minireview

Lipoprotein metabolism in diabetes mellitus

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I. INTRODUCTION

Diabetes mellitus is almost always associated with changes in plasma lipoproteins. To understand the mechanism of the changes in lipoproteins that occur in diabetes mellitus and how they may influence the development of the cardiovascular disease that accompanies this disorder, we must examine lipoprotein metabolism. The purpose of this review is to summarize observations from this and other laboratories on lipoprotein metabolism in human diabetics, to evaluate the possible mechanisms of diabetes-associated changes in lipoprotein metabolism, and to define directions for future research. As will be evident, there are multiple abnormalities of lipoprotein metabolism, primarily in VLDL and HDL, but also to some extent in LDL, which can potentially explain the increased atherogenesis in human diabetics.

This review will consider separately studies of lipoprotein metabolism in the two major forms of human diabetes as defined by the National Diabetes Data Group (1) and the World Health Organization (2). The two forms of diabetes differ in their basic mechanisms of development and in physiologic characteristics such as associations with obesity, age, and insulin; thus, lipoprotein metabolism may differ in the two forms. It should be emphasized, however, that the two forms of this disease share the common characteristics of hyperglycemia and both microvascular and macrovascular complications, and it is possible that lipoproteins are related to the etiology of the cardiovascular disease in the two forms of diabetes in similar ways.

II. LIPOPROTEIN METABOLISM IN NON-INSULIN-DEPENDENT DIABETES MELLITUS

The most common form of human diabetes is non-insulin-dependent diabetes (NIDDM); this is also referred to as Type II, maturity onset, or non-ketotic diabetes (1, 2). It most often occurs after age 40, and is very often associated with obesity. Individuals with NIDDM

Abbreviations: VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; FCR, fractional catabolic rate; LPL, lipoprotein lipase; LCAT, lecithin:cholesterol acyltransferase; IVFTT, intravenous fat tolerance test.

often have high concentrations of insulin both fasting and postprandially, although the time course of secretion may be altered. Since they are hyperglycemic, individuals with NIDDM can be said to have a relative deficiency of insulin. The main reason for this inability for insulin to induce adequate glucose disposal is that subjects with NIDDM are insulin-resistant; that is, there appears to be a defect(s) at the cellular level that impedes insulin-mediated glucose disposal. Free fatty acids are also elevated in individuals with NIDDM, although it is not certain whether this is because of their insulin resistance or because of other hormonal derangements. Individuals with NIDDM are not dependent on insulin therapy, although some may receive insulin after failure of weight loss or oral hypoglycemic therapy. Thus, it is possible to study lipoprotein metabolism in NIDDM in the absence of therapy.

A. VLDL metabolism in NIDDM

The most common alteration of lipoproteins in NIDDM is an elevation in VLDL, as reflected by either increased total triglyceride or VLDL triglyceride concentrations (3–23). Some reports, especially the earlier descriptions of diabetic hypertriglyceridemia (3, 4), stressed individuals with extremely high levels of plasma and VLDL triglycerides; it is clear, however, from the studies of large populations (9, 11, 12, 16, 19, 23), including the Pima Indians (21) who have a virtual absence of genetic hyperlipemia (24), that NIDDM generally produces only a 50–100% elevation in plasma VLDL or total triglycerides. It is, thus, likely that NIDDM subjects with total triglyceride concentrations greater than 300–400 mg/dl are those who also have other genetic defects in lipoprotein metabolism (25), the expression of which may be exacerbated by hyperglycemia.

1. Metabolism of VLDL triglyceride in NIDDM. Abnormalities in both production and clearance of VLDL triglyceride have been reported in NIDDM. Several studies (26–33) have observed an overproduction of VLDL triglyceride **(Table 1).** This elevation in VLDL production is more pronounced in diabetics with very high triglyceride values (26, 28, 31, 33) but it is also observed in subjects with more modest elevations in plasma triglyceride (26, 34, 35). In the two studies where no significant overproduction was observed (27, 36), individuals had either very mild elevations in triglyceride, mild hyperglycemia, or no elevations in plasma free fatty acids. That the increase in VLDL triglyceride production is in some way induced directly by hyperglycemia is suggested by the observations that the overproduction decreases after glycemia is improved, regardless of the method of therapy (26, 31–34).

In addition to inducing an overproduction of VLDL triglyceride, non-insulin-dependent diabetes appears to be associated with a defect in clearance of VLDL triglyceride. Decreased fractional catabolic rates (FCR) have been observed in VLDL triglyceride metabolism (26–28, 30, 31, 33–36) and also in studies using Intralipid infusions (intravenous fat tolerance tests) (7, 37, 38). This decreased fractional catabolic rate decreased as glycemia decreased (7, 31, 33, 34, 36), further evidence for a diabetes-induced effect on VLDL clearance.

Some studies of patients with NIDDM, especially those with greatly elevated triglycerides, did not show consistent clearance defects (26, 29, 31, 32). One possibility is that the interpretation of kinetic data for VLDL-triglyceride (and for other lipoproteins) is influenced in part by the mathematical analysis of the specific activity curves. Earlier studies used single exponential analysis of the data (26–30) whereas later studies have employed multicompartmental modeling (31–36). In addition, the interpretation of the differences in FCR must be evaluated in view of the fact that the diabetics and nondiabetics are compared at different levels of VLDL triglyceride.

2. Metabolism of VLDL apolipoprotein B in non-insulin-dependent diabetics. Although there are fewer studies of VLDL apoB metabolism in NIDDM, results indicate there is a clearance defect similar to that for VLDL triglyceride, whereas VLDL apoB production may be influenced primarily by obesity. Subjects with NIDDM have a decrease in fractional catabolic rate for VLDL apoB (30, 34, 35). Haffner et al. (39) found slower clearance of chylomicron apoB in hyperlipidemic subjects with NIDDM. The proportional decrease in clearance of VLDL apoB was similar to that observed for VLDL triglyceride (34, 35).

Studies to date suggest there may be an overproduction of VLDL-apoB in NIDDM, but this may be modulated by obesity, which is associated with greatly increased production of VLDL apoB (40, 41). Sigurdsson, Nicoll, and Lewis (28) observed increased production rates for VLDL apoB in a group of non-insulin-dependent diabetics with hyperlipidemia compared to normolipidemic controls. Kissebah et al. (30) also observed that VLDL apoB production was increased in both normolipidemic and in hyperlipemic mildly diabetic subjects. The subjects studied in these groups were mildly obese, averaging approximately 120% of ideal body weight. On the other hand, in two studies in our laboratory (34, 35) among more obese diabetics, individuals with non-insulin-dependent diabetes did not have an elevation in VLDL apoB production compared to weight-matched controls. These data suggest that, although obese diabetics have higher VLDL apoB production compared to lean individuals, in obese subjects with NIDDM VLDL apoB production may be maximally stimulated and therefore diabetes has a greater influence on VLDL triglyceride production.

Finally, a greater proportion of the VLDL apoB in NIDDM is metabolized without conversion to LDL (direct removal or shunt pathway) (30, 35). We have

TABLE 1. Metabolism of VLDL-TG in NIDDM

Reference	Patients	Obesity (% ideal body wt)	Total Triglyceride	Fasting Glucose	Transport	FCR	Comments
		%	*mg/dl*	*mg/dl*			
Lewis et al. (37)	10M/12F	112	all but 3 below 300	Mean 188	NA	↓	Measured by IVFTT. FCR increased after therapy
Nikkila and Kekki (26)		115	< 400	> 110	↑		Single exponential analysis
Nikkila and Kekki (26)		115	< 400	> 110	↑		Single exponential analysis
Nikkila and Kekki (26)		115	> 400	> 110	↑	↓	Single exponential analysis
Sigurdsson et al. (28)	2M/1F	100–123	> 1000	160–240	↑	↓	Single exponential analysis
Kissebah et al. (27)	8M/8F	Mean 108	Mean 381	Mean 132		↓	Single exponential analysis
Kissebah et al. (27)	4M/3F	Mean 125	Mean 242	Mean 133	↑	↓	Single exponential analysis
Kissebah et al. (30)	5M/4F	Mean 120	Mean 121	Mean 127	↑	↑	Single exponential analysis
Kissebah et al. (30)	5M/6F	Mean 118	Mean 326	Mean 150	↑		Single exponential analysis
Kissebah et al. (30)	4M/4F	Mean 122	Mean 366	Mean 181	↑	↓	Single exponential analysis
Paisley et al. (7)	14M/12F	Mean 94	All but 3 < 264	Random > 322	NA	↓	Measured by IVFTT
Greenfield (29)	11M/11F	131	Mean 387	Mean 264	↑	NA	Single exponential analysis
Abrams et al. (31)	14M	Mean 115	Mean 617	Mean 280	↑	↓ in 10/14	Multicompartmental analysis
Ginsberg and Grundy (32)	7M/2F	110–123	Mean 739	Mean 261	↑		Multicompartmental analysis
Howard et al. (36)	10M	Mean 152	Mean 167	Mean 217		↓	Multicompartmental analysis
Dunn et al. (33)	4M/2F	Mean 95	Mean 1302	Mean 207	↑	↓	Multicompartmental analysis
Vessby et al. (38)	12M/8F	Mean 102	Mean 431	Mean 203	NA	↓	Measured by IVFTT
Taskinen et al. (34)	6M/9F	Mean 171	Mean 212	Mean 242	↑	↓	Multicompartmental analysis
Howard et al. (35)	10M	Mean 163	Mean 189	Mean 216	↑	↓	Multicompartmental analysis

demonstrated that this increased direct removal of VLDL is related to the larger triglyceride-rich particles found in NIDDM (34, 35) (see section IIA4).

3. Lipoprotein lipase activity in NIDDM. Studies of lipoprotein lipase in diabetes have been reviewed and summarized recently (42); therefore emphasis will be focused on possible relationships between observations on lipoprotein lipase and the changes in metabolism of VLDL (and later HDL) observed in diabetics. The evaluation of these relationships is confounded by problems of measurement. One method of determining LPL is by measurement after injection of heparin, but it is not clear how heparin-stimulated plasma activity reflects actual tissue metabolic capacity for VLDL and chylomicron degradation. Activity is also measured from adipose tissue or muscle obtained by needle biopsies, but it is difficult to relate activity measured in small pieces of tissue to that in whole body tissue stores. Nevertheless, a general pattern has emerged suggesting there is decreased lipoprotein lipase activity in NIDDM. This finding is consistent with the observed retardation of VLDL clearance. Decreases have been observed in the late phase of postheparin lipolytic activity (43), in the acute phase postheparin lipoprotein lipase activity of individuals with NIDDM (44), and in the early and late phases of postheparin LPL in normolipemic male NIDDM subjects (45). On the other hand, in several studies, especially when the subjects were not hyperlipemic, decreases in postheparin LPL were not found (15, 34, 46). Decreases have been observed in adipose tissue lipoprotein lipase in subjects with NIDDM (15, 34, 36) and this decrease paralleled the decrease in FCR for VLDL triglyceride and VLDL apoB (34). No differences have been described in skeletal muscle LPL activity in NIDDM subjects (15, 34, 36).

Although the data on lipoprotein lipase are not entirely consistent, they suggest that one of the effects of NIDDM on lipoprotein metabolism might be a decrease in lipoprotein lipase activity, which is consistent with the observed decrease in the clearance of VLDL. This possibility is supported by several studies showing that improved diabetic control, regardless of the method of therapy, usually results in increased lipoprotein lipase activity (34, 43, 46).

4. VLDL composition and in vitro metabolism in NIDDM. There appear to be changes in the composition of VLDL in NIDDM which may either reflect or be the cause of alterations in VLDL metabolism. Several studies have suggested that diabetics may have a large, triglyceride-rich VLDL (34, 35, 47). In addition, our studies with the Pimas have demonstrated that this enrichment in VLDL triglyceride content, as measured by an increase in the ratio of triglyceride apoB in VLDL, appears to revert to normal after sulfonylurea therapy (34). The altered ratio of triglyceride/apoB in VLDL may be a reflection of the disproportionate influence of NIDDM on VLDL triglyceride production compared to that on apoB production. The presence of large VLDL particles in NIDDM is consistent with observations of a higher proportion of direct removal of VLDL (30, 35), since kinetic studies in nondiabetics have indicated that large triglyceride-rich particles are less efficiently converted to LDL (48, 49). The presence of a greater proportion of large VLDL particles, on the other hand, is not consistent with the decreased VLDL clearance in NIDDM, since large triglyceride-rich

VLDL should be more rapidly degraded by lipoprotein lipase (50).

Another alteration in VLDL composition in NIDDM may be a change in the distribution of the smaller apoproteins, apoC and apoE. This would have important implications for VLDL metabolism, since apoCs control the activity of lipoprotein lipase (51, 52) and apoEs influence the affinity for binding to receptors (53, 54). Increases in the proportions of apoC and apoE in relation to other components of VLDL in NIDDM have been reported (20, 55); this may retard liver uptake of VLDL in diabetics, since the rate of uptake of VLDL by the liver in in vitro studies has been observed to correlate inversely with the content of apoC (56). On the other hand, Stalenhoef et al. (57), in a careful quantification of apoCs in VLDL from NIDDM subjects, found a normal distribution of apoC-II and apoC-III.

Less work has been done on the content of apoE in VLDL in NIDDM. Our laboratory found no change in apoE relative to the apoB content of VLDL in NIDDM, although apoE concentration was decreased in proportion to VLDL triglyceride (34). However, an increased proportion of apoE in the VLDL in NIDDM and a lower ratio of E3/E2 has been reported (58, 59). Interpretation of apoE measurements performed on ultracentrifugally isolated VLDL is difficult, however, since apoE may be lost from particles during the isolation procedure. Finally, there is in vitro evidence that VLDL isolated from non-insulin-dependent diabetics have altered metabolic properties. VLDL isolated from normotriglyceridemic patients with NIDDM results in a greater cellular accumulation of lipids in mouse peritoneal macrophages than does VLDL isolated from either normotriglyceridemic or hypertriglyceridemic nondiabetic control subjects (60). The VLDL particles in this study, however, were triglyceride-enriched, indicating that the altered in vitro activity might be the result of altered particle composition.

5. Summary and comments. **(Fig. 1)** The data at the present time suggest that there are multiple alterations in VLDL metabolism in non-insulin-dependent diabetes mellitus. NIDDM appears to induce an overproduction of VLDL triglyceride and, to a lesser extent, of VLDL apoB. FCR for both VLDL triglyceride and apoB are lower and are associated with lower activities of LPL. Finally, there are indications that the VLDL particle in NIDDM has altered composition.

The mechanism for the overproduction of VLDL is not clear. The most likely explanation is that it is a result of the increased flow of substrates, particularly glucose and free fatty acids, to the liver. There are few studies, however, that address the relationship between VLDL triglyceride production in NIDDM subjects and the levels or turnover of these substrates. In our studies of Pima Indians with NIDDM in which the relationships between VLDL metabolism and the concentrations of glucose or free fatty acids were examined, no direct correlations were observed (34, 61). We have postulated that this failure to observe a correlation is probably a reflection of the fact that the concentrations of glucose and free fatty acids are not directly related to that small proportion of the total turnover that is devoted to VLDL triglyceride production (61).

Another possibility is that overproduction of VLDL triglyceride in NIDDM is induced by hyperinsulinemia (62). Although individuals with NIDDM have a relative insulin deficiency, they often have higher insulin levels than nondiabetics. Some workers have observed a correlation between VLDL production and insulin concentrations (63, 64). On the other hand, we were unable to show a significant correlation between insulin concentrations and production rates for VLDL triglyceride in NIDDM subjects (34, 36, 61), and studies in isolated hepatocytes have even demonstrated an inhibitory effect of insulin on VLDL production (65, 66). The most likely explanation, as suggested by Reaven and Greenfield (67), is that insulin has a permissive effect on VLDL production, in that some insulin is necessary but that VLDL production does not increase further when insulin concentrations are raised above a threshold level. Recent data from our laboratory have shown a significant positive correlation between VLDL triglyceride and insulin resistance, as measured by the euglycemic clamp technique, independent of insulin concentration (68). This suggests that the elevated VLDL in NIDDM may be directly related to insulin resistance rather than insulin concentrations per se.

The removal defect for VLDL in NIDDM is most likely due to a deficiency in lipoprotein lipase; in this case it is likely than insulin plays a definite role, since LPL is an insulin-dependent enzyme (69). It is not clear, however, whether the deficiency of lipoprotein lipase in NIDDM is due to the altered secretion of insulin or is a reflection of the insulin resistance.

The cause and significance of the altered VLDL composition in NIDDM are not as clear. The triglyceride enrichment of VLDL may be because triglyceride production appears to be stimulated to a greater extent than apoB production, and the altered VLDL composition may result in the increased proportion of VLDL metabolized without conversion to LDL. More information is needed about the distribution of apoC and apoE in VLDL in NIDDM, because of the potential importance of these apoproteins in the control of VLDL metabolism.

B. LDL metabolism in NIDDM

There are no consistent changes observed in LDL concentrations in NIDDM; although, in the absence of changes in LDL concentrations in NIDDM, there could be potentially detrimental changes in LDL metabolism with regard to their atherogenic potential. Many studies

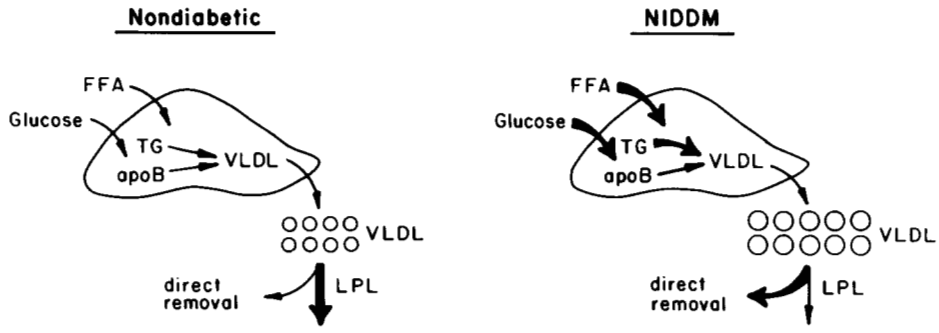

Fig. 1. Multiple changes in VLDL metabolism in NIDDM. Increased influx of FFA and glucose induce a disproportionate increase in triglyceride production, although apoB production may also be elevated, especially if subjects are obese. VLDL in plasma are increased in number and enriched in triglyceride, as indicated by the large circles (apoC and E may also be altered). Clearance is decreased because of lower amounts of LPL, but there is more direct removal of VLDL.

have shown that LDL cholesterol concentrations in NIDDM are similar to those of control subjects (16, 17, 70–73). On the other hand, increases in LDL cholesterol have been observed in some groups of diabetics (12, 21, 74–77).

1. *Metabolism of LDL apoB.* Little work has been reported on LDL metabolism in NIDDM. In NIDDM subjects with relatively severe hyperglycemia, the FCR for LDL apoB is reduced (35, 78). In mildly hyperglycemic NIDDM individuals, there may be increased LDL production as well (78).

2. *Composition and in vitro metabolism of LDL in NIDDM.* The LDL in non-insulin-dependent diabetics appears to have altered composition which may lead to abnormal metabolism, and this has been supported by in vitro studies. An increase in the proportion of triglyceride in LDL has been rather consistently observed (15, 21, 47, 79). In addition, in some diabetics the LDL may be polydisperse on ultracentrifugal analysis (80); this finding is supported by data from Gonen et al. (81) who showed that the LDL from NIDDM subjects has an increased ratio of cholesterol to apoB, implying the presence of larger LDL particles. There is in vitro evidence that the LDL from diabetics might have altered metabolic properties. Hiramatsu, Bierman, and Chait (82) observed decreased binding of LDL from hypertriglyceridemic (>500 mg/dl) diabetic subjects to skin fibroblasts. They showed that the decline in binding was inversely related to the ratio of triglyceride/protein in LDL, whether the LDL was isolated from hypertriglyceridemic diabetics or from nondiabetics. This suggests that the triglyceride enrichment of LDL in NIDDM results in altered LDL metabolism. Kraemer et al. (79), on the other hand, examined binding, internalization, and degradation of LDL from NIDDM individuals with mild hyperglycemia and showed that LDL from diabetics with moderate elevations in plasma glucose were not modified sufficiently to alter their normal binding and degradation by fibroblasts or to cause increased uptake by mouse peritoneal macrophages.

3. *Glucosylation of LDL.* The interaction of LDL with its receptor can be inhibited by various chemical modifications of the lysine and arginine residues of apoB (83). This suggests that the nonenzymatic glucosylation of apoB, a process occurring in diabetics because of their increased ambient glucose levels, could result in altered LDL metabolism. Glucosylation of approximately 40% of lysine residues completely blocks receptor-mediated LDL catabolism in vivo (84). Even though the extent of glucosylation of LDL in diabetics with moderate hyperglycemia is only approximately 2–5% (85), it has been shown (86) that this degree of glucosylation of lysine residues decreases LDL catabolism by 5–25% as measured by both degradation in cultured normal human fibroblasts and turnover in guinea pigs. Glucosylated LDL also appear to have altered interaction with endothelial cells (87); thus glucosylation of LDL in NIDDM may accelerate its deposition in vessel walls.

4. *Cholesteryl ester transfer in NIDDM.* Cholesteryl ester transfer among plasma lipoproteins is a critical step in the formation and metabolism of cholesterol esters. A consistent pattern of abnormal net cholesterol transport and transfer, as measured in vitro, has been shown in the plasma of patients with NIDDM (88, 89). The transfer of LCAT-synthesized cholesteryl esters to VLDL and LDL was inhibited, with a concomitant increase in their transfer to HDL. This abnormal metabolic pattern was reversed by insulin therapy (88). Finally, the block in cholesteryl ester transfer activity in patients with NIDDM is correlated with an increase in free cholesterol content of both LDL and VLDL in NIDDM. Therefore,

in NIDDM free cholesterol may be spontaneously lost to HDL, and this abnormal cholesteryl ester transfer may be related to an increased risk for atherosclerosis.

5. *Summary and comments.* **(Fig. 2)** In summary, the few in vivo studies have shown a decrease in fractional catabolic rate for LDL in NIDDM. In addition, in vitro studies of LDL from NIDDM subjects have shown altered binding that may be related to the increased triglyceride content. Finally, the evidence suggests that the in vivo nonenzymatic glucosylation of LDL may result in decreased LDL clearance.

The decreased clearance of LDL in NIDDM in vivo may simply be a result of the altered LDL composition. However, LDL binding in vitro is stimulated by insulin (90). Thus the defect in LDL clearance in NIDDM may be due to relative insulin deficiency. This possibility is supported by the observation that the FCR for LDL in NIDDM is positively correlated with plasma insulin and the insulin response to an oral glucose challenge (78).

If a clearance defect is a characteristic of NIDDM, why do many diabetics not show increases in their LDL concentrations? The answer may be found in the results of the combined studies of VLDL and LDL turnover in NIDDM (Fig. 2) which have shown that there was increased direct removal of VLDL apoprotein B in NIDDM. Thus, we have proposed (35) that concentrations of LDL in NIDDM are influenced by two opposing mechanisms. On the one hand, decreased clearance leads to increased LDL, whereas on the other, increased direct removal of VLDL leads to lower production of LDL. The resultant concentration, thus, may be dependent on the relative magnitude of these two processes and the net result, in many cases, may be no significant change in LDL concentration. Nevertheless, these alterations in the flux of both VLDL remnants and LDL particles may have atherogenic potential, in that they could possibly lead to increased deposition of LDL cholesterol in vessel walls. Furthermore, the in vitro studies of LDL binding also suggest there may be alterations of LDL interactions with cells in NIDDM which are not reflected in changes in concentration of LDL.

C. HDL metabolism in non-insulin-dependent diabetes

Almost as common as the observation of increased VLDL in NIDDM is the finding that HDL cholesterol concentrations are lower in individuals with NIDDM (6, 8, 13–18, 20–23, 47, 73, 91–93).

1. *HDL metabolism in NIDDM.* To date there has been only one report of HDL turnover in NIDDM (94). The data showed a decreased rate of HDL synthesis, as measured by apoA-I kinetics. In addition, there were significant positive correlations between HDL turnover and plasma HDL cholesterol and apoA-I protein concentrations. Brewer et al. (personal communication), however, have observed increased clearance of HDL in NIDDM with chylomicronemia.

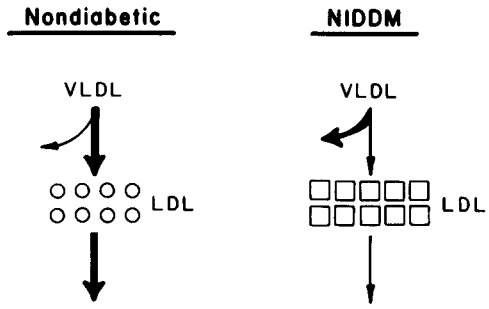

Fig. 2. Opposing changes influencing concentrations of LDL in NIDDM. Decreased fractional clearance of LDL may lead to increased LDL, but this may be counteracted by increased direct removal of VLDL, the precursor of LDL. In addition, altered LDL particle composition and glucosylation (as diagrammed by the change from circles to squares) may inflence LDL clearance or interaction with cells.

2. *HDL composition and in vitro metabolism in NIDDM.* The decreased HDL in NIDDM is mostly reflected in decreases in the HDL_2 subfraction (21, 23, 77, 95). However, we have also observed decreases in HDL_3 in measures of the Pima Indian diabetic population (21). Although total HDL composition will differ depending on the relative proportion of the subfractions, several studies suggest that there is altered HDL composition or distribution in NIDDM. As with LDL, an increased proportion of triglyceride has been observed in HDL (17, 20, 77, 95). This increased triglyceride is accompanied by an altered distribution of HDL particles (96). In addition, an increase in the ratio of cholesterol to protein in HDL has been reported (55). Studies of Pima diabetics (95), as in other populations (20, 55, 97), indicate that the apoA-I content of HDL may be preferentially depleted in NIDDM. In addition, we have demonstrated an increase in the ratio of both cholesterol and phospholipid to apoA-I in the HDL_2 of NIDDM, and these ratios decreased after improvement in glycemic control. Finally, Witztum et al. (98) have shown that, although nonenzymatic glucosylation of HDL accelerates its catabolism in guinea pigs, no change is observed in its uptake by mouse peritoneal macrophages. The effect of glucosylation on HDL metabolism has not been examined using HDL isolated from diabetic humans.

3. *Hepatic lipase in NIDDM.* Although it is not completely understood how hepatic lipase acts in the regulation of HDL, it is possible that the lower HDL concentrations in NIDDM may in part be attributable to higher hepatic lipase activity. Hepatic lipase is elevated in obese female NIDDM subjects (99) and increased in thin male NIDDM individuals (31), the activity in the latter group decreasing after normalization of glycemia with insulin therapy. We have recently shown that hepatic lipase activity is somewhat higher in obese Pima NIDDM sub-

jects and it decreased significantly after normalization of glycemia with sulfonylurea therapy (34).

4. *Summary and comments.* **(Fig. 3)** The only study to date of in vivo HDL metabolism in NIDDM showed a decreased production of HDL (94). There are also reports of altered HDL composition, and hepatic lipase activity appears to be lower in NIDDM.

The finding of lower HDL turnover is consistent with lower VLDL clearance and LPL activity since HDL, especially HDL_2, increases during the lipolytic process (100). An elevated hepatic lipase activity may also contribute to decreased HDL concentrations, since it also plays a key role in the metabolism of HDL (101). Thus, changes in lipoprotein and hepatic lipases may act in concert to decrease HDL in NIDDM (Fig. 3). There are several indications that the HDL in NIDDM may be of altered composition. This in part may be a reflection of alterations in the delipidation cascade which is involved in its formation. This altered composition may in turn alter its "antiatherogenic" properties. Finally, we have observed a negative relationship between insulin resistance and HDL cholesterol which is independent of VLDL concentrations (68). This raises the possibility that insulin resistance per se in some way influences HDL concentrations.

III. LIPOPROTEIN METABOLISM IN INSULIN-DEPENDENT DIABETES MELLITUS

The second and less common form of human diabetes is insulin-dependent diabetes (IDDM); this form is also referred to as Type I, juvenile onset, or ketosis-prone diabetes (1, 2). Its onset is usually before the age of 20, and it is characterized by insulin deficiency resulting from an autoimmune destruction of the pancreatic B cells. Individuals with IDDM are rarely obese, but they also have some degree of insulin resistance when poorly controlled. They require insulin therapy, and in the absence of insulin they become ketoacidotic.

A consideration of lipoprotein metabolism in IDDM is influenced by their obligatory requirement for insulin therapy. Thus, a spectrum of situations is possible from the totally insulin-deficient ketoacidotic state with greatly elevated glucose, free fatty acids, ketones, and lipolytic hormones such as glucagon and epinephrine, to that seen when continuous insulin infusion therapy is administered where an excess of insulin in peripheral plasma is found and glucose and fatty acid levels are close to normal. All degrees of insulinization result, however, in a nonphysiological distribution of insulin with higher levels in the peripheral circulation than in the portal. In the following sections an attempt will be made to differentiate between these various degrees of control and, thus, situations that vary in the amount of insulin present.

A. VLDL metabolism in IDDM

Extreme elevations in VLDL have been recognized to be a common occurrence in diabetic ketoacidosis (3, 102), the stage in which insulin concentrations are minimal. On the other hand, VLDL in individuals with IDDM receiving adequate therapy need not be elevated (9, 103–109), and it is now well established that VLDL triglyceride elevations in IDDM are often well correlated with degree of diabetic control (81, 105, 110–113).

1. *VLDL metabolism in IDDM.* In untreated IDDM subjects the fractional catabolic rate for endogenous triglyceride is decreased (26, 114) and the clearance rate for exogenous triglycerides (Intralipid) is lower (37). Thus, in extreme insulin deficiency, clearance is impaired, probably because of the dependency of the enzyme lipoprotein

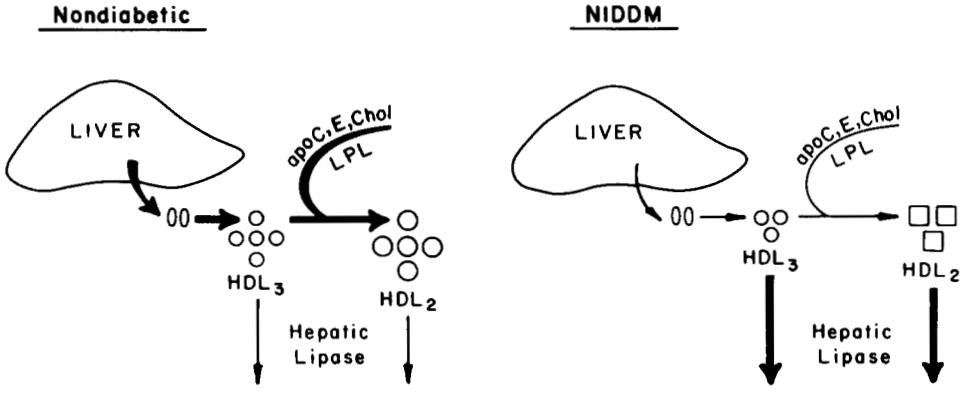

Fig. 3. Changes of HDL in NIDDM. HDL production is decreased in NIDDM, in part due to lower LPL activity. In addition, increased hepatic lipase activity accelerates its catabolism. There is a lower proportion of HDL_2 because of lower LPL activity. Also, particle composition, especially in HDL_2 is altered (as diagrammed by the change from circles to squares).

lipase on insulin (69). In the early stages of insulin deficiency there is increased production of VLDL (26), probably because of the increase in free fatty acid mobilization. This enhanced VLDL secretion falls off in the later stages of ketoacidosis because of a drop in hepatic protein synthesis secondary to the insulin deficiency (115). In poorly controlled but nonketotic IDDM patients, both overproduction and decreased clearance are observed. Ginsberg et al. (116) showed both increased synthesis and decreased clearance of VLDL triglyceride in a group of insulin-deficient Type I diabetics, and Greenfield et al. (29) observed an increase in VLDL triglyceride production in insulin-dependent diabetics under moderate control. Kinetic studies of VLDL triglyceride on a group of IDDM subjects on adequate conventional therapy showed normal production rates and fractional catabolic rates compared to weight- and age-matched controls (117). Institution of continuous subcutaneous insulin infusion in this study resulted in a significant fall in VLDL triglyceride production rates to levels below those observed in the nondiabetic subjects. There was no change in the mean FCR for VLDL triglyceride after insulin infusion. A similar drop in plasma VLDL triglyceride production was observed after treatment with the artificial beta cell in a group of Type I diabetics (118). These latter two studies indicate that rigorous insulin therapy can result in decreased rates of VLDL production and subnormal levels of VLDL triglyceride. There have been no studies reported of VLDL apoB metabolism in IDDM.

2. *Lipoprotein lipase in IDDM.* In untreated IDDM individuals the concentrations of serum triglyceride correlate inversely with postheparin plasma lipoprotein lipase activity (44). After initiation of insulin therapy, VLDL triglyceride falls in parallel with a rise in tissue LPL activities (44, 119). Thus, lipoprotein lipase is low in the insulin-deficient state and increases upon institution of insulin therapy.

3. *Summary and comments.* **(Fig. 4)** The diagram in Fig. 4 presents a possible scheme of lipoprotein metabolism in various stages of control of IDDM. During severe ketoacidosis, when there is severe insulin deficiency, hypertriglyceridemia is caused primarily by a deficiency in lipoprotein lipase activity, and triglyceride overproduction may not occur even in the presence of elevated free fatty acids. As insulin therapy is instituted, the situation changes. In moderate control, that is with suboptimal insulin administration, there is overproduction of VLDL because of the increased free fatty acids and also some deficiency in VLDL clearance. As stringent control is instituted, with large amounts of peripheral insulin, clearance is normal; VLDL production rates may fall to subnormal levels since excess insulin may suppress hepatic VLDL formation (65, 66). IDDM subjects in this situation will have normal or even low normal levels of circulating VLDL triglyceride.

It should be noted that other factors may also be involved in the derangement of VLDL in IDDM. Intestinal VLDL lipoprotein secretion has been shown to be increased in insulin-deficient animals (120), and there are most likely changes in VLDL composition similar to those described for NIDDM (section IIA4). Various routes of insulin administration also may have differential effects on lipid metabolism, since peritoneal insulin infusion has been shown to decrease plasma glucose while resulting in increased levels of triglycerides (121).

B. LDL metabolism in IDDM

Over the spectrum of degrees of glycemic control in IDDM, LDL concentration appears to vary with the extent of hyperglycemia. LDL has been shown to be increased in poorly controlled IDDM subjects (111–113). LDL cholesterol levels appear to correlate with the degree of control (81, 110–112). However, in many individuals with IDDM, LDL are normal or not different from age- and weight-matched controls (103–106, 108, 122), and some IDDM subjects on pump therapy (112, 123) have LDL concentrations considerably below that of controls.

1. *LDL metabolism in IDDM.* Very little work has been done on LDL metabolism in IDDM. Rosenstock, Vega, and Raskin (123) showed that the fractional catabolic rate for LDL in IDDM subjects on conventional therapy or after 3 weeks of continuous subcutaneous insulin infusion was similar to that of nondiabetic controls. Improvement in control resulted in a decrease in the production rate for LDL apoB to levels below those of nondiabetic controls.

2. *LDL composition and in vitro metabolism in IDDM.* There may be an increased cholesterol to apoB ratio in the LDL of individuals with IDDM (81) but this has not been related to any metabolic parameter. Low density lipoproteins isolated from poorly controlled diabetics are taken up and degraded by fibroblasts at a lower rate than LDL isolated from normal subjects (124). When glucose concentrations are lowered by insulin therapy, binding properties of LDL return to normal. Futhermore, exposure of cells to lipoprotein-deficient serum obtained from poorly controlled diabetic patients enhances the binding deficiency, (125) and it has been postulated that membrane changes might be induced in IDDM which result in altered LDL binding.

3. *Summary and comments.* (Fig. 4) LDL concentrations in IDDM, as with VLDL, appear to decrease with increasing extent of insulin administration, but few metabolic studies have been performed to elucidate the mechanisms involved. In uncontrolled Type I diabetics, LDL fractional clearance is probably decreased, since insulin appears to potentiate LDL binding to its receptor. With increasing control, LDL metabolism may return to normal. Glucosylated LDL and defects in cholesteryl ester transfer may also occur in IDDM as has been described for NIDDM (sections IIB2 and 3) but to date no

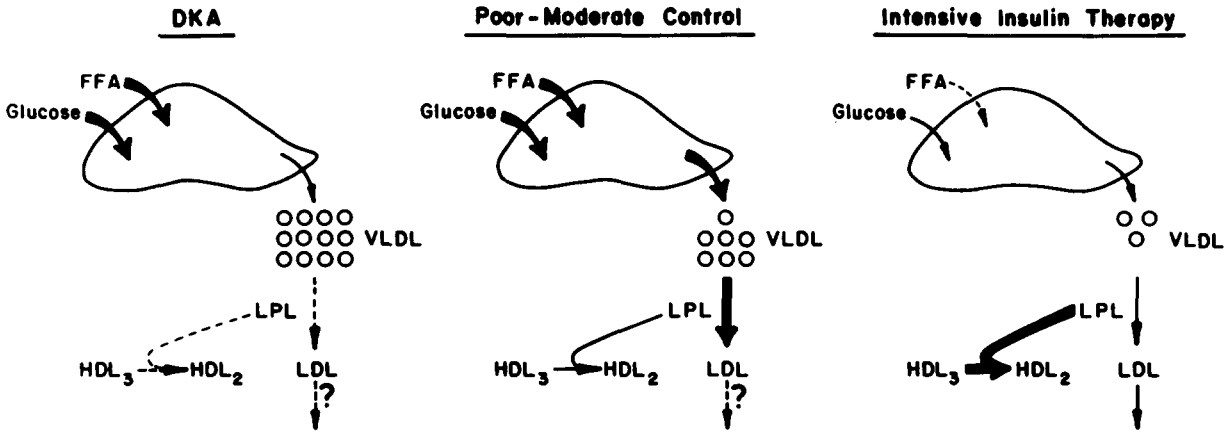

Fig. 4. Spectrum of lipoprotein changes in IDDM with various degrees of control. In extreme insulin deficiency (DKA), LPL activity is minimal and VLDL production is low. This results in little transfer to the HDL compartment and thus high VLDL and low HDL. In poor to moderate control, VLDL may be elevated both because of suboptimal LPL and because of overproduction induced by elevated FFA and glucose. LDL may be elevated because of increased VLDL and inadequated insulin for optimal clearance. On intensive insulin therapy VLDL production drops, probably because of decrease availability of FFA; LPL activity is optimal, resulting in increased production of HDL.

studies have been performed on glucosylation or cholesteryl ester transfer in IDDM. It is also plausible that insulin deficiency may lead to LDL overproduction because of increased influx of VLDL, its precursor, or because of impaired removal of VLDL remmnants by the liver. An abnormal VLDL particle may also influence its conversion to LDL. Further studies of lipoprotein metabolism in IDDM subjects with various degrees of insulinization would provide an opportunity to elucidate the role of insulin in the processes that control plasma LDL.

C. HDL metabolism in IDDM

A number of observations indicate that plasma HDL are low in untreated insulin-deficient diabetics (69, 111–113). Response of HDL to insulin therapy is slower than that of VLDL (109) but HDL increases with degree of glycemic control and, in many studies of IDDM, HDL has been shown to be not altered (108, 110, 126) or even higher (103–106, 122) than in age-, sex-, and weight-matched controls. HDL may also be higher in those on pump therapy (112, 123).

1. *Metabolism of HDL in IDDM.* There have been no studies of HDL metabolism in individuals with IDDM. It has been postulated (42) that one factor responsible for the decrease in HDL in poorly controlled subjects is low lipoprotein lipase activity, which leads to the reduced formation of HDL particles during impaired lipolysis of VLDL. In insulin-treated diabetics, both HDL cholesterol and phospholipids have been shown to correlate positively with postheparin plasma lipoprotein lipase activity (109).

2. *Hepatic lipase activity in IDDM.* An inverse correlation has been observed between HDL and postheparin plasma hepatic lipase activity (101). Preliminary data suggest that hepatic lipase activity may be lower in well-controlled IDDM subjects (109), and associated with a higher ratio of HDL_2/HDL_3. Thus, the role of this enzyme in regulating HDL levels and the influence that insulin may have on this process is similar to that postulated for NIDDM (section IIC3).

3. *HDL composition in IDDM.* When HDL is elevated in well-controlled IDDM subjects it is generally due to an increase in the HDL_2 subfraction (85, 106, 107, 109). These observations confirm the hypothesis that insulin action, whether through lipoprotein lipase or other means, results in an increased transfer of material to the HDL_2 compartment. As in NIDDM, preliminary data indicate there may also be alterations in HDL composition in IDDM. HDL_3 is smaller and triglyceride-rich in those IDDM individuals who have lower HDL concentrations (96). Abnormal contents of both triglycerides and apoA-I have been observed in the HDL in IDDM (126), and Scherthaner et al. (97) have also reported that apoA-I and apoA-II are decreased. Both apoA-I and apoA-II have also been reported to be glucosylated in patients with IDDM (127). As in NIDDM, altered HDL particle composition may be a reflection of an altered delipidation cascade but, on the other hand, may also profoundly influence the function of the HDL particles.

4. *Summary and comments.* (Fig. 4) As with VLDL a spectrum of changes in HDL occurs in IDDM which depends on the degree of glycemic control. Insulin deficiency is associated with decreased HDL, probably due to

LPL deficiency, whereas either suboptimal or optimal insulinization leads to normal or even elevated amounts of HDL, the latter occurring because of the abnormally high peripheral concentrations of insulin necessary to achieve adequate insulin delivery to the liver. This system would appear to be a good opportunity to explore the role of insulin in the regulation of HDL, an important issue in view of the possibility that reduced or altered HDL may play a role in the increased atherogenesis observed in IDDM.

IV. CONCLUSIONS AND QUESTIONS

There are multiple changes in lipoprotein metabolism in both insulin-dependent and non-insulin-dependent diabetes. However, there are many gaps in our understanding of the mechanisms of these changes, the sequence in which they occur, and, in particular, their relevance to the atherosclerotic process. More metabolic studies, especially of LDL and HDL, are needed in both kinds of diabetes. In addition, several areas of metabolic investigation can be singled out, because there are preliminary data that appear to be of interest or because there are areas that are important for the full understanding of the influence of diabetes on lipoprotein metabolism.

A) What is the significance of the altered lipoprotein composition that appears to occur in all three major lipoprotein fractions in diabetics?

Although thorough epidemiologic investigations of risk factors for cardiovascular disease in diabetes are not available, several workers (128) have proposed that coronary heart disease in diabetics may be more closely associated with alterations in triglyceride concentrations than in the nondiabetic. De Wikinski, Henao, and Figueroa (129) have reported that there may be β-VLDL in NIDDM. It must be determined whether there are alterations in content or composition of VLDL remnants in diabetes, as suggested in some studies (129), because of the relative importance of these in the atherogenic process (130). Thorough studies are also required of the apoC and E distribution in diabetic VLDL. Similarly, the occurrence of polydispersity in diabetic LDL must be determined and the metabolic consequences of the increased LDL triglyceride understood. Lastly, HDL composition, especially the relative proportions of apoA-I and apoA-II must be more thoroughly evaluated and related to HDL metabolism in diabetes.

B. What is the role of insulin in the alterations in lipoproteins in diabetes mellitus?

As recently summarized (131), insulin plays important roles at three points in lipoprotein metabolism. Minimum amounts are needed for lipid synthesis and lipoprotein production in the liver, and minimum amounts are needed for lipoprotein lipase production and lipase-catalyzed intravascular hydrolysis of triglyceride-rich particles. Insulin may also be needed for the optimum expression of the receptor-mediated endocytosis of apoB- and E- containing lipoproteins (90). Reduction of plasma LDL cholesterol has been observed after continuous intravenous insulin infusion (132) and in vivo insulin stimulates LDL degradation (133). Careful studies must be performed to evaluate the role of insulin in the alterations in VLDL, LDL, and HDL seen in the two forms of diabetes. Varying the extent of insulin therapy may be a useful tool to examine the metabolic action of insulin on various aspects of lipoprotein metabolism. This latter approach may be especially important in helping to understand how (and if) hyperinsulinemia is atherogenic.

C. Does insulin resistance play a role in the abnormalities in lipoprotein metabolism in diabetes?

It has been proposed that in NIDDM insulin resistance and the subsequent hyperinsulinemia are responsible for VLDL triglyceride overproduction (62). More recently our laboratory has demonstrated significant positive correlations between VLDL concentrations and degree of insulin resistance and negative correlations between HDL concentrations and degree of insulin resistance (68) which were independent of each other. These observations suggest that alterations associated with the insulin-resistant state in the liver, adipocyte, or muscle may directly influence plasma lipoprotein concentrations. Alternatively, it is possible that elevated lipoproteins, especially VLDL, may induce insulin resistance by impairing cell insulin action.

D) How is plasma glucose related to lipoproteins?

A common denominator in all forms and stages of diabetes is hyperglycemia. In many of the studies of VLDL and HDL in diabetes, lowering of glucose, regardless of the mode of therapy, resulted in decreases in VLDL and increases in HDL. One possible interpretation is that many of the changes in VLDL and HDL are directly attributable to hyperglycemia. This may be plausible in the case of elevated VLDL where the increased plasma glucose and deficit in glycogen storage would stimulate hepatic triglyceride formation. Glucose has been shown to potentiate the lipolytic responsiveness of human adipocytes in vitro (134), which would lead to increased fatty acid flux to the liver. On the other hand, Hollenbeck et al. (135) noted that, in NIDDM, treatment with insulin, even with normalization of plasma glucose levels, did not restore the HDL concentrations to normal, implying that factors in addition to hyperglycemia are causing the lower HDL.

E) How do the elevations in FFA in diabetes influence lipoproteins?

Elevations in FFA in diabetes are consistently observed and are related to the degree of hyperglycemia (136). It is most plausible that the elevated FFA induce increased VLDL triglyceride production in NIDDM and in uncontrolled IDDM. Although increased VLDL triglyceride output is observed in diabetics with high FFA (34), direct correlations between FFA concentrations and VLDL triglyceride production are rately observed (95), and this is most likely due to the fact that only a small portion of FFA turnover is attributable to VLDL production (95, 137). Early metabolic studies have suggested a majority of VLDL triglyceride is derived from plasma FFA. It remains to be determined whether this is the case in diabetes, and how free fatty acids and glucose interact in influencing triglyceride production in diabetics.

F) What is the role of nonenzymatic glucosylation in the lipoprotein abnormalities in diabetes?

As discussed in section IIB3 and IIIB2, there is evidence that glucosylation of the lysine residues of LDL, even to the extent observed in diabetics with moderate hyperglycemia, leads to impaired in vitro metabolism of LDL. It remains to be directly demonstrated that alterations of LDL to the extent found in the average diabetic result in altered in vivo metabolism in humans. In addition, there are other possible areas of lipoprotein metabolism that may be influenced by glucosylation. The receptors themselves may be glucosylated and thus have impaired function, although Lorenzi et al. (87) showed that in vitro growth of endothelial cells in high glucose did not affect LDL receptor function. Another possibility is that other apolipoproteins such as A-I, A-II, C, or E are glucosylated (128). In addition, it has been shown that nonenzymatic glucosylation products on collagen covalently trap low density lipoproteins (138). Finally, the extent of the influence of glucosylation on HDL metabolism (98) must be further explored.

G) Are there alterations in plasma exchange proteins that influence atherogenesis in diabetes?

As summarized in section IIB4, the data from in vitro studies suggest that there are changes in rates of cholesteryl ester flux in plasma and lipoproteins isolated from diabetics. Moreover, lipoproteins from diabetics are enriched in free cholesterol. An almost universal observation appears to be an increase in triglyceride content in VLDL, LDL, and HDL of diabetics. It is possible, therefore, that the triglyceride exchange process is also altered in diabetic subjects. The implications for altered cholesteryl ester and triglyceride exchange in terms of lipoprotein metabolism and atherogenic potential must be further examined.

H) Are there sex differences in the influences of diabetes on lipoprotein metabolism?

Diabetes appears to induce greater increases in cardiovascular mortality in women than in men (70). Ganda, Soeldner, and Gleason (139) have reported that the increase in triglyceride and decrease in HDL cholesterol in offspring of NIDDM individuals are greater in women than in men, and several other studies have suggested greater changes in VLDL and HDL concentrations in diabetic women than in men (21, 93). Lipoprotein metabolic studies should thus be compared in diabetic men and women to determine the metabolic basis for the epidemiologic evidence that diabetes equalizes the cardiovascular disease risk in men and women.

I) Would generic studies be useful in elucidating the links between diabetes mellitus, lipoprotein metabolism, and atherosclerosis?

Recently, the gene for the C3-complement type has been shown to be linked with familial hypercholesterolemia (140), and DNA sequences flanking the insulin gene on chromosome 11 appear to confer risk of atherosclerosis (141). These observations raise the intriguing possibility that genetic studies may be able to assist the physiologist in the elucidation of mechanisms which control lipoprotein metabolism in diabetes and how they are related to atherogenesis.

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