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In-treatment HDL cholesterol levels and development of new diabetes mellitus in hypertensive patients: The LIFE Study

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Abstract

Aims Although hypertensive patients with low baseline HDL cholesterol levels have a higher incidence of diabetes mellitus, whether changing levels of HDL over time are more strongly related to the risk of new diabetes in hypertensive patients has not been examined.

Methods Incident diabetes mellitus was examined in relation to baseline and in-treatment HDL levels in 7485 hypertensive patients with no history of diabetes randomly assigned to losartan- or atenolol-based treatment.

Results During 4.7 ± 1.2 years follow-up, 520 patients (6.9%) developed new diabetes. In univariate Cox analyses, compared with the highest quartile of HDL levels (> 1.78 mmol/l), baseline and in-treatment HDL in the lowest quartile (< 1.21 mmol/l) identified patients with > 5-fold and > 9 fold higher risks of new diabetes, respectively; patients with baseline or in-treatment HDL in the 2nd and 3rd quartiles had intermediate risk of diabetes. In multivariable Cox analyses, adjusting for randomized treatment, age, sex, race, prior anti-hypertensive therapy, baseline uric acid, serum creatinine and glucose entered as standard covariates, and in-treatment non-HDL cholesterol, Cornell product left ventricular hypertrophy, diastolic and systolic pressure, BMI, hydrochlorothiazide and statin use as time-varying covariates, the lowest quartile of in-treatment HDL remained associated with a nearly 9-fold increased risk of new diabetes (hazard ratio 8.7, 95% CI 5.0–15.2), whereas the risk of new diabetes was significantly attenuated for baseline HDL < 1.21 mmol/l (hazard ratio 3.9, 95% CI 2.8–5.4).

Conclusions Lower in-treatment HDL is more strongly associated with increased risk of new diabetes than baseline HDL level.

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Introduction

The high and increasing prevalence of hyperglycaemia and Type 2 diabetes mellitus [1] and the associated greater risk of cardiovascular disease [2,3] make a better understanding of the risk factors for diabetes an important area of investigation. There is a well-established association between blood pressure and insulin resistance [4–6], although this relationship partially reflects parallel effects of obesity and age [4,5]. Moreover, hypertension and diabetes frequently coexist, with the combination associated with a 2- to 3-fold increased risk of cardiovascular disease [2,3,7]. These findings, taken together with the increased long-term cardiovascular risk associated with the development of new diabetes in hypertensive patients [2], suggest that prevention of diabetes in hypertensive patients may have prognostic benefit.

Low levels of HDL cholesterol have been implicated in the development of insulin resistance and diabetes [8–16]. Low HDL levels correlate significantly with increased insulin resistance and fasting insulin levels [8,9] and low levels of HDL at baseline measurement predict low insulin-sensitivity index values and increased insulin resistance at subsequent follow-up [9,10]. Low baseline HDL levels have also been strongly linked to the development of diabetes in the general population [11,12], Pima Indians [13,14], subjects with

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pre-diabetes [15] and in the current population of hypertensive patients with electrocardiographic left ventricular hypertrophy [16].

However, HDL levels decrease with age and weight gain [17] and often in response to increasing statin therapy. As a consequence, it is unclear if a single, baseline measurement of HDL will best stratify diabetes risk or whether changing levels of HDL over time would more strongly reflect the risk of diabetes. Therefore, the purpose of the present study was to compare the predictive value of baseline and in-treatment HDL levels for development of diabetes and to determine whether HDL remained associated with a higher diabetes risk after adjusting for the potential confounding effects of risk factors, including hydrochlorothiazide [18] and statin therapy [19], on diabetes incidence, and for the previously demonstrated relations of randomized treatment allocation, prior anti-hypertensive treatment and in-treatment electrocardiographic left ventricular hypertrophy to new diabetes in the current study population [16,20].

Subjects and methods

Patient selection and treatment

The LIFE Study enrolled 9193 hypertensive patients with electrocardiographic left ventricular hypertrophy by Cornell voltage-duration product and/or Sokolow-Lyon voltage criteria on a screening electrocardiographic in a prospective, double-blind randomized study that compared cardiovascular morbidity and mortality with use of losartan-based treatment as opposed to atenolol-based treatment, as previously described in detail [20,21]. The study was approved by all ethics committees concerned and all participants gave informed written consent. The 1195 patients with diabetes mellitus at study baseline [16,20] and 513 additional patients without diabetes who were missing baseline HDL levels were excluded, leaving 7485 patients who were at risk of developing diabetes in the present study. The 513 patients with missing baseline HDL levels were similar to the 7485 patients included in the study with respect to age, gender, randomized treatment allocation, baseline systolic pressure, plasma glucose and severity of electrocardiographic left ventricular hypertrophy by Cornell product criteria.

Blinded treatment was begun with losartan 50 mg or atenolol 50 mg daily and matching placebo of the other agent, with up-titration of study medication to 100 mg and addition of hydrochlorothiazide and other anti-hypertensive therapies to achieve a pressure of $\leq$ 140/90 mmHg as previously reported [21].

Electrocardiography and lipid measurements

Study electrocardiogram were obtained at baseline, 6 months and yearly follow-up until study termination or patient death and were interpreted as previously reported [20,21]. Cornell product > 2440 mm × ms or Sokolow-Lyon voltage > 38 mm were used to identify left ventricular hypertrophy [20,21].

Serum total cholesterol and HDL were measured in two central laboratories as previously reported [22]. LDL cholesterol and triglycerides were not measured. Non-HDL cholesterol was calculated as total cholesterol minus HDL. Treatment of lipids was at the discretion of study investigators, but all treatment was reported [22].

Endpoint determination

New-onset diabetes was a pre-specified secondary endpoint in LIFE and was initially defined according to 1985 World Health Organization criteria [16,23]. Because new recommendations for the diagnosis of Type 2 diabetes were published by the World Health Organization in 1999 while the LIFE study was in progress [24], it was decided that all patients who were diagnosed with new-onset diabetes would be included in analyses regardless of whether the diagnosis was based on 1985 or 1999 criteria [16,23,24].

Statistical analyses

Data management and analysis were performed with SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD for continuous variables and proportions for categorical variables. Differences in prevalences were compared using χ^2 analyses and of mean values using the unpaired *t*-test.

The relation of new-onset diabetes to HDL was assessed using Cox proportional hazards models with patients categorized into quartiles according to HDL levels at baseline; the risk of new diabetes was calculated comparing each of the first three quartiles of HDL against the highest quartile of HDL. The predictive value of baseline HDL was determined using baseline quartiles of HDL entered as standard covariates in the Cox models; the predictive value of in-treatment levels of HDL was determined using baseline and in-treatment quartiles of HDL entered as time-varying covariates. Independence of the relationship of new-onset diabetes to baseline and in-treatment HDL was evaluated in multivariable Cox models that adjusted for randomized treatment with losartan vs. atenolol, age, sex, race, prior anti-hypertensive therapy, baseline uric acid, serum creatinine and glucose entered as standard covariates and, for in-treatment non-HDL cholesterol, Cornell product left ventricular hypertrophy, diastolic and systolic pressure, BMI, hydrochlorothiazide and statin use treated as time-varying covariates. Baseline HDL was also included as a standard covariate in the multivariable Cox analyses examining in-treatment HDL. Analyses were also performed stratifying the population by sex, age, prior anti-hypertensive treatment, randomized treatment allocation, treatment with a statin at any time during the study, median baseline serum glucose and BMI, median of the average systolic blood pressure during treat-

ment and the median decrease in electrocardiographic left ventricular hypertrophy by Cornell product and Sokolow-Lyon voltage during the study, using in-treatment HDL entered as a continuous variable for simplicity of these analyses. For all tests, a two-tailed P-value < 0.05 was required for statistical significance.

The relationship of incident diabetes over time to changing quartiles of HDL during treatment was illustrated using a modified Kaplan–Meier method [25] implemented in SAS release 8.2 (SAS Institute, Cary, NC, USA) on the WIN_PRO platform. Using this method, HDL quartile assignment is updated each year and patients may be variably included in one curve or another at different times during follow-up. These modified Kaplan–Meier curves illustrate the results of time-varying covariate analyses.

Results

During mean follow-up of 4.7 ± 1.2 years, new-onset diabetes mellitus developed in 520 patients (6.9%). Demographic and clinical characteristics of patients according to development of diabetes are compared in Table 1. As previously reported [16], patients who developed diabetes were more likely to have had prior anti-hypertensive treatment, less likely to have been randomized to losartan-based therapy, more obese, had higher serum glucose, creatinine and uric acid levels, and lower total cholesterol levels.

Blood pressure and electrocardiographic left ventricular hypertrophy measurements at baseline and changes in these measurements between baseline and last in-study determination or last measurement prior to development of diabetes are shown in Table 2. Patients who developed diabetes had higher baseline systolic pressures, greater decreases in systolic and diastolic pressure, more severe baseline left ventricular hypertrophy by Cornell product and less severe baseline left ventricular hypertrophy by Sokolow-Lyon voltage, but had similar changes in diastolic pressure and both electrocardiographic left ventricular hypertrophy criteria compared with patients without diabetes.

HDL and non-HDL cholesterol levels at baseline and at each year of treatment in relation to the development of diabetes are shown in Table 3. Baseline and yearly in-treatment HDL levels were significantly lower in patients who developed diabetes. In contrast, non-HDL cholesterol

Table 2 Baseline and change from baseline to last in-study measurement of blood pressure and electrocardiographic left ventricular hypertrophy in relation to development of new diabetes mellitus

Variables	No diabetes (n = 6965)	New diabetes (n = 520)	P-value
Baseline measurements			
Systolic blood pressure (mmHg)	174 ± 14	177 ± 14	< 0.001
Diastolic blood pressure (mmHg)	98 ± 9	99 ± 9	0.090
Cornell voltage-duration product (mm × ms)	2805 ± 1038	2980 ± 1146	< 0.001
Sokolow-Lyon voltage (mm)	30.3 ± 10.4	29.1 ± 10.2	0.015
Change from baseline to last measurement*			
Systolic blood pressure (mmHg)	–29 ± 20	–32 ± 19	0.010
Diastolic blood pressure (mmHg)	–17 ± 10	–19 ± 10	< 0.001
Cornell voltage-duration product (mm × ms)	–210 ± 849	–223 ± 908	0.747
Sokolow-Lyon voltage (mm)	–3.9 ± 7.3	–4.4 ± 7.3	0.147

*Change from baseline to last in-study measurement or last measurement prior to diagnosis of new diabetes.

Table 1 Baseline demographic and clinical characteristics in relation to development of new diabetes mellitus

Variables	No diabetes (n = 6965)	New diabetes (n = 520)	P-value
Age (years)	66.9 ± 7.0	66.5 ± 6.8	0.166
Sex (% female)	54.3	51.3	0.190
Race (% black)	5.0	5.6	0.559
Randomized to losartan (%)	50.9	42.3	< 0.001
History of ischaemic heart disease (%)	14.8	14.8	0.990
History of myocardial infarction (%)	5.8	6.2	0.730
History of heart failure (%)	1.5	1.9	0.389
History of stroke (%)	3.8	4.4	0.479
History of peripheral vascular disease (%)	5.4	6.2	0.464
Current smokers (%)	16.8	16.2	0.683
Prior anti-hypertensive treatment (%)	70.4	80.2	< 0.001
BMI (kg/m^2)	27.5 ± 4.5	30.5 ± 5.2	< 0.001
Serum glucose (mmol/l)	5.41 ± 0.95	6.50 ± 1.60	< 0.001
Serum creatinine (μmol/l)	85.8 ± 19.9	89.3 ± 20.5	< 0.001
Total cholesterol (mmol/l)	6.09 ± 1.11	5.91 ± 1.16	< 0.001
Non-HDL cholesterol (mmol/l)	4.55 ± 1.10	4.60 ± 1.14	0.304
Uric acid (μmol/l)	328 ± 78	359 ± 73	< 0.001
Urine albumin:creatinine ratio (mg/mM)	5.8 ± 28.1	7.0 ± 20.4	0.359

Table 3 Baseline and in-treatment HDL and non-HDL cholesterol levels in relation to development of new diabetes mellitus

Variables	No diabetes (n = 6965)	New diabetes (n = 520)	P-value
HDL cholesterol (mmol/l)*			
Baseline	1.54 ± 0.44	1.30 ± 0.37	< 0.001
Year 1	1.38 ± 0.40	1.18 ± 0.32	< 0.001
Year 2	1.37 ± 0.37	1.18 ± 0.32	< 0.001
Year 3	1.43 ± 0.36	1.23 ± 0.30	< 0.001
Year 4	1.47 ± 0.37	1.26 ± 0.33	< 0.001
Year 5	1.49 ± 0.37	1.27 ± 0.30	< 0.001
Non-HDL cholesterol (mmol/l)†			
Baseline	4.55 ± 1.10	4.60 ± 1.14	0.304
Year 1	4.68 ± 1.12	4.70 ± 1.12	0.671
Year 2	4.70 ± 1.10	4.71 ± 1.12	0.783
Year 3	4.51 ± 1.05	4.44 ± 1.08	0.181
Year 4	4.34 ± 1.01	4.29 ± 1.04	0.321
Year 5	4.33 ± 1.04	4.12 ± 1.00	< 0.001

*P < 0.001 for no diabetes vs. new diabetes by repeated-measures ANOVA.
†P = 0.353 for no diabetes vs. new diabetes by repeated-measures ANOVA.

Table 4 Baseline and in-treatment hydrochlorothiazide and statin use in relation to development of new diabetes mellitus

Variables	No diabetes (n = 6965)	New diabetes (n = 520)	P-value
Hydrochlorothiazide use			
Baseline (%)	0.9	1.0	0.825
Year 1 (%)	67.0	78.1	< 0.001
Year 2 (%)	66.8	78.1	< 0.001
Year 3 (%)	66.3	76.0	< 0.001
Year 4 (%)	65.7	73.5	< 0.001
Year 5 (%)	52.7	58.1	0.021
Statin use			
Baseline (%)	7.1	8.8	0.157
Year 1 (%)	5.7	7.5	0.101
Year-2 (%)	22.2	31.9	< 0.001
Year 3 (%)	21.4	31.5	< 0.001
Year 4 (%)	20.5	31.2	< 0.001
Year 5 (%)	19.6	30.0	< 0.001

levels at baseline and at each of the first 4 years of the study did not differ between patients who did and did not develop diabetes, but were significantly lower at year 5 in patients who developed diabetes.

Because both hydrochlorothiazide and statin therapy have been implicated in the development of diabetes [18,19], the relationship of baseline and in-treatment hydrochlorothiazide and statin use to development of diabetes are examined in Table 4. By protocol design [23], use of hydrochlorothiazide was uncommon at baseline and increased substantially by year 1. Hydrochlorothiazide therapy at baseline was similar in patients with and without new-onset diabetes, but became significantly more common at each in-treatment year in patients who developed diabetes. Statin therapy was relatively uncommon and similar in patients with and without new diabetes at baseline and year 1 of the study, but was significantly more common in patients with new diabetes from year 2 to year 5 of the study.

The relationship of new-onset diabetes to quartiles of HDL cholesterol levels at baseline and during treatment is shown in Table 5 and Fig. 1. In univariate Cox analyses, compared with the highest quartile of HDL levels (HDL > 1.78 mmol/l), baseline and in-treatment HDL in the lowest quartile (< 1.21 mmol/l) identified patients with > 5-fold and > 9-fold higher risk of new diabetes, respectively; patients with baseline or in-treatment HDL in the 2nd and 3rd quartiles had intermediate increased risk of diabetes. In multivariable Cox analyses, the lowest quartile of in-treatment HDL remained associated with a nearly 9-fold increased risk of new diabetes, whereas the adjusted risk of new diabetes associated with a baseline HDL < 1.21 mmol/l was significantly attenuated. The full multivariable Cox model for prediction of new diabetes by quartiles of in-treatment HDL is shown in Table 6. Of note in a parallel multivariable Cox model adjusting for the same variables, lower in-treatment HDL treated as a continuous variable remained strongly associated with new-onset diabetes, with each 1 SD of the baseline mean lower in-treatment HDL (0.44 mmol/l) associated with a greater than 3-fold higher adjusted risk of new diabetes (hazard ratio 3.46, 95% CI 2.79–4.26, P < 0.001). The association between lower serum HDL and an increased risk of new diabetes was statistically similar in all subsets of the population (Table 7).

Discussion

These findings demonstrate that lower in-treatment levels of HDL during anti-hypertensive therapy are more strongly associated with increased risk of new-onset diabetes than baseline HDL levels. The greater predictive value of low in-treatment HDL persists and is not attenuated in multivariable models that adjust for other known and potential risk factors for diabetes, the possible impact of concurrent treatment with hydrochlorothiazide and statins [18,19], and the previously demonstrated impacts of losartan vs. atenolol treatment, previous anti-hypertensive therapy and in-treatment electrocardiographic left ventricular hypertrophy on diabetes risk is this population [16,20]. These findings support the value of serial measurement of HDL to better estimate diabetes risk in hypertensive patients.

Low HDL levels have been related to insulin resistance and to increased fasting insulin levels [8,9]. More importantly,

Table 5 Univariate and multivariable Cox regression analyses to assess the relation of new-onset diabetes mellitus to quartiles of baseline and in-treatment HDL cholesterol levels

Analysis	Hazard ratios (95% CI) Quartile 1 HDL < 1.22	Quartile 2 HDL 1.22–1.47	Quartile 3 HDL 1.48–1.78	Quartile 4 HDL > 1.78
Univariate Cox model				
Baseline HDL	5.1 (3.8–6.9)	2.8 (2.0–3.8)	2.1 (1.5–2.9)	1
In-treatment HDL	9.1 (5.9–13.8)	3.7 (2.4–5.8)	2.0 (1.3–3.3)	1
Multivariate Cox model*				
Baseline HDL	3.9 (2.8–5.4)	2.4 (1.7–3.4)	1.9 (1.3–2.7)	1
In-treatment HDL†	8.7 (5.0–15.2)	3.6 (2.2–6.1)	2.0 (1.2–3.4)	1

*Adjusted for randomized treatment with losartan vs. atenolol, age, sex, race, prior anti-hypertensive therapy, baseline uric acid, serum creatinine and glucose entered as standard covariates, and for in-treatment non-HDL cholesterol, Cornell product left ventricular hypertrophy, diastolic and systolic pressure, BMI, hydrochlorothiazide and statin use treated as time-varying covariates.
†Also adjusted for baseline HDL cholesterol level.

Table 6 Full multivariable Cox regression model relating new-onset diabetes mellitus to quartiles of in-treatment HDL cholesterol levels and other predictor variables*

Variables	Hazard ratio	95% CI	*P*-value
In-treatment HDL cholesterol quartile			
Quartile 1 (< 1.22 mmol/l)	8.7	5.0–15.2	< 0.001
Quartile 2 (1.22–1.47 mmol/l)	3.6	2.2–6.1	< 0.001
Quartile 3 (1.48–1.78 mmol/l)	2.0	1.2–3.4	0.005
Quartile 4 (> 1.78 mmol/l)	1 (reference group)	—	—
Age (per 7.0 years)	1.11	1.01–1.22	0.040
Sex (female)	1.65	1.33–2.04	< 0.001
Race (black)	0.93	0.62–1.40	0.739
Prior anti-hypertensive treatment	1.24	0.99–1.54	0.060
Randomized treatment with losartan	0.77	0.64–0.91	0.003
Baseline HDL cholesterol (per 0.44 mmol/l)	1.18	0.82–1.71	0.381
Baseline serum glucose (per 1.05 mmol/l)	1.70	1.61–1.78	< 0.001
Baseline serum creatinine (per 19.9 μmol/l)	0.96	0.85–1.06	0.388
Baseline uric acid (per 78 μmol/l)	1.26	1.17–1.37	< 0.001
In-treatment non-HDL cholesterol (per 1.10 mmol/l)	0.65	0.59–0.71	< 0.001
In-treatment BMI (per 4.6 kg/m^2)	1.40	1.30–1.51	< 0.001
In-treatment systolic blood pressure (per 14 mmHg)	1.27	1.17–1.36	< 0.001
In-treatment diastolic blood pressure (per 9 mmHg)	1.39	1.26–1.52	< 0.001
In-treatment Cornell product left ventricular hypertrophy	1.07	0.89–1.28	0.475
In-treatment statin use	1.04	0.74–1.29	0.708
In-treatment hydrochlorothiazide use	1.36	1.12–1.66	0.002

*Hazard ratios for continuous variables calculated for 1 SD of the baseline mean value.

low HDL levels at baseline measurement predict low insulin-sensitivity index values 13 years later [9], increased insulin resistance at 8-year follow-up [10] and subsequent development of diabetes [11–16]. In the Framingham Offspring study [11,12], low baseline HDL was associated with a nearly 2.2-fold higher risk of diabetes after adjustment for age, sex, BMI, fasting glucose and triglyceride levels, waist circumference and a measure of insulin resistance at baseline. Lower baseline HDL was also associated with an increased risk of new diabetes in population-based studies of Pima Indians [13,14] and in 830 pre-diabetic subjects enrolled in the Insulin Resistance Atherosclerosis Study (IRAS) [15]. Finally, in an earlier analysis of findings from the LIFE study, in which only baseline predictor variables were included [16], each mmol/l decrease in baseline HDL was associated with a nearly 2.8-fold increased risk of new diabetes after adjusting for randomized and prior anti-hypertensive treatment, baseline glucose, BMI and systolic pressure.

The current study extends these previous findings to a large population of hypertensive patients, demonstrating that HDL at baseline is a strong predictor of new-onset diabetes after adjusting for numerous other possible diabetes risk factors. More importantly, the current study demonstrates that in-treatment HDL, treated as a time-varying covariate in Cox analyses, has substantially better predictive power than baseline HDL for the development of new diabetes. Persistence or development of an HDL < 1.21 mmol/l (the lowest quartile at LIFE study baseline) during treatment was associated with a nearly 9-fold increased adjusted risk of new diabetes developing during nearly 5 years' mean follow-up, compared with a 3.9-fold higher risk associated with baseline values in the same quartile after similar multivariable adjustment. Moreover, low

Table 7 Multivariable Cox analyses to assess the predictive value of in-treatment HDL for new-onset diabetes in relevant subgroups of the study population

Subgroup	New diabetes (*n*)	Hazard ratio*	95% CI	*P*-value for interaction
Sex				
Female (n = 4050)	267	3.27	2.35–4.55	0.354
Male (n = 3435)	253	4.22	3.18–5.59	
Age				
< 65 years (n = 2881)	204	3.51	2.51–4.90	0.145
≥ 65 years (n = 4604)	316	3.98	3.01–5.26	
Prior anti-hypertensive treatment				
No (n = 2167)	103	2.79	1.74–4.49	0.459
Yes (n = 4901)	417	4.08	3.20–5.16	
Randomized treatment				
Atenolol (n = 3721)	300	2.98	2.23–3.99	0.062
Losartan (n = 3764)	220	4.99	3.64–6.76	
Treatment with a statin at any time during study				
No (n = 5740)	351	3.51	2.71–4.55	0.417
Yes (n = 1745)	169	4.31	2.93–6.35	
Median baseline serum glucose				
≤ 5.30 mmol/l (n = 3802)	91	3.70	2.29–6.01	0.442
> 5.30 mmol/l (n = 3683)	429	3.26	2.58–4.12	
Median baseline BMI				
≤ 27.14 kg/m^2 (n = 3727)	135	2.92	1.97–4.32	0.898
> 27.14 kg/m^2 (n = 3758)	385	4.09	3.16–5.26	
Median of the average systolic blood pressure during treatment				
< 147 mmHg (n = 3825)	250	3.65	2.67–4.98	0.983
≥ 147 mmHg (n = 3660)	270	3.95	2.94–5.36	
Median decrease in Cornell product left ventricular hypertrophy during treatment				
≤ 223 mm × ms (n = 3665)	251	3.71	2.71–5.07	0.948
> 223 mm × ms (n = 3820)	269	3.74	2.79–5.07	
Median decrease in Sokolow-Lyon voltage left ventricular hypertrophy during treatment				
≤ 3.5 mm (n = 3840)	252	4.30	3.14–5.86	0.810
> 3.5 mm (n = 3645)	268	3.34	2.50–4.49	

*Hazard ratio for each 1 SD of mean of baseline HDL (0.44 mmol/l) with lower HDL entered as a continuous variable adjusted for the same covariates as in Table 5.

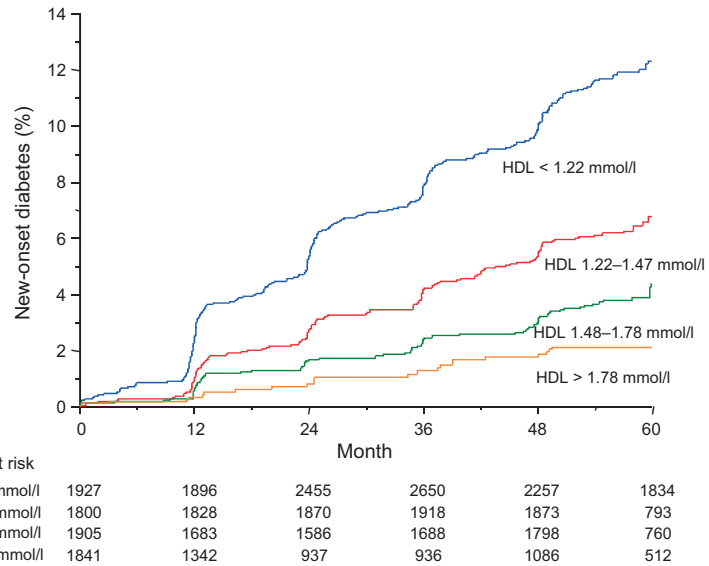

FIGURE 1 Survival curves illustrating the rate of new-onset diabetes mellitus in relation to quartiles of in-treatment HDL cholesterol levels.

in-treatment HDL remained associated with a markedly increased diabetes risk when HDL was considered as a continuous variable. Importantly, the predictive value of low in-treatment HDL persisted after adjusting for the previously demonstrated decreased risk associated with randomization to losartan and increased risks associated with prior anti-hyper-

tensive treatment [16], the slightly increased risk reported for statin therapy [19], the potential risk associated with changing levels of BMI and use of hydrochlorothiazide [18] during the study, baseline serum glucose levels and other potential risk factors, and the previously demonstrated decreased risk of diabetes associated with in-treatment resolution or absence of electrocardiographic left ventricular hypertrophy by Cornell product criteria [20].

The predictive value of in-treatment HDL for new-onset diabetes was similar in all subgroups examined (Table 7). Particularly of note, lower in-treatment HDL had statistically similar predictive value in groups defined by prior antihypertensive treatment, randomized treatment allocation to either losartan or atenolol, and by median baseline values of BMI and serum glucose, despite the markedly different incidence of diabetes in these subgroups. In addition, there was no significant interaction of in-treatment HDL with statin use in this study, suggesting that neither the potential impact of statins on HDL levels nor the possible relationship of incidence diabetes to statin use [19] significantly contributes to the impact of low HDL on diabetes risk.

Cell-based and clinical studies suggest a number of possible mechanisms via which HDL may play a role in plasma glucose control and development of diabetes. In isolated human and rat pancreatic β-cells [26], HDL appeared to counter the negative effects of oxidized LDL on insulin secretion. Moreover, incubation of cultured murine pancreatic β-cells with HDL significantly increased acute-phase, glucose-stimulated insulin and reversed the blunting of this effect by oxidized LDL [27], with the absence of any changes in insulin gene or protein expression, suggesting that HDL may be directly stimulating insulin secretion. Among 13 patients with Type 2 diabetes, a 4-h infusion of reconstituted HDL produced a greater fall in plasma glucose and greater increases in plasma insulin and the homeostasis model assessment of β-cell function index than matching placebo [27]. In addition, acetyl-CoA carboxylase β phosphorylation in skeletal muscle biopsies was increased by 70% after reconstituted HDL infusion and HDL increased glucose uptake by 177% in primary human skeletal muscle cell cultures established from patients with Type 2 diabetes, suggesting activation of the AMP-mediated protein kinase pathway [27]. These experiments in patients with Type 2 diabetes provide a putative framework for how low HDL could promote the development of diabetes via worsening glycaemic control by decreasing plasma insulin and attenuating skeletal muscle glucose uptake and suggest that low HDL cholesterol in patients who develop diabetes may be a marker of hepatic insulin resistance.

Study limitations

Several limitations of our study warrant review. First, inclusion criteria of hypertension and electrocardiographic left ventricular hypertrophy by either Cornell product or Sokolow-Lyon voltage increased the risk of new-onset diabetes in the population; as a consequence, our findings may not be representative of other lower-risk populations. Second, the absence of triglyceride measurements in the LIFE study does not allow determination whether in-treatment HDL levels would remain predictive of diabetes after adjusting for the demonstrated predictive value of baseline and changes in triglyceride levels over time [28]. Third, the absence of fasting insulin levels or more sophisticated measures of insulin resistance makes it impossible to determine from the current analyses whether the association of low HDL levels with incident diabetes is a direct one or rather a reflection of the association of low HDL with increased hepatic insulin resistance [26,27].

Implications

First, these findings suggest that tracking HDL levels over time may provide important insights into the risk of developing diabetes. Second, these findings raise the possibility that therapies aimed at raising HDL levels could reduce the risk of diabetes in high-risk populations with low HDLs. This possibility is supported by the recent post hoc analysis of the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, which compared the effect of the combination of torcetrapib, a cholesteryl ester transfer protein inhibitor, and atorvastatin with atorvastatin alone on glycaemic control in a subset of 6661 patients with diabetes [29]. Patients on the combination of torecetrapib and atorvastatin had significantly lower 3-month plasma glucose levels and insulin levels, lower insulin resistance and lower 6-month HbA_{1c} levels [29]. Although ILLUMINATE was terminated early because of an excess of deaths and cardiovascular events in the torcetrapib arm of the study [30], there is increasing evidence that this increase in harm may have been attributable to off-target effects of torcetrapib that produce an increase in blood pressure, serum sodium and bicarbonate, and a decrease in serum potassium [30]. However, as noted above, the association of low HDL levels with incident diabetes could also be explained by increased insulin resistance. As a consequence, additional studies which examine direct markers of insulin resistance, and further study of both the safety and efficacy of other cholesteryl ester transfer protein inhibitors that do not appear to share these off-target effects will be required in order to assess whether treatment to increase HDL levels may be of clinical value in preventing the development of diabetes or whether low HDL levels are solely a marker of increased insulin resistance.

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Competing interests

PMO has received grant support from Merck and Co. Inc., serves on a medical advisory board for GE Medical Systems and as a consultant to Novartis. DAH is employed by Merck and Co. Inc. SEK has served as a consultant to Bayer, Boehringer-Ingelheim, and Takeda, received grants from the Norwegian Government and Norwegian Council on Cardiovascular Diseases, received payments for lectures from AstraZeneca, Menarini and Sanofi Aventis, and received royalties from Gyldendal. LHL has received honoraria and travel support from Merck and Co. Inc. BD has received grant support, honoraria, support for travel, participation in planning committees and administrative activities from Merck and Co. Inc., has served on the board of Mintage Scientific, has served as a consultant to and received honoraria from Merck and Co. Inc, Novartis, Boehringer-Ingelheim, Daiichi Sankyo and Pfizer, and owns stock or stock options in Mintage Scientific. RBD has received grant support, consulting fees, honoraria and travel support from Merck and Co. Inc. and serves on a medical advisory boards for Novartis and GE Medical Systems. BPW has nothing to declare.

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