Effects of a Short-Acting Insulin Analog (Insulin Lispro) Versus Regular Insulin on Lipid Metabolism in Insulin-Dependent Diabetes Mellitus

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Insulin Lispro (IL) is a short-acting insulin analog that better reproduces the physiological postprandial insulin profile. The aim of this study was to compare the effects of intensive insulin therapy on lipid metabolism using preprandial IL and regular insulin (RI) in 10 insulin-dependent diabetes mellitus (IDDM) subjects. The mean hemoglobin A_{1c} (HbA_{1c}) at baseline was 7.13% ± 1.2% and did not change after both treatments. In IDDM patients, total cholesterol and triglyceride levels appeared lower after RI than after IL. The low-density lipoprotein (LDL) to high-density lipoprotein (HDL) ratio significantly decreased only after RI (baseline, 2.01 ± 0.6; IL, 1.88 ± 0.6; RI, 1.71 ± 0.5, $P < .05$). Although no very–low-density lipoprotein (VLDL) composition abnormalities were observed at baseline, the protein content was lower ($P < .05$) after IL (8.13% ± 2.93%) than after RI (11.93% ± 3.41%). Intermediate-density lipoprotein (IDL) protein depletion at baseline (6.14% ± 6.84%) was normalized after both treatments (IL, 11.09% ± 12.14%; RI, 10.38% ± 16.68%, $P < .05$). LDL, HDL, HDL_2, and HDL_3 composition abnormalities were similar after both treatments and did not normalize. IDDM and control subjects showed similar LDL subfraction distribution at baseline and after both treatments. Two-hour postprandial VLDL composition alterations, although improved after RI, completely normalized after IL ($P < .05$). Lipoprotein lipase (LPL) and cholesteryl ester transfer protein (CETP) activities were similar to the control group and did not change after both treatments. Hepatic lipase (HL) activity was lower in diabetic patients (39.6 ± 35.2 *v* 87.0 ± 27.1 U/L, $P < .01$) and remained lower after both treatments. In conclusion, in IDDM patients, IL (injected immediately before the meal) may offer small different effects on lipoprotein metabolism versus RI (injected 30 minutes before the meal) that, taken together, do not seem relevant.

PLASMA very–low-density, intermediate-density, and low-density lipoprotein (VLDL, IDL, and LDL) concentrations and composition are determined by the rate of hepatic VLDL synthesis and clearence. The major factors that regulate VLDL synthesis are plasma insulin concentrations and substrate availability.[1] Lipolytic activity (lipoprotein lipase [LPL] and hepatic lipase [HL]) represents the key step of the VLDL metabolic cascade and is mainly regulated by plasma insulin levels. LPL is considered most effective on VLDL, whereas HL has been shown to be active on IDL and high-density lipoprotein (HDL) metabolism. In addition, cholesteryl ester transfer protein (CETP) catalyzes the exchange of cholesteryl esters, triglycerides, and other neutral lipids between all plasma lipoprotein classes.[2] On the other hand, an increased proportion of small and dense LDL particles have been observed in insulin-dependent diabetes mellitus (IDDM) subjects in poor glycemic control,[3] and it has been related to an enhanced cardiovascular risk.[4] This abnormality may be in relation to changes in lipolytic activities or in postprandial lipoprotein metabolism due to the unphysiological plasma insulin profile obtained after injection of the current rapid insulin preparations. Insulin Lispro [Lys (B28), Pro (B29)-human insulin] (IL) is a rapid insulin analog in which amino acids 28 and 29 of the B-chain have been exchanged, resulting in a reduction of the capacity of the molecule to self-associate.[5] This monomeric insulin has already proved to be faster in subcutaneous absorption than regular insulin (RI). IL better reproduces the physiological postprandial plasma insulin levels than RI,[6-9] and consequently, it is more effective in decreasing postprandial hyperglycemia after the first 2 hours of injection.[10,11]

The consequences of the different pharmacokinetics of IL versus RI on lipid metabolism in IDDM patients have been limited to a few studies focused only on plasma lipid concentrations.[11] Since more comprehensive information in this field was needed, we aimed to compare in IDDM subjects the effects of intensive insulin therapy using preprandial IL versus RI on postheparin plasma LPL and HL activities, CETP activity, fasting VLDL, IDL, LDL, and HDL composition, LDL subfraction distribution, HDL subfractions, and 2-hour postprandial VLDL composition.

SUBJECTS AND METHODS

Subjects

Multiple Institutional Review Board approval for this study was obtained, and informed consent was provided by all of the subjects. Ten type I diabetic subjects (two males and eight females aged 29.0 ± 6.5 years; BMI, 24.1 ± 2.6 kg/m^2; diabetes duration, 5.5 ± 5.0 years) and 10 age-, sex-, and BMI-matched healthy control subjects were included (age, 29.4 ± 5.3 years; BMI, 24.1 ± 2.2 kg/m^2). All patients were free of diabetic complications or other diseases known to affect lipid metabolism. None were taking any drugs other than insulin. All patients have previously been treated with subcutaneous multiple insulin injections (RI before each meal and intermediate insulin (NPH) before dinner or at bedtime).

Study Design

Patients were included in a 6-month randomized, open, crossover study, 3 months with IL and 3 months with RI. IL and RI were injected in subcutaneous abdominal tissue immediately and 30 minutes before

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main meals, respectively. Long-acting insulin (Humulin ultralente) was also administered before breakfast (20%) and dinner (80%). Patients recieved an isocaloric diet providing 50% to 55% carbohydrate and 30% to 35% fat.

All patients were studied before (baseline) and after 3 months of multiple insulin injections with either IL or RI. Each study was performed after an overnight fast of 12 hours. After blood samples were obtained, patients injected their usual morning insulin dose (ultralente plus RI or IL) and were provided with their usual breakfast (mean breakfast composition: 66.6% ± 14.8% carbohydrate, 23.2% ± 8.3% protein, and 10.7% ± 16.2% fat). Two hours after starting breakfast, blood samples were also obtained. The breakfast composition for every diabetic patient was identical to that of the corresponding matched healthy subject.

Specimen Collection and Biochemical Procedures

Venous blood was obtained in fluoride tubes for glucose and in EDTA tubes for lipoprotein and hemoglobin A_{1c} (HbA_{1c}) determinations. Blood specimens to determine lipolytic activities were obtained 15 minutes after injection of sodium heparin 50 IU/kg and placed into chilled heparinized tubes kept on ice. All samples were immediately centrifuged at 4°C and stored at −80°C for no longer than 1 month until analyzed.

Glucose was determined by a fully enzymatic method adapted to a Hitachi 747 autoanalyzer (Boehringer, Mannheim, Germany). The HbA_{1c} level was measured by high-performance liquid chromatography ([HPLC] reference range, 4.3% to 6.1%).

Lipoprotein isolation was performed by a double-ultracentrifugation procedure as described in our laboratory.[12] In short, VLDL was isolated by previous flotation ultracentrifugation (100,000× *g* at 15°C for 18 hours). The infranatant (2 mL) was adjusted to density 1,250 kg/L with KBr and saccharose, and then 5 mL 1,210-kg/L solution and 5 mL distilled water were overlayered. IDL, LDL, and HDL were isolated by aspiration after density gradient ultracentrifugation. Six LDL subfractions were isolated by gradient ultracentrifugation with the method of Griffin et al[13] with some modifications performed in our laboratory.[14] HDL subfractions (HDL_2 and HDL_3) were isolated by flotation ultracentrifugation with density adjustment (1.100 g/mL).

Total cholesterol and triglyceride content in plasma and in each lipoprotein fraction were measured enzymatically (CHOD-PAP ref 172626 and GOP-PAP ref 701912, respectively; Boehringer). The content of phospholipid in lipoprotein particles was determined by enzymatic methods (Phospholip B-test, ref 54009; Wako Chemicals, Osaka, Japan). The protein content in lipoprotein particles was measured by the method of Bradford.[15] Lipoprotein mass was calculated as the sum of the four-component mass (cholesterol, triglyceride, phospholipid, and protein) expressed in milligrams per liter.

The Lp(a) level was measured by an enzyme-linked immunosorbent assay (ELISA) method commercially available (Terumo Medical, Elkton, MD) and standardized against all Lp(a) isoforms.

LPL activity was assayed following the procedure described by Ramirez et al[16] with few modifications. In short, LPL activity was measured by the production of tritiated-FFA from tritiated-triolein after blockage of HL with a specific antibody provided by Dr Monique Robert (Biochemistry Department, Faculty of Biology, University of Barcelona). HL activity was measured by a similar method, but by blocking LPL activity with high concentrations of NaCl (1.5 mol/L). Both lipolytic activity assays are expressed as units per liter and showed a within- and between-assay imprecision lower than 2% and 4%, respectively.

CETP activity was determined by measuring the transfer of [cholesteryl-1,2,6,7-^{3}H (*N*)]-oleate from HDL_3 to LDL. Briefly, after incubation of labeled HDL_3 and LDL with a serum sample, HDL_3 and LDL were separated by gel filtration chromatography. CETP is expressed as nanomoles of labeled cholesteryl ester transferred per milliliter of serum per hour. Within- and between-assay imprecision was 6.6% and 11%, respectively.

Statistical analysis

The Shapiro-Wilks test was performed to verify normal distribution of the variables. All variables that were not normally distributed (plasma triglyceride, VLDL-C, and Lp (a)) were logarithmically transformed. To compare the composition of the lipoproteins, we used both the percentage of each constituent and the logarithmic ratio of different constituents. An ANOVA was used to compare the three periods (Baseline [B], IL, and RI), followed by a paired *t* test with Bonferroni correction. Comparison of results between the diabetics and the control group was performed by a nonpaired *t* test. The association between variables was analyzed by linear correlation (Pearson's correlation coefficient).

In all cases, a probability value of .05 or less was accepted as statistically significant. All data are presented as the mean ± SD.

RESULTS

Metabolic Parameters and Lipid Levels

Metabolic parameters of the diabetic patients and control subjects are shown in Table 1. The BMI, insulin requirements, and HbA_{1c} did not change during the study.

Plasma lipid and lipoprotein concentrations, including Lp(a), in diabetic patients did not differ from those of the control group (Table 2), with the exception of total cholesterol and the LDL/HDL ratio, which significantly ($P < .05$) decreased during RI treatment. Total cholesterol and triglyceride levels appeared lower during RI versus IL treatment. In all cases, lipid concentrations remained within the normal range.

Fasting VLDL, IDL, and LDL Composition

Compared with the control group (687 ± 637 mg/L), diabetic patients at baseline showed similar VLDL mass (433 ± 271 mg/L) and composition expressed as either the concentration of each lipoprotein constituent (data not shown) or the percent contribution of each constituent to the total lipoprotein mass (Fig 1A). No significant changes were observed after both treatments (IL, 498 ± 386 mg/L; RI, 379 ± 224 mg/L); however, after IL, the protein content of VLDL particles was lower ($P < .05$) and the ratio of lipid to protein was higher (14.0 ± 9.7 *v* 7.9 ± 1.9, $P < .05$), with the differences in the lipid content due to triglyceride rather than cholesterol, as indicated by a higher triglyceride to protein ratio (10.8 ± 4.2 *v* 5.0 ± 1.1, $P < .05$) and a similar cholesterol to protein ratio (3.3 ± 5.3 *v* 1.3 ± 0.3) compared with RI treatment. IDL mass in diabetic subjects at baseline was similar to that of the control group

Table 1. Metabolic Parameters of the IDDM and Control Subjects

Parameter	IDDM Patients			Control Subjects
	Baseline	IL	RI	
BMI (kg/m²)	24.1 ± 2.6	23.9 ± 2.5	23.5 ± 2.3	24.1 ± 2.2
HbA_{1c} (%)	7.13 ± 1.2	7.06 ± 1.3	6.82 ± 0.8	NA
Insulin (U/kg/d)	0.64 ± 0.2	0.66 ± 0.3	0.67 ± 0.2	NA
Glycemia (mmol/L)				
Fasting	8.96 ± 4.2*	9.11 ± 4.1†	10.2 ± 4.0†	4.74 ± 0.4
2-h postprandial	8.12 ± 3.5*	8.79 ± 4.1*	9.57 ± 4.0†	4.59 ± 0.4

Abbreviation: NA, not assayed.

*$P < .05$, †$P < .01$: *v* the control group.

Table 2. Plasma Lipid and Lipoprotein Concentrations (mmol/L) in the IDDM and Control Subjects

Parameter	IDDM Patients			Control Subjects
	Baseline	IL	RI	
Triglyceride	0.74 ± 0.3	0.82 ± 0.3	0.65 ± 0.2†	0.96 ± 0.6
Cholesterol				
Total	4.74 ± 0.7	4.58 ± 0.5	4.23 ± 0.4*†	4.68 ± 0.7
VLDL	0.17 ± 0.1	0.19 ± 0.1	0.14 ± 0.1	0.23 ± 0.2
LDL	2.78 ± 0.6	2.68 ± 0.8	2.48 ± 0.4	2.73 ± 0.8
HDL	1.46 ± 0.4	1.57 ± 0.3	1.56 ± 0.4	1.62 ± 0.4
LDL/HDL ratio	2.01 ± 0.6	1.88 ± 0.6	1.71 ± 0.5*	1.79 ± 0.6
Lp(a) (mg/dL)	11.2 ± 13.8	11.3 ± 13.3	11.5 ± 14.6	14.9 ± 14.2

*$P < .05$ *v* baseline.
†$P < .05$ *v* IL.

(84.00 ± 129 *v* 99.32 ± 76 mg/L) and decreased ($P < .05$) after IL (26.59 ± 14 mg/L) and after RI (29.24 ± 26 mg/L). At baseline, IDL particles of IDDM patients showed a lower ($P < .05$) content of protein than those of the control group, with a higher lipid to protein ratio (27.8 ± 47.7 *v* 15.3 ± 20.6, $P < .05$). This alteration disappeared after both treatments (Fig 1B). No further compositional modifications of IDL particles were seen after the treatments.

LDL mass in the diabetic subjects at baseline (2,443 ± 503 mg/L) was similar to that of the control group (2,434 ± 637 mg/L), and only after RI treatment did it significantly ($P < .001$) decrease (RI, 2,088 ± 370 mg/L; IL, 2,366 ± 534 mg/L). Concerning LDL composition, initially, LDL particles from IDDM patients appeared depleted of phospholipid, with a lower phospholipid to protein ratio compared with the control group (1.8 ± 0.2 *v* 1.5 ± 0.3, $P < .05$). After both treatments, they became enriched in cholesterol and depleted in protein (Fig 2A), as indicated by the increase ($P < .05$) in the cholesterol to protein ratio (baseline, 2.3 ± 0.3; IL, 3.1 ± 0.3; RI, 2.9 ± 0.4).

LDL Subfraction Distribution

LDL subfraction distribution was similar in the diabetic patients at baseline and in the control group, with a predominance of phenotype A (large and buoyant LDL) in both groups (70% and 80%, respectively). After both treatments, no significant changes in LDL subfraction distribution were observed, and the predominance of phenotype A was still present (IL, 90%; RI, 90%).

HDL, HDL_2, and HDL_3

HDL mass, which was similar in the diabetic patients at baseline (3,171 ± 727 mg/L) and in the control subjects (3,785 ± 708 mg/L), was decreased with both treatments (IL, 2,987 ± 719 mg/L; RI, 2,995 ± 898 mg/L, $P < .05$) compared with the control group.

Concerning HDL composition, the triglyceride content at baseline, which was similar in the diabetic and nondiabetic patients, increased with both treatments (Fig 2B), and there was an increase ($P < .05$) in the triglyceride to protein ratio (baseline, 0.05 ± 0.01; IL, .09 ± 0.03; RI, 0.12 ± 0.13) and cholesterol to protein ratio (baseline, 0.3 ± 0.1; IL, 0.4 ± 0.1; RI, 0.7 ± 0.7). The cholesterol content increased after both treatments compared with that of the control subjects (Fig 2B).

Regarding HDL subfractions, HDL_3 but not HDL_2 mass was lower in IDDM patients at baseline and after both treatments as compared with the control group. Composition abnormalities of HDL_2 and HDL_3 (increased cholesterol and phospholipid and decreased protein content) were observed at baseline and after both treatments (data not shown).

Postheparin Plasma Lipolytic Activities

Postheparin plasma LPL activity at baseline did not show any difference in IDDM subjects versus the control group (105.0 ± 29.7 *v* 97.5 ± 27.6 U/L; Fig 3), and did not change after treatment with either IL or RI. In contrast, the postheparin plasma HL activity at baseline was significantly lower in diabetic patients ($P < .001$) than in the control subjects and remained lower after both treatments (Fig 3). When the LPL/HL ratio was considered, diabetic patients at baseline showed a higher ratio than the control group (4.94 ± 4.69 *v* 1.27 ± 0.65, $P < .05$), and no significant changes were observed after both treatments (IL, 3.85 ± 3.38; RL, 2.17 ± 1.43).

CETP Activity

CETP activity expressed as nanomoles of labeled cholesteryl ester transferred per milliliter serum per hour was similar in the

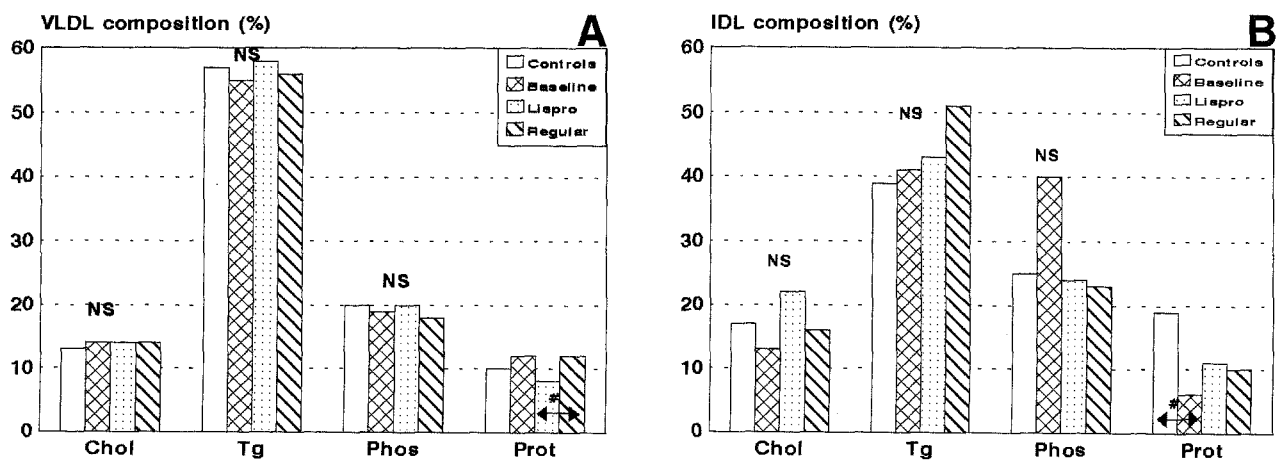

Fig 1. (A) Fasting VLDL and (B) IDL composition in control subjects and IDDM patients at baseline and after IL and RI treatments. Chol, %cholesterol; Tg, %triglyceride; Phos, %phospholipid; Prot, %protein. *$P < .01$, #$P < .05$. NS, nonsignificant differences.

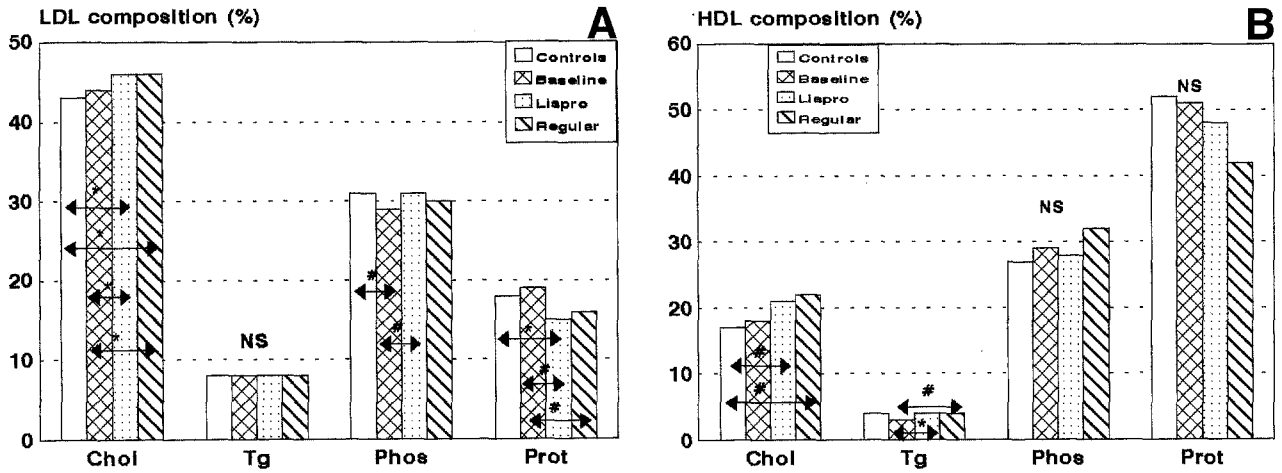

Fig 2. (A) Fasting LDL and (B) HDL composition in control subjects and IDDM patients at baseline and after IL and RI treatments. Chol, %cholesterol; Tg, %triglyceride; Phos, %phospholipid; Prot, %protein. *$P < .01$, #$P < .05$. NS, nonsignificant differences.

diabetic patients at baseline (128.2 ± 27.4) and the control group (118.0 ± 22.0). No changes were observed after one or the other treatment (IL, 123.6 ± 23.6; RL, 119.5 ± 29.2).

Two-Hour Postprandial Plasma Lipid Concentrations and VLDL Composition

Two hours after breakfast, total plasma cholesterol and triglyceride levels in IDDM patients were similar to those of the control group, but were lower after RI than after IL (Table 3).

Two-hour postprandial VLDL mass in diabetic subjects at baseline (158.0 ± 80 mg/L) and in the control subjects (316.0 ± 332 mg/L) was not different and remained unchanged after IL (177.0 ± 110 mg/L) and RI (151.0 ± 151 mg/L). Nevertheless, the lipid to protein ratio was higher in diabetic patients at baseline compared with the control group (19.4 ± 5.6 *v* 10.8 ± 6.6, $P < .05$), and was corrected only after IL (11.1 ± 3.8, $P < .05$). Both the triglyceride to protein and cholesterol to protein ratios, which were also higher in diabetic patients at baseline, were corrected only after IL, due to normalization of the protein content (Table 3).

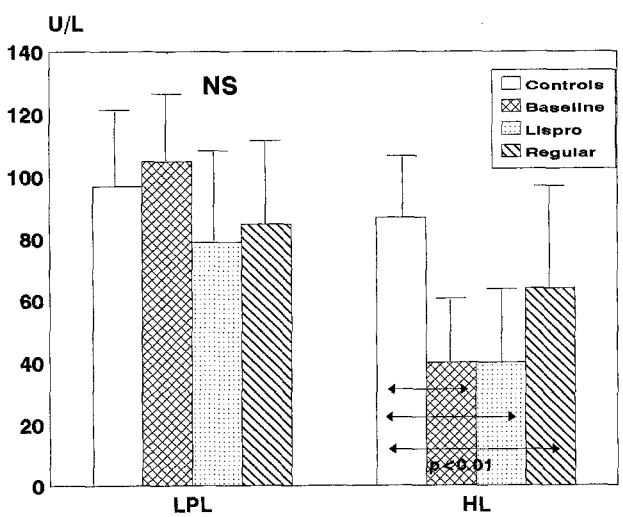

Fig 3. Postheparin plasma LPL and HL activities in control subjects and IDDM patients at baseline and after IL and RI treatments. NS, nonsignificant differences.

DISCUSSION

The pharmacokinetics of IL better reproduce the physiological postprandial plasma insulin levels when IL is injected immediately before the meal, in comparison to RI injected 30 minutes before.[6-9] Since the insulin concentration is a major factor in the regulation of the synthesis and catabolism of lipoproteins, it is important to know the effects of intensive insulin therapy using IL on lipoprotein metabolism. In the present study, the meal composition was identical under any tested treatment, and no significant differences in postprandial plasma glucose, HbA_{1c}, BMI, and insulin requirements were observed after both treatments. Therefore, any differences in lipid and lipoprotein concentrations and composition using one or the other treatment could be attributed to differences in insulin pharmacokinetics. There is no clear explanation to justify the differences in total cholesterol and the LDL/HDL ratio between baseline and the RI period, but a better adherence to diet recommendations during the follow-up period cannot be discounted.

Table 3. Two-Hour Postprandial Plasma Lipid Concentrations and VLDL Composition (expressed as % of each constituent to total lipoprotein mass) in the IDDM and Control Subjects

2-Hour Postprandial	IDDM Patients			Control Subjects
	Baseline	IL	RI	
Cholesterol (mmol/L)	4.64 ± 0.7	4.59 ± 0.5	4.22 ± 0.5†‡	4.38 ± 0.5
Triglyceride (mmol/L)	0.60 ± 0.2	0.55 ± 0.2	0.48 ± 0.2‡	0.72 ± 0.4
VLDL				
% cholesterol	13.3 ± 2.5*	10.9 ± 4.5†	9.31 ± 3.8†	9.56 ± 3.8
% triglyceride	64.7 ± 6.9	63.2 ± 14.4	70.5 ± 7.8	63.9 ± 8.5
% phospholipid	17.7 ± 5.3	14.2 ± 4.6†	15.2 ± 3.9	15.2 ± 3.8
% protein	4.30 ± 2.1*	11.7 ± 15.0	5.05 ± 6.0*	11.4 ± 6.5

*$P < .05$ *v* controls.
†$P < .05$ *v* baseline.
‡$P < .05$ *v* IL.

According to previous studies,[17,18] our group of well-controlled IDDM subjects showed lipid and lipoprotein concentrations similar to those of the control group. However, both total plasma cholesterol and triglycerides appeared lower with RI treatment versus IL. This finding agrees with the report by Taskinen,[19] who also reported subnormal lipid levels in chronically insulin-treated IDDM patients, probably due to peripheral hyperinsulinism after RI administration. The same group[20] postulated that triglyceride levels above 1.7 mmol/L increased the prevalence of small and dense LDL and consequently the risk to develop coronary heart disease. In the present study, triglyceride levels after both treatments were far from this threshold and, consequently, far from a potential atherogenic risk. We have no explanation for the larger decrease of the LDL/HDL ratio after RI; however, no significant differences existed between the ratios obtained after both treatments. In addition, all ratios observed were favorable from an atherogenic point of view.

The similarity in VLDL mass and composition between diabetic patients at baseline and the control group agrees with one study[21] but disagrees with others[3,22] that observed abnormalities in VLDL composition despite good glycemic control. The lack of differences in VLDL mass may be due to the great variability of the method and the small number of individuals included in the study. The differences in VLDL composition observed between both treatments (higher lipid to protein ratio with similar cholesterol to protein ratio after IL) indicate that there is no cholesterol enrichment in VLDL particles after the utilization of IL, which is known to be more atherogenic. In the present study, the postprandial triglyceride and cholesterol response of both the IDDM patients under any treatment and the control subjects was similar and reflected the close relationship between fasting and postprandial triglycerides.[23-24] However, 2-hour postprandial VLDL particles in IDDM subjects showed a high lipid to protein ratio that improved with both treatments, but only corrected with IL. The absence of relevant abnormalities in the postprandial triglyceride response and VLDL composition in IDDM subjects compared with the matched controls may be due to the low-fat mixed meal used for the study and the obtainment of blood samples in a very early postprandial stage.

Regarding LDL particles, only after RI was the mass decreased, although in terms of composition, neither IL nor RI normalized the alterations and LDL particles appeared cholesterol-enriched and protein-depleted after both treatments, as already reported in other studies.[25] In agreement with James and Pometta,[3] the LDL subfraction distribution of IDDM subjects in good glycemic control showed a predominance of large and buoyant LDL particles, and the distribution was not influenced by any of the treatments. Concerning HDL, all observed changes in mass or content (enrichment in cholesterol and triglyceride) did not differ between both treatments, and have already been reported.[22,26] Furthermore, no relevant changes in HDL subfractions and CETP activity were observed with both treatments, which were similar to the control group. By contrast, other groups who have reported an accelerated transfer in chronically insulin-treated IDDM patients attribute the disturbance to the peripheral hyperinsulinism.[27,28]

As far as we know, there are few studies on IDL composition and mass in IDDM,[21,22,25] which are not in agreement. Winocour et al[25] found IDL particles to be depleted in protein and enriched in phospholipid, and Ruotolo et al[21] observed increased triglyceride content (although phospholipid content was not taken into account). However, Rivellese et al[22] did not observe any differences in IDL composition when comparing IDDM patients and a matched control group. These discrepancies could be attributed to different gradient densities used to isolate lipoproteins, which can be misleading in terms of IDL isolation.[25] In agreement with Winocour et al,[25] in our study, IDL at baseline was depleted of protein, and after both treatments, the composition normalized. The IDL mass, which was similar to the control level at baseline, decreased after both treatments. These changes could be attributed to a more effective lipolysis of VLDL to LDL after both treatments. However, no changes in the main lipolytic enzyme (LPL) in relation to the control group or between both treatments were observed. Moreover, plasma HL activity, an enzyme involved in the last step of the triglyceride-rich lipoprotein catabolism cascade, was lower in IDDM subjects than in the control group and remained low after both treatments, which cannot explain the changes in IDL mass and composition. The findings in LPL and HL activities agree with those reported by Patti et al[29,30] in patients treated with multiple insulin doses, but disagree with other studies that report increased LPL activity in IDDM subjects on subcutaneous insulin therapy as a consequence of peripheral hyperinsulinism and the relative portal hypoinsulinemia.[31-33] Discrepancies between studies may be explained at least in part by differences in the design. This study and those from Patti et al[29,30] were comparable, since they were performed in well-controlled IDDM patients treated with multiple doses of insulin and well matched to control subjects. Regarding HL activity, most of the studies report no differences between IDDM and control subjects[21,34] or between IDDM patients with and without treatment.[35] However, in agreement with Patti et al,[29,30] we observed lower HL activity and a higher LPL/HL ratio in IDDM subjects than in the control group. Although HL activity was not significantly influenced by both treatments, the LPL/HL ratio tended to improve to levels closer to the control group. This reduced HL activity could be a consequence of lower hepatic insulin levels (one of the main regulators of HL activity) achieved with subcutaneous insulin delivery and a reduction of potential substrate for HL due to an improved lipolysis of VLDL and IDL, reported in well-controlled IDDM subjects during intensive insulin therapy.[36,37]

In conclusion, compared with RI (injected 30 minutes before the meal), there appear to be subtle differences in lipoprotein metabolism using IL (injected immediately before the meal), such as a less pronounced decrease in fasting and 2-hour postprandial triglyceride and cholesterol levels and the fasting LDL/HDL ratio, an increase in the fasting VLDL lipid to protein ratio, and a complete normalization of 2-hour postprandial VLDL protein depletion. These differences together do not seem relevant, and we can conclude that IL offers effects similar to RI on lipoprotein metabolism in IDDM patients.

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