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Clinical Research Article

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Low-Density Lipoprotein Cholesterol Is Associated With Insulin Secretion

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Abbreviations: AUC, area under the curve; BMI, body mass index; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; DI, disposition index; HDL, high-density lipoprotein; HMG-CoA, hydroxy-3-methylglutaryl-CoA; IGI, insulinogenic index; Matsuda ISI, insulin sensitivity estimate as proposed by Matsuda and DeFronzo; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; OGTT, oral glucose tolerance test; tSNE, *t*-distributed stochastic neighbor embedding

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Abstract

Context: Pharmacological lowering of low-density lipoprotein (LDL) cholesterol potently reduces cardiovascular risk while concurrently increasing type 2 diabetes risk.

Objective: The aim of this study was to investigate the relationship between LDL cholesterol concentrations and insulin secretion and glucagon levels.

Methods: A total of 3039 individuals without cholesterol-lowering therapy, but with increased risk for diabetes, underwent routine blood tests and a 5-point oral glucose tolerance test (OGTT). Glucagon concentrations, insulin secretion, and insulin clearance indices were derived from the OGTT.

Results: There was no association between LDL cholesterol and fasting glucagon ($P = .7$, $\beta = -.01$) or post–glucose load glucagon levels ($P = .7$, $\beta = -.07$), but we detected significant positive associations of LDL cholesterol and C-peptide–based indices of insulin secretion (area under the curve $[AUC]_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$: $P < .001$, $\beta = .06$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P < .001$, $\beta = -.08$). In contrast, we found a negative association of insulin-based insulin secretion indices with LDL concentrations (insulinogenic index: $P = .01$, $\beta = -.04$; disposition index: $P < .001$, $\beta = -.06$). LDL cholesterol levels, however, were positively associated with insulin clearance assessed from C-peptide and insulin

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concentrations, both in the fasting state and post–glucose load ($P < .001$, $\beta = .09$ and $P < .001$, $\beta = .06$, respectively).

Conclusion: As C-peptide based indices reflect insulin secretion independent of hepatic clearance, our results indicate lower insulin secretion in case of lesser LDL cholesterol. This could explain deteriorating glycemic control in response to cholesterol-lowering drugs.

Key Words: LDL cholesterol, insulin secretion, type 2 diabetes, glucagon, insulin clearance

Dyslipidemia is characterized by low levels of high-density lipoproteins (HDLs), hypertriglyceridemia, high total and low-density lipoprotein (LDL) cholesterol concentrations, as well as an increased proportion of small dense lipoproteins. Changes in lipoprotein particles and their concentrations, especially increased levels of proatherogenic LDL particles, play an important role in the development of cardiovascular diseases. It is well established that statin treatment is very effective in lowering LDL cholesterol levels and therefore in preventing cardiovascular events (1-3).

Statins inhibit hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), the key enzyme for cholesterol synthesis in the liver (4). Despite the beneficial effects on the cardiovascular system, statin therapy is unfortunately linked to an increased risk for type 2 diabetes, especially in individuals prone to the disease (5, 6). Recently, data from several meta-analyses of randomized, controlled trials with statins and population-based studies of patients taking statins were summarized. In these studies, incidence rates for new-onset diabetes mellitus range from 28% to 43% (7). Another review reported a range of 9% to 12% in 2 meta-analyses of statin trials and of 18% to 99% in 5 population-based studies (8). Swerdlow et al tested whether the observed effects are a consequence of the mode of action of statins—the inhibition of HMG-CoA reductase (9). Single-nucleotide variations (formerly single-nucleotide polymorphisms) in the HMG-CoA reductase gene were therefore used as proxies for its inhibition by statins and were indeed associated with a higher risk for type 2 diabetes (9). This associative study, however, cannot differentiate between the effects of lower LDL and the consequences of altered enzyme activity.

Other genetic studies detected loss-of-function mutations in *PCSK9*, the gene encoding proprotein convertase subtilisin/kexin type 9. These variants are associated with lower LDL cholesterol levels and protect against coronary heart disease (10) but were also linked to higher fasting glucose concentrations and an increased risk of type 2 diabetes in a mendelian randomization study (11). Accordingly, short-term *PCSK9* inhibitor therapy was found to be related to a significant elevation of plasma glucose levels and glycated hemoglobin (12). Finally, cross-sectional data from the Netherlands demonstrate that patients with familial hypercholesterolemia show a significantly higher prevalence of type 2 diabetes than their unaffected relatives, with variability by mutation type (13).

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion from pancreatic β cells. Insulin resistance alone is insufficient to cause type 2 diabetes, as long as the β cell remains able to compensate for the increased demand for insulin. Once this compensatory mechanism reaches its physiological limits, glucose levels increase and patients progress toward overt type 2 diabetes.

Mechanistic studies suggest an impact of LDL cholesterol on the structure and function of pancreatic islets (14-16); however, this has not yet been comprehensively studied in humans. LDL cholesterol and diabetes risk might either be directly linked at the molecular level, for example, in the pancreatic islets, or this might be coincidence in a metabolic state that goes along with both lower LDL cholesterol and higher diabetes risk.

We therefore aimed to investigate the association between LDL cholesterol concentrations and the key pathogenic mechanism of type 2 diabetes, insulin secretion, in a cohort with increased risk for the disease.

Materials and Methods

Participants

Data from 3039 White individuals from the southern part of Germany who had participated in the Tübingen Family Study were analyzed. The individuals participated in different studies on the pathogenesis of type 2 diabetes between 1993 and 2017. All participants underwent metabolic characterization including a detailed medical history and physical examination, routine blood tests (fasting state) and a 5-point oral glucose tolerance test (OGTT) (17). Selection of the present study cohort was based on the absence of treatment with cholesterol-lowering drugs and the availability of complete clinical data. The participant characteristics are presented in Table 1.

Table 1. Characteristics of the study participants

Characteristics	
No.	3039
Sex, F/M	2001/1038
Age, y	42 ± 0.25
BMI	31.2 ± 0.2
WHR[a]	0.88 ± 0.004
Fasting blood glucose, mmol/L	5.31 ± 0.01
2-h blood glucose, mmol/L	6.69 ± 0.04
Fasting glucagon, pg/mL[b]	69.23 ± 1.06
$AUC_{Glucagon}$, pg/mL[c]	115.18 ± 2.03
HbA_{1c}, %[d]	5.5 ± 0.01
Glucose tolerance, NGR/ prediabetes/diabetes	1833/1055/151
Total cholesterol, mg/dL[e]	194.64 ± 0.70
LDL cholesterol, mg/dL[f]	119.20 ± 0.61
HDL cholesterol, mg/dL[g]	53.74 ± 0.26
Triglycerides, mg/dL[h]	124.49 ± 2.14
Liver fat content, %[i]	6.8 ± 0.2
Insulin sensitivity, Matsuda ISI[j]	12.05 ± 0.16
$IGI_{0\text{-}30min}$[k]	190.84 ± 3.96
$AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$[l]	190.09 ± 1.37
$AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$[m]	299.38 ± 1.84
Disposition index[n]	1969 ± 70
Fasting insulin clearance, $C\text{-}Pep_{0min}/Ins_{0min}$[o]	9.16 ± 0.10
Insulin clearance during OGTT, $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Insulin(0\text{-}120min)}$[p]	4.80 ± 0.04

Data are means ± SEM.

Abbreviations: AUC, area under the curve; C-Pep, C-peptide; F, female; HDL, high-density lipoprotein; IGI, insulinogenic index; ISI, insulin sensitivity index; LDL, low-density lipoprotein; M, male; NGR, normal glucose regulation; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

Data were available for the following numbers of individuals: [a]N = 3002; [b]N = 595; [c]N = 385; [d]N = 2913; [e]N = 3038; [f]N = 3012; [g]N = 3013; [h]N = 3037; [i]N = 998; [j]N = 2971; [k]N = 2982; [l]N = 2963; [m]N = 2945; [n]N = 2959; [o]N = 2968; and [p]N = 2919.

Oral Glucose Tolerance Test

A 5-point 75-g OGTT was performed after an overnight fasting period of at least 8 hours, and venous blood samples were drawn at time points 0, 30, 60, 90, and 120 minutes for the determination of plasma glucose, insulin, and C-peptide. A total of 1833 participants showed normal glucose regulation, 1055 prediabetes, and 151 individuals fulfilled the diagnostic criteria for diabetes. In a subset of 595 participants, fasting glucagon was measured; in 387 participants glucagon was assessed at all time points.

Laboratory Measurements

Plasma glucose was measured using a YSI 2300 glucose analyzer (YSI). Serum insulin and C-peptide were determined by immunoassay with the ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics). Glucagon was measured as previously described for the Tübingen Family Study cohort (18). Total, HDL, LDL cholesterol, and triglycerides were measured on the ADVIA XPT Clinical Chemistry System (Siemens Healthcare Diagnostics). Glycated hemoglobin measurements were performed in the central laboratory of the University Hospital of Tübingen using the Tosoh A1c analyzer HLC-723G8 (Tosoh Bioscience GmbH).

Calculations

Insulin secretion indices were derived from the OGTT with insulin and C-peptide concentrations given in picomole per liter (pmol/L), and glucose concentration given in millimole per liter (mmol/L). Areas under the curve (AUCs) of insulin, C-peptide, glucose, and glucagon concentrations during the entire 120 minutes of the OGTT were calculated according to the trapezoid method as $0.5 \times (0.5 \times c_{0min} + c_{30min} + c_{60min} + c_{90min} + 0.5 \times c_{120min})$ with c equal to concentration. $AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$ was calculated as $(C\text{-}Pep_{0min} + C\text{-}Pep_{30min})/(Glc_{0min} + Glc_{30min})$ (19). Insulinogenic index ($IGI_{0\text{-}30min}$) was calculated as $(Ins_{30min} - Ins_{0min})/(Glc_{30min} - Glc_{0min})$ (19). Insulin sensitivity derived from the OGTT was estimated as proposed by Matsuda and DeFronzo (Matsuda ISI) (20) as $10\,000/\sqrt{(Glc_{0min} \times Ins_{0min} \times Glc_{mean} \times Ins_{mean})}$. Disposition index (DI) was calculated as IGI × ISI (19). Fasting insulin clearance was calculated as $C\text{-}Pep_{0min}/Ins_{0min}$ with $C\text{-}Pep_{0min}$ equal to fasting C-peptide; insulin clearance during the OGTT was calculated as $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Insulin(0\text{-}120min)}$.

Single-Cell Data

Recently published single cell expression profiles (21) were analyzed for expression of *LDLR*. A *t*-distributed stochastic neighbor embedding (tSNE) plot from 2544 pancreatic single-cell data sets was generated. For this, we used the top 250 expressed genes with a perplexity parameter of 30 and a θ of 0.4. Then, we assigned each cell to a probable cell type based on the highest expression of the cell type–specific marker genes. Next, we plotted the log-transformed LDL receptor (*LDLR*) expression on these cells.

Statistical Analyses

Prior to statistical evaluation, variables with skewed distribution were log-transformed. For multiple linear regression analysis, the standard least-squares method was applied and the variable of interest was used as dependent variable, LDL cholesterol concentration as

independent variable, and sex, age, body mass index (BMI), and Matsuda ISI (for all insulin and C-peptide–based secretion parameters except DI and glucagon secretion during the OGTT) as confounding variables. Data are presented as means ± SEM. For illustrative purposes we divided the cohort into LDL cholesterol quartiles and compared them by analysis of variance (Fig. 1). A *P* value less than or equal to .05 was considered statistically significant. The statistical software package JMP 13.0.0 (SAS Institute Inc) was used. Single-cell data were analyzed using R (version 3.6.1) and the Rtsne library (version 0.15).

Results

Low-Density Lipoprotein Receptor Expression in Human Pancreatic Islets

The basis for a possible effect of LDL cholesterol levels on human islets is the expression of LDLRs in pancreatic tissue. We therefore sought single-cell data from Enge et al. (21) and observed *LDLR* expression in all major endocrine cells types of the pancreas (Fig. 2).

Association Between Low-Density Lipoprotein Cholesterol Levels and Glucagon Concentrations

Because *LDLR* expression was present in α cells, we first analyzed possible links to glucagon secretion at fasting as well as during an OGTT. There was no association between LDL cholesterol and fasting glucagon levels ($P = .7$, $\beta = -.01$ adjusted for sex, age, and BMI, $P = .04$, $\beta = .09$ unadjusted, respectively). There was also no significant association between fasting LDL and glucagon secretion during the OGTT ($P = .2$, $\beta = -.07$ adjusted for sex, age, and BMI, $P = .4$, $\beta = .05$ unadjusted, respectively) (see Table 2). We detected no significant interaction with BMI (all $P \geq .5$).

Association between Low-Density Lipoprotein Cholesterol Levels and Insulin Secretion

We next analyzed the relation of LDL with insulin secretion from pancreatic β cells and detected statistically significant positive associations of LDL cholesterol and C-peptide–based indices of insulin secretion ($AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$: $P < .001$, $\beta = .06$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P < .001$, $\beta = .08$; see Fig. 1). This remained significant after adjustment of LDL cholesterol for HDL cholesterol ($AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$: $P < .001$, $\beta = .06$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P < .001$, $\beta = .08$) (see Table 2) or for triglyceride levels, though the association was only at the trend level for $AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$ ($P = .09$, $\beta = .03$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P = .005$, $\beta = .05$), respectively (22).

Adjusting LDL cholesterol for fasting blood glucose levels or the area under the blood glucose curve during the OGTT revealed comparable association (all $P \leq .002$) (22). Additionally we found a significant interaction between LDL cholesterol and glucose tolerance on insulin secretion ($AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$ and $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$, $P = .004$, $\beta = -1.28$ and $P = .03$, $\beta = -.97$, respectively). This interaction remained significant after adjusting for sex, age, BMI, and insulin sensitivity, at least for $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$ ($P = .02$, $\beta = -.79$). Therefore, we stratified our cohort by glucose tolerance. Whereas C-peptide–based insulin secretion was not linked with LDL cholesterol in individuals with prediabetes or treatment-naive diabetes (all $P \geq .2$), there was a significant association in those with normal glucose regulation $AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$: $P < .001$, $\beta = .09$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P < .001$, $\beta = .1$ adjusted for sex, age, BMI, and Matsuda ISI). No interaction with sex was present, however ($AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$: $P = .9$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P = .3$), indicating a comparable relation in both sexes. We also found no interaction with BMI ($AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$: $P = .8$; $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$: $P = .6$). In contrast to the C-peptide–based indices, we found a negative association between LDL concentrations and insulin secretion when analyzing insulin-based insulin secretion indices (insulinogenic index [ISI]: $P = .01$, $\beta = -.04$; DI: $P < .001$, $\beta = -.06$; see Fig. 2). This remained significant after adjustment for HDL cholesterol (ISI: $P = .01$, $\beta = .04$; DI: $P = .001$, $\beta = -.06$) (see Table 2). For the insulin-based ISIs, we detected no significant interaction with glucose tolerance, sex, or BMI (all $P \geq .1$).

Association Between Low-Density Lowering Cholesterol Levels and Insulin Clearance

After secretion into the portal vein, insulin undergoes hepatic extraction as well as peripheral clearance. In comparison, C-peptide is not extracted by the liver, but reaches the systemic circulation to a full extent before being cleared in the kidneys. Because insulin and C-peptide show different elimination kinetics, we next performed an analysis for estimates of fasting and post–load insulin clearance. LDL cholesterol levels were directly associated with fasting insulin clearance as well as clearance during the OGTT ($P < .001$, $\beta = .09$ and $P < .001$, $\beta = .06$, respectively) (see Table 2). This relationship did not interact with glucose

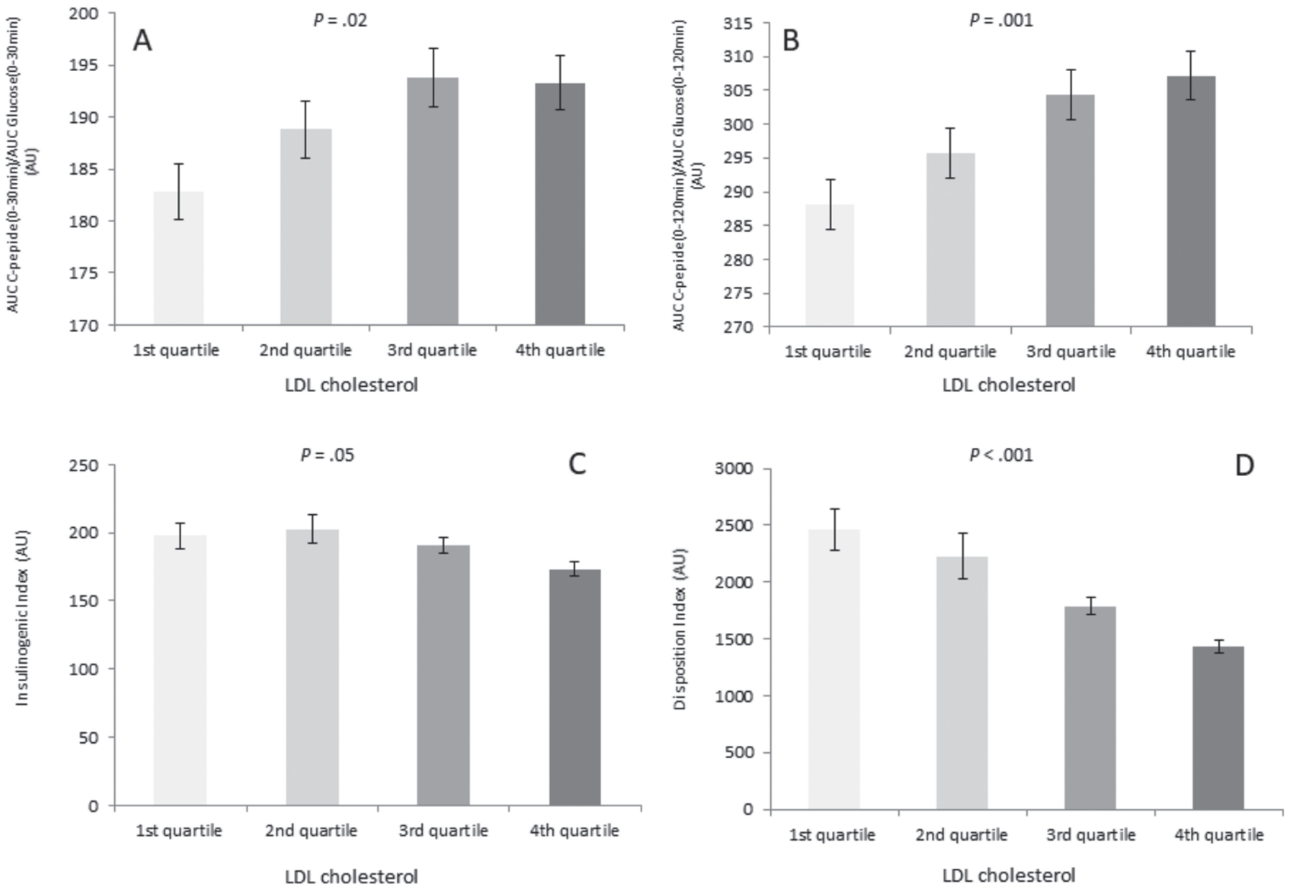

Figure 1. Low-density lipoprotein (LDL) cholesterol levels and insulin secretion. Displayed are C-peptide–based insulin secretion parameter A, area under the curve $(AUC)_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$; B, $AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$ and insulin-based secretion parameter; C, insulinogenic index; and D, disposition index after stratification of participants in LDL cholesterol quartiles. Bars represent means + SEM. *P* values are for comparison of LDL quartiles by analysis of variance for illustrative purpose, while *P* values from continuous models are reported in the text.

tolerance (fasting insulin clearance: $P = .06$; clearance during OGTT: $P = .9$) or BMI (fasting insulin clearance: $P = .8$; clearance during OGTT: $P = .96$).

Discussion

Lowering LDL cholesterol levels has beneficial effects on the cardiovascular system but is unfortunately linked to increased risk for type 2 diabetes. Based on previous experimental data (14-16), we hypothesized that LDL cholesterol is linked via its receptor to pancreatic islet function. Therefore, we now investigated the relevance for humans and addressed whether LDL cholesterol levels are linked to insulin secretion from pancreatic β cells or to α-cell function. Such a relationship could contribute to the widely observed association between LDL cholesterol–lowering and diabetes risk.

All cells in the islets of Langerhans express LDL receptors. Whereas glucagon levels were unrelated to LDL cholesterol, we observed significant associations with insulin secretion. Notably, C-peptide–based indices were positively but insulin-based ones were negatively associated with LDL cholesterol. This was due to an association of LDL cholesterol with insulin clearance.

In 1997 Grupping et al showed that human islet β cells isolated from donor pancreas express LDL-binding sites that fulfill the properties of LDLRs (23). In 2017 Enge et al. provided single-cell data from human pancreatic cells (21). Using this data set, we identified *LDLR* expression in all major endocrine cells. α Cells secrete glucagon, which works antagonistically to insulin. Additionally, postchallenge changes in glucagon contribute to glycemia after an OGTT and are therefore important in regulating postprandial glucose metabolism (18). Because the hormone affects blood glucose levels and single-cell data showed *LDLR* expression on α cells, we first investigated the association between LDL cholesterol levels and glucagon secretion. As we did not find links between LDL

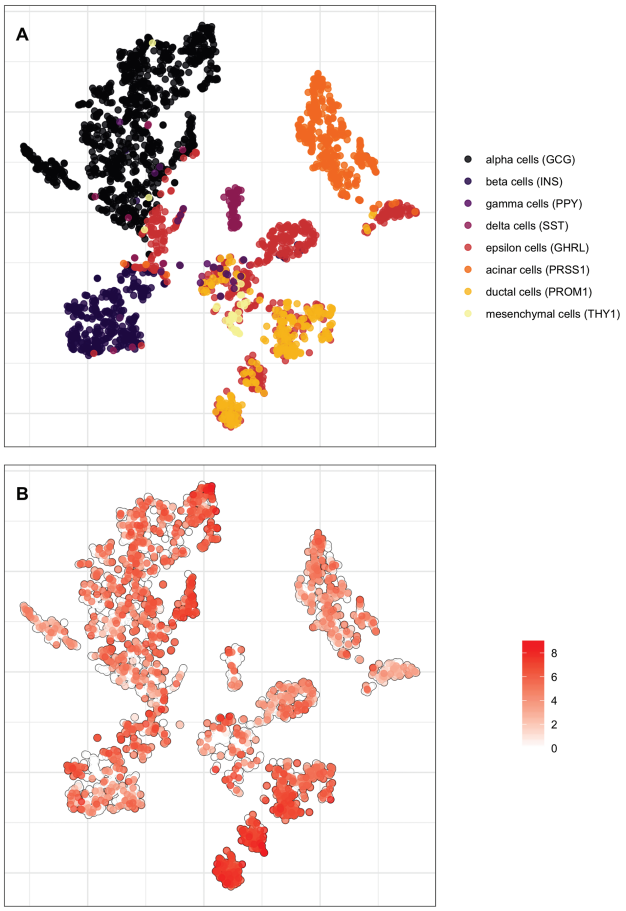

Figure 2. Low-density lipoprotein receptor (LDLR) expression across pancreatic cells. Recently published single-cell expression profiles (21) were analyzed for expression of *LDLR*. A *t*-distributed stochastic neighbor embedding (tSNE) plot from 2544 pancreatic single-cell data sets was generated. A, We assigned each cell to a probable cell type based on the highest expression of the cell type–specific marker genes indicated in the figure legend in parentheses. B, Next, we plotted the log-transformed *LDLR* expression on these cells with high expression indicated in dark red.

cholesterol and glucagon, this hormone is most likely not involved in increased diabetes risk in the case of LDL-lowering therapy. The function of LDLRs on α-cell biology, however, remains to be determined.

Insulin is synthesized and released from pancreatic β cells. When glucose levels rise, insulin and its cleavage fragment C-peptide are released in equimolar amounts. The ability to secret sufficient amounts of insulin is the most important component for physiological control of glucose concentrations in the body. We detected a significant, positive association between fasting LDL concentrations and C-peptide–based estimates for insulin secretion. As these indices reflect insulin secretion independent of hepatic clearance, they are the superior estimates of insulin secretion in our present setting. Our results indicate that higher LDL cholesterol levels could promote insulin secretion from pancreatic β cells. This link could explain the observations in various clinical studies in which lowering of LDL levels by statin therapy results in a deterioration of glucose control (5-8). Natali and colleagues detected no link between LDL cholesterol and insulin secretion (24). This study is not, however, entirely comparable to our present analysis because the sample size was smaller and individuals with higher cholesterol concentrations were excluded. Of note, potential LDL effects on insulin secretion appear to be affected by glucose control and seem to be blunted in prediabetes and diabetes. Thus, LDL-lowering therapy might raise diabetes risk especially in still-metabolically healthy individuals. In case of already impaired glycemia, other pathomechanisms might superimpose LDL effects on pancreatic β cells.

Recently, Klimentidis et al. identified 31 genetic loci that are associated with lower circulating LDL cholesterol and increased diabetes risk. The identified variants are linked with genes that affect de novo fatty acid synthesis, hepatic lipid uptake, and export and insulin action. Of note, 5 of the identified loci were associated with insulin secretion, including *SLC2A2* (25). This gene encodes the glucose transporter 2, which is essential for postload hepatic glucose uptake that will subsequently enter hepatic de novo lipogenesis. Further genetic loci like *C2CD4A/B*, *MICAL3*, *HNF1A-OASL*, and *GIPR* were previously described to be associated with insulin secretion (26-30) and have now been linked to circulating LDL cholesterol (25). Molecular mechanisms that mediate this association remain unknown.

While HDL cholesterol and triglycerides are also associated with insulin secretion, the link between LDL cholesterol and insulin secretion was independent of these potential confounders in our present analysis (22).

Although our data on LDL cholesterol and C-peptide–based analyses of insulin secretion are well in line with previous findings on diabetes risk, we unexpectedly detected an inverse correlation for the tested insulin-based estimates of insulin secretion (IGI and DI). Thus, our results at first glance appear controversial. As insulin and C-peptide undergo different elimination mechanisms with a high hepatic first-pass clearance of insulin (31), we next investigated possible links between LDL cholesterol and insulin clearance that could potentially explain these contrary results. Indeed, fasting and stimulated insulin clearance both were directly associated with LDL concentrations. Accordingly, with increasing LDL cholesterol concentrations, more insulin is extracted by the liver, explaining the inverse correlation of insulin-based and C-peptide–based estimates for insulin secretion. In humans, the liver is the most LDLR-abundant organ and accounts for more than 70% of the total LDL clearance from plasma (32). We therefore hypothesize that hepatic mechanisms that decrease circulating LDL cholesterol

Table 2. Association of low-density lipoprotein cholesterol levels with glucagon, insulin secretion, and insulin clearance

	*P*unadj	β ± SE	r^2	*P*adj, age, sex, BMI	β ± SE	r^2	*P*adj, age, sex, BMI, Matsuda ISI	β ± SE	r^2	*P*adj, age, sex, BMI, HDL	β ± SE	r^2	*P*adj, age, sex, BMI, Matsuda ISI, HDL	β ± SE	r^2
Association of LDL cholesterol with glucagon secretion															
Fasting glucagon levels	.04	0.07 ± 0.05	0.006	.73	–0.01 ± 0.06	0.16	.53	–0.02 ± 0.05	0.22	.63	–0.02 ± 0.05	0.16	.53	–0.02 ± 0.05	0.22
Glucagon secretion during OGTT	.38	0.05 ± 0.06	–0.001	.15	–0.07 ± 0.06	0.13	.16	–0.07 ± 0.06	0.13	.14	–0.08 ± 0.06	0.12	.17	–0.07 ± 0.06	0.13
Association of LDL cholesterol with C-peptide–based insulin secretion indices															
$AUC_{C\text{-}Peptide(0\text{-}30min)}/AUC_{Glucose(0\text{-}30min)}$	< .001	0.07 ± 0.02	0.005	< .001	0.08 ± 0.02	0.2	< .001	0.06 ± 0.02	0.28	< .001	0.07 ± 0.02	0.21	< .001	0.07 ± 0.02	0.28
$AUC_{C\text{-}Peptide(0\text{-}120min)}/AUC_{Glucose(0\text{-}120min)}$	< .001	0.11 ± 0.04	0.007	< .001	0.09 ± 0.02	0.08	< .001	0.08 ± 0.02	0.16	< .001	0.09 ± 0.02	0.09	.02	0.04 ± 0.03	0.16
Association of LDL cholesterol with insulin-based insulin secretion indices															
IGI	.16	–0.03 ± 0.05	<.001	.10	–0.03 ± 0.05	0.13	.01	–0.04 ± 0.05	0.20	.07	–0.03 ± 0.05	0.14	.01	–0.04 ± 0.05	0.20
DI	< .001	–0.178 ± 0.05	<.001	< .001	–0.06 ± 0.05	0.13	[a]	[a]	[a]	.001	–0.06 ± 0.05	0.14	[a]	[a]	[a]
Association of LDL cholesterol with insulin clearance indices															
Fasting insulin clearance	.42	–0.01 ± 0.03	<.001	< .001	–0.06 ± 0.03	0.2	< .001	0.09 ± 0.02	0.49	< .001	0.06 ± 0.03	0.2	< .001	0.09 ± 0.02	0.49
Insulin clearance during OGTT	< .001	–0.09 ± 0.03	0.007	.36	0.02 ± 0.02	0.26	< .001	0.06 ± 0.02	0.62	.22	0.02 ± 0.02	0.27	< .0001	0.0538 ± 0.0157	0.62

For multiple linear regression analysis, the standard least-squares method was applied with LDL cholesterol concentration as the independent variable. *P* values were given unadjusted (first column) or adjusted for covariates age, sex, and BMI.

Abbreviations: AUC, area under the curve; BMI, body mass index; DI, disposition index; HDL, high-density lipoprotein; IGI, insulinogenic index; ISI, insulin sensitivity index; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test.

[a] Matsuda ISI was added as an additional covariate for all parameters except DI (second and third column). The last 2 columns show *P* values after additional adjustment for HDL cholesterol concentrations. β are given ± SE.

levels concurrently enhance the liver's insulin clearance capacity. The carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), a transmembrane glycoprotein, could possibly link LDL cholesterol levels and insulin clearance. Animal research suggests a link between CEACAM1, a key component of hepatic insulin clearance, and lipid metabolism in the liver. However, the detailed molecular pathways and their potential link to LDL metabolism remain elusive (33, 34).

Among the limitations of this study is the use of estimates for insulin secretion and clearance. Both physiological processes are complex and influenced by several further components, and insulin secretion and clearance can be overestimated or underestimated. Furthermore, the results are based only on a cross-sectional analysis and did not apply the gold-standard measurements of insulin secretion, using well-established estimates from the OGTT. Further prospective analyses are necessary in an experimental setting, in which LDL cholesterol levels are actively decreased by cholesterol-lowering drugs. Additionally, only White individuals were included in this analysis, and we cannot rule out that ethnicity affects the described associations. Nevertheless, the observed effects are not likely to outweigh the benefits of LDL-lowering strategies in patients with increased LDL cholesterol levels. On the other hand, our data may suggest that benefits and risks in patients with reduced insulin secretory capacity should be carefully evaluated before commencing an LDL-lowering strategy.

Taken together, our present results demonstrate that all major endocrine cells show *LDLR* expression in the pancreas. While we did not find an association between LDL cholesterol levels and glucagon secretion from pancreatic α cells, a positive association was observed for LDL concentrations and C-peptide–based estimates for insulin secretion. Decreased insulin secretion in case of lower LDL cholesterol could underlie the observation of deteriorated glycemic control in response to LDL-lowering drugs. The observed inverse correlation of LDL cholesterol concentrations and insulin-based estimates for insulin secretion is a result of enhanced insulin clearance in case of higher LDL levels. CEACAM1 as a key component of hepatic insulin clearance could possibly link hepatic insulin clearance and LDL metabolism in the liver, for which molecular mechanisms are not identified so far. Accordingly, our data suggest that LDL cholesterol levels and insulin secretion and clearance might be directly linked. A detailed understanding of the underlying complex biology will aid the way to novel approaches to preserve β-cell function and prevent diabetes in patients who require LDL cholesterol–lowering therapy.

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