Low Synthesis and High Absorption of Cholesterol Characterize Type 1 Diabetes

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OBJECTIVE — Streptozotocin-induced type 1 diabetes in experimental animals inhibits cholesterol synthesis and increases cholesterol absorption. In contrast to human type 2 diabetes, virtually no information is available on cholesterol synthesis and absorption in type 1 diabetes.

RESEARCH DESIGN AND METHODS — We studied the variables of cholesterol metabolism in 27 patients with type 1 diabetes and in 10 patients with type 2 diabetes matched for body weight, using cholesterol precursor sterol ratios to cholesterol as surrogate markers of synthesis, and those of cholestanol and plant sterols of cholesterol absorption. Glucose control was good in all subjects.

RESULTS — Total and HDL cholesterol and LDL triglycerides were higher in type 2 than in type 1 diabetes. Serum sterols, measured also in VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL, were transported up to >90% by LDL and HDL in type 1 diabetes. The ratios of all absorption sterols in serum and in each lipoprotein were higher, and those of the synthesis markers, especially cholestenol and lathosterol, were lower in type 1 than in type 2 diabetes.

CONCLUSIONS — In contrast to type 2 diabetes, the findings in type 1 diabetes could be related to low expression of ABC G/5 G/8 genes, resulting in high absorption of cholesterol and sterols in general and low synthesis of cholesterol.

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Dyslipidemia characterizes patients with type 2 diabetes, showing normal or modestly increased cholesterol, small dense LDL, reduced HDL cholesterol, and modestly increased serum triglycerides with altered metabolism of triglyceride-rich lipoproteins (1). Cholesterol absorption efficiency and serum plant sterols, reflecting cholesterol absorption (2), are low in type 2 diabetes (3,4), and synthesis of cholesterol and its biliary and fecal elimination are increased (3,5,6). Type 1 diabetes has less advanced dyslipidemia (7), yet obliterating arterial disease, both microvascular and macrovascular, develops frequently, and myocardial infarction is also an important cause of death in these patients. The relatively normal lipid pattern is apparently a reason that scientific interest has been less frequently focused to metabolism of serum lipids in patients with type 1 than type 2 diabetes. For instance, there is virtually no information on cholesterol absorption or synthesis in patients with type 1 diabetes. However, serum plant sterols were increased in a group of poorly controlled patients with type 1 diabetes but no more at intensified insulin treatment (8). That lack of insulin might actually improve cholesterol absorption and downregulate hepatic cholesterol synthesis is indicated by streptozotocin-induced diabetes in experimental animals (9). To this end, our intention was to study cholesterol metabolism in type 1 diabetes, and in the present study we investigated surrogate markers of cholesterol absorption and synthesis by measuring serum noncholesterol sterols in patients with type 1 diabetes and compared the results with those in type 2 diabetes. From among the noncholesterol sterols, ratios of cholestenol, desmosterol, and lathosterol to cholesterol reflect cholesterol synthesis (2), whereas those of cholestanol, campesterol, and sitosterol are markers of cholesterol absorption (2). In addition to the total serum values of different noncholesterol sterols, their concentrations and ratios to cholesterol were studied in different lipoproteins, VLDL, IDL, LDL, and HDL, which were separated with ultracentrifugation.

RESEARCH DESIGN AND METHODS

— From among type 1 diabetic patients of our endocrine outpatient department, 27 men and women, age 18–46 years with a BMI of 23 ± 1 kg/m^2 (mean ± SE) on a good glucose balance with a constant insulin dose, volunteered for the study (Table 1). The type 2 diabetes group included 10 patients selected on the basis of identical body weight with the type 1 patients and without insulin therapy. They were aged 43–67 years with a BMI of 23 ± 1 kg/m^2 and also on good glucose control. The subjects in either group did not use statins or other hypolipidemic agents. The patients had been advised to consume a diet recommended for diabetes in general, but no dietary analyses were made. Fasting blood samples were obtained in the morning at ~8:00 A.M. in both groups before the morning insulin dose in type 1 diabetic subjects. The research protocol was accepted by the Ethics Committee of our department (University of Helsinki).

Serum cholesterol and triglycerides were measured with commercial kits (CHOD-PAP and GPO-PAP; Roche Diagnostics, Mannheim, Germany). Blood glucose and glucose hemoglobin were as-

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Abbreviations: IDL, intermediate-density lipoprotein.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic and clinical data and serum lipids (in millimoles/liter) in type 1 and type 2 diabetic subjects*

Variables	Type 1 diabetes	Type 2 diabetes
n	27	10
Age (years)	33 ± 3	61 ± 3*
Male/Female	15/12	8/2
BMI (kg/m^2)	23 ± 1	23 ± 1
Glycated hemoglobin (%)	7.4 ± 0.4	ND
Blood glucose (mmol/l)	ND	8.4 ± 0.9
Total cholesterol	4.27 ± 0.19	5.56 ± 0.43*
VLDL cholesterol	0.24 ± 0.02	0.57 ± 0.28
IDL cholesterol	0.17 ± 0.01	0.17 ± 0.03
LDL cholesterol	2.89 ± 0.18	3.42 ± 0.27
HDL cholesterol	0.97 ± 0.06	1.40 ± 0.12*
Total triglycerides	0.85 ± 0.07	1.14 ± 0.18
VLDL triglycerides	0.40 ± 0.05	0.67 ± 0.16
IDL triglycerides	0.07 ± 0.01	0.08 ± 0.01
LDL triglycerides	0.18 ± 0.01	0.23 ± 0.01*
HDL triglycerides	0.15 ± 0.01	0.13 ± 0.01

Data are means ± SE. The lipoprotein lipid values are recovery corrected. *$P < 0.05$ vs. type 1 diabetes.

sayed by the routine hospital methods. VLDL, IDL, LDL, and HDL were separated with ultracentrifugation. Noncholesterol sterols (of which ratios to cholesterol of cholestenol, desmosterol, and lathosterol reflect cholesterol synthesis as well as squalene, a nonsteroid precursor of cholesterol, and those of cholestanol, campesterol, and sitosterol, markers of cholesterol absorption) were measured with gas liquid chromatography from nonsaponifiable material of serum or lipoprotein fractions (10). The results of squalene and noncholesterol sterols are given either as micrograms/deciliter so as to see their distribution and concentrations in different lipoproteins or as microgram/milligram of cholesterol ratios in which cholesterol was obtained from the same gas liquid chromatography run. The ratios to cholesterol "normalizes" the low concentrations of squalene and noncholesterol sterols in the triglyceride-rich lipoproteins VLDL and IDL.

Means ± SE were calculated, and the statistical difference between the control and diabetic groups was calculated by two-sided Student's *t* test, using $P < 0.05$ as the limit for statistical significance. Logarithmic transformations were performed when appropriate.

RESULTS

Cholesterol and triglycerides

Table 1 shows that serum total and HDL cholesterol and LDL triglyceride levels were higher in type 2 than in type 1 diabetic subjects. Body weight was unchanged in the participants during the study. The type 2 diabetic subjects were older than subjects with type 1 diabetes, but the lipid and sterol values were not related to age.

Concentrations of noncholesterol sterols and squalene

From among the serum concentrations of noncholesterol sterols, those reflecting cholesterol synthesis were all lower in type 1 than type 2 diabetic subjects, whereas those of the cholesterol absorption markers and squalene were similar (Table 2). The concentrations were low especially in triglyceride-rich lipoproteins, e.g., IDL cholestanol was 5 vs. 120 μg/dl in LDL of type 1 diabetes. Additional data in Fig. 1 (shown for squalene, lathosterol, and sitosterol) indicate that the serum concentrations are reflected mainly by LDL and HDL. Namely, ~55% in type 1 and ~60% in type 2 diabetes of serum noncholesterol sterols were transported by LDL with the respective transport by HDL being 34–39% and 23–30%, respectively. Relatively high amounts of noncholesterol sterols were found in HDL in type 1 diabetes, such that concentrations of the absorption sterols were higher ($P < 0.05$) in the HDL of type 1 than type 2 diabetic subjects. Owing to accumulation of squalene to triglyceride-rich lipoproteins, its transport by LDL remained low, especially in type 2 diabetic subjects. Respective distributions of noncholesterol sterols were roughly similar to those of cholesterol (Fig. 1).

Ratios of noncholesterol sterols and squalene to cholesterol

Table 3 shows that the ratios to cholesterol (in terms of microgram/milligram of cholesterol) of the synthesis marker sterols in serum were lower, significantly for cholestenol and lathosterol ($P < 0.01$), in type 1 than type 2 diabetic subjects, whereas those of the absorption markers were correspondingly higher ($P < 0.001$ for all). Despite marked differences in noncholesterol sterol concentrations in different lipoproteins, the ratios were more homogenous but not identical in different lipoproteins, as shown in Table 3. Lathosterol ratios were significantly lower in all lipoprotein fractions of type 1 than type 2 diabetic subjects, whereas the respective difference occurred only for LDL and HDL cholestenol. The cholestenol and lathosterol ratios were highest in triglyceride-rich lipoproteins and lowest in LDL for cholestenol and in HDL for lathosterol. The ratios of squalene were

Table 2—*Concentration (in micrograms/deciliter) of squalene and noncholesterol sterols in serum of type 1 and type 2 diabetic subjects*

Variable	Type 1 diabetes	Type 2 diabetes
n	27	10
Cholestanol	251.3 ± 15.5	239.0 ± 17.6
Campesterol	620.9 ± 52.5	522.8 ± 60.0
Sitosterol	345.6 ± 28.0	287.9 ± 29.6
Squalene	86.1 ± 5.8	74.6 ± 14.9
Cholestenol	18.9 ± 1.6	34.5 ± 5.6*
Desmosterol	110.9 ± 6.1	161.5 ± 26.9
Lathosterol	200.0 ± 14.2	364.7 ± 42.9*

Data are means ± SE. *$P < 0.05$ vs. type 1 diabetes.

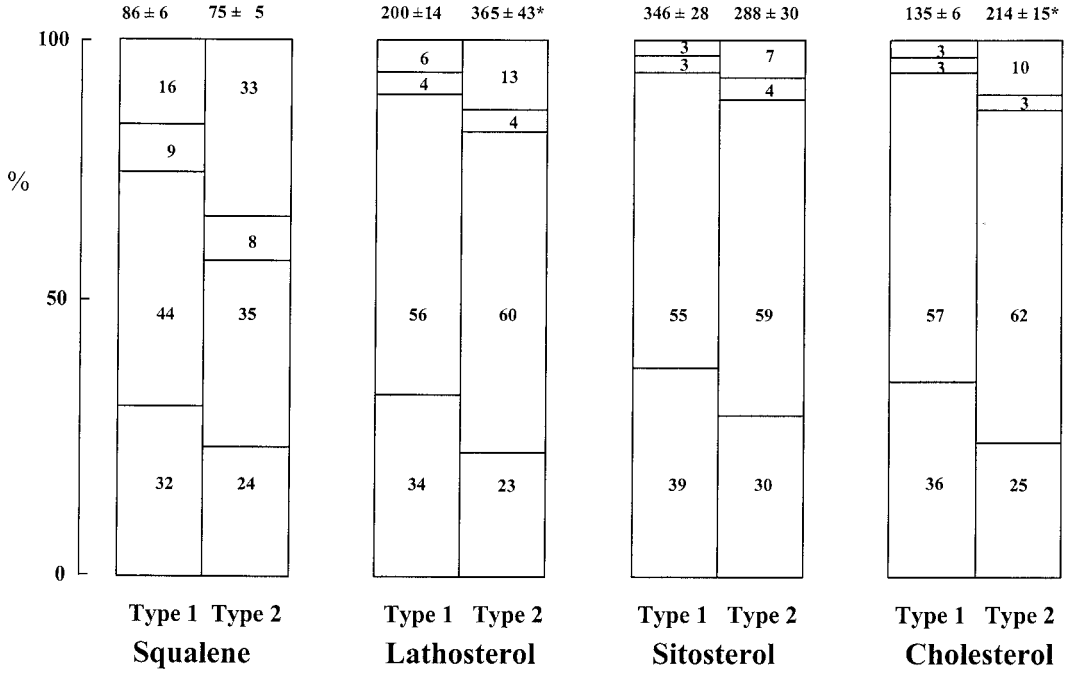

Figure 1—*The percent distribution of squalene, lathosterol, sitosterol, and cholesterol concentrations in different lipoproteins in type 1 and type 2 diabetes. The total concentrations of the respective sterols and squalene are given at the* top *of each column. The lipoproteins are in the following order from top: VLDL, IDL, LDL, and HDL. *Significantly different from type 1 diabetes.*

Table 3—*Serum cholesterol*, squalene, and noncholesterol sterols† in type 1* (n = *27) and type 2* (n = *10) diabetic subjects*

Variables	VLDL	IDL	LDL	HDL	Serum
Cholesterol					
Type 1	5.6 ± 0.6	4.1 ± 0.4	76.7 ± 4.4	48.5 ± 2.2	135.1 ± 5.7
Type 2	21.1 ± 10.8	6.7 ± 1.3	132.6 ± 10.4‡	54.0 ± 4.7	214.4 ± 15.2‡
Cholestanol					
Type 1	123.4 ± 4.5	134.1 ± 4.4	156.5 ± 5.2	181.9 ± 7.8	163.5 ± 5.7
Type 2	91.8 ± 4.6‡	85.8 ± 3.8‡	114.5 ± 5.6‡	133.3 ± 6.1‡	116.9 ± 6.4‡
Campesterol					
Type 1	366.9 ± 20.9	402.2 ± 20.6	404.7 ± 20.8	421.0 ± 22.4	409.4 ± 21.4
Type 2	237.4 ± 20.1‡	260.3 ± 24.0‡	253.0 ± 23.1‡	263.2 ± 24.3‡	254.7 ± 23.4‡
Sitosterol					
Type 1	169.6 ± 9.4	214.3 ± 10.0	221.0 ± 12.1	255.2 ± 14.3	230.7 ± 12.7
Type 2	132.4 ± 13.7‡	200.5 ± 25.4	134.0 ± 12.3‡	163.6 ± 14.2‡	142.1 ± 13.3‡
Squalene					
Type 1	209.9 ± 17.2	164.0 ± 12.1	40.2 ± 2.1	47.2 ± 5.9	51.1 ± 2.5
Type 2	130.4 ± 30.0‡	132.5 ± 31.5	20.9 ± 1.8‡	34.9 ± 3.5	34.7 ± 4.1
Cholestenol					
Type 1	20.1 ± 2.1	26.4 ± 3.2	8.9 ± 0.9	13.6 ± 1.0	11.2 ± 0.9
Type 2	23.0 ± 3.8	24.4 ± 6.0	15.2 ± 1.6‡	18.4 ± 2.0‡	16.1 ± 1.6‡
Desmosterol					
Type 1	54.4 ± 3.2	49.0 ± 3.6	63.9 ± 3.3	70.9 ± 3.8	65.4 ± 3.3
Type 2	63.8 ± 6.2	57.5 ± 8.9	79.8 ± 8.6	76.5 ± 7.5	75.5 ± 6.5
Lathosterol					
Type 1	164.5 ± 12.8	165.6 ± 12.4	122.6 ± 8.8	120.8 ± 9.5	124.7 ± 9.2
Type 2	222.3 ± 22.8‡	231.0 ± 21.1‡	171.2 ± 8.2‡	165.1 ± 9.6‡	173.1 ± 4.1‡

Data are mean ± SE. $n = 27$ for type 1 diabetes and $n = 10$ for type 2 diabetes. *Milligram/deciliter; †10^2 × micrograms/milligrams of cholesterol. All sterols measured by gas liquid chromatography from each lipoprotein fraction. ‡$P < 0.05$ vs. type 1 diabetes.

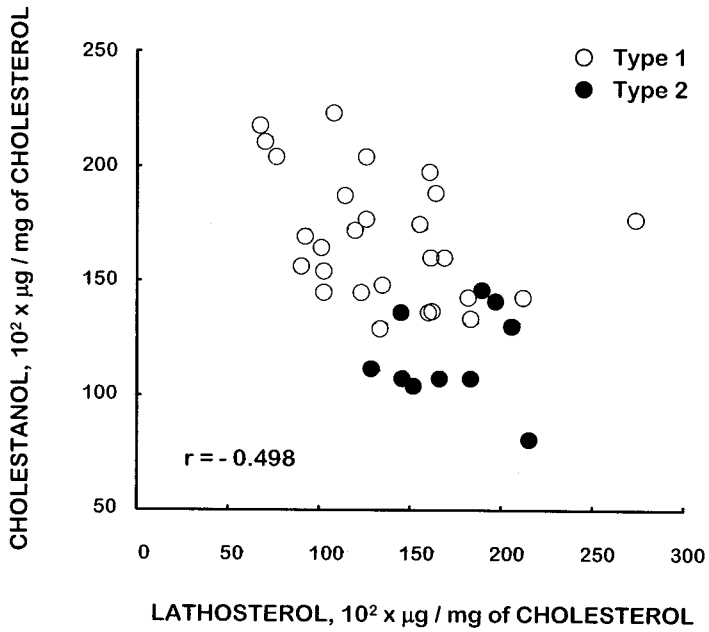

Figure 2—*Correlation of lathosterol and cholestanol ratios with each other in serum (*r *= −0.498;* P *= 0.003).* ○*, type 1 diabetes;* ●*, type 2 diabetes.*

surprisingly higher in VLDL and LDL of type 1 than type 2 diabetic subjects, and the markedly high ratios in the triglyceride-rich lipoproteins decreased when moved to LDL in both groups. In contrast to the ratios of squalene, cholestenol, and lathosterol, those of desmosterol increased when moved from the triglyceride-rich lipoproteins to LDL and HDL in both groups. The ratios only tended to be lower in subjects with type 1 than type 2 diabetes.

The ratios of cholestanol, campesterol, and sitosterol were significantly higher in all lipoprotein fractions (except IDL sitosterol) of type 1 than type 2 diabetic subjects. The ratios of the absorption sterols were usually lowest in VLDL, surprisingly high in IDL (except cholestanol in type 2), and usually highest in HDL. Despite markedly higher absorption sterol ratios in type 1 than type 2 diabetic subjects, their relative distributions were roughly similar in lipoproteins of type 1 and 2 diabetic subjects. The ratios of the absorption markers correlated negatively with those of the synthesis markers as shown for cholestanol and lathosterol in Fig. 2.

The mean ratios in serum underestimated those of squalene, cholestenol, and lathosterol in VLDL and IDL and the absorption markers in HDL, whereas the mean ratios overestimated desmosterol in VLDL and IDL and absorption markers mainly in VLDL.

CONCLUSIONS — The major novel findings of the present study were the increased ratios to cholesterol of the serum sterols reflecting absorption of cholesterol of type 1 versus type 2 diabetes and decreased ratios of the sterols reflecting synthesis of cholesterol. The findings can be interpreted to indicate high absorption and low synthesis of cholesterol in the patients with type 1 as compared with type 2 diabetes. These differences were present also in various lipoproteins.

Is there then any evidence in the literature for the finding that patients with type 1 diabetes have high absorption and low synthesis of cholesterol? The answer is yes, but only for experimental diabetes. Namely, streptozotocin-induced diabetes (insulin deficient) in rats hypertrofies intestinal mucosal function enhancing fat and cholesterol absorption and reducing hepatic cholesterol synthesis (9). Serum plant sterols, campesterol and sitosterol, have been shown to be increased over twofold in rats (11). The values improved with insulin treatment.

Correspondingly, significantly increased campesterol and sitosterol ratios to cholesterol have been found in one study of poorly controlled patients with type 1 diabetes (8). The values were normalized with intensified insulin treatment. However, no comparison was made with type 2 diabetes, and cholesterol precursors were not measured so that changes in cholesterol synthesis could not be evaluated. Earlier studies have measured cholesterol metabolism mainly in type 2 diabetes, but the results have been confusing because of different durations of the disease, different insulin and drug doses, variable glycemic control, and a variable clinical picture of the study populations (5,6,12–15). One of these studies included a small group of type 1 diabetic patients exhibiting actually slightly reduced cholesterol synthesis and fecal output of neutral sterols as compared with control subjects (13). Cholesterol absorption percentage measured in two brothers with type 1 diabetes was exceptionally high, ~60% in both of them, despite marked bile acid malabsorption (16). High absorption efficiency was associated with high cholestanol and plant sterol ratios to cholesterol in serum but also with increased precursor sterol ratios of cholesterol and high cholesterol synthesis as measured by the sterol balance technique. Bile acid malabsorption was responsible for increased cholesterol synthesis despite increased cholesterol absorption. Increased administration of dietary cholesterol under controlled conditions seemed to increase LDL cholesterol more effectively in type 1 diabetic subjects than in matched control subjects (17). On the other hand, reduction of dietary cholesterol with modification of fat intake has been observed to effectively reduce serum cholesterol in type 1 diabetes (18). Thus, to our knowledge, no general conclusion has been made in the literature that cholesterol absorption was high and synthesis correspondingly low in type 1 diabetes.

The findings of high cholesterol absorption and low cholesterol synthesis as indicated by serum noncholesterol sterols in patients with type 1 diabetes in the present study suggest that variables of cholesterol metabolism are opposite to those in type 2 diabetes. In the latter patients, cholesterol absorption efficiency has frequently been found to be low (3,13,19), ratios of cholestanol and plant sterols to cholesterol are also low in serum (3,4,19), whereas synthesis of cholesterol measured with either the ratios of the precursor sterols to cholesterol or sterol balance technique are high (3,5,6,12,15),

and biliary secretion and fecal output of cholesterol is elevated (3,5,6). The findings are also found in obese subjects (20,21) but are detectable also in type 2 diabetic subjects without obesity (22) or in non diabetic subjects with a high-normal glucose level (23). Insulin resistance seems to be an important factor in modifying cholesterol metabolism when metabolic syndrome includes most clinical and laboratory findings of type 2 diabetes. What then are the factors regulating cholesterol metabolism in opposite directions in the two forms of diabetes?

Our hypothesis is that the ABC transport system regulates cholesterol absorption and synthesis also in the two types of diabetes. Briefly, current research indicates that ABC G/5 and G/8 genes are almost exclusively expressed in intestinal enterocytes and liver (24). In transgenic mice or in overexpression of the two genes in mice, serum plant sterol levels and sterol absorption are reduced, and cholesterol synthesis and biliary and fecal secretion of cholesterol are increased (25). Thus, the changes in cholesterol metabolism in these mice are identical to those in type 2 diabetes. Accordingly, resemblance of cholesterol metabolism in obesity (20) and type 2 diabetes (3,19) to that found in overexpression of the ABC G/5 G/8 genes has to be emphasized.

On the other hand, knockout of the ABC G/5 G/8 genes in mice changes serum sterol pattern (25) to resemble that seen in hereditary sitosterolemia, a metabolic disease caused by mutation of the ABC G/5 G/8 genes (24,26). In fact, downregulated expression of the two genes increases cholesterol and plant sterol absorption and prevents their biliary secretion, resulting in enhanced serum plant sterol and cholesterol levels. However, subsequently increased hepatic cholesterol inhibits cholesterol synthesis, preventing extensive increase of serum cholesterol and lowers biliary and fecal secretion of cholesterol (27). We propose that in type 1 diabetes, the expression of the ABC G/5 G/8 genes are downregulated, probably due to lack of effective insulin action, resulting in increased intestinal cholesterol and plant sterol absorption and their reduced biliary secretion. Owing to enhanced accumulation of cholesterol, hepatic cholesterol synthesis is downregulated, precursor sterol ratios are reduced, and LDL cholesterol is normal or slightly increased, with age extensively increased values occurring mainly during poor glycemic control (28). Cholestanol and plant sterol ratios are increased and seem to characterize type 1 diabetes.

Even though the ratios to cholesterol in serum of different sterols were not exactly the same as those in different lipoproteins, the mean ratios of both absorption and synthesis markers in serum seemed to discover the difference between type 1 and type 2 diabetes. A reason for the different expression of desmosterol might be that this side chain-unsaturated sterol was synthesized also in peripheral tissues from where it was released into circulation analogously to cholesterol by reverse transport. Recent studies have indicated that precursor sterols with a good proportion of desmosterol are released to medium HDL and LDL during cell cultures (29). Cholestenol, lathosterol, and squalene are apparently mostly originating from the liver, released in VLDL in circulation, and further to IDL during lipolysis of VLDL. Reduced conversion of squalene to desmosterol might increase its serum level in type 1 diabetes.

The ratios of the absorption sterols were lowest in VLDL and highest in HDL in both diabetic groups. Their high ratios in HDL might point to reversed transport of these sterols from tissues to the liver by HDL itself or after transfer to LDL by cholesteryl ester transfer protein. The high ratio of plant sterols in IDL of type 2 diabetic patients might reflect its low hepatic uptake. On the other hand, impaired biliary secretion of the absorption sterols in type 1 diabetes could increase their hepatic sterol content. This phenomenon, in association with possible low hepatic cholesterol synthesis, could have produced VLDL with high absorption sterol ratios to cholesterol. However, the increase of plant sterols in type 1 diabetes was highest in HDL and was >60% higher than in type 2 diabetes.

The present findings suggest that increased cholesterol absorption in type 1 diabetes could be a primary factor in modifying cholesterol metabolism such that the homeostatic mechanism decreases cholesterol synthesis, a factor that could keep LDL cholesterol concentration quite normal. The findings could be explainable by altered expression of the ABC G/5 G/8 genes or a specific occurrence of their polymorphism. The most important point at the moment was to carry out direct measurements of cholesterol absorption percentage and synthesis of cholesterol by sterol balance technique in type 1 diabetes during conventional and intensified insulin treatment and to proceed with an intervention study in which the serum cholesterol level is reduced by inhibiting cholesterol absorption, e.g., by plant stanol ester margarine. Our future research project is along these investigation lines.

References

1. Howard BV: Lipoprotein metabolism in diabetes. *Curr Opin Lipidol* 5:216–220, 1994
2. Miettinen TA, Tilvis RS, Kesäniemi YA: Serum plant sterols and cholesterol precursors reflect cholesterol absorption and synthesis in volunteers of a randomly selected male population. *Am J Epidemiol* 131:20–31, 1990
3. Simonen PP, Gylling HK, Miettinen TA: Diabetes contributes to cholesterol metabolism regardless of obesity. *Diabetes Care* 25:1511–1515, 2002
4. Sutherland WH, Scott RS, Lintott CJ, Robertson MC, Stapely SA, Cox C: Plasma noncholesterol sterols in patients with non-insulin dependent diabetes mellitus. *Horm Metab Res* 24:172–175, 1992
5. Abrams JJ, Ginsberg H, Grundy SM: Metabolism of cholesterol and triglycerides in nonketotic diabetes mellitus. *Diabetes* 31:903–910, 1982
6. Bennion LJ, Grundy SM: Effects of diabetes mellitus on cholesterol metabolism in man. *N Engl J Med* 296:1365–1371, 1977
7. Winocour PH, Durrington PN, Ishola M, Anderson DC: Lipoprotein abnormalities in insulin-dependent diabetes mellitus. *Lancet* 1:1176–1178, 1986
8. Kojima H, Hidaka H, Matsumura K, Fujita Y, Yamada S, Haneda M, Yasuda H, Kikkawa R, Kashiwagi A: Effect of glycemic control on plasma plant sterol levels and post-heparin diamine oxidase activity in type 1 diabetic patients. *Atherosclerosis* 145:389–397, 1999
9. Young NL, Lopez DR, McNamara DJ: Contributions of absorbed dietary cholesterol and cholesterol synthesized in small intestine to hypercholesterolemia in diabetic rats. *Diabetes* 37:1151–1156, 1988
10. Miettinen TA: Cholesterol metabolism during ketoconazole treatment in man. *J Lipid Res* 29:43–51, 1988
11. Kojima H, Omoto Y, Hidaka H, Aoki T, Nakamura T, Kawabata T, Konaka K, Kashiwagi A, Kikkawa R, Shigeta Y: Increased plasma post-heparin diamine ox-

idase activity and plant sterol levels in streptozotocin diabetic rat. *Biochem Biophys Res Commun* 186:398–404, 1992
12. Andersen E, Hellström P, Hellström K: Cholesterol and bile acid metabolism in middle-aged diabetics. *Diabetes Metab* 12: 261–266, 1986
13. Briones ER, Steiger DL, Palumbo PJ, O'Fallon WM, Langworthy AL, Zimmerman BR, Kottke BA: Sterol excretion and cholesterol absorption in diabetics and nondiabetics with and without hyperlipidemia. *Am J Clin Nutr* 44:353–361, 1986
14. Saudek CD, Brach E: Cholesterol metabolism in diabetes: I. The effect of diabetic control on sterol balance. *Diabetes* 27:1059–1064, 1978
15. Naoumova RP, Cummings MH, Watts GF, Rendell NB, Taylor GW, Sönksen PH, Thompson GR: Acute hyperinsulinaemia decreases cholesterol synthesis less in subjects with non-insulin-dependent diabetes mellitus than in non-diabetic subjects. *Eur J Clin Invest* 26:332–340, 1996
16. Gylling H, Miettinen TA: Cholesterol absorption and cholesterol and bile acid synthesis in two brothers with IDDM and diarrhoea. *Diabetes Care* 17:1345–1347, 1994
17. Romano G, Tilly-Kiesi MK, Patti L, Taskinen M-R, Pacioni D, Cassader M, Riccardi G, Rivellese AA: Effects of dietary cholesterol on plasma lipoproteins and their subclasses in IDDM patients. *Diabetologia* 41:193–200, 1998
18. Kaufmann RL, Assal JPh, Soeldner JS, Wilmshurst EG, Lemaire JR, Gleason RE, White P: Plasma lipid levels in diabetic children: effect of diet restricted in cholesterol and saturated fats. *Diabetes* 24:672–679, 1975
19. Simonen P, Gylling H, Howard AN, Miettinen TA: Introducing a new component of the metabolic syndrome: low cholesterol absorption. *Am J Clin Nutr* 72:82–88, 2000
20. Miettinen TA, Gylling H: Cholesterol absorption efficiency and sterol metabolism in obesity. *Atherosclerosis* 153:241–248, 2000
21. Nestel PJ, Schreibman PH, Ahrens EH Jr: Cholesterol metabolism in human obesity. *J Clin Invest* 52:2389–2397, 1973
22. Simonen PP, Gylling H, Miettinen TA: Body weight modulates cholesterol metabolism in non-insulin dependent type 2 diabetics. *Obes Res* 10:328–335, 2002
23. Strandberg TE, Salomaa V, Vanhanen H, Miettinen TA: Associations of fasting blood glucose with cholesterol absorption and synthesis in nondiabetic middle-aged men. *Diabetes* 45:755–761, 1996
24. Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH: Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 290:1771–1775, 2000
25. Yu L, Li-Hawkins J, Hammer RE, Berge KE, Horton JD, Cohen JC, Hobbs HH: Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. *J Clin Invest* 110:671–680, 2002
26. Lee M-H, Lu K, Hazard S, Yu H, Shulenin S, Hidaka H, Kojima H, Allikmets R, Sakuma N, Pegoraro R, Srivastava AK, Salen G, Dean M, Patel SB: Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption. *Nat Genet* 27:79–83, 2001
27. Miettinen TA: Phytosterolaemia, xanthomatosis and premature atherosclerotic arterial disease: a case with high plant sterol absorption, impaired sterol elimination and low cholesterol synthesis. *Eur J Clin Invest* 10:27–35, 1980
28. Glasgow AM, August GP, Hung W: Relationship between control and serum lipids in juvenile-onset diabetes. *Diabetes Care* 4:76–80, 1981
29. Heino S, Lusa S, Somerharju P, Ehnholm C, Olkkonen VM, Ikonen E: Dissecting the role of the Golgi complex and lipid rafts in biosynthetic transport of cholesterol to the cell surface. *Proc Natl Acad Sci U S A* 97:8375–8380, 2000