Plasma Lipid and Lipoprotein Disorders in IDDM

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Abnormal lipoprotein metabolism contributes to the increased risk of premature atherosclerosis in people with insulin-dependent (type I) diabetes. Although hypertriglyceridemia is common in those with untreated IDDM, treatment with conventional insulin therapy usually restores fasting lipoprotein profiles to nondiabetic levels. Intensive insulin therapy improves glycemic control and lipoprotein concentrations, but does not ameliorate the changes in lipoprotein composition described in people with IDDM. Some of these persistent changes in lipoprotein composition have been attributed to peripheral hyperinsulinemia associated with s.c. insulin therapy. The recent availability of implantable insulin-infusion pumps for treatment of IDDM has allowed the study of the effect of i.p. insulin delivery on lipoprotein metabolism. i.p. insulin therapy is capable of maintaining near normal plasma glucose levels while reducing the peripheral hyperinsulinemia. Although results have been contradictory, studies of i.p. insulin therapy may eventually help to determine whether some of the observed changes in lipoprotein metabolism and composition in people with IDDM are due to the peripheral hyperinsulinemia associated with s.c. insulin therapy. *Diabetes* 41(Suppl. 2):102–06, 1992

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IDDM, insulin-dependent diabetes; CHD, coronary heart disease; VLDL, very-low-density lipoprotein; LDL cholesterol, low-density lipoprotein cholesterol; HDL cholesterol, high-density-lipoprotein cholesterol; VLDL-TG, very-low-density-lipoprotein triglyceride; apoB, apolipoprotein B; DCCT, Diabetes Control and Complications Trial; CSII, continuous s.c. insulin infusion; CPII, continuous i.p. insulin infusion; CVII, continuous i.v. insulin infusion.

Insulin has important regulatory effects on plasma lipid as well as glucose metabolism, which explains why IDDM is associated with significant abnormalities of lipoprotein metabolism. The importance of lipid and lipoprotein disorders in IDDM is due to the increased risk of atherosclerosis. Long-term studies from the Joslin Clinic demonstrate the excess cardiovascular mortality in patients with IDDM (1). In juvenile-onset IDDM, the cumulative mortality by age 55 yr due to CHD was 35% for both men and women, compared with 8% for aged matched nondiabetic men and 4% for nondiabetic women in the Framingham Heart Study.

Although diabetes appears to be an independent cardiovascular risk factor, abnormalities in lipid and lipoprotein metabolism in diabetic people also contribute to the observed excess in cardiovascular risk (2). In IDDM patients with CHD, increases in total and LDL cholesterol and decreases in HDL cholesterol are more common than in IDDM patients without CHD (3). In addition, one proposed explanation for the increased cardiovascular risk in diabetic women compared with men is that diabetes appears to have a greater adverse effect on lipid and lipoprotein levels in women than in men (4). Various mechanisms are responsible for abnormal lipoprotein metabolism in people with IDDM, and these depend on the relative insulin deficiency, the degree of diabetic control, the method of insulin administration, and the sex of the individual.

UNTREATED OR POORLY CONTROLLED IDDM

Uncontrolled IDDM is often associated with elevated plasma lipid levels, and insulin treatment usually restores lipid levels to normal. In a study of diabetic patients with ketoacidosis, Weidman et al. (5) examined the effect of treatment on plasma lipid levels. Before insulin therapy, elevated cholesterol and triglyceride levels were due to

accumulation of triglyceride-rich lipoproteins, chylomicrons, and VLDL. Insulin therapy resulted in a decrease in triglycerides to normal levels in most patients within 24 h. LDL cholesterol was low initially and did not change with therapy. HDL cholesterol levels were also low but increased significantly after 24 h.

The mechanism responsible for the development of hyperlipidemia in people with uncontrolled IDDM is due to the effect of insulin on adipose tissue lipoprotein lipase activity. Acute insulin deficiency initially causes an increase in free fatty acid mobilization from adipose tissue, resulting in increased secretion of VLDL-TG from the liver. With longer-term insulin deficiency, the liver converts free fatty acids into ketone bodies, and VLDL-TG secretion diminishes. At the same time, lipoprotein lipase activity falls (6), resulting in impaired clearance of VLDL and chylomicrons from the plasma (7). Treatment of the diabetic ketoacidosis with insulin rapidly corrects these metabolic abnormalities and clears the lipemia.

CONVENTIONAL TREATMENT OF IDDM

Most studies show a pattern of moderate plasma lipid and lipoprotein abnormalities in IDDM patients treated adequately with conventional insulin therapy. Nikkila and Hormila (8) examined 170 middle-aged insulin-requiring diabetic patients and compared their values with nondiabetic control subjects of the same age and sex. Plasma cholesterol, VLDL-C, LDL-C, and triglyceride levels in the diabetic subjects were similar to those in the nondiabetic subjects, but HDL-C levels were significantly higher than in nondiabetic subjects. Sosenko et al. (9) studied 105 juvenile patients with IDDM and compared them with their nondiabetic siblings. They reported that poor diabetic control, as determined by HbA_{1c} and fasting glucose levels, were associated with increases in total cholesterol, VLDL-C, LDL-C, and triglyceride. However, the diabetic patients with good metabolic control had lipid levels similar to their nondiabetic siblings. HDL-C was normal and not affected by diabetic control.

Walden et al. (4) also reported moderate lipid abnormalities in 111 patients with IDDM compared with age-, weight-, and sex-matched control subjects. Men with IDDM had slightly higher mean total triglycerides (1.7%) and total cholesterol levels (4.6%), the latter mainly due to increased HDL-C. However, the differences observed in the women with IDDM were greater. The women with IDDM had a 66% higher mean total triglyceride level and 22% higher total cholesterol, due to increased VLDL-C (33%), LDL-C (24%), and HDL-C (11%) levels compared with nondiabetic control subjects. These authors concluded that diabetes had a greater adverse effect on lipoprotein concentrations in diabetic women than in diabetic men.

The effect of IDDM on HDL levels remains controversial. Although several large studies reported normal HDL levels in people with IDDM compared with nondiabetic control subjects others reported moderate elevations of HDL-C. Eckel et al. (10) reported high-normal HDL-C levels and increased apolipoprotein A-I–A-II ratio in IDDM patients compared with control subjects, consistent with increased HDL_2 in the diabetic subjects. Mattock et al. (11) also reported increased HDL-C and HDL_2-C in men with IDDM, but not in women. On the other hand, Bagdade and Subbaiah (12) reported that the increase in HDL-C in men with IDDM is due to increased HDL_3-C rather than HDL_2-C. In contrast, Bergman et al. (13) reported decreased HDL-C in IDDM due to decreased HDL_2-C and HDL_3-C in men and to decreased HDL_3-C in women.

Several studies also confirmed the importance of diabetic control on plasma lipoprotein abnormalities in people with IDDM. Lopes-Virella et al. (14) studied 106 patients with IDDM and divided them into three groups (good, fair, and poor control) based on 24-h glycosuria and HbA_{1c} levels. Total cholesterol, VLDL-C, LDL-C, and triglyceride levels were increased in the group with poor control, and HDL-C levels decreased, compared with the groups with fair and good control. Glasgow et al. (15) also reported a positive correlation between diabetes control and serum cholesterol, triglyceride, and VLDL-C + LDL-C in 147 children with IDDM. HDL-C levels were not correlated with control for the group as a whole, but did correlate with fasting blood glucose when the patients were analyzed individually. Elkeles et al. (16) studied the relationship between HDL-C and diabetes control in insulin-requiring diabetic subjects and reported that HDL-C did not correlate with HbA_1 levels.

Gonen et al. (17) examined plasma lipoproteins and apoproteins in 109 patients with IDDM. HbA_1 levels were positively correlated with LDL-C, triglyceride, and apoB levels, but not with HDL-C levels. The strongest correlation was between apoB levels and HbA_1, and the authors suggested that apoB is a particularly sensitive indicator of alterations in glycemic control. Semenkovich et al. (18) reported plasma lipids in a group of 544 patients with IDDM. HbA_1 correlated positively with total cholesterol, triglyceride, and LDL-C and negatively with HDL-C.

Sosenko et al. (19) examined the longitudinal relationship between plasma lipids and diabetes control (HbA_1) in 124 young patients with IDDM during 1 yr. Control correlated with fluctuations in total cholesterol, VLDL-C, LDL-C, and triglyceride levels, but not HDL-C levels. Ostlund et al. (20) also studied longitudinal changes in plasma lipids in 212 people with IDDM over an average interval of 3.7 yr. Changes in cholesterol and triglyceride correlated with changes in glycohemoglobin, and improved diabetic control was closely associated with reduced plasma lipid levels. In addition, increased insulin dose was independently associated with increased plasma triglyceride levels, but not related to plasma cholesterol levels.

One of the largest studies to examine plasma lipid and lipoprotein levels in people with IDDM is the DCCT (21). The DCCT is a multicenter, randomized clinical trial in North America designed to determine whether intensive diabetes treatment will affect early vascular complications. Fasting cholesterol, triglyceride, HDL-C, and LDL-C were measured during screening in 1569 healthy IDDM patients between the ages of 13 and 39 yr and with 1 to 15 yr of diabetes, and were compared with values obtained in nondiabetic individuals by the Lipid Re-

search Clinics prevalence study (22). When age-matched groups of IDDM patients and nondiabetic subjects were compared, men with IDDM and older women with IDDM (ages 25–39 yr) had similar lipid and lipoprotein profiles to nondiabetic subjects. The only group with abnormal values were the younger (ages 13–24 yr) women with IDDM, who had higher total cholesterol and LDL-C and lower HDL-C levels. Metabolic control, measured by HbA_{1c}, and body weight correlated positively with total and LDL cholesterol and triglyceride levels, but not with HDL-C levels.

INTENSIVE INSULIN THERAPY

The effect of intensive s.c. insulin therapy on plasma lipid and lipoprotein metabolism was also studied. Pietri et al. (23) compared the effect of 3 wk of improved diabetic control with either conventional therapy or CSII using insulin infusion pumps in diabetic patients studied on a metabolic ward. They found a significant decrease in triglyceride and VLDL-C levels with both treatments, but a decrease in total cholesterol and LDL-C occurred only in the CSII therapy group.

Dunn et al. (24) studied the effect of CSII therapy with insulin pumps on lipoprotein levels in ambulatory patients. They observed decreases in total cholesterol, VLDL-C, LDL-C, and triglycerides within 2 to 4 wk of treatment. These changes were maintained over 6 mo and were associated with maintaining the glycosylated hemoglobin levels within the normal range. In addition, significant increases in HDL-C levels were observed after 2 to 3 mo of CSII therapy. Falko et al. (25) confirmed the finding of an increase in HDL cholesterol with insulin pump therapy in ambulatory diabetic patients.

Lopes-Virella et al. (26) studied the effect of 2–3 wk of intensive insulin therapy in 55 subjects with IDDM on a metabolic ward. Twenty-two of the subjects were treated with CSII, and the rest were treated with multiple doses of s.c. regular insulin. Total, VLDL, and LDL cholesterol, total and VLDL triglycerides, and apoB levels significantly decreased, and HDL-C and apoA-I levels increased with intensive insulin therapy. The effects were more pronounced in patients admitted with poor diabetic control compared with those initially classified with fair control. Gonen et al. (17) also reported the effect of CSII pump in six patients with IDDM. Most of their subjects also exhibited a reduction in LDL-C and apoB levels and increases in HDL-C and apoA-I levels.

INTRAPERITONEAL INSULIN THERAPY

The recent availability of implantable insulin-infusion pumps (27) has permitted the study of different routes of insulin administration on lipoprotein metabolism. Intensive s.c. insulin therapy results in normalization of plasma glucose levels, but at the expense of elevated peripheral insulin concentrations. Implantable insulin pumps permit chronic i.p. insulin therapy and are now successfully used in people with IDDM to nearly normalize plasma glucose and insulin profiles and restore the normal portal-peripheral insulin gradient present in nondiabetic individuals.

Because of the possible effect of insulin on production of VLDL from the liver, as well as action on the enzymes lipoprotein lipase and hepatic lipase, there has been considerable interest in the effect of i.p. insulin therapy on lipoprotein metabolism. Unfortunately, the results have been contradictory. Monnier et al. (28) compared CPII to CSII and found increased cholesterol and apoB levels with CPII. They suggested that this result was due to increased cholesterol and apoB synthesis by the liver with CPII therapy. Selam et al. (29) also compared the effect of i.p. and s.c. insulin administration on plasma lipids. They observed no change in total cholesterol, LDL-C, or apoB levels, but an increase in triglycerides and decrease in HDL-C after 6 mo of i.p. insulin therapy. On the other hand, Ruotolo et al. (30) found lower VLDL triglycerides and apoB and higher HDL and HDL_3 cholesterol with CPII.

Thompson and Dunn (31) also studied the effect of different routes of insulin administration on lipoprotein metabolism. Fifteen IDDM subjects were studied after 3 mo of intensive s.c. insulin therapy and after 6 mo of either i.p. or i.v. insulin therapy with an implantable insulin pump. No change in plasma lipid, lipoprotein cholesterol, or apoB and apoA-I levels were observed with i.v. insulin therapy. However, in the CPII group, a progressive increase in fasting and postprandial plasma triglycerides and transient increase in LDL-C were observed.

ABNORMAL LIPOPROTEIN METABOLISM AND COMPOSITION

VLDL metabolism in patients with treated IDDM depends on diabetic control. In patients with poorly controlled but nonketotic IDDM, both overproduction and decreased clearance of VLDL can occur (32). With adequately treated conventional therapy, plasma triglyceride levels are usually normal or only slightly elevated, and these patients tend to have normal production and clearance of VLDL-TG. Institution of CSII with insulin-infusion pumps results in a marked drop in plasma triglycerides due to decreased VLDL-TG production (33). A similar fall in plasma VLDL-TG production is observed after treatment with CVII using the artificial β-cell (34). These latter two studies show that intensive insulin therapy can result in decreased rates of VLDL-TG production, leading to subnormal levels of plasma triglyceride, despite the development of moderate hyperinsulinemia. On the other hand, i.p. insulin therapy with an implantable pump has been reported to decrease VLDL levels because of decreased production and increased clearance of VLDL apoB, but has little effect on VLDL-TG kinetics (30).

Compositional changes in VLDL from people with IDDM were described. VLDL from normolipidemic IDDM patients are enriched with cholesterol and apoB and depleted in triglycerides compared with that of nondiabetic subjects (35). This abnormal composition suggests the presence of smaller and possibly more atherogenic VLDL. Improved glycemic control with intensive s.c. insulin therapy improves but does not completely normalize the abnormal composition (35,36). Georgopoulis and Saudek (37) examined composition of triglyceride-rich lipoproteins after i.p. insulin therapy with implantable

pumps and found improvement, but attributed this change to the associated improvement in glycemic control.

Dunn et al. (38) also studied the effect of different routes of insulin delivery (s.c., i.p., or i.v.) with implantable insulin pumps but with similar levels of glycemic control on lipoprotein metabolism and composition. Fifteen IDDM subjects were studied after 3 mo of intensive s.c. insulin therapy and after 6 mo of either CPII or CVII. There were no significant differences in patient weights, daily insulin dose, or HbA_{1c} among the three methods of insulin delivery, but 24-h free insulin levels were significantly lower with i.p. than with s.c. or i.v. insulin therapy. Fasting and postprandial triglyceride levels were slightly higher after i.p. insulin therapy, but VLDL composition as estimated by VLDL cholesterol–triglyceride ratios and triglyceride-apoB ratios improved with i.p. insulin therapy. On the other hand, no change in fasting or postprandial triglyceride levels or VLDL composition was observed with i.v. insulin therapy. These changes were associated with significantly lower lipoprotein lipase activity with i.p. insulin compared with s.c. or i.v. insulin therapy. Thus, i.p. insulin therapy resulted in improvements of VLDL composition probably related to lower free insulin concentrations and decreased lipoprotein lipase activity.

There are several mechanisms postulated to be responsible for abnormal LDL metabolism in IDDM. *1*) Nonenzymatic glucosylation of LDL-apoB interferes with normal LDL catabolism mediated by the LDL receptor (39,40). Nonenzymatic glucosylation of LDL was shown to inhibit uptake and degradation of LDL by endothelial cell (41). *2*) Binding of LDL to its receptor is impaired, independent of LDL glucosylation (42). LDL uptake and binding to fibroblasts isolated from patients with poorly controlled IDDM is slower than from nondiabetic control subjects, and insulin therapy restores LDL binding to normal (43). Insulin stimulates LDL catabolism (44), and this process may be related to stimulation of LDL receptor activity (45,46). *3*) Studies of LDL metabolism in conventionally treated IDDM patients demonstrated that LDL-apoB synthesis and clearance are similar to those in nondiabetic subjects (47). However, improvement in control with CSII resulted in a decrease in LDL apoB production to levels below those observed in nondiabetic control subjects.

The mechanism for the low HDL in people with untreated IDDM is probably related to low lipoprotein lipase activity, which can lead to reduced formation of HDL during impaired lipolysis of VLDL (48). Studies in rabbits with alloxan-induced diabetes also suggest that low HDL levels are due to decreased HDL apo A-I synthetic rates (49). The rise in HDL-C levels with CSII appears to be due to increases in both HDL_2 and HDL_3 cholesterol fractions (50). This increase may be related to the high peripheral insulin levels with CSII, which can increase adipose tissue lipoprotein lipase activity (51,52). Alterations in surface and core lipids of HDL in people with IDDM also were reported (12,53). These compositional changes are postulated to be atherogenic by impairing reverse cholesterol transport and are not reversed by intensive s.c. insulin therapy (54). In contrast, i.p. insulin therapy improves cholesterol ester transfer and HDL composition towards normal (55).

CONCLUSION

In summary, although levels of plasma lipids and lipoproteins in IDDM are affected by metabolic control, these changes are moderate if good metabolic control is maintained. Total, VLDL, and LDL cholesterol and triglyceride levels in people with IDDM treated adequately with conventional insulin therapy are similar or only slightly elevated compared with age-matched nondiabetic individuals. HDL-C levels may be low in uncontrolled IDDM, but in adequately insulinized diabetic patients, HDL-C levels are normal or slightly elevated compared with nondiabetic subjects of the same age and sex. On the other hand, with intensive insulin therapy, particularly with CSII with insulin-infusion pumps, VLDL, LDL-C, and apoB levels decrease, and HDL-C and apoA-I levels increase. These changes may be partly at the expense of peripheral hyperinsulinemia associated with intensive insulin therapy. I.p. insulin therapy with implantable insulin pumps may be able to maintain near-normal plasma glucose levels while reducing peripheral hyperinsulinemia. The potential benefit of this form of therapy on lipoprotein metabolism and composition remains to be determined.

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