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Insulin sensitivity in type 2 diabetes is closely associated with LDL particle size

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Summary

Principles: Small dense LDLs have been found to be associated with type 2 diabetes (T2DM). This association has been observed in the context of decreased HDL cholesterol and increased triglycerides.

Methods: In the present study the relationship between LDL particle size and insulin sensitivity was assessed in 46 patients with T2DM (mean age 60 (11) years, HbA1c 7.6 (0.8) %). 75 g oral glucose tolerance testing was performed and composite insulin sensitivity index was calculated by the method of Matsuda and de Fronzo (ISI(comp)). Additional parameters included BMI, waist circumference, blood pressure, HDL cholesterol, triglycerides and LDL cholesterol. LDL particle size was measured by gradient gel electrophoresis.

Results: Log ISI(comp) correlated most strongly with LDL particle size (R = 0.61), less closely with HDL cholesterol (R = 0.48) and plasma triglycerides (R = –0.45) and not at all with LDL cholesterol (R = 0.001), as supported by multiple regression analyses where log ISI(com) was associated with LDL particle size (p = 0.004) and HDL cholesterol (p = 0.027) but not with triglycerides and LDL cholesterol.

Conclusion: Log ISI(comp) estimated by a formula using endogenous insulin levels is very closely associated with LDL particle size in patients with T2DM. Our data suggest that smaller LDL particle size reflects the impact of insulin resistance on lipoprotein metabolism more strictly than do the traditional lipid parameters.

Key words: type 2 diabetes; insulin sensitivity; LDL particle size; plasma triglycerides; HDL cholesterol

Introduction

The worldwide incidence of type 2 diabetes mellitus is increasing and accounts for 6–12% of total health care expenditure in industrialised countries [1]. Hypertriglyceridaemia, low HDL cholesterol and an increased fraction of small dense LDL particles are frequent lipid abnormalities in insulin resistance and type 2 diabetes mellitus [2–4], and are associated with increased cardiovascular mortality [5, 6]. An association of LDL particle size with the cluster of risk factors that characterise the insulin resistance syndrome has also been demonstrated [7] and there is strong evidence that small dense LDL particles can be added to the group of changes described as syndrome X, also termed the metabolic syndrome [3, 8, 9].

The aim of the present study was to investigate the association of LDL particle size and of traditional lipid parameters, particularly HDL cholesterol and triglycerides with insulin sensitivity, in a cohort of patients with type 2 diabetes mellitus.

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Methods

Patients were recruited from April 2001 to June 2002. Patients with type 2 diabetes treated by diet alone, metformin or repaglinide at the Division of Endocrinology, Diabetes and Clinical Nutrition and Medical Policlinic of Zurich University Hospital were asked in the routine medical consultation to participate in the study. Exclusion criteria were symptomatic CHD, autonomic neuropathy and treatment with insulin or insulin sensitising agents. 46 patients who agreed to participate in the study were enrolled and all of them were included in the

final analysis. Written informed consent was obtained and the study was approved by the local medical ethics committee.

All patients were interviewed during the visit. Information was collected on the duration of diabetes, hypertension, smoking habits and current treatment. Patients on sulfonylurea were changed to repaglinide two weeks before sampling. Overnight fasting blood samples were drawn while the subjects remained in a sitting position and blood was centrifuged within 30 min. Plasma for analysis for LDL particle size was frozen at –80 °C until further analysis. Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ALT, uric acid and hs-CRP were determined at Zurich University Hospital Institute for Clinical Chemistry. Total cholesterol, HDL cholesterol, triglycerides, ALT and uric acid, were analysed on a Roche Modular Analytics System using commercial assays from Roche Diagnostics (Rotkreuz, Switzerland) with a maximum inter-assay variation of 2.3%, 6.8%, 4.2%, 5.7%, and 3.1%, respectively. LDL cholesterol was calculated according to the formula of Friedewald [10]. Hs-CRP was determined on an Immulite 2000 chemiluminescence analyser using commercial reagents from Diagnostic Products Corporation (Los Angeles, USA) with a maximum inter-assay variation of 6.3% and a detection limit of 0.1 mg/L.

A standard oral glucose tolerance test was performed with a 75 g glucose load after an overnight fast. In the morning an intravenous catheter was inserted into an antecubital vein. Blood samples were obtained at baseline (mean of two samples) and 30, 60, 90, and 120 min after the glucose load.

Venous blood samples were drawn into sodium fluoride-containing tubes for determination of plasma glucose. Plasma glucose was measured by the glucose oxidase technique (Beckman Analyzer; Beckman, Fullerton, CA, USA). Insulin was measured in serum samples by solid phase radioimmunoassay (CIS Bio international, Oris Industries, Gif-Sur-Yvette, France) with a cross-reactivity of 14% for proinsulin and 0.1% for C-peptide; normal overnight fasting range stated by the manufacturer was 30 to 138 pmol/L; lower limit of detection 14 pmol/L. HbA1c was measured by DCA 2000 (Bayer Diagnostics, Zurich, Switzerland). Composite insulin sensitivity index [ISI(comp)] was calculated by the method of Matsuda and DeFronzo using the 75 g OGTT [11]: ISI(comp) = 10000 / square root of $Gluc_0$(mg/dl)xIns_0(mU/L)x$Gluc_{Mean}$(mg/dl)xIns_{Mean}(mU/L). HOMA-IR was calculated as proposed by Matthews [12]: Ins_0(mU/l)x$Gluc_0$(mmol/l)/22.5. Insulinogenic index was calculated as proposed by Wareham [13] as the ratio of the increment of plasma insulin to plasma glucose at 30 min after the glucose load: Ins_{30}(pmol/L)-Ins_0(pmol/L)/$Gluc_{30}$(mmol/l). Ins_t and $Gluc_t$ represent the insulin and glucose concentrations at time t during the OGTT. Ins_{mean} and $Gluc_{mean}$ represent the mean insulin and glucose concentrations during the OGTT.

Nondenaturing polyacrylamide gradient gel electrophoresis (GGE) of plasma was performed at 10–14 °C in 2–16% polyacrylamide gradient gels. Gels were subjected to electrophoresis for 24 h at 125 V in tris borate buffer (pH 8.3) as described elsewhere [14, 15]. Gels were fixed and stained for lipids in a solution containing oil red O in 60% ethanol at 55 °C. Gels were placed on a light source and photographed with a Canon G3 digital camera. Migration distance for each absorbance peak was determined and the molecular diameter corresponding to each peak was calculated from a calibration curve generated from the migration distance of size standards of known diameter, which includes carboxylated latex beads (Duke Scientific, Palo Alto, CA), thyroglobulin and apoferritin (HMW Std, Pharmacia, Piscataway, NJ) having a molecular diameter of 380 Å, 170 Å and 122 Å, respectively, and lipoprotein calibrators of previously determined particle size.

Statistical analysis

Data are presented as means with standard deviations or medians with interquartile ranges. Evaluations were performed using Statistica version 6 and SPSS version 14.0. Bivariate correlation coëfficients R mean Pearson's parametric calculations. Multiple regression analyses were performed on LDL particle size, HDL cholesterol, triglycerides and LDL cholesterol, taking patient characteristics and baseline data as independent variables. Highly skewed values were normalised by logarithmic transformation. A stepwise backward elimination procedure was chosen with $p \geq 0.10$ as exclusion criterion leading to the final models presented with 2–6 variables. Occurrence of collinearity was resolved by exclusion of correlated variables. P-values <0.05 were considered statistically significant.

Results

Subject characteristics

46 patients (33 men and 13 women) with type 2 diabetes were included in the study and underwent oral glucose challenge. Baseline characteristics of the patients are shown in table 1. Average duration of diabetes was 7.2 (SD 6.6) years and HbA1c 7.6 (0.8) % at recruitment. Glucose lowering therapy consisted of diet only in 13 (28%) patients ; 18 patients (39%) were treated with either repaglinide or metformin and 15 patients (33%) with both agents. 42 patients (91%) had a BMI over 25 kg/m^2 with a mean of 30 (4) kg/m^2 in the study population. Waist circumference was ≥94 cm in 29 of the 33 men and ≥80 cm in 12 of the 13 women, with a mean of 104 (10) cm. 34 (74%) had blood pressure ≥130/80 mm Hg or were treated with antihypertensive drugs. 6 (13%) patients were on statin therapy and 8 (17%) patients were smokers. Fasting, 2 h-postload plasma glucose, indices determined during the OGTT, LDL particle size, lipid parameters and other laboratory data are shown in table 1.

Correlation of LDL particle size, HDL cholesterol, triglycerides and LDL cholesterol with indices of insulin sensitivity

Figure 1 shows the correlation of LDL particle size and the traditional lipid parameters with both indices of insulin sensitivity. Of the four lipid parameters, LDL particle size showed the strongest correlation with log ISI(comp) ($R = 0.61$, $p < 0.001$) and log HOMA-IR ($R = –0.53$, $p = 0.001$). A weaker but still significant correlation was found for HDL cholesterol and triglycerides

with both indices. On the other hand, there was no correlation between LDL cholesterol and log ISI(comp) and log HOMA.

The relations of log ISI(comp) with LDL particle size and the three traditional lipid parameters of figure 1 were tested for significance by multiple regression analysis, including patient characteristics and baseline parameters (table 2). Log ISI(comp) remained significantly associated with LDL particle size (p = 0.004) and HDL cholesterol (p = 0.027), but not with triglycerides and LDL cholesterol.

Discussion

In the present study correlation analysis suggested, and multiple regression analysis afforded evidence, that LDL particle size in type 2 diabetes was by far the strongest marker of insulin sensitivity and stronger than traditional lipid parameters. To the best of our knowledge this is the first time this association has been clearly shown, (1) within a group of patients with type 2 diabetes, (2) using indices derived from endogenous insulin values (thus more closely addressing the importance of insulin sensitivity at ambient insulin levels than does the hyperinsulinaemic clamp method and preferentially addressing insulin sensitivity in skeletal muscle), and (3) using the sensitive lipid gel methodology.

Table 1

Demographic, clinical and laboratory baseline data of 46 patients with type 2 diabetes.

	Patients with type 2 diabetes (n = 46)
Age, y	60 (11)
Male gender, %	72
Body mass index, kg/m^2	30 (4)
Waist circumference, cm	104 (10)
Arterial hypertension, %	74
Smoking, %	17
Diabetes duration, y	7.2 (6.6)
Repaglinide therapy, %	46
Metformin therapy, %	59
Statin treatment, %	13
Laboratory data	
Haemoglobin A1c, %	7.6 (0.8)
Fasting plasma glucose, mmol/l	8.7 (2.2)
2-h-postload plasma glucose, mmol/l	16.2 (3.2)
Insulin sensitivity index*	1.7 (1.3–2.7)
HOMA-IR†	7.9 (5.2–6.8)
Insulinogenic index‡	6.9 (3.5–14)
ALT, U/L	24 (16–34)
Uric acid, mmol/L	344 (287–391)
Hs-CRP, mg/L	2.6 (1.4–7.2)
LDL particle size, Å	266 (9)
HDL cholesterol, mmol/L	1.4 (0.4)
LDL cholesterol, mmol/L	3.5 (0.9)
Triglycerides, mmol/L	1.5 (0.8)

Values are % of patients, means with SD or medians with interquartile range.

* Composite insulin sensitivity index [ISI(comp)] was calculated as proposed by Matsuda and DeFronzo [11] 10 000 / square root of $Gluc_0$(mg/dl)xIns_0(mU/L) x $Gluc_{Mean}$(mg/dl)xIns_{Mean}(mU/L).

† HOMA-IR was calculated as proposed by Matthews [12]: Ins_0(mU/L)x$Gluc_0$(mmol/l)/22.5.

‡ Insulinogenic index was calculated as proposed by Wareham [13] Ins_{30}(pmol/L)-Ins_0(pmol/L)/$Gluc_{30}$(mmol/l).

Ins_t and $Gluc_t$ represent the insulin and glucose concentrations at time t during the OGTT. Ins_{mean} and $Gluc_{mean}$ represent the mean insulin and glucose concentrations during the OGTT.

It is well known that hypertriglyceridaemia, low HDL cholesterol and decreased LDL particle size are frequent lipid abnormalities in insulin resistance and type 2 diabetes mellitus [2–4, 20–24] and are associated with an increased risk of cardiovascular disease [5, 16–18]. In addition, an association of LDL particle size with the cluster of risk factors that characterise insulin resistance and the metabolic syndrome has also been demonstrated [7, 9], while there is strong evidence that the smaller denser LDL particles can be added to the group of changes described as syndrome X or metabolic syndrome [3, 8]. The present study suggests that determination of two standard key markers of diabetic dyslipidaemia – plasma triglycerides and HDL cholesterol – does not necessarily replace the analysis of apo-B-containing atherogenic particles such as small dense LDL. One reason for this finding may be that LDL size remains relatively stable over time, in contrast to plasma triglycerides which exhibit more marked alterations depending on the prandial state.

To avoid confounding by hyperglycaemia, the relationship between insulin resistance and lipoproteins has often been studied in normal subjects. However, the issue may be more complex but equally relevant in patients with type 2 diabetes; in the latter condition there may be not only impaired clearance of LDLs but also increased, hyperglycaemia-driven hepatic output of triglyceride-rich VLDL,1 as suggested in a study using stable isotopes [19].

In morbidly obese women with normoglycaemia, impaired glucose tolerance (IGT) and non-insulin-dependent diabetes mellitus (NIDDM) Barakat et al. found a decrease in plasma insulin and triglyceride levels and an increase in LDL size following gastric bypass surgery, while cholesterol and LDL cholesterol levels remained unchanged [20]. Haffner et al. have shown that LDL particle size is correlated with impaired glucose tolerance in non-diabetic subjects [21]. Importantly, Reaven and colleagues

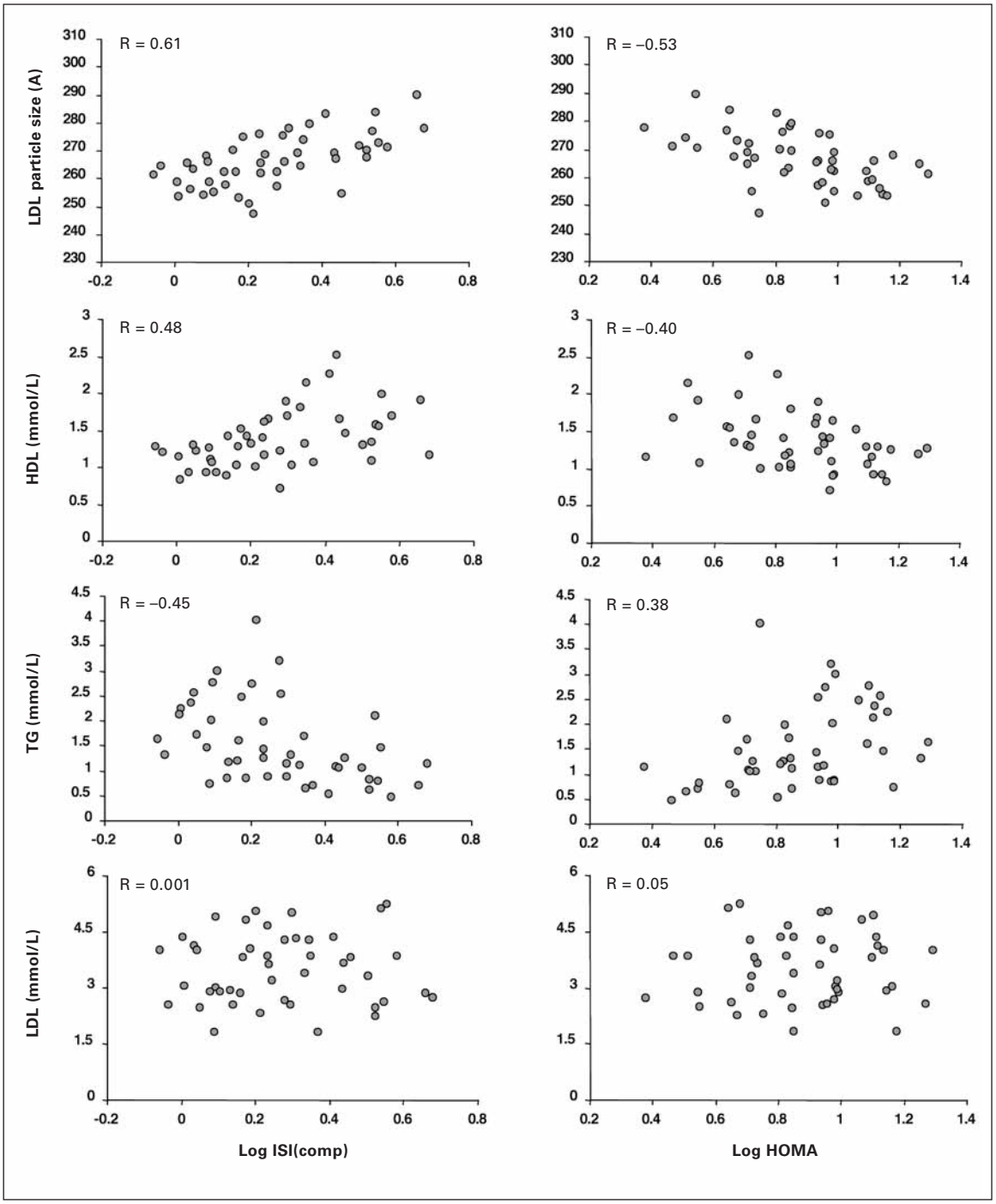

Figure 1

Correlation analysis of LDL particle size, plasma HDL cholesterol, plasma triglycerides and LDL cholesterol with log ISI(comp) and log HOMA, respectively. Correlation analyses were done using Pearson's correlation. For calculations and abbreviations of log ISI(comp) and log HOMA see footnote table 1.

have demonstrated that among 100 normal adults, those with pattern B (predominance of small dense LDL particles) were more insulin resistant than those with pattern A, as judged by an oral glucose challenge, and that this relationship persisted even when differences in gender, age and the degree of obesity were taken into consideration [22]. On the basis of these data it has been suggested that the pattern B phenotype may reflect insulin resistance. Using nuclear magnetic resonance and hyperinsulinaemic clamps to compare insulin sensitive, insulin resistant individuals and untreated patients with type 2 diabetes it has been shown that insulin resistance was associated with an increase in VLDL size and a decrease in LDL particle size. However, no multivariate analysis to test whether the associations between altered lipoprotein sizes and insulin resistance are independent of the traditional lipid parameters within the group of patients with type 2 diabetes, such as HDL cholesterol and triglycerides, was reported in this paper [23] and, to the best of our knowledge, has not been so far. A strong inverse relationship between LDL particle size and triglycerides has been demonstrated in the literature, as summarised in [17]. Festa and colleagues demonstrated an inverse relation of LDL particle size and proinsulin concentrations, but in a heterogeneous population [24]. The studies summarised above and our present data are in contrast to a study by Lahdenpera et al., who, using euglycaemic clamping, found no difference in lipid, lipoprotein concentrations and LDL particle size distribution between the more insulin re-

Table 2

Multiple stepwise backward regressions on LDL particle size, HDL cholesterol, triglycerides, LDL cholesterol with log ISI(comp) and demographic and laboratory data of 46 patients with type 2 diabetes.

Dependent variable	Independent var. (final model)	Regression coeff. B	95% CI of B	Regression coeff. Beta	Signif. (p-value)	Partial correlation	R^2 (adjusted)
LDL particle size	ISI comp (log)	7.3	2.4–12.1	0.347	0.004	0.42	0.56
	Triglycerides (log)	–9.4	-13.5–5.3	–0.526	<0.001	–0.57	
HDL cholesterol (log)	Gender	–0.29	-0.44 – -0.15	–0.479	<0.001	–0.55	0.62
	Statin treatment	0.22	0.05–0.38	0.269	0.010	0.40	
	lSI comp (log)	0.16	0.02–0.29	0.251	0.027	0.34	
	Triglycerides (log)	–0.22	-0.35 – -0.09	–0.423	0.001	–0.48	
	LDL-chol.	0.11	0.04–0.17	0.351	0.003	0.46	
	hs-CRP (log)	–0.07	-0.13 – -0.02	–0.305	0.008	–0.41	
Triglycerides (log)	HDL-chol. (log)	–0.73	-1.15 – -0.31	–0.386	0.001	–0.48	0.62
	LDL-chol.	0.20	0.09–0.31	0.350	0.001	0.48	
	LDL particle size	–0.03	-0.04 – -0.02	–0.486	<0.001	–0.57	
LDL cholesterol	Statin treatment	–0.83	-1.49 – -0.17	–0.305	0.015	–0.36	0.38
	HDL-chol. (log)	1.95	1.02–2.88	0.582	<0.001	0.55	
	Triglycerides (log)	1.18	0.68–1.68	0.667	<0.001	0.59	

CI: confidence interval; Beta: standardised regression coefficient. R^2:coefficient of determination

sistant and less insulin resistant subjects [25]. In their study LDL particle size was not associated with insulin-stimulated glucose uptake and serum insulin. The reason for these contrasting findings is unclear. Our data suggest that smaller LDL particle size reflects the impact of insulin resistance on lipoprotein metabolism more strictly than do the traditional lipid parameters. However, these associations cannot be interpreted as causal relationships.

There are a number of potentially confounding factors in the present study. Six subjects were under treatment with statins. Hypolipidaemic treatment with statins may result in a shift to larger LDL particles [26, 27]. Thus, these patients may have had even smaller LDL particles before initiation of hypolipidaemic treatment. Thirty-three patients were male and thirteen female. It is known that LDL particle size in women is larger than in men. However, antidiabetic therapy and gender were included in the multivariate regression analysis and did not remain in the final model for LDL particle size. Taken together, our data show that determination of LDL particle size provides information on the dyslipidaemic pattern characteristic of type 2 diabetes beyond that provided by measuring triglycerides and HDL cholesterol. Insulin resistance was most closely reflected by lower LDL particle size, which may not only represent an excellent marker but possibly also a mediator of the cardiovascular harm associated with insulin resistance in patients with type 2 diabetes.

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