. The Institutional Review Board of the Sheba medical center approved this study on the basis of strict maintenance of participants' anonymity during database analyses. No individual consent was obtained.

The present study population comprised Caucasian men and women who visited the Institute for Preventive Medicine during the years 2000–2013 and had HDL-C levels from their first two baseline visits. Low HDL was defined as <40 mg/dl for men and <50 mg/dl for women according to the NCEP ATP III guidelines [8]. Subjects with known coronary artery disease, or abnormal exercise stress test at the baseline visit were excluded from the analysis. Final sample size included 12,867 subjects who were followed up, examined and interviewed annually at yearly intervals over a mean follow up of 6 ± 3 years. Participants were encouraged to perform regular physical activity, nutritional counseling was given when needed (e.g. obesity or dysglycemia) and annual medical follow-up was ensued. Baseline characteristics, cardiovascular risk factors and laboratory characteristics of subjects were not included in the final analysis (due to loss to follow up or missing HDL-C levels at baseline) and were not statistically different from the characteristics of the included subjects (data not shown).

2.2. Definitions and endpoint

In the primary analysis of the present study, subjects were grouped into three HDL-C change groups based on HDL-C levels at the first and second landmark visits. Group I: persistently-high HDL-C concentrations on both landmark visits (HH); Group II: persistently-low HDL-C concentrations on both landmark visits (LL); and Group III: subjects with high HDL-C in a single (either first or second) follow-up visit (LH/HL). In a secondary analysis, Group III subjects were further categorized into those who changed their HDL-C levels between the first and second visits from low to high (LH) or those who had a corresponding reduction between the two visits (HL).

The primary end point of the present study was the first occurrence of a cardiovascular event during follow-up. This outcome was defined as significant coronary heart disease requiring intervention (therapeutic percutaneous coronary intervention (PCI)) or acute coronary syndrome (defined according as the combination of ischemic symptoms and ECG changes of new ischemia with or without evidence of loss of viable myocardium). Outcomes were reported at the yearly visit and approved by the attending physician. The study was designed as a landmark study (i.e. with follow-up for cardiovascular events beginning after the second assessment of HDL-C levels). Since all-cause mortality occurred in only a small minority of study subjects (n = 112 [0.86%]), all analyses were further repeated for the secondary end point that included the first occurrence of a cardiovascular event (as defined above) or all-cause mortality.

3. Statistical analysis

Baseline clinical characteristics were compared among the three HDL-C change groups (LL, LH/HL, HH) by either using one-way ANOVA for continuous variables or chi-square test for categorical variables. The probability of the development of a first CVD event during follow-up by the prespecified HDL-C change groups was estimated and graphically displayed according to the method of Kaplan and Meier, with comparison of cumulative events across strata by the log-rank test. In this analysis follow-up was initiated after the second landmark visit.

Multivariate Cox proportional hazard regression modeling was carried out to evaluate how HDL-C change groups were associated with the development of the composite CVD outcome, incorporating HDL-C levels at consecutive follow-up visit (up to 8 annual visits) as a time-dependent covariate in the multivariate models. In this analysis subjects in the LL or HH groups at the second follow-up visit were moved into the LH/HL group if their HDL-C category was changed at any subsequent visit, thereby incorporating the 3 HDL-C change groups as a time-dependent covariate. Pre-specified covariates in the multivariate models included age, gender, smoking status (yes/no), obesity (>30 kg/m^2), self-reported regular physical activity (yes/no), LDL and HDL cholesterol levels and lipid lowering therapy. All statistical analyses were performed with SPSS (ver. 20.0) statistical software.

4. Results

Among the 12,867 study subjects, the mean age was 49 ± 10 and 9265 (72%) of the subjects were men. There were 2145 (17%) active smokers, 1714 (13%) obese and 7900 (61%) physically active subjects.

Table 1
Baseline characteristics of study population.[a]

	LL N = 3184	LH/HL N = 2334	HH N = 7519
Age, years	48 ± 10	48 ± 10	49 ± 11
Gender, male	2445 (77%)	1649 (72%)	5171 (70%)
BMI	27 ± 4	27 ± 4	25 ± 4
Obesity	649 (22%)	363 (17%)	702 (10%)
Active smokers	715 (25%)	414 (19%)	1016 (15%)
Physically active	1651 (57%)	1331 (62%)	4918 (70%)
Systolic BP (mm Hg)	126 ± 18	124 ± 18	124 ± 19
Diastolic BP (mm Hg)	80 ± 10	80 ± 10	78 ± 13
Hemoglobin (g/dl)	14.8 ± 1.3	14.7 ± 1.3	14.6 ± 1.5
Creatinine (mg/dl)	1.06 ± 0.17	1.04 ± 0.17	1.04 ± 0.16
Glucose (mg/dl)	96 ± 24	92 ± 19	91 ± 19
Uric acid (mg/dl)	6 ± 1	5 ± 1	5 ± 1
Total cholesterol (mg/dl)	188 ± 34	193 ± 35	199 ± 34
LDL-C (mg/dl)	120 ± 28	124 ± 29	124 ± 30
HDL-C (mg/dl)	36 ± 5	42 ± 7	54 ± 12
Triglyceride (mg/dl)	169 ± 89	142 ± 79	110 ± 57
Lipid lowering therapy[b]	57 (2%)	50 (2%)	150 (2%)

BMI: body mass index. BP: blood pressure. LDL-C: low density lipoprotein cholesterol. HDL-C: high density lipoprotein cholesterol. LL: low concentration of HDL-C on both visits. LH/HL: high HDL-C in a single follow-up visit. HH: high HDL-C concentration on both visits. SI conversion factors: to convert cholesterol to mmol/l, multiply values by 0.0259.

[a] All comparisons were statistically significant (p < 0.01 for overall comparison) with the exception of lipid lowering therapy.

[b] Statin — 88%, fibrate — 10%, others (niacin and ezetemibe) — 2%, of them only 3% were on more than one lipid lowering agent.

Only 257 (2.2%) subjects were on chronic lipid lowering drug therapy (statin — 88%, fibrate — 10%, others [niacin and ezetemibe] — 2%, of them only 3% were on more than one lipid lowering agent).

There were 3164 (25%) subjects in the LL group, 7426 (58%) subjects in the HH group, and 2277 (18%) subjects in the LH/HL group. The latter group included 1357 (60%) LH subjects (i.e. those with low HDL-C concentration in the first and high concentrations in the second visit) and 920 (40%) HL subjects (i.e. those with high HDL-C levels in the first and low HDL-C levels in the second visit).

Baseline clinical and laboratory characteristics of study subjects by the prespecified HDL-C change groups are presented in Table 1. The 3 groups displayed significant differences in all baseline characteristics. Notably, compared with HH and LH/HL groups, LL group subjects were more likely to be males, had higher levels of fasting glucose, were more likely to be active smokers, were less likely to be physically active,

Table 2
Baseline characteristics at landmark visits.[a]

	Landmark visit 1	Landmark visit 2
BMI	26 ± 4	26 ± 4
Obesity	1753 (13%)	1773 (14%)
Active smokers	2145 (17%)	2039 (16%)
Physically active	7900 (61%)	8862 (69%)
Systolic BP (mm Hg)	124 ± 19	124 ± 17
Diastolic BP (mm Hg)	79 ± 12	78 ± 10
Hemoglobin (mg/dl)	14.7 ± 1.4	14.6 ± 1
Creatinine (mg/dl)	1.05 ± 0.16	1.04 ± 0.2
Glucose (mg/dl)	92 ± 20	91 ± 18
Uric acid (mg/dl)	5.4 ± 1.4	5.5 ± 1.4
Total cholesterol (mg/dl)	196 ± 34	195 ± 34
LDL-C (mg/dl)	123 ± 29	122 ± 28
HDL-C (mg/dl)	47.5 ± 12.5	48.1 ± 12.1
Low HDL-C (mg/dl)	4521 (35%)	4084 (32%)
Triglyceride (mg/dl)	130 ± 74	130 ± 72
Lipid lowering drugs[b]	257 (2.0%)	348 (2.7%)

All comparisons were statistically significant (p < 0.01) with the exception of BMI, obesity rates and triglycerides level. BP: blood pressure. BMI: body mass index. LDL-C: low density lipoprotein cholesterol. HDL-C: high density lipoprotein cholesterol. SI conversion factors: to convert cholesterol to mmol/l, multiply values by 0.0259.

[a] Average time interval between first and second visits was 467 ± 265 days.

[b] Include statin and fibrate based medications.