Intraperitoneal Insulin Infusion Improves the Depletion in Choline-Containing Phospholipids of Lipoprotein B Particles in Type I Diabetic Patients

B. Guerci, B. Igau, O. Ziegler, T. Crea, J.-C. Fruchart, P. Drouin, and C. Fievet

Insulin-dependent diabetes mellitus (IDDM) is characterized by altered composition of atherogenic lipoproteins, especially a depletion in choline-containing phospholipids (PL) of apolipoprotein (apo) B lipoproteins (LpB). To determine the effects of continuous intraperitoneal (IP) insulin infusion (CIPII) on this qualitative lipoprotein abnormality, we compared lipoprotein profiles of 14 IDDM patients treated by continuous subcutaneous insulin infusion (CSII) and at 2 and 4 months after treatment with CIPII using an implantable pump. IDDM patients were in fair metabolic control and were compared with 14 healthy control subjects matched for sex, age, body mass index, and plasma lipids. The following parameters were studied: hemoglobin A_{1c} (HbA_{1c}), monthly blood glucose, daily insulin dose (units per kilogram per day), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, apo A-I, and apo B. Choline-containing PL were assessed in plasma and in apo B– and no-apo B–containing lipoprotein particles (LpB and Lp no B). As compared with the control group, plasma PL and LpB-PL were significantly lower in IDDM patients treated by CSII (2.95 ± 0.26 *v* 3.30 ± 0.45 mmol/L, $P < .05$, and 1.09 ± 0.45 *v* 1.68 ± 0.33 mmol/L, $P < .01$, respectively). No significant differences were observed for Lp no B lipid determinations between both groups. After initiation of CIPII, IDDM patients did not experience any significant changes in mean values for body mass index, HbA_{1c}, and monthly blood glucose throughout the study. Daily insulin doses were identical to those observed before IP therapy. Lipid parameters remained unchanged in IDDM patients (TC, TG, HDL and LDL cholesterol, apo A-I, and apo B). A moderate but progressive elevation of plasma PL was noted, and after 4 months of CIPII, PL and LpB-PL levels were no longer significantly different between IDDM patients and controls. The increase in plasma and LpB choline-containing PL observed after 2 and 4 months of CIPII is not linked to changes in blood glucose control, body weight, or daily insulin requirements. These changes may be related to the route of insulin administration, which may be accompanied by a reduction of lipoprotein lipase (LPL) activity and consequently a reduction of phospholipase activity. These results suggest that IP insulin delivery may be a more physiological route that increases the choline-containing PL content of LpB particles.

DIABETES is associated with increased cardiovascular morbidity and mortality in general and increased coronary heart disease (CHD) incidence in particular.[1] The true nature of this relationship remains unclear, and the role of plasma lipids and lipoproteins is still not proven.[2] In general, adequately controlled insulin-dependent diabetes mellitus (IDDM) patients have almost normal concentrations of the major lipoproteins,[3] and it has been proposed that atherogenesis is better associated with subtle qualitative abnormalities of the structure of certain lipoproteins and therefore with functional alterations.[4] Chemically modified lipoproteins such as glycated and oxidized low-density lipoproteins (LDLs) have been identified in the plasma of IDDM patients,[5-7] and many reports have emphasized the role of both these types of modification in atherogenesis.[8-10] Other lipoprotein changes may also occur, and alterations in core- and surface-lipid components that might affect functional lipoprotein properties have been addressed.[11-13] If intensive insulin treatment is now known to reverse a number of quantitative abnormalities in plasma lipids in IDDM patients,[14] in contrast, persistence of some atherogenic disturbances in lipoprotein lipid composition has been shown even when metabolic control was good and plasma lipids were normal.[15]

Through their effects on lipolytic enzymes, hepatic production of very–low-density lipoproteins, LDL and high-density lipoprotein (HDL) receptor activity, and proliferation of human arterial smooth muscle cells,[4,16] insulin resistance and hyperinsulinemia are now considered potent atherogenic risk factors for CHD.[17] Since in IDDM patients elevated peripheral insulin concentrations are most likely a result of the nonphysiologic route of continuous subcutaneous insulin infusion (CSII), an alternative method that delivers insulin via the intraperitoneal (IP) route has been investigated. Despite unanimous improvement of blood glucose control of patients treated with continuous IP insulin infusion (CIPII), controversial results are reported concerning the changes in lipoprotein profiles.[18-21] In a recent study, we have shown a depletion in the choline-containing phospholipid (PL) content of apolipoprotein (apo) B–containing lipoproteins in fairly controlled IDDM patients treated using intensified conventional insulin therapy.[22] To determine the effects of IP insulin infusion on this qualitative lipoprotein abnormality, we compare here the lipoprotein profiles of 14 IDDM patients receiving therapy by CSII and at 2 and 4 months after treatment with CIPII using an implantable pump.

SUBJECTS AND METHODS

Patients

The study group consisted of 14 diabetic patients (five women and nine men). All had IDDM diagnosed according to National Diabetes Data Group criteria[23] and were C-peptide–negative, confirmed after a 1-mg intravenous glucagon test (< 0.3 nmol/L). These patients were volunteers for the implantation program. They had been selected from 120 diabetic patients treated with CSII at

From the Service de Médecine G du Centre Hospitalo-Universitaire et Département de Nutrition et des Maladies Métaboliques de l'Université de Nancy I, Hôpital Jeanne d'Arc, Toul; and SERLIA et INSERM U325, Institut Pasteur, Lille, France.

Submitted January 26, 1995; accepted August 29, 1995.

Supported by le Centre d'Investigation Clinique-INSERM/CHU de NANCY.

Address reprint requests to B. Guerci, MD, Service de Médecine G, Hôpital Jeanne d'Arc, B.P. 303, 54201 Toul Cedex, France.

0026-0495/96/4504-0004$03.00/0

our outpatient clinic.[24] Inclusion criteria were as follows: (1) CSII duration more than 1 year (range, 1.2 to 6.7), (2) fair metabolic control, (3) good compliance with home blood glucose monitoring, and (4) hypoglycemia awareness. The duration of diabetes was 16.4 ± 11.1 years (mean ± SD). The age of the patients was 40 ± 6.2 years, and body mass index was 24.2 ± 2.1 kg/m^2. None had a recent episode of ketoacidosis, and none were taking any drug known to influence lipid and lipoprotein metabolism except insulin. Patients with hyperlipidemia, high levels of lipoprotein(a), thyroid or liver disease, diabetic or nondiabetic renal disease, urinary tract infection, pregnancy, acute or chronic inflammatory syndrome, alcoholism, or malnutrition were not included in the study. None had proteinuria or microalbuminuria (microalbuminuria was defined as an albumin excretion rate of 20 to 200 μg/min). None of the patients had macrovascular complications, and only one was affected with background retinopathy. One case of hypertension was reported and treated with a calcium antagonist. Patients were instructed to follow a weight-maintaining diet (15% of calories as protein, 35% as fat, and 50% as carbohydrate) given as three main meals and two to three snacks per day throughout the study.

Fourteen nondiabetic subjects were volunteers selected to have a sex ratio (five women and nine men), age (39 ± 6.5 years), and body mass index (24.4 ± 2.2 kg/m^2) comparable to those of the diabetic patients. They were in good health, and none were taking any medication that could influence lipoprotein metabolism. None of these patients had a history of diabetes mellitus and hyperlipidemia. Absence of diabetes was documented by normal fasting blood glucose.

All subjects gave informed consent before participating in the study, and the project was approved by the Ethics Committee of the Centre Hospitalier Universitaire de Nancy.

Study Protocol

Surgical pump implantation. Diabetic patients were studied before and at 2 and 4 months after initiation of exclusively IP insulin administration (IP-2 and IP-4, respectively); this procedure has been previously described.[25] They were implanted with MiniMed pump MIP 2001 (MiniMed Technologies, Sylmar, CA). The pump was equipped with a bilaminate polyethylene outer-coated–silicon inner-coated catheter. The programers are battery-operated telemetry systems, and their functions include modification of current basal and premeal bolus rates and recording of pump status and residual volume of insulin in the reservoir. Semisynthetic human insulin (HOE 21 PH; Hoechst, Frankfurt, Germany) was used at a concentration of 400 U/mL. Surgical pump implantation was performed under general anesthesia. A subcutaneous pocket was created in the lower left quadrant of the anterior abdominal wall. A prefilled pump was placed in the pocket and sutured to the fascia of the abdominal wall muscles. The distal portion of the catheter was inserted into the peritoneal cavity.

Metabolic monitoring. Capillary glucose values were recorded in the patients' memory meters (Glucometer M memory meter; Miles Elkhart, IN). Data recorded in the glucometer were transferred to a computer and handled by the Glucofacts program (Glucofacts Data Management System; Miles) to calculate mean blood glucose levels over time, standard deviations in blood glucose levels, and frequency of hypoglycemia, ie, number of blood glucose determinations less than 3.5 mmol/L monthly. The memory of the pump communicator was transferred to computer memory at each visit for recording insulin requirements, ie, basal rate and preprandial bolus. Hemoglobin A_{1c} (HbA_{1c}) levels were measured at baseline before implantation and then every 2 months.

Methods

Laboratory procedures. Blood sampling was performed after a 12-hour overnight fast. HbA_{1c} was assessed using high-performance liquid chromatography on Biorex resins (BioRad, Richmond, CA; normal range, 4.2% to 5.6%), and plasma glucose was determined by a glucose oxidase technique (Beckman Glucose Analyzer; Beckman, Fullerton, CA). Blood lipid determinations were made on fresh serum stored at 4°C. Total cholesterol (TC), triglycerides (TG), and choline-containing PL were determined by enzymatic methods (kits from Boehringer, Mannheim, Germany).[26-28] HDL cholesterol was determined after precipitation of apo B–containing lipoproteins by phosphotungstic acid/manganese (Boehringer). LDL cholesterol was calculated by the Friedewald formula.[29] Apo A-I and apo B were quantified by immunonephelometry on a Behring Nephelometer Analyzer (Behring werke, Marburg, Germany). Plasma C-peptide level was measured by radioimmunoassay (CIS Biointernational, Gif sur Yvette, France) after an overnight fast. Urinary albumin concentration, measured by laser nephelometry (Behring), was taken as the mean of three 12-hour overnight urine collections over a 3-month period. Apo B–containing lipoprotein particles (LpB) were selectively precipitated using concanavalin A.[30,31] The supernatant was recovered by pipetting and then assessed for TC and PL levels. These determinations corresponded to TC and PL contents in no–apo B–containing particles (Lp no B-TC and Lp no B-PL, respectively). TC and PL of LpB (LpB-TC and LpB-PL) were determined by subtracting the above results from those obtained for total plasma. Details of the concanavalin A precipitation test procedure and the specificity, reproducibility, and accuracy for diabetic samples have been published elsewhere.[22] In particular, we have ensured that results obtained with this procedure were not altered by nonenzymatic glycation of apolipoproteins. Interassay coefficients of variation for total lipids, lipoprotein subfractions, and apolipoproteins were all less than 6%.

Statistical Analysis

Results are expressed as the mean ± SD. Comparison of diabetic patients and controls was made using the nonparametric Mann-Whitney *U* test for unpaired series, and between diabetic patients (IP *v* subcutaneous) using the nonparametric Wilcoxon test for paired series. ANOVA was performed by the nonparametric Kruskal-Wallis test for repeated determinations. The Spearman rank correlation coefficient test was used for testing correlations between different variables. Statistical significance is implied by P less than .05. Statistical analysis was performed using the Statview program (Statview II; Brain Power, Calabasas, CA).

RESULTS

Diabetic patients were in fair metabolic control, with HbA_{1c} levels close to the normal range (Table 1). After initiation of CIPII, IDDM patients did not experience any significant changes in mean values for body mass index, HbA_{1c}, and monthly blood glucose levels throughout the study. Only blood glucose standard deviations were significantly improved after 2 and 4 months of CIPII as compared with CSII. Daily insulin doses were slightly increased after 2 months of CIPII, but after 4 months, insulin requirements were similar to those observed before IP therapy.

At baseline (end of the CSII therapy), plasma choline-containing PL were significantly lower in diabetic patients. TC, TG, LDL cholesterol, and apo B tended to be lower, but differences did not reach statistical significance (Table

Table 1. Effects of IP Insulin Treatment on Clinical and Metabolic Parameters (mean ± SD)

Parameter	Baseline	IP-2	IP-4
HbA_{1c} (%)	6.01 ± 0.60	5.59 ± 0.46	5.90 ± 0.63
Monthly blood glucose (mmol/L)	7.78 ± 0.70	7.54 ± 0.48	7.55 ± 0.47
Blood glucose standard deviation (mmol/L)	3.36 ± 0.40	2.98 ± 0.64*	3.03 ± 0.53*
Insulin dose (U/kg/d)	0.60 ± 0.13	0.69 ± 0.15*	0.64 ± 0.14
Body mass index (kg/m^2)	24.4 ± 2.20	24.2 ± 2.10	24.2 ± 1.80

NOTE. Baseline, CSII; IP, IP insulin therapy after 2 (IP-2) and 4 (IP-4) months of treatment.

*$P < .01$ *v* baseline.

2). Lipid determinations for LpB and Lp no B particles at baseline are reported in Table 3. Choline-containing PL content in LpB particles from IDDM patients treated with CSII was significantly lower as compared with that in control subjects ($P < .01$). This was confirmed when this depletion in choline-containing PL content was expressed in terms of apo B. The LpB-PL/apo B ratio was significantly lower in diabetic patients versus control subjects ($P < .05$). Despite a tendency to higher values, no significant differences were observed for Lp no B lipid determinations between groups.

During CIPII, mean values of TC, TG, HDL cholesterol, and apo A-I were not significantly altered, whereas HDL cholesterol and apo A-I levels decreased in eight of 14 patients. A moderate but progressive elevation of plasma PL was noted, and after 4 months of CIPII, PL levels were no longer significantly different between diabetic patients and controls (Table 2). During CIPII, LpB-PL increased (Table 3) in 12 of 14 patients (Fig 1), and after 4 months, there was no significant difference between diabetic patients and healthy controls. The LpB-PL/apo B ratio increased significantly versus baseline (Table 3). The LpB-PL/apo B ratios of diabetic patients after 4 months of CIPII and controls were not significantly different, suggesting that CIPII improved the choline-containing PL depletion of apo B–containing particles. LpB-TC was not significantly modified.

Table 2. Plasma Lipid and Lipoprotein Levels in IDDM Patients on the Two Modes of Insulin Administration and in Control Subjects (mean ± SD)

		Diabetic Patients		
Parameter	Controls	Baseline	IP-2	IP-4
TC (mmol/L)	5.27 ± 0.93	4.97 ± 0.65	4.95 ± 0.73	5.01 ± 0.59
TG (mmol/L)	1.21 ± 0.45	1.10 ± 0.40	1.12 ± 0.48	1.13 ± 0.56
Total PL (mmol/L)	3.30 ± 0.45	2.95 ± 0.26*	2.97 ± 0.29*	3.02 ± 0.39
LDL cholesterol (mmol/L)	3.17 ± 0.88	2.94 ± 0.69	2.96 ± 0.83	3.01 ± 0.63
HDL cholesterol (mmol/L)	1.54 ± 0.40	1.57 ± 0.38	1.48 ± 0.36	1.49 ± 0.35
Apo A-I (mg/dL)	155 ± 26	157 ± 18	148 ± 23	153 ± 26
Apo B (mg/dL)	112 ± 29	95 ± 26	98 ± 25	99 ± 24

NOTE. Baseline, CSII; IP, IP insulin therapy after 2 (IP-2) and 4 (IP-4) months of treatment.

*$P < .05$ *v* controls.

Table 3. LpB and Lp no B Lipid Contents in IDDM Patients on the Two Modes of Insulin Administration and in Control Subjects (mean ± SD)

		Diabetic Patients		
Parameter	Controls	Baseline	IP-2	IP-4
Lp B-PL (mmol/L)	1.68 ± 0.33	1.09 ± 0.45†	1.25 ± 0.58*	1.36 ± 0.58§
Lp B-PL/apo B	1.53 ± 0.20	1.17 ± 0.45*	1.32 ± 0.70	1.39 ± 0.59‡
Lp B-TC (mmol/L)	3.69 ± 0.88	3.35 ± 0.77	3.59 ± 0.94	3.51 ± 0.86
Lp no B-PL (mmol/L)	1.62 ± 0.38	1.88 ± 0.61	1.81 ± 0.46	1.75 ± 0.55
Lp no B-TC (mmol/L)	1.48 ± 0.41	1.62 ± 0.49	1.36 ± 0.46	1.50 ± 0.46

NOTE. Baseline, CSII; IP, IP insulin therapy after 2 (IP-2) and 4 (IP-4) months of treatment.

*$P < .05$ *v* controls.

†$P < .01$ *v* controls.

‡$P < .05$ *v* baseline.

§$P < .01$ *v* baseline.

DISCUSSION

In this study, IDDM patients treated by CSII and in good metabolic control had a normal routine blood lipid profile but reduced plasma and LpB choline-containing PL. After 4 months of CIPII using an implantable pump, total and LpB choline-containing PL increased without significant modifications of blood glucose control.

The lipid and lipoprotein profiles of patients treated by CSII confirm our previous finding in patients treated by intensive conventional insulin therapy.[22] Some reports have

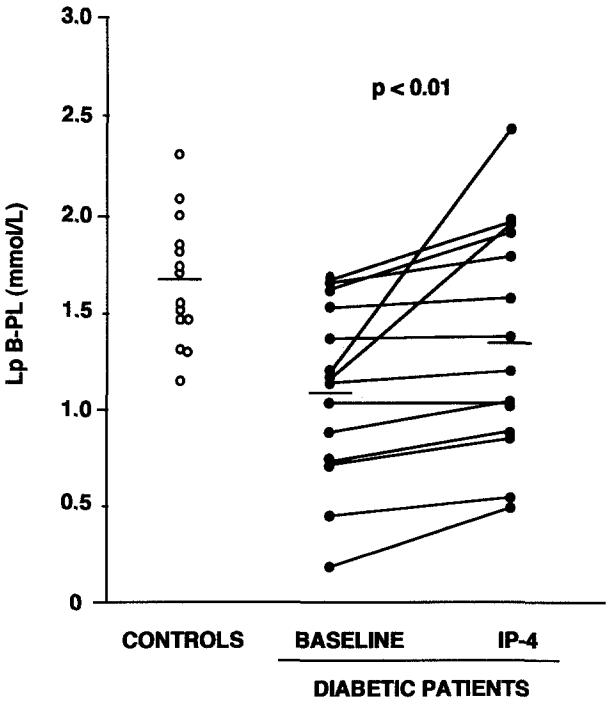

Fig 1. Effect of CIPII on choline-containing LpB-PL. (○) Individual levels of LpB-PL in the control group. (●) Individual levels of LpB-PL in the diabetic group at baseline (end of CSII therapy) and after 4 months CIPII by programable pump. (—) Mean.

emphasized the important metabolic role of the surface-lipid components of lipoproteins, ie, free cholesterol and PL,[32-35] and an altered free cholesterol to lecithin ratio has been described in plasma and lipoprotein fractions from IDDM men.[13] This ratio had been previously proposed as a potent index of CHD risk.[36]

Compositional abnormalities of plasma lipoproteins have been reported to be a consequence of poor metabolic control.[37] However, these abnormalities are not always corrected by a long period of optimized blood glucose control,[38,39] or persist in patients with normal body weight and near-normal HbA_{1c}, as indicated by our results. Another factor that can modulate plasma lipids in IDDM is the route of insulin administration. Conventional insulin therapy results in peripheral hyperinsulinemia and a negative portal-peripheral insulin gradient.[40] High peripheral insulin levels may induce an overstimulation of lipoprotein lipase (LPL) activities and therefore an increased lipolytic degradation of TG-rich lipoproteins, which characterizes well-controlled diabetic patients under intensive insulin therapy.[41] The slight reduction of TG levels we observed in patients during CSII as compared with controls may be a reflection of this increased LPL activity. Although the mechanism of the depletion of plasma PL and LpB-PL in IDDM patients remains unclear, it might also be related to an increased LPL activity through the phospholipase specificity of the enzyme.

The specific effects of IP insulin administration on plasma lipids and lipoproteins remain controversial. Moreover, interpretation of the data may be biased by confounding factors such as major improvement of blood glucose control. Therefore, we have chosen to study adequately controlled diabetic patients to allow us to evaluate only the impact of the IP route of insulin administration on lipid metabolism. However, it is always possible that the additional 2 to 4 months of insulin therapy could influence the increase in LpB choline-containing PL, rather than the switch from CSII to CIPII. Ideally, the protocol should have compared an IDDM group that continued to be treated by CSII and another IDDM group that was switched to treatment with CIPII, to show strictly specific effects of the route of insulin administration.

In our series, the increase in plasma and LpB choline-containing PL observed after 2 and 4 months of CIPII is not linked to changes in blood glucose control, body weight, or daily insulin requirements. The only change was a decrease in the blood glucose standard deviation, which may be linked to the IP insulin administration, but this might have contributed to the changes in lipids.[42] These lipid changes may be related to the route of insulin administration. IP insulin administration is associated with a positive portal-systemic insulin gradient.[43] According to Bagdade et al,[44] this may be accompanied by a reduction of LPL activity and consequently a reduction of phospholipase activity. This hypothesis may explain the increase in PL and LpB-PL observed in our study. However, recently, Ruotolo et al[21] measured LPL activity in type I diabetic patients after 3 and 9 months of CIPII. They did not observe any clear modification of enzyme activity. Unfortunately, glycemic control was not similar before and after IP infusion, and it is difficult to know whether the changes in lipoprotein metabolism were due to improved glycemic control, delivery mode of insulin, or a combination of several factors.

The influence of hepatic lipase activity on these compositional changes remains to be established. Ruotolo et al[21] reported a progressively increased activity that was significant after 9 months of IP insulin therapy.

In conclusion, we found an increase in choline-containing PL content of plasma and LpB lipoprotein particles when IDDM patients were treated using CIPII as compared with CSII. These modifications seem to be linked to the IP route of insulin administration. However, this hypothesis deserves further study.

REFERENCES

1. Kannel WB, McGee DL: Diabetes and cardiovascular disease. The Framingham Study. JAMA 241:2035-2038, 1979

2. Kannel WB: Lipids, diabetes, and coronary heart disease: Insights from The Framingham Study. Am Heart J 110:1100-1107, 1985

3. Taskinen M-R: Hyperlipidaemia in diabetes. Clin Endocrinol Metab 4:743-775, 1990

4. Bierman EL: Atherogenesis in diabetes. Arterioscler Thromb 12:647-656, 1992

5. Curtiss LK, Witztum JL: Plasma apolipoproteins AI, AII, B, CI and E are glucosylated in hyperglycemic diabetic subjects. Diabetes 34:452-461, 1985

6. Calvo C, Ponsin G, Berthezene F: Characterization of the non enzymatic glycation of high density lipoprotein in diabetic patients. Diabete Metab 14:264-269, 1988

7. Bowie A, Owens D, Collins P, et al: Glycosylated low density lipoprotein is more sensitive to oxidation: Implications for the diabetic patient? Atherosclerosis 102:63-67, 1993

8. Witztum JL, Mahoney EM, Branks MJ, et al: Nonenzymatic glycosylation of low-density lipoprotein alters its biologic activity. Diabetes 31:283-291, 1982

9. Morel DW, Chisolm GM: Antioxidant treatment of diabetic rats inhibits lipoprotein oxidation and cytotoxicity. J Lipid Res 30:1827-1834, 1989

10. Duell PB, Oram JF, Bierman EL: Nonenzymatic glycosylation of HDL and impaired HDL-receptor–mediated cholesterol efflux. Diabetes 40:377-384, 1991

11. Eckel RH, Albers JJ, Cheung MC, et al: High density lipoprotein composition in insulin-dependent diabetes mellitus. Diabetes 30:132-138, 1981

12. Slotte JP, Chait A, Bierman EL: Cholesterol accumulation in aortic smooth muscle cells exposed to low density lipoproteins: Contribution of free cholesterol transfer. Arteriosclerosis 8:750-758, 1988

13. Bagdade JD, Subbaiah PV: Whole plasma and high-density lipoprotein subfraction surface lipid composition in IDDM men. Diabetes 38:1226-1230, 1989

14. Pietri A, Dunn FL, Raskin P: The effect of improved diabetic control on plasma lipid and lipoprotein levels. Diabetes 29:1001-1005, 1980

15. Bagdade JD, Helve E, Taskinen M-R: Effects of continuous insulin infusion therapy on lipoprotein surface and core lipid composition in insulin-dependent diabetes mellitus. Metabolism 40:445-449, 1991

16. Stout RW: Overview of the association between insulin and atherosclerosis. Metabolism 34:7-12, 1985 (suppl 1)

17. Pyörälä K: Hyperinsulinaemia as a predictor of atheroscle-

rotic vascular disease: Epidemiological evidence. Diabete Metab 17:87-92, 1991

18. Selam JL, Kashyap M, Alberti KG, et al: Comparison of intraperitoneal and subcutaneous insulin administration on lipids, apolipoproteins, fuel metabolites and hormones in type I diabetes mellitus. Metabolism 38:908-912, 1989

19. Ruotolo GR, Micossi P, Galimberti G, et al: Effects of intraperitoneal versus subcutaneous insulin administration on lipoprotein metabolism in type I diabetes. Metabolism 39:598-604, 1990

20. Georgopoulos A, Saudek CD: Normalization of composition of triglyceride-rich lipoprotein subfractions in diabetic subjects during insulin infusion with programmable implantable medication system. Diabetes Care 15:19-26, 1992

21. Ruotolo G, Parlavecchia M, Taskinen M-R, et al: Normalization of lipoprotein composition by intraperitoneal insulin in IDDM. Diabetes Care 17:6-12, 1994

22. Fiévet C, Ziegler O, Parra HJ, et al: Depletion in choline-containing phospholipids of LpB particles in adequately controlled type I insulin-dependent diabetes mellitus. Diabete Metab 16:64-69, 1990

23. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979

24. Ziegler O, Kolopp M, Got I, et al: Reliability of self-monitoring of blood glucose by CSII-treated patients with type I diabetes. Diabetes Care 12:184-188, 1989

25. Renard E, Lauton D, Bonifaci C, et al: Experience with intraperitoneal insulin infusion from implantable programmable systems in type I (insulin-dependent) diabetes mellitus previously treated by external pumps. Diabete Metab 19:364-371, 1993

26. Fruchart JC, Duthilleul P, Daunizeau A, et al: Dosage du cholestérol total à l'aide d'une méthode enzymatique utilisant un monoréactif. Pharm Biol 24:227-229, 1980

27. Ziegenhorn J, Baril K, Deeg R: Improved kinetic method for automated determination of serum triglycerides. Clin Chem 26:973-979, 1980

28. Takayama M, Itoh S, Nagasaki T, et al: A new enzymatic method for determination of serum choline-containing phospholipids. Clin Chim Acta 79:93-98, 1977

29. Friedewald WT, Levy RI, Fredrickson DS: Estimations of serum low density lipoprotein cholesterol concentration without use of preparative ultracentrifugation. Clin Chem 18:499-502, 1972

30. McConathy W, Alaupovic P: Studies on the interaction of concanavalin A with the major density classes of human plasma lipoproteins: Evidence for the specific binding of lipoprotein B in its associated and free forms. FEBS Lett 41:174-176, 1974

31. Pascal M, Wülfert E: Evaluation of a new precipitation procedure for estimating high density lipoprotein cholesterol: Precipitation of apolipoprotein B associated cholesterol with concanavalin A. Ann Biol Clin 39:343-350, 1981

32. Fielding CJ: The origin and properties of free cholesterol potential gradients in plasma, and their relation to atherogenesis. J Lipid Res 25:1624-1628, 1984

33. Johnson WJ, Bamberger MJ, Latta RA, et al: The bidirectional flux of cholesterol between cells and lipoproteins: Effects of phospholipid depletion of high density lipoprotein. J Biol Chem 261:5766-5776, 1986

34. Morton RE: Free cholesterol is a potent regulator of lipid transfer protein function. J Biol Chem 263:12235-12241, 1988

35. Borensztajn J, Getz GS, Hotlar TJ: Uptake of chylomicron remnants by the liver: Further evidence for the modulating role of phospholipids. J Lipid Res 29:1087-1096, 1988

36. Kuksis A, Myher JJ, Geher K, et al: Decreased plasma phosphatidylcholine/free cholesterol ratio as an indicator of risk for ischemic vascular disease. Arteriosclerosis 2:296-302, 1982

37. James RW, Pometta D: Differences in lipoprotein subfraction composition and distribution between type I diabetic men and control subjects. Diabetes 39:1158-1164, 1990

38. Rivellese A, Riccardi G, Romano G, et al: Presence of very low density lipoprotein compositional abnormalities in type I (insulin-dependent) diabetic patients: Effects of blood glucose optimisation. Diabetologia 31:884-888, 1988

39. Rivellese A, Romano G, Patti L, et al: Persistent lipoprotein composition abnormalities in long-term well controlled insulin-dependent diabetic patients. Diab Nutr Metab 5:99-105, 1992

40. Wredling R, Liu D, Lins P-E, et al: Variation of insulin absorption during subcutaneous and peritoneal infusion in insulin-dependent diabetic patients with unsatisfactory long-term glycaemic response to continuous subcutaneous insulin infusion. Diabete Metab 17:456-459, 1991

41. Shumak SL, Zinman B, Zuniga-Guarjardo S, et al: Triglyceride-rich lipoprotein metabolism during acute hyperinsulinemia in hypertriglyceridemia humans. Metabolism 37:461-466, 1988

42. Hanaire-Broutin H, Broussolle C, Jeandidier N, et al: Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM. Diabetes Care 18:388-392, 1995

43. Nelson JA, Stephen R, Landau ST, et al: Intraperitoneal insulin administration produces a positive portal-systemic blood insulin gradient in unanesthetized, unrestrained swine. Metabolism 31:969-972, 1982

44. Bagdade JD, Dunn FL, Eckel RH, et al: Intraperitoneal insulin therapy corrects abnormalities in cholesteryl ester transfer and lipoprotein lipase activities in insulin-dependent diabetes mellitus. Arterioscler Thromb 14:1933-1939, 1994