Quantitative and Qualitative Lipoprotein Abnormalities in Diabetes Mellitus

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In people with diabetes, the concentration of an individual lipoprotein or apolipoprotein can be highly variable and is totally different in the two major forms of the disease. Alterations in the concentrations of major lipids and lipoproteins are well characterized in both IDDM and NIDDM. In general, the lipoprotein pattern is antiatherogenic in individuals with IDDM who are treated and have optimal glycemic control. In contrast, NIDDM is associated with atherogenic changes of serum lipids and lipoproteins regardless of the mode of treatment. In people with both types of diabetes, the distribution of apoE phenotype seems to be similar to that in nondiabetic populations. IDDM patients with microalbuminuria show atherogenic changes of lipoproteins and have elevated levels of Lp(a), which is a risk factor of coronary artery disease. Whether glycemic control influences the concentration of Lp(a) is still an open question. An important issue is that the concentration of a lipoprotein can be normal without excluding compositional abnormalities that are potentially atherogenic. Such alterations are present in people with both IDDM and NIDDM. Consequently, it has been questioned whether the target values to start treatment should be lower in diabetic than in nondiabetic populations. *Diabetes* 41(Suppl. 2):12–17, 1992

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IDDM, insulin-dependent diabetes; NIDDM, non-insulin-dependent diabetes; apoE, apolipoprotein E; Lp(a), lipoprotein A; CHD, coronary heart disease; FFA, free fatty acid; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Sf, svedberg flotation unit; BMI, body mass index; NCEP, National Cholesterol Education Program; NHANES, Second National Health and Nutrition Examination Survey; PROCAM, Prospective Cardiovascular Munster study; NS, not significant.

Because atherosclerotic complications, particularly coronary heart disease, are the leading causes of death in people with diabetes, the recognition of both quantitative and qualitative abnormalities that signify the risk of CHD is essential. The concentration and metabolism of plasma lipoproteins in people with diabetes are influenced first by factors specific to the diabetic state, that is, type of diabetes, glycemic control, insulin resistance, transport rate of FFA, nephropathy, and the type and method of treatment. Secondly, insulin has multiple sites of actions on the metabolism of VLDL-IDL-LDL cascade and HDL. Thus, diabetes itself can cause severe perturbations of lipoprotein metabolism. In addition, the factors that influence serum lipids and lipoproteins in the general population operate also in the diabetic population. Therefore, it is not unexpected that the concentration and composition of an individual lipoprotein can be highly variable and also are completely different in people with the two types of diabetes.

QUANTITATIVE CHANGES OF LIPOPROTEINS IN IDDM

Spectrum of lipoprotein abnormalities. In well- and moderately well-controlled IDDM patients, the levels of total cholesterol and triglycerides are commonly similar to those in nondiabetic individuals (1,2). The concentrations of VLDL and LDL are normal or even subnormal. Reduced concentration of plasma apoB is consistent with the lowering of apoB-containing particles (3). Raised HDL cholesterol levels in IDDM patients were first reported by Nikkila and Hormila (4) and were confirmed in several but not all studies (4–7). The elevation of HDL cholesterol is mainly attributed to raised HDL_2 cholesterol (7,8). In agreement, the concentration of plasma apoA-I is slightly elevated or within normal range, whereas the level of apoA-II does not differ from that of nondiabetic individuals (9).

Quantitative variation of lipoproteins in IDDM. Of the many factors that influence the concentration of plasma lipoproteins in IDDM, glycemic control, method of insulin administration, and nephropathy are the most important in clinical practice. When metabolic control is poor, the major lipid abnormality is hypertriglyceridemia, but elevation of serum total and LDL cholesterol also occurs. Insulin deficiency, due to inadequate insulin administration or to the omission of insulin therapy, is associated with decreased clearance of triglyceride-rich particles because lipoprotein lipase activity is diminished (2). Subsequently, in ketoacidosis, plasma can be clearly lipemic due to a marked elevation of both chylomicrons and VLDL, whereas the concentration of HDL cholesterol is low. Optimization of insulin therapy rapidly restores LPL activity and corrects the abnormalities of VLDL metabolism, but the response of HDL occurs more slowly. Overall, the effect of glycemic control on lipid values is emphasized by the fact that cholesterol concentration fell by 0.1 mM (3.87 mg/dl; 2.2%) and plasma triglyceride level by 0.08 mM (7.1 mg/dl; 8%) for each percentage-point fall of glycohemoglobin in a random IDDM population (10). In effect, intensive insulin treatment, which normalizes the glycemic control, lowers serum lipoproteins even within normal range. Consequently, many IDDM patients have subnormal concentrations of VLDL and LDL. The route of insulin delivery is also physiologically important. Insulin delivery s.c. by conventional regimens results in peripheral hyperinsulinemia, whereas hypoinsulinemia supervenes in portal circulation. Recently, two studies compared the effects of i.p. versus s.c. insulin delivery on serum lipids and lipoproteins (11,12). Unfortunately, the results were partly inconsistent, and therefore, further studies are required to establish if i.p. insulin regimen is more beneficial than conventional insulin regimens for lipoprotein metabolism (12).

In IDDM patients with clinical nephropathy and overt albuminuria, the concentrations of total cholesterol, triglycerides, VLDL, and LDL are elevated, whereas those of HDL cholesterol and apoA-I are reduced (2). By and large, the atherogenic lipoprotein profile is thought to contribute to the excess cardiovascular mortality in IDDM patients with nephropathy (13). Importantly, there is emerging evidence that abnormalities of serum lipids and lipoproteins occur in IDDM patients with only microalbuminuria (14–17). Overall, the atherogenic indices—LDL–HDL cholesterol and apoA-I–apoB ratios—are increased in IDDM patients with microalbuminuria.

Recently, heavy proteinuria in nondiabetic patients was reported to be associated with elevation of plasma Lp(a) levels (18). The concentration of plasma Lp(a) is a marker for excess early risk of CHD (19). Recent discovery of the homology between Lp(a) and plasminogen promoted the idea that Lp(a) acts at the interface of atherosclerosis and thrombosis. Consequently, the question arose whether Lp(a) is a special marker for CHD in IDDM patients with micro- or macroalbuminuria (20). Recently, Jenkins et al. (21) reported that Lp(a) levels were similar in IDDM patients without microalbuminuria and in nondiabetic individuals. Two studies demonstrated a relationship between Lp(a) and glycosylated hemoglobin (22,23) that contradicts the results of Jenkins et al. (21). Importantly, Jenkins et al. reported raised Lp(a) levels in IDDM patients with microalbuminuria and macroalbuminuria (21). Taken together, these preliminary results advocate Lp(a) as a potential candidate for an additional risk factor of CHD in IDDM patients with kidney disease.

TABLE 1
ApoE allele frequencies ± SD in IDDM and NIDDM patients

	IDDM patients (n = 71)	NIDDM patients (n = 60)	P
ε_4	0.190 ± 0.034	0.158 ± 0.034	NS
ε_3	0.761 ± 0.051	0.808 ± 0.054	NS
ε_2	0.049 ± 0.045	0.033 ± 0.049	NS

Data from M.J. Koistinen et al., unpublished observations. Significance of differences between allele frequencies of IDDM and NIDDM patients were calculated by χ^2 test. Standard deviations of apoE allele frequencies were calculated as described (25).

ApoE has genetic polymorphism determined by three common alleles, ε_2, ε_3, and ε_4, giving rise to six genotypes (24). ApoE polymorphism influences serum total and LDL cholesterol levels in the general population. The ε_4 allele is associated with the elevations of serum total and LDL cholesterol and apoB, whereas the ε_2 allele has the opposite effect. Because of these effects, the effect of apoE polymorphism on serum lipids in people with diabetes has been the object of recent studies. Table 1 shows that the allele frequencies of apoE in IDDM patients are similar to those in random Finnish populations (25). Similarly, Winocour et al. (26) reported that in IDDM patients, the allele frequencies of apoE did not differ from those observed in healthy control subjects. However, Winocour et al. (26) observed an unexpected increase in ε_2 homozygosity in IDDM patients. Furthermore, ε_2 homozygosity was associated with increased susceptibility to hypertriglyceridemia in IDDM patients. In contrast, ε_2 homozygosity was not increased in our IDDM group, but the ε_2 allele frequency is lower in Finns than in other white populations (26). We found that in IDDM patients, the effects of apoE locus on serum total and LDL cholesterol and apoB levels were similar to those in nondiabetic populations (Table 2) (26).

QUALITATIVE ABNORMALITIES OF LIPOPROTEINS IN IDDM

The lack of overt abnormalities of lipoproteins levels in IDDM patients with fair to good glycemic control does not exclude the possibility that there are compositional alterations that may be atherogenic. All major lipoproteins have structural heterogeneity that is attributed to discrete subpopulations. James and Pometta (27) reported that in poorly controlled IDDM patients, both VLDL and LDL subfractions have multiple abnormalities considered to be atherogenic. First, in poorly controlled IDDM patients, all three VLDL subclasses ($VLDL_1$ Sf > 100, $VLDL_2$ Sf 60–100, and $VLDL_3$ Sf 20–60) were increased. Interest-

TABLE 2
Concentrations of serum triglycerides; serum total, LDL, and HDL cholesterol; and apoB by apoE phenotypes in IDDM and NIDDM patients

	IDDM patients			NIDDM patients		
	E4/4, E4/3 (n = 23)	E3/3 (n = 41)	E3/2 (n = 7)	E4/4, E4/3 (n = 17)	E3/3 (n = 39)	E3/2 (n = 4)
Triglyceride (mM)	1.4 ± 1.0	1.4 ± 0.6	1.0 ± 0.6	1.8 ± 0.9	2.3 ± 1.7	2.5 ± 2.3
Cholesterol (mM)	6.4 ± 1.0	5.6 ± 1.0*	5.5 ± 1.0†	6.4 ± 1.5	5.8 ± 1.1	4.0 ± 2.5
LDL cholesterol (mM)	4.2 ± 1.0	3.6 ± 0.8*	3.5 ± 1.0	4.3 ± 1.4	3.6 ± 1.1	2.8 ± 0.4*
HDL cholesterol (mM)	1.4 ± 0.3	1.4 ± 0.3	1.6 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.4
ApoB (mM)	108 ± 29	91 ± 26	85 ± 24†	121 ± 49	118 ± 31	96 ± 52

Data from M.J. Koistinen et al., unpublished observations.
*P < 0.01, †P < 0.05, vs. patients with E4/4 or 4/3 phenotypes in each group.

ingly, VLDL subclasses contained relative excess of non-apoB apolipoproteins (apoCs and apoEs). Second, LDL distribution demonstrated atherogenic modification with relative excess of small dense LDL (Sf 3–6) compared with normal LDL (Sf 6–12). Finally, LDL particles in particular were triglyceride rich but depleted in esterified cholesterol. Improvement of glycemic control was associated with a fall-in large VLDL particles ($VLDL_1$ and $VLDL_2$) particularly. Rivellese et al. (28) observed an increased prevalence of triglyceride-poor but cholesterol ester–rich small VLDL in normolipidemic IDDM patients. Of physiological relevance is that diabetic VLDL and LDL in vitro induces abnormal responses of cellular cholesterol metabolism in human macrophages (29,30). Bagdade et al. (31,32) showed that in IDDM patients, lipoprotein particles also display distinct abnormalities in the distribution of surface and core lipids. First, IDDM patients have a higher free cholesterol-lecithin ratio, which is an index of CHD risk (33), in plasma and VLDL + LDL fraction. Second, there are subtle reductions of different phospholipids in HDL that may compromise the function of HDL in reverse cholesterol transfer. Recently, we reported that these alterations are not fully reversed after the achievement of optimal glycemic control (34). Importantly, the compositional changes cannot be suspected from the measurement of the concentrations of serum lipids.

PREVALENCE OF HYPERLIPIDEMIAS IN IDDM

Unfortunately, the data on the prevalence of hyperlipidemias in IDDM patients among different populations are insufficient. Recently, Winocour et al. (35) reported that in adults with IDDM, hypertriglyceridemia occurred in 31% of cases and hypercholesterolemia in 27% of cases. The cutoff values were >6.5 mM (251.6 mg/dl) for serum cholesterol and >2.25 mM (199.1 mg/dl) for serum triglycerides. Overall, the prevalence of hypertriglyceridemia and combined hyperlipidemia was more common in men with IDDM than in nondiabetic control men. In contrast, hypercholesterolemia was, if anything, less common in men with IDDM than in nondiabetic men. We also examined the prevalence of dyslipidemias in young adults (mean age 32 yr) with IDDM attending the diabetic outpatient clinic of Helsinki University Hospital (Table 3). The cutoff values were >5.0 mM (193.5 mg/dl) for cholesterol and >2.0 mM (177 mg/dl) for triglycerides, which represent the target values recommended by the Finnish consensus panel. In this cohort of consecutive IDDM patients (n = 57 for men and n = 53 for women), the prevalence of moderate hypercholesterolemia (>6.5 mM [251.55 mg/dl]) was similar in IDDM patients and in a random population of nondiabetic control subjects matched for sex, age, and BMI (8.6 vs. 11.3% for men and 5.7 vs. 6.0% for women). The prevalence of mild hypercholesterolemia (>5 mM [193.5 mg/dl]) was lower in men and women with IDDM than in nondiabetic groups (40 vs. 59% and 26 vs. 58%). In men with IDDM, the frequency of hypertriglyceridemia was similar to that in nondiabetic men (19 vs. 22%). Women with IDDM more frequently had hypertriglyceridemia than nondiabetic women (13 vs. 6%). Overall, in young adults with IDDM, the prevalence of dyslipidemias is now, if anything, less than in the nondiabetic population.

QUANTITATIVE LIPOPROTEIN ABNORMALITIES IN NIDDM

Spectrum of lipoprotein abnormalities. Raised serum and VLDL triglycerides and low levels of HDL cholesterol are the most frequent lipid abnormalities in NIDDM patients (1,2,4). Usually, the elevation of serum triglycerides is moderate, 1.5- to 3-fold compared with nondiabetic subjects matched for sex, age, and BMI. Some NIDDM patients with poor glycemic control may have

TABLE 3
Frequency (%) of hyperlipidemias in IDDM patients

	Men		Women	
	IDDM (n = 57)	Control (n = 97)	IDDM (n = 53)	Control (n = 81)
Cholesterol (mM)				
>5.0	40	59	26	58
>6.5	8.6	11.3	5.7	6.0
Triglycerides (mM)				
>2.0	19	22	13	6

IDDM patients represent 110 consecutive patients who attended diabetic outpatient clinic of Meilahti Hospital and had measurements of serum cholesterol and triglycerides January to March 1990. Nondiabetic control subjects were matched for age and BMI with IDDM subjects and represent participants in a lipid survey during 1989.

severe hypertriglyceridemia and milky serum. Such patients commonly have concomitant genetic hyperlipidemias or other secondary causes of dyslipidemias. The concentration of HDL cholesterol is on average reduced by 10–20%. In most studies, but not all, the concentrations of apoA-I and HDL cholesterol–apoA-I ratio were reported to be reduced (2,4,6,36,37). In NIDDM patients with fair to good control, the levels of serum total and LDL cholesterol do not strikingly differ from those of control populations (37). Despite this, the concentration of apoB has been reported to be elevated (37,38). The quantitative changes are present in cross-sectional studies independently of the method of therapy as well as in undiagnosed patients (39). Undoubtedly, in people with NIDDM, the lipoprotein profile is atherogenic.

Variation in lipoprotein concentrations. In practice, the main modulators of lipoproteins in NIDDM are glycemic control, insulin resistance, obesity, and nephropathy. Recently, the effect of apoE polymorphism has become of major interest. As in people with IDDM, the concentrations of serum and VLDL triglyceride and apoB are closely related to the variables of glycemic control in NIDDM populations (1,2,40). Overall improvement of glycemic control, regardless of the method of treatment, is associated with a decrease of serum total and VLDL triglycerides and a slight fall in serum total and LDL cholesterol. The response of HDL cholesterol is less consistent. In particular, intensive insulin therapy seems to be effective in correcting the quantitative abnormalities of lipoproteins in NIDDM (41).

The association of raised VLDL and low HDL cholesterol levels with insulin resistance is well documented in both nondiabetic and NIDDM populations (40–43). In humans, the rate of glucose disposal, measured by the euglycemic clamp procedure, is inversely related to the concentration of serum triglycerides but positively to that of HDL cholesterol. In NIDDM patients, the levels of serum triglyceride increase by the tertiles of glucose-disposal rate and, as in nondiabetic individuals, both high VLDL triglyceride and low HDL cholesterol are closely related to the degree of insulin resistance (40). Taken together, these observations are strong evidence that insulin resistance is an important regulator of lipoprotein levels in people with NIDDM. Obesity is highly prevalent in NIDDM patients. Recent data suggest that obesity has a particularly deleterious effect on the concentration of lipoproteins in NIDDM (44). Overall, quantitative abnormalities of lipoproteins are more frequent and more severe in obese NIDDM patients than in obese nondiabetic subjects (44). It remains to be established whether this unfavorable interaction between obesity and NIDDM is related to more severe insulin resistance.

Because apoE polymorphism contributes to the differences of lipoprotein concentrations at the population level, it is of interest to know whether it contributes to the variation of serum lipids and lipoproteins in NIDDM patients as it does in the nondiabetic population. In people with NIDDM, the apoE genotype frequencies do not differ from those in matched nondiabetic populations (45–47). Interestingly, it was reported that Japanese NIDDM patients with the ε_2 allele are more susceptible to developing hypertriglyceridemia than those without it (48). However, the contribution of the apoE gene locus to the variation of LDL cholesterol is influenced by ethnic background (49). This variation may explain why Shriver et al. (47) could not confirm the association of the ε_2 allele and hypertriglyceridemia in a group of Mexican Americans with NIDDM. Overall, the effect of the apoE gene locus on lipoproteins was similar in NIDDM and nondiabetic groups. Because the prevalence of the ε_4 allele is more frequent in Finns than in other white populations, we evaluated its effect on serum total and LDL cholesterol in NIDDM patients. Again, the apoE gene frequencies in the NIDDM group were similar to those in the nondiabetic population (Table 1; 26). The effects of the apoE gene locus on serum total and LDL cholesterol and apoB levels were similar to those in a nondiabetic Finnish population (Table 2; 26). Thus, it is possible that the effect of the apoE gene locus on the variation of lipoprotein levels in NIDDM is indeed population specific.

QUALITATIVE LIPOPROTEIN ABNORMALITIES

In most studies, but not all, NIDDM patients are reported to have subtle abnormalities in the composition of lipoproteins that cannot be detected from the measurements of the lipoprotein concentrations (2). Kinetic studies show that poorly controlled NIDDM patients secrete mainly large VLDL particles (Sf 100–400). In agreement, VLDL particles have a high triglyceride-apoB ratio (50). Even in strictly normolipidemic NIDDM patients, the cholesterol-apoB ratio is increased in VLDL + IDL fraction (Sf 12–400; 51). In addition, VLDL shows alterations in its apolipoprotein distribution with relative increase of apoE compared with apoCs (36,52). A detailed examination of the VLDL subclass profile revealed that all VLDL subclasses are elevated and appear to be enriched in free and esterified cholesterol (53). In several studies, LDL was found to be enriched in triglycerides (1,2). However, LDL fraction separated by ultracentrifugation in the density range of 1.006–1.063 g/L includes also VLDL remnants and IDL particles, and, thus, the compositional changes of LDL may be confounded by quantitative changes of IDL or remnants. In fact, the concentration of IDL is increased in NIDDM patients (54). However, a close examination of LDL subfractions revealed an aberrant profile. In NIDDM patients with poor control, the LDL_3 fraction was elevated, whereas the LDL_2 fraction was lower than in control subjects (53). Overall, the LDL_2 fraction represents normal LDL, whereas LDL_3 comprises small dense particles considered to be particularly atherogenic (55). Finally, alterations in lipids of both surface matrix and core also are present in lipoproteins of NIDDM patients as in those of IDDM patients. Bagdade et al. (56) reported that the free cholesterol-lecithin ratio in total plasma and VLDL and LDL is higher than in control subjects. In addition, the sphingomyelin-lecithin ratio was abnormal in VLDL and HDL subfractions. On the whole, the compositional alterations of lipoproteins are improved but not fully corrected with improvement of glycemic control, although the concentrations of lipoproteins are normalized (53,56). The observed qualitative

abnormalities of lipoproteins are important because they may interfere with the physiological function of lipoproteins and, thus, may be potentially atherogenic.

PREVALENCE OF QUANTITATIVE LIPOPROTEIN ABNORMALITIES

Compared with IDDM patients, quantitative abnormalities of lipoproteins are more common in NIDDM patients. The prevalence of hypertriglyceridemia varies between 20 and 60% in different studies, being two- to threefold higher than in nondiabetic populations of the same age (1,2,4). In the San Antonio Heart Study, 23% of diabetic patients had hypertriglyceridemia or low HDL cholesterol levels independently of racial background (Mexican American vs. non-Hispanic whites; 57). Overall, more than 40% of NIDDM subjects were hyperlipidemic according to the criteria of NCEP compared with only 20% in the nondiabetic population. In agreement, hypertriglyceridemia and/or low HDL cholesterol were found in 19% of NIDDM patients in a recent survey from Finland (37). In this cohort, 54% of NIDDM patients had serum cholesterol >6.5 mM (251.6 mg/dl), which was similar to that observed in the nondiabetic population. In the Finnish cohort, only 10% of the NIDDM subjects had a cholesterol level below the target value of 5 mM (193.5 mg/dl). Overall, the prevalence of hypercholesterolemia in NIDDM patients reflects that in the background population. Recent data from the NHANES study indicate that 70% of people with diagnosed diabetes and 77% with undiagnosed diabetes have high or borderline-high total cholesterol and warrant dietary treatment (58). In addition, the data from the PROCAM study indicate that the prevalence of combined hyperlipidemia is much higher in the diabetic population than in the general population (59).

REFERENCES

1. Howard BJ: Lipoprotein metabolism in diabetes mellitus. *J Lipid Res* 28:613–28, 1987
2. Taskinen M-R: Hyperlipidaemia in diabetes. *Clin Endocrinol Metab* 4:743–75, 1990
3. Winocour PH, Durrington PN, Ishola M, Anderson DC: Lipoprotein abnormalities in insulin-dependent diabetes mellitus. *Lancet* 2:1176–78, 1986
4. Gibbons GF: Hyperlipidaemia of diabetes. *Clin Sci* 71:477–86, 1986
5. Durrington PN: Serum high density lipoprotein cholesterol subfractions in type I (insulin-dependent) diabetes mellitus. *Clin Chim Acta* 120:21–28, 1982
6. Schernthaner G, Kostner GM, Dieplinger H, Prager R, Mühlhauser I: Apolipoproteins (A-I, A-II, B), Lp(a) lipoprotein and lecithin: cholesterol acyltransferase activity in diabetes mellitus. *Atherosclerosis* 49:277–93, 1983
7. Mattock MB, Salter AM, Fuller JH, Omer T, Gohari R-El, Sharon D, Keen RH: High density lipoprotein subfractions in insulin-dependent diabetic and normal subjects. *Atherosclerosis* 45:67–79, 1982
8. Taskinen M-R, Kuusi T, Nikkilä EA: Regulation of HDL and its subfractions in chronically insulin treated patients with type 1 diabetes. In *Diabetes, Obesity and Hyperlipidemias*. Crepaldi A, Tiengo A, Baggio G, Eds. Amsterdam, Elsevier Science Publishers, 1985, p. 251–59
9. Eckel RH, Albers JJ, Cheung MC, Wahl PW, Lindgren FT, Bierman EL: High density lipoprotein composition in insulin-dependent diabetes mellitus. *Diabetes* 30:132–38, 1981
10. Ostlund RE, Semenkovich CF, Schechtman KB: Quantitative relationship between plasma lipids and glycohemoglobin in type 1 diabetes. *Diabetes Care* 12:332–36, 1989
11. Selam J-L, Kashyap M, Alberti KGMM, Lozano J, Hanna M, Turner D, Jeandidier N, Chan E, Charles MA: Comparison of intraperitoneal and subcutaneous insulin administration on lipids, apolipoproteins, fuel metabolites, and hormones in type 1 diabetes mellitus. *Metabolism* 38:908–12, 1989
12. Ruotolo G, Micossi P, Galimberti G, Librenti MC, Petrella G, Marcovina S, Pozza G, Howard BV: Effects of intraperitoneal versus subcutaneous insulin administration on lipoprotein metabolism in type 1 diabetes. *Metabolism* 39:598–604, 1990
13. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T: Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. *Diabetologia* 30:144–48, 1987
14. Vannini P, Ciavarella A, Flammini M, Bargossi AM, Forlani G, Borgnino LC, Orsoni G: Lipid abnormalities in insulin-dependent diabetic patients with albuminuria. *Diabetes Care* 7:151–54, 1984
15. Dullaart RPF, Dikkeschei LD, Doorenbos H: Alterations in serum lipids and apolipoproteins in male type 1 (insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 32:685–89, 1989
16. Jones SL, Close SF, Mattock MB, Jarrett RJ, Keen H, Viberti GC: Plasma lipid and coagulation factor concentrations in insulin dependent diabetics with microalbuminuria. *Br Med J* 298:487–90, 1989
17. Watts GF, Naumova R, Slavin BM, Morris RW, Houlston R, Kubal C, Shaw KM: Serum lipids and lipoproteins in insulin-dependent diabetic patients with persistent microalbuminuria. *Diabetic Med* 6:25–30, 1989
18. Karádi I, Romics L, Domán J, Kaszás I, Hesz' A, Kostner GM: Lp(a) lipoprotein concentration in serum of patients with heavy proteinuria of different origin. *Clin Chem* 35:2121–23, 1989
19. Loscalzo J: Lipoprotein(a): a unique risk factor for atherothrombotic disease. *Arteriosclerosis* 10:672–79, 1990
20. Robbins DC, Howard BV: Lipoprotein(a) and diabetes. *Diabetes Care* 14:347–49, 1991
21. Jenkins AJ, Steele JS, Janus ED, Best JD: Increased plasma apolipoprotein(a) levels in IDDM patients with microalbuminuria. *Diabetes* 40:787–90, 1991
22. Levitsky L, Scanu AM, Gould SH: Lipoprotein(a) levels in black and white children and adolescents with IDDM. *Diabetes Care* 14:283–87, 1991
23. Haffner SM, Tuttle KR, Rainwater DL: Decrease of lipoprotein(a) with improved glycemic control in IDDM subjects. *Diabetes Care* 14: 302–307, 1991
24. Davignon J, Gregg RE, Sing CF: Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis* 8:1–21, 1988
25. Ehnholm C, Lukka M, Kuusi T, Nikkilä E, Utermann G: Apolipoprotein E polymorphism in the Finnish population: gene frequencies and relation to lipoprotein concentrations. *J Lipid Res* 27:227–35, 1986
26. Winocour PH, Tetlow L, Durrington PN, Ishola M, Hillier V, Anderson DC: Apolipoprotein E polymorphism and lipoproteins in insulin-treated diabetes mellitus. *Atherosclerosis* 75:167–73, 1989
27. James R, Pometta D: Differences in lipoprotein subfraction composition and distribution between type 1 diabetic men and control subjects. *Diabetes* 39:1158–64, 1990
28. Rivellese A, Riccardi G, Romano G, Giacco R, Patti L, Marotta G, Annuzzi G, Mancini M: Presence of very low density lipoprotein compositional abnormalities in type 1 (insulin-dependent) diabetic patients: effects of blood glucose optimisation. *Diabetologia* 31: 884–88, 1988
29. Lyons TJ, Klein RL, Baynes JW: Stimulation of cholesteryl ester synthesis in human monocyte-derived macrophages by LDL from type 1 diabetic subjects: the influence of non-enzymatic glycosylation of LDL. *Diabetologia* 30:916–23, 1987
30. Klein RL, Lyons IM, Lopes-Virella MR: Interaction of very-low-density lipoprotein isolated from type 1 (insulin-dependent) diabetic subjects with human monocyte–derived macrophages. *Metabolism* 38:1108–14, 1989
31. Bagdade JD, Subbaiah PV: Abnormal high-density lipoprotein composition in women with insulin-dependent diabetes. *J Lab Clin Med* 113:235–40, 1989
32. Bagdade JD, Subbaiah PV: Whole-plasma and high-density lipoprotein subfraction surface lipid composition in IDDM men. *Diabetes* 38:1226–30, 1989
33. Kuksis A, Myher JJ, Geher K, Jones GJ, Breckenridge WC, Feather T, Hewitt D, Little JA: Decreased plasma phosphatidylcholine/free cholesterol ratio as an indicator of risk for ischemic vascular disease. *Arteriosclerosis* 2:296–302, 1982
34. 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* 40:445–49, 1991
35. Winocour PH, Durrington PN, Ishola M, Hillier VF, Anderson DC: The prevalence of hyperlipidaemia and related clinical features in insulin-dependent diabetes mellitus. *Q J Med* 70:265–76, 1989
36. Weisweiler P, Schwandt P: Type 1 (insulin-dependent) versus type 2 (non-insulin-dependent) diabetes mellitus: characterization of serum lipoprotein alterations. *Eur J Clin Invest* 17:87–91, 1987
37. Rönnemaa T, Laakso M, Kallio V, Pyörälä K, Marniemi J, Puukka P:

Serum lipids, lipoproteins, and apolipoproteins and the excessive occurrence of coronary heart disease in non-insulin-dependent diabetic patients. *Am J Epidemiol* 130:632–45, 1989
38. Billingham MS, Milles JJ, Bailey CJ, Hall RA: Lipoprotein subfraction composition in non-insulin-dependent diabetes treated by diet, sulphonylurea, and insulin. *Metabolism* 38:850–57, 1989
39. Laakso M, Voutilainen E, Sarlund H, Aro A, Pyörälä K, Penttilä I: Serum lipids and lipoproteins in middle-aged non-insulin-dependent diabetics. *Atherosclerosis* 56:271–81, 1985
40. Laakso M, Sarlund H, Mykkänen L: Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance. *Arteriosclerosis* 10:223–31, 1990
41. Taskinen M-R, Kuusi T, Helve E, Nikkilä EA, Yki-Järvinen H: Insulin therapy induces antiatherogenic changes of serum lipoproteins in noninsulin-dependent diabetes. *Arteriosclerosis* 8:168–77, 1988
42. Abbott WGH, Lillioja S, Young AA, Zawadzki JK, Yki-Järvinen H, Christin L, Howard BV: Relationships between plasma lipoprotein concentrations and insulin action in an obese hyperinsulinemic population. *Diabetes* 36:897–904, 1987
43. Garg A, Helderman HJ, Koffler M, Ayuso R, Rosenstock J, Raskin P: Relationship between lipoprotein levels and in vivo insulin action in normal young white men. *Metabolism* 37:982–87, 1988
44. Laakso M, Pyörälä K: Adverse effects of obesity on lipid and lipoprotein levels in insulin-dependent and non-insulin-dependent diabetes. *Metabolism* 39:117–22, 1990
45. Eto K, Watanabe K, Iwashima Y, Morikawa A, Oshima E, Sekiguchi M, Ishii K: Apolipoprotein E polymorphism and hyperlipemia in type 2 diabetics. *Diabetes* 35:1374–82, 1986
46. Imari Y, Koga S, Ibayashi H: Phenotypes of apolipoprotein E and abnormalities in lipid metabolism in patients with non-insulin-dependent diabetes mellitus. *Metabolism* 37:1134–38, 1988
47. Shriver MD, Boerwinkle E, Hewett-Emmett D, Hanis CL: Frequency and effects of apolipoprotein E polymorphism in Mexican-American NIDDM subjects. *Diabetes* 40:334–37, 1991
48. Eto M, Watanabe K, Sato T, Makino I: Apolipoprotein-ε_2 and hyperlipoproteinemia in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 69:1207–12, 1989
49. Utermann G: Apolipoprotein E polymorphism in health and disease. *Am Heart J* 113:433–39, 1987
50. Taskinen M-R, Packard CJ, Shepherd J: Effect of insulin therapy on metabolic fate of apolipoprotein B–containing lipoproteins in NIDDM. *Diabetes* 39:1017–27, 1990
51. Iwai M, Yoshino G, Matsushita M, Morita M, Matsuba K, Kazumi T, Baba S: Abnormal lipoprotein composition in normolipidemic diabetic patients. *Diabetes Care* 13:792–96, 1990
52. Klein RL, Lyons TJ, Lopes-Virella MF: Metabolism of very low- and low-density lipoproteins isolated from normolipidaemic type 2 (non-insulin-dependent) diabetic patients by human monocyte–derived macrophages. *Diabetologia* 33:299–305, 1990
53. James RW, Pometta D: The distribution profiles of very low density and low density lipoproteins in poorly-controlled male, type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 34:246–52, 1991
54. Kasama T, Yoshino G, Iwatani I, Iwai M, Hatanaka H, Kazumi T, Oimomi M, Baba S: Increased cholesterol concentration in intermediate density lipoprotein fraction of normolipidemic non-insulin-dependent diabetics. *Atherosclerosis* 63:263–66, 1987
55. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM: Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA* 260:1917–21, 1988
56. Bagdade JD, Buchanan WE, Kuusi T, Taskinen M-R: Persistent abnormalities in lipoprotein composition in noninsulin-dependent diabetes after intensive insulin therapy. *Arteriosclerosis* 10:232–39, 1990
57. Stern MP, Patterson JK, Haffner SM, Hazuda HP, Mitchell BD: Lack of awareness and treatment of hyperlipidemia in type II diabetes in a community survey. *JAMA* 262:360–64, 1989
58. Harris MI: Hypercholesterolemia in diabetes and glucose intolerance in the U.S. population. *Diabetes Care* 14:366–74, 1991
59. Assmann G, Schulte H: The Prospective Cardiovascular Münster (PROCAM) study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J* 116:1713–24, 1988