DYSLIPIDAEMIA IN DIABETES MELLITUS

REVIEW OF THE MAIN LIPOPROTEIN ABNORMALITIES AND THEIR CONSEQUENCES ON THE DEVELOPMENT OF ATHEROGENESIS

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SUMMARY - Lipid abnormalities in diabetic patients are likely to play an important role in the development of atherogenesis. These lipid disorders include not only quantitative but also qualitative abnormalities of lipoproteins which are potentially atherogenic. Both types are present in non-insulin-dependent diabetes (NIDDM) and poorly controlled insulin-dependent diabetes (IDDM), whereas only qualitative abnormalities are observed in well- and moderately well-controlled IDDM. The main quantitative abnormalities are increased triglyceride levels related to elevated VLDL and IDL and decreased HDL-cholesterol levels due to a drop in the HDL2 subfraction. The increase of triglyceride-rich lipoproteins in plasma is related to higher VLDL production by the liver and a decrease in their clearance. Metabolic abnormalities of triglyceride-rich lipoproteins are more pronounced in the postprandial period. The decrease in HDL-cholesterol is related to increased HDL catabolism. Qualitative abnormalities include changes in lipoprotein size (large VLDL, small LDL), increase of triglyceride content of LDL and HDL, glycation of apolipoproteins, and increased susceptibility of LDL to oxidation. These qualitative abnormalities impair the normal metabolism of lipoproteins and could thus promote atherogenesis. The physiopathology of lipid disorders in diabetes mellitus is multifactorial and still imperfectly known. However, such factors as hyperglycaemia and insulin resistance (in NIDDM) are likely to play an important role.

Key-words: lipids, diabetes mellitus, lipoproteins.

RÉSUMÉ - La dyslipidémie du diabétique : revue des principales anomalies lipoprotéiques et de leurs conséquences sur les gros vaisseaux. La plus grande fréquence et sévérité des accidents cardiovasculaires, au cours du diabète, est favorisée par plusieurs facteurs parmi lesquels les anomalies du métabolisme lipidique, qui apparaissent en première ligne. Il est observé, chez le patient diabétique, des anomalies quantitatives et qualitatives des lipoprotéines, potentiellement athérogènes. On distingue le diabète non insulino-dépendant, où sont rencontrées des anomalies quantitatives et qualitatives des lipoprotéines, du diabète insulino-dépendant traité, où ne sont observées, en règle, que les anomalies qualitatives. Les anomalies quantitatives comportent principalement une hypotriglycéridémie, liée à une augmentation des lipoprotéines riches en triglycérides (VLDL, IDL), ainsi qu’une baisse du HDL-cholestérol, par diminution des particules HDL2. La majoration du nombre des lipoprotéines riches en triglycérides apparaît liée à une augmentation de production hépatique des VLDL ainsi qu’à un ralentissement de leur catabolisme. Les anomalies métaboliques des lipoprotéines riches en triglycérides sont encore plus marquées en période postprandiale. La baisse du HDL-cholestérol est secondaire à un catabolisme accru des HDL. Parmi les anomalies qualitatives, on retient essentiellement une modification de taille des lipoprotéines (VLDL de grande taille, petites LDL), un enrichissement en triglycérides des LDL et HDL, une glycation des apolipoprotéines, une oxydabilité accrue des lipoprotéines et plus particulièrement des LDL. Ces anomalies qualitatives modifient le métabolisme normal des lipoprotéines et favorisent le développement de lésions athérosclérotiques. La physiopathologie des troubles du métabolisme lipidique, au cours du diabète, est complexe et multifactorielle. Cependant, il apparaît clair que l’hyperglycémie et l’insulino-résistance (au cours du diabète non insulino-dépendant) jouent un rôle majeur.

Mots-clés : lipides, diabète sucré, lipoprotéines.
Atherosclerotic complications, particularly coronary heart disease, are the leading causes of death in individuals with diabetes [1, 2]. One of the most important factors contributing to the greater severity and frequency of atheroma in diabetes is the alteration in lipoproteins observed among diabetic patients [3]. Both quantitative and qualitative lipid abnormalities are associated with diabetes, leading to the alteration of lipoprotein metabolism, kinetics, and binding to membrane receptors. Both types of lipid abnormalities are encountered in non-insulin-dependent diabetes mellitus (NIDDM), but only qualitative lipid abnormalities are present in well- and moderately well-controlled insulin-dependent diabetes mellitus (IDDM). In diabetes, the concentration and metabolism of plasma lipoproteins are influenced by different factors such as hyperglycaemia, insulin resistance, and the type and method of treatment. Because insulin has multiple sites of action on lipoprotein metabolism, insulin resistance in NIDDM and insulin deficiency in poorly controlled IDDM are associated with pronounced lipid abnormalities. This review will provide a brief description of human lipoprotein metabolism and consider the role of insulin in lipid metabolism and the lipid abnormalities observed in NIDDM and IDDM.

**BRIEF REVIEW OF LIPOPROTEIN METABOLISM**

Lipoproteins, which transport non-water-soluble cholesterol and triglycerides in plasma, are spherical particles composed of a central core of non-polar lipids (cholesterol esters, triglycerides) and a surface monolayer of phospholipids, free cholesterol and apolipoproteins. Lipoproteins are classified according to their density as chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). More recently, greater attention has been paid to another lipoprotein, lipoprotein (a) [Lp(a)], which is associated with increased cardiovascular risk [4]. However Lp(a) does not share the same metabolic pathways as the other lipoproteins. An overview of lipoprotein metabolism is shown in Figure 1.

![Figure 1. Lipoprotein metabolism in humans. VLDL: Very Low Density Lipoprotein; IDL: Intermediate Density Lipoprotein, LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; LPL: Lipoprotein Lipase; HL: Triglyceride Hepatic Lipase; CETP: Cholesteryl ester Transfer protein; LCAT: lecithin-cholesterol acyl transferase; FFA: Free Fatty Acids; LRP: LDL-receptor related protein; B/E rec.: B/E receptor (LDL receptor); TG: Triglycerides, Chol: Cholesterol; PL: Phospholipids; Apo: Apolipoproteins; CE: Cholesterol Esters.](image-url)
Chylomicrons

Chylomicrons, the largest lipoprotein particles, are responsible for the transport of dietary triglycerides and cholesterol. They are produced by the enterocyte and secreted into the lymphatic circulation before entering the bloodstream. In plasma, triglycerides of chylomicrons are quickly hydrolysed by lipoprotein lipase. The residual particle depleted of triglycerides, known as the chylomicron remnant, is cleared by the liver through the LDL-receptor-related protein (LRP).

VLDL and IDL

VLDL particles, which are secreted by the liver, consist of endogenous triglycerides (55% to 65%), cholesterol, phospholipids and apolipoproteins (B100 as well as C and E). The triglycerides of VLDL particles are hydrolysed in plasma by lipoprotein lipase. As VLDL become progressively depleted of triglycerides, a portion of the surface, including phospholipids and apolipoproteins C and E, is transferred to HDL. This metabolic cascade leads to the formation of IDL particles, which are either cleared from the circulation by receptors in the liver, including the B/E receptor and possibly the LRP, or further metabolised to form LDL.

LDL

LDL particles are the final products of the VLDL-IDL-LDL cascade. LDL is the main cholesterol-bearing lipoprotein in plasma, and each LDL particle contains one molecule of apoB. Clearance of LDL is normally mediated by the B/E receptor located on hepatic and peripheral cell surfaces. LDL particles play a key role in the pathogenesis of atherosclerosis.

HDL

HDL are secreted by the hepatocyte as small cholesterol-poor lipoproteins containing apolipoproteins A, C and E. In plasma, surface components of chylomicron remnants and VLDL are transferred to HDL during the lipolytic process. HDL particles subsequently become enlarged, i.e. HDL₃ and then HDL₂.
Within HDL particles, cholesterol ester is produced by the action of lecithin-cholesterol acyl transferase (LCAT) on free cholesterol and lecithin. HDL particles, which are cleared by the liver, play a central role in the reverse cholesterol pathway (transfer of cholesterol from peripheral cells to the liver for subsequent secretion in bile) and appear to be protective against atherogenesis.

**Lp(a)**

Lp(a) is a subclass of the LDL fraction, consisting of LDL complexed to a large glycoprotein, apo(a), resembling plasminogen [4]. Individual concentrations of Lp(a) are predominantly determined by genetic factors. Lp(a) is synthesised by the liver and is thought to be cleared by the B/E receptor. Elevated Lp(a) levels are associated with increased atherosclerosis, possibly because Lp(a) inhibits plasminogen binding and stimulates gene expression of PA I-1.

**Lipid transfer proteins**

The metabolism of plasma lipoproteins is largely influenced by lipid transfer proteins, including two which play an important role in lipid metabolism: cholesteryl ester transfer protein (CTEP) and phospholipid transfer protein (PLTP). CETP facilitates the transfer of triglycerides from VLDL toward LDL and HDL, and of cholesteryl esters from LDL and HDL toward VLDL [5]. PLTP facilitates the transfer of phospholipids, but also of lipopolysaccharides, free cholesterol and α-tocopherol, between lipoproteins and is also an important determinant of the size distribution of HDL particles [6]. Any modification of CETP or PLTP activity is likely to promote significant quantitative and qualitative abnormalities of lipoproteins.

### ROLE OF INSULIN ON LIPID METABOLISM

Insulin plays a central role in the regulation of lipid metabolism. The main sites of insulin action on lipoprotein metabolism are shown in Figure 2. In adipose tissue, insulin inhibits lipolysis by blocking lipase. Insulin is a potent activator of lipoprotein lipase, promoting the catabolism of triglyceride-rich lipoproteins, and it inhibits VLDL production by the liver. Insulin promotes the clearance of LDL, stimulates apoB/E receptor (LDL-receptor) activity and enhances LDL degradation via the LDL-receptor pathway [7, 8]. Insulin also plays an important role in HDL metabolism since it activates LCAT activity and modulates hepatic triglyceride lipase activity [9].

### LIPID ABNORMALITIES IN NIDDM

Both quantitative and qualitative lipid abnormalities are observed in NIDDM patients [10-16]. The prevalence of dyslipidaemia is very common in NIDDM [17, 18]. Data from the United Kingdom Prospective Diabetes Study (UKPDS) have shown that the effect of NIDDM on plasma lipoprotein levels is more pronounced in women than in men [19], which partly explains why cardiovascular risk is proportionally higher in female diabetic patients. The main lipid quantitative abnormalities in NIDDM are hypertriglyceridaemia and low HDL-cholesterol level. Lipid qualitative abnormalities are present in all lipoproteins. Hyperglycaemia and insulin resistance supposedly play important roles in the physiopathology of dyslipidaemia in NIDDM. Both the quantitative and qualitative lipid abnormalities observed in NIDDM are likely to promote atherogenesis. The main lipoprotein modifications in NIDDM are shown in Table I.

#### TABLEAU I. Main lipoprotein modifications in NIDDM.

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Plasma level</th>
<th>metabolism modifications</th>
<th>Qualitative abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>↑</td>
<td>Increased production</td>
<td>Size ↑; TG and cholesterol content; Glycation of apolipoproteins</td>
</tr>
<tr>
<td>LDL</td>
<td>↓ or ↑</td>
<td>Decreased clearance</td>
<td>Size ↓; Density ↑; TG content; Glycation of apoB; Oxidation</td>
</tr>
<tr>
<td>HDL</td>
<td>↓</td>
<td>Increased catabolism</td>
<td>HDL2/HDL3 ratio ↑; TG content; Glycation of apoA1</td>
</tr>
</tbody>
</table>

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Triglyceride-rich lipoproteins

Plasma triglyceride level is frequently increased in NIDDM, mainly in relation to a higher VLDL level [10, 11, 13]. The triglyceride-rich lipoprotein pool is significantly increased in NIDDM, including an augmentation of both VLDL and IDL [20-22]. Steiner et al. have recently shown that 70% of the increase in triglyceride-rich lipoproteins is due to an augmentation of their number [22].

One determinant of diabetic hypertriglyceridaemia is overproduction of VLDL-triglycerides [23], which is attributed to the increased flow of substrates, glucose and free fatty acids to the liver and also to hepatic resistance to the inhibitory effect of insulin on VLDL secretion [24-27]. It has been shown that the suppressive effect of insulin on VLDL secretion is significantly reduced in obese and NIDDM patients [26, 27]. The increase in the production of VLDL-triglycerides is accompanied by an overproduction of VLDL apo B in NIDDM [23, 28]. Some data suggest that overproduction of VLDL-triglycerides may be greater than that of apo B in NIDDM, resulting in the formation of larger triglyceride-rich VLDL particles [15, 29]. Moreover, NIDDM patients have reduced clearance of VLDL-triglycerides [23, 28], which is more pronounced when the degree of hyperglycaemia is high. This defect in VLDL catabolism reflects reduced lipolytic activity on these lipoproteins. In fact, decreased activity of adipose tissue lipoprotein lipase has been observed in some studies [29, 30]. Moreover, VLDL from NIDDM patients have altered metabolic properties, with increased cellular accumulation of lipids in macrophages, which contributes to the formation of foam cells [25].

Several qualitative abnormalities of VLDL have been described in NIDDM patients. VLDL, in NIDDM, are present as large particles enriched in triglycerides and cholesterol [13, 15, 20, 31]. Moreover, VLDL have shown alterations in their apolipoprotein distribution, with a relative increase of apo E compared to apo Cs [32, 33]. Other changes in VLDL composition occurring in NIDDM include glycation of apo C and E [34]. The latter may inhibit binding to the B/E receptor and thus impair its catabolism [35]. It has been suggested that the glycation of apo C II, a cofactor of lipoprotein lipase, could contribute to lesser activation of the enzyme [36].

Impaired LDL clearance is observed in NIDDM, and decreased affinity of LDL from diabetic patients for the apo B/E receptor has been observed [39]. A part of this reduced LDL clearance has been attributed to insulin resistance since LDL binding is stimulated by insulin [7, 23, 28].

Important qualitative abnormalities are observed in LDL from NIDDM patients. Smaller higher-density LDL particles (known as subclass B) are more prevalent in NIDDM [40, 41]. The presence of small dense LDL in NIDDM patients appears to be mainly related to hypertriglyceridaemia [42]. It seems likely in NIDDM that hypertriglyceridaemia related to increased triglyceride-rich lipoproteins stimulates CETP activity, promoting the transfer of triglycerides to LDL particles and leading to the formation of small dense triglyceride-rich LDL. However, it has been shown that small LDL is independently associated with increased HbA1c [43]. Individuals with increased small dense LDL (subclass B) have a higher risk of developing coronary heart disease [44]. In fact, small dense LDL have a reduced affinity for the apo B/E receptor, with an increased accumulation in macrophages, and show a greater susceptibility to oxidation [45]. Other alterations in LDL composition include increased triglyceride content and an elevated free cholesterol/lecithin ratio [10, 11, 46]. Another important qualitative abnormality is the glycation of apo B, which is likely to have a significant effect on LDL metabolism [47]. It has been shown that glycation of 2 to 5% can reduce LDL catabolism by 5 to 25% [48]. Moreover, glycation of apo B results in the stimulation of foam cell formation as a result of uptake of glycated LDL by macrophages and increased LDL oxidation [49, 50]. Glycated LDL decrease fibrinolysis, increase platelet aggregation and stimulate the expression of cell adhesion molecules by endothelial cells [16].

Another lipoprotein modification with marked atherogenic potential is increased LDL oxidation, which is partly promoted by glycation of apo B [16]. Many studies have shown that glycated LDL can be more easily oxidised [50, 51] and have thus likely to play an important role in the development of atherogenesis. Oxidative modification of LDL results in rapid uptake by macrophages, leading to foam cell formation. Oxidised LDL have been reported to damage endothelial and smooth muscle cells [16], produce chemotactic effects on monocytes and increase the number of monocytes adhering to the endothelium by promoting the expression of intercellular adhesion molecule 1 (ICAM 1). Furthermore, glycated and oxidised LDL stimulate the immune system to form antibodies. The resulting immune complexes are taken up by macrophages, thereby stimulating foam cell formation and the release of cytokines (TNFα, IL1) which further injure the endothelium and amplify the atherogenic process [16].
HDL

NIDDM is associated with a decrease in the HDL-cholesterol level related to a decrease in the HDL$_2$ subfraction [10, 37, 52]. Reduced HDL$_2$ in NIDDM is correlated with both hypertriglyceridaemia and obesity [53]. Insulin resistance is likely to have an important influence on the concentration of HDL in NIDDM [13, 14]. The decrease in HDL observed in NIDDM is mainly due to increased HDL catabolism with augmented triglyceride hepatic lipase activity [54, 55]. Impaired VLDL clearance and lower lipoprotein lipase activity are also likely to decrease the transformation of HDL$_2$ into HDL$_3$. Furthermore, reverse cholesterol transfer is impaired in NIDDM, in relation to inhibition of LCAT production of cholesteryl esters [56].

HDL particles from NIDDM patients show several qualitative abnormalities. They are enriched in triglyceride [57], which is likely to make lipoprotein more vulnerable to destruction by lipases [58]. Furthermore, it has recently been shown that the increased transfer of triglycerides between triglyceride-rich lipoproteins and HDL, owing to CETP, promotes HDL catabolism [59]. Glycation of apoA-I in NIDDM is directly correlated with plasma glucose level [60]. It has been shown that apoA-I glycation decreases HDL receptor binding and may impair intracellular cholesterol efflux [61].

Lp(a)

Though some studies have reported increased Lp(a) levels among NIDDM patients, most large studies have found that Lp(a) levels and isoforms are not different in NIDDM [62, 63]. However, increased Lp(a) has been shown to be an independent risk factor for atherosclerotic cardiovascular disease in NIDDM [64, 65].

Lipid postprandial abnormalities

The interest in postprandial studies has been great since Zilversmit hypothesised that the development of atherosclerosis could be a postprandial phenomenon [70]. In NIDDM, an increase in plasma triglycerides and triglyceride-rich lipoprotein levels was observed after an oral fat load [71, 72]. Postprandial lipid abnormalities occur early in the development of diabetes since they can already be noted in non-diabetic insulin-resistant subjects [73]. A correlation between the level of insulin resistance and postprandial triglyceride concentrations has been found by Jeppesen et al., which suggests that insulin resistance plays a key role in postprandial lipid abnormalities in NIDDM [74]. These postprandial lipid abnormalities are very likely to promote atherogenesis in NIDDM.

LIPID ABNORMALITIES IN IDDM

Important lipid quantitative abnormalities related to insulin deficiency have been noted in untreated or poorly-treated IDDM. In these situations, highly increased triglyceride-rich lipoproteins (VLDL and chylomicrons) are observed in relation to reduced lipoprotein lipase activity, increased LDL-cholesterol due to reduced HDL catabolism, and decreased HDL-cholesterol [10].

In well- and moderately well-controlled IDDM, VLDL and LDL concentrations are normal or even subnormal, whereas HDL-cholesterol is frequently increased [10]. The rise in HDL-cholesterol is mainly attributable to an increase in HDL$_2$ particles [12], which could be related to overactivation of lipoprotein lipase activity resulting from peripheral hyperinsulinaemia in IDDM patients treated with subcutaneous insulin. Lp(a) concentration is not augmented in IDDM patients without nephropathy [63]. However, increased Lp(a) levels have been reported in IDDM patients with micro- and macroproteinuria [75]. Nephropathy in IDDM patients is also associated with other lipid quantitative abnormalities, such as increased total cholesterol, triglycerides, VLDL and LDL and decreased HDL-cholesterol [12].

The lack of overt abnormalities for lipoprotein levels in IDDM patients with fair to good glycaemic control does not exclude the possibility of qualitative abnormalities, which may be atherogenic.

An enrichment of VLDL in cholesterol ester is observed in IDDM [76]. VLDL from IDDM patients induce abnormal responses of cellular cholesterol metabolism in human macrophages in vitro [77]. As in NIDDM subjects, glycation of apo C and E occurs in VLDL from IDDM patients, causing the same effects on atherogenicity.

LDL particles of IDDM patients are triglyceride-rich [10], and the proportion of small dense LDL is also increased in IDDM [12]. These compositional
abnormalities are more apparent in poorly controlled IDDM patients [78]. Other qualitative abnormalities include an increased free cholesterol/lecithin ratio, which is an index of cardiovascular risk [12]. Moreover, glycation of apo B occurs in IDDM. Lopes-Virella et al. showed that LDL from IDDM patients (HbA1c ranging from 6.4 % to 10.5 %) stimulated more cholesteryl ester synthesis and accumulation in human monocyte-derived macrophages than did LDL from non-diabetic controls [79]. This seems to have been due to glycation since cholesteryl ester synthesis by macrophages was correlated with the extent of LDL glycation. Furthermore, increased LDL oxidation has been observed in IDDM patients [16]. HDL particles from IDDM patients may show some qualitative abnormalities. Subtle reductions of phospholipids have been reported that may compromise the function of HDL in reverse cholesterol transfer [80]. Moreover, enrichment of HDL in triglycerides has been noted in IDDM patients [81]. Thus, several lipoprotein qualitative abnormalities in IDDM could promote atherogenesis. Importantly, these compositional changes cannot be suspected from measurement of serum lipid concentrations. Moreover, increased CETP activity has been noted in IDDM [82, 83]. The acceleration of cholesteryl ester transfer may be harmful as it loads to more atherogenic cholesteryl rich apo B-containing lipoproteins, which may be redirected to non hepatic sites of catabolism such as arterial wall macrophages. This could contribute to the development of macrovascular disease in IDDM, even when plasma lipids are normal. If hyperglycaemia is likely to play an important role in promoting lipid qualitative abnormalities in IDDM (such as apolipoprotein glycation), the subcortaneous mode of insulin administration, leading to peripheral hyperinsulinaemia, could also contribute to some compositional changes of lipoproteins. Indeed, it has been shown that intraperitoneal insulin administration, which mimics physiological insulin secretion in the portal vein to avoid peripheral hyperinsulinaemia, is able to restore CETP and lipoprotein lipase activities to normal, decrease triglyceride content in LDL and HDL, and normalise the HDL_{2}/HDL_{3} ratio [84, 85].

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