New insight into the pathophysiology of lipid abnormalities in type 2 diabetes

B Vergès

SUMMARY
Lipid abnormalities in patients with type 2 diabetes 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. The main quantitative abnormalities are increased triglyceride levels, related to an augmented hepatic production of VLDL and a reduction of both VLDL and IDL catabolism, and decreased HDL-Cholesterol levels due to an accelerated HDL catabolism. The main qualitative abnormalities include large VLDL particles (VLDL₁), relatively rich in triglycerides, small dense LDL particles, increase in triglyceride content of LDL and HDL, glycation of apolipoproteins and increased susceptibility of LDL to oxidation. Moreover, although plasma LDL-cholesterol level is usually normal in type 2 diabetic patients, LDL particles show significant kinetic abnormalities, such as reduced turn-over, which is potentially harmful. The pathophysiology of lipid abnormalities in type 2 diabetes is not yet totally explained. However, insulin resistance and the "relative" insulin deficiency, observed in patients with type 2 diabetes, are likely to play a crucial role since insulin has an important function in the regulation of lipid metabolism. In addition, it is not excluded that adipocytokines, such as adiponectin, could play a role in the pathophysiology of lipid abnormalities in type 2 diabetes.

Key-words: Type 2 diabetes · Lipids · Lipoproteins · VLDL · LDL · HDL.

RÉSUMÉ
Physiopathologie des anomalies lipidiques observées dans le diabète de type 2 : données nouvelles
Les anomalies lipidiques observées chez les patients diabétiques de type 2 ont une responsabilité importante dans la plus grande fréquence et gravité des accidents cardio-vasculaires propres au diabète de type 2. La dyslipidémie du diabète de type 2 est caractérisée par la présence d’anomalies quantitative et qualitatives des lipoprotéines, toutes potentiellement athérogènes. Les principales anomalies quantitatives sont représentées par l’hypertriglycéridémie, secondaire à une augmentation de la production hépatique des VLDL et à un ralentissement du catabolisme des VLDL et IDL, et par la diminution des concentrations plasmatiques de HDL-cholestérol, liée à l’augmentation du catabolisme des HDL. Les principales anomalies qualitatives comprennent la présence de VLDL de grande taille (VLDL₁), relativement riches en triglycérides, de LDL petites et denses, enrichissement en triglycérides des LDL et HDL, glycation des apolipoprotéines et une augmentation de l’oxydation des LDL. En outre, bien que le niveau de LDL-cholestérol plasmatique soit en règle normal, chez les patients diabétiques de type 2, il est observé des modifications significatives de la cinétique des LDL, en particulier un ralentissement de leur turn-over, potentiellement délétère. La physiopathologie précise de la dyslipidémie du diabète de type 2 n’est pas encore parfaitement connue. Cependant, l’insulinorésistance et la carence « relative » en insuline, observées dans le diabète de type 2, apparaissent jouer un rôle important puisque l’insuline exerce des fonctions essentielles dans le contrôle du métabolisme lipidique. En outre, il n’est pas exclu que les adipocytokines, en particulier l’adiponectine, puissent être impliquées dans la physiopathologie des anomalies lipidiques du diabète de type 2.

Mots-clés : Diabète de type 2 · Lipides · Lipoprotéines · VLDL · LDL · HDL.
Cardiovascular disease [CVD] is the major cause of morbidity and mortality in patients with type 2 diabetes and CVD risk is 2 - 4 that of non-diabetic subjects [1-4]. Abnormalities of lipid metabolism, observed in type 2 diabetes, are one of the major factors contributing to vascular risk [1, 5]. Diabetic dyslipidemia includes not only quantitative lipid abnormalities but also qualitative and kinetic lipid abnormalities, which are potentially atherogenic. Insulin resistance plays a key role in the pathophysiology of lipid abnormalities in type 2 diabetes. Other factors, such as adipocytokines (adiponectine, for instance) could also be involved in the development of lipid abnormalities in type 2 diabetic patients. This review, after providing a brief description of human lipoprotein metabolism, and a concise report about the role of insulin on lipid metabolism, will present lipid abnormalities observed in type 2 diabetes and discuss their pathophysiological mechanisms.

Brief review of human 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 generally classified according to their density as chylomicrons, Very Low Density Lipoprotein (VLDL), Intermediate Density Lipoprotein (IDL), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL). An overview of lipoprotein metabolism is shown in Figure 1.

Chylomicrons

Chylomicrons, the largest lipoprotein particles, are responsible for the transport of dietary triglycerides and cholesterol. Chylomicrons are composed of triglycerides (85%-90%), cholesterol esters, phospholipids and apolipoproteins (mainly apoB48 but also apoA-I and apoA-IV). The formation of chylomicrons takes place in the enterocytes, and the process associating the lipid components (triglycerides, cholesterol esters, phospholipids) and apoB48 is performed by the MTP (Microsomal Tranfer Protein). Chylomicrons are secreted into the lymphatic circulation before entering the bloodstream. In plasma, triglycerides of chylomicrons are hydrolyzed by lipoprotein lipase leading to the formation of smaller, triglyceride-poorer particles known as chylomicron-remnants. Chylomicron-remnants are cleared by the liver through LDL B/E receptor or LRP (LDL-receptor related protein).

VLDLs and IDLs

VLDL particles, which are secreted by the liver consist of endogenous triglycerides (55% to 65%), cholesterol, phospholipids and apolipoproteins (apoB100 as well as apoCs and apoE). In the hepatocyte, the formation of VLDL occurs in two major steps. In the first step, which takes place in the rough endoplasmatic reticulum, apoB is cotranslationally and post-translationally lipidated by the MTP (Microsomal Tranfer Protein). MTP transfers lipids (mainly triglycerides but also cholesterol esters and phospholipids) to apoB. This first step leads to the formation of pre-VLDL [6]. In the second step, pre-VLDL is converted to VLDL in the smooth membrane compartment. This
step is driven by ADP ribosylation factor-1 (ARF-1) and its activation of phospholipase D, needed for the formation of VLDL from pre-VLDL [6].

In plasma, triglycerides of VLDLs are hydrolyzed by lipoprotein lipase. As VLDLs become progressively depleted in triglycerides, a portion of the surface including phospholipids and apolipoproteins C and E is transferred to HDLs. This metabolic cascade leads to the formation of IDL particles, which are either cleared by the liver through LDL B/E receptors or further metabolized to form LDLs. The enzyme, hepatic lipase, which has both triglyceride lipase and phospholipase activities, is involved in this metabolic process generating LDL particles from IDLs.

**LDLs**

LDL is the final product of the VLDL-IDL-LDL cascade. LDL is the main cholesterol-bearing lipoprotein in plasma. Each LDL particle contains one molecule of apoB100, which plays an important role in LDL metabolism. Clearance of LDL is mediated by the LDL B/E receptor. Seventy percent of LDL B/E receptors are located on hepatic cells and 30% on the other cells of the body.

**HDLs**

HDL particles are secreted by the hepatocyte as small lipid-poor lipoproteins, containing mostly apoA-I, which receive, in the circulation, phospholipids, apoCs and apoE from chylomicrons and VLDLs. Nascent or lipid-poor HDLs get from peripheral cells free cholesterol and phospholipids through ABCA1 transporter (ATP Binding Cassette A1 transporter), allowing the transport of free cholesterol and phospholipids from the cell cytoplasm into the HDL particles. Within HDL particles free cholesterol is esterified by LCAT (Lecithin Cholesterol AcylTransferase) leading to the formation of HDL \(_2\) particles. The fusion of 2 HDL \(_2\) particles, that is promoted by PLTP (Phospholipid Transfer Protein), leads to the formation of one larger size HDL \(_2\) particle. HDL \(_2\) lipoproteins, rich in cholesterol ester, are degraded by hepatic lipase and endothelial lipase, leading to the formation of HDL remnant particles that are cleared by the liver after recognition by the SR-B1 receptor (Scavenger Receptor class B type 1).

**Lipid transfer proteins**

Lipoprotein metabolism is largely influenced by lipid transfer proteins. Among these, two play an important role: CETP (Cholesteryl Ester Transfer Protein) and PLTP (Phospholipid Transfer Protein). CETP facilitates the transfer of triglycerides from triglyceride-rich lipoproteins (mainly VLDL) toward HDL and LDL and the reciprocal transfer of cholesteryl esters from HDL and LDL toward VLDL. PLTP facilitates the transfer of phospholipids and \(\alpha\)-tocopherol between lipoproteins. PLTP is also involved in the formation of HDL \(_2\) particles from HDL \(_3\) particles. Any modification of CETP or PLTP activities is likely to promote significant qualitative abnormalities of lipoproteins.

![Figure 2](image)

**Figure 2**

Role of insulin on lipid metabolism

Insulin plays a central role in the regulation of lipid metabolism. The main sites of action of insulin on lipoprotein metabolism are shown in Figure 2.

In adipose tissue, insulin inhibits hormone-sensitive lipase. Thus, insulin has an anti-lipolytic action. It promotes storage of triglycerides in the adipocytes and reduces secretion in the circulation of free fatty acids from adipose tissue.

Insulin inhibits VLDL production from the liver. In normal subjects, it has been shown that insulin induces a 67% decrease of VLDL-triglyceride production and a 52% decrease of VLDL-apoB production [7, 8]. Insulin reduces VLDL production by diminishing circulating free fatty acids (due to its antilipolytic effect), which are substrates for VLDL, but also by a direct inhibitory effect in the hepatocyte [8]. Insulin is a potent activator of lipoprotein lipase (LPL), promoting the catabolism of triglyceride-rich lipoproteins. Insulin not only enhances LPL activity [9] but also has a direct positive effect on the LPL gene, promoting LPL synthesis [10]. Insulin promotes the clearance of LDL by increasing LDL B/E receptor expression and activity [11, 12]. Insulin acts also on HDL metabolism by activating LCAT and hepatic lipase activities [13]. An inhibitory effect of insulin on PLTP activity has been demonstrated in normal subjects and type 2 diabetic patients [14]. It has also been shown that insulin reduces CETP activity. However, this inhibitory effect is more likely to be the consequence of the insulin-induced reduction of free fatty acids in the circulation than a direct inhibitory action on CETP [15].

Lipid abnormalities observed in type 2 diabetes

Prevalence of dyslipidemia is very common in type 2 diabetes [16-18]. Both quantitative and qualitative lipoprotein abnormalities are observed in type 2 diabetic patients [19-25]. The main quantitative lipid abnormalities are hypertriglyceridaemia and low HDL-cholesterol levels. Qualitative lipid abnormalities are present in all lipoproteins in type 2 diabetes. Both quantitative and qualitative lipoprotein abnormalities are likely to promote atherosclerosis in type 2 diabetic patients. Main lipoprotein modifications are shown in Table I and in Figure 3.

Triglyceride-rich lipoproteins

Plasma triglyceride level is frequently increased in type 2 diabetes, mainly due to an increased number of VLDL particles [19, 23]. An augmented number of IDL particles is also observed in type 2 diabetic patients [26, 27].

One determinant of diabetic hypertriglyceridaemia is overproduction of VLDL-triglycerides [28] which is attributed to the increased availability of lipids in hepatocytes but also to hepatic resistance to the inhibitory effect of insulin on VLDL production [29-31]. The increased lipid pool in hepatocytes is due to the augmented flux of free fatty acids into the liver [32] and possibly to exaggerated de novo lipogenesis. Indeed, an elevated level of Sterol Regulatory Element-Binding Protein-1c (SREBP-1c) is observed in liver of insulin-resistant animals [33, 34]. The augmentation of SREBP-1c expression in the liver is followed by the activation of key enzymes of de novo lipogenesis: acetyl-CoA carboxylase and Fatty acid synthase. If a part of VLDL overproduction, in type 2 diabetic patients, has been shown to be secondary to the augmented free fatty acid plasma level [35], many studies indicate that the decrease of the inhibitory effect of insulin on hepatic VLDL production is likely to play the major role [8, 31]. Indeed, the inhibitory effect of insulin on hepatic VLDL production has been demonstrated in several studies [7, 8, 36-42]. Insulin has been shown to inhibit the assembly and secretion of VLDL particles by increasing apoB degradation and reducing the expression of MTP in hepatocytes [37, 38, 41]. Interestingly, an increased expression of MTP leading to enhanced VLDL assembly has been observed in insulin-resistant hamsters and in obese diabetic mice [42, 43]. Furthermore, significant per-

<table>
<thead>
<tr>
<th>Table I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main lipid abnormalities in type 2 diabetes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Plasma level</th>
<th>Kinetic abnormalities</th>
<th>Qualitative abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>(hypertriglyceridaemia)</td>
<td>• production</td>
<td>• Large VLDL (VLDL1) • Glycation</td>
</tr>
<tr>
<td>LDL</td>
<td>Normal or slightly</td>
<td>• catabolism</td>
<td>• Small dense LDL (TG-rich LDL) • Oxidation • Glycation</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td>• catabolism</td>
<td>• TG-rich HDL • Glycation</td>
</tr>
</tbody>
</table>
New insight into the pathophysiology of lipid abnormalities in type 2 diabetes

Turbations in the assembly and secretion of VLDL particles are observed in type 2 diabetic patients. Normally, insulin through activation of Phosphoinositide 3-kinase (PI 3-kinase) stimulates the transformation of PIP2 (Phosphoinositol biphosphate) into PIP3 (Phosphoinositol triphosphate). The insulin-induced reduction of PIP2, which is an activator of ARF-1 and Phospholipase D, leads to a decrease in the activation of both ARF-1 and Phospholipase D which are involved in VLDL assembly [6]. In type 2 diabetes, a defective activation of PI 3-kinase is noted, secondary to the insulin resistant state. This reduced activation of PI 3-kinase, in type 2 diabetes induces an excess of PIP2 which activates ARF-1 and Phospholipase D leading to increased VLDL assembly.

Thus VLDL overproduction, in type 2 diabetes, seems to be mainly due to hepatic resistance to the inhibitory effect of insulin on VLDL production. This mechanism occurs early since it is already observed in obese insulin resistant subjects without diabetes [7, 44]. Moreover, the increased VLDL-triglyceride production is accompanied by an augmented production of VLDL-apoB, in type 2 diabetic patients [28, 45]. Some data suggest that overproduction of VLDL-triglycerides may be greater than that of VLDL-apoB, in type 2 diabetes, resulting in the formation of larger triglyceride-rich VLDL particles (VLDL1) [46].

Type 2 diabetic patients have also reduced catabolism of VLDL particles which is an additive factor promoting diabetic hypertriglyceridemia. This has been shown by in vivo kinetic studies with radio isotopes [28, 46] and with stable isotopes [47]. Moreover, a significant reduction of IDL catabolism is also noted in type 2 diabetic patients [47]. This defect in VLDL and IDL catabolism reflects mainly the reduced activity of lipoprotein lipase, which is in charge of the degradation of triglycerides within VLDL and IDL particles. Indeed a decreased activity of adipose tissue lipoprotein lipase has been shown in type 2 diabetes [46, 48, 49]. Since insulin is an activator of lipoprotein lipase, we may think that the decrease of its activity may be due to relative insulin deficiency and/or insulin resistance, observed in type 2 diabetes.

Type 2 diabetic patients show not only fasting hypertriglyceridemia but also significant postprandial lipemia. Indeed, several studies have reported an increased plasma triglyceride response to an oral fat load in type 2 diabetic patients [50, 51]. In type 2 diabetic patients, the majority of plasma triglyceride-rich lipoproteins during the postprandial state are VLDL1 particles [52, 53]. The excessive postprandial lipemia in type 2 diabetes is secondary to the failure of insulin to suppress VLDL1 production, particularly postprandially, to a reduced delipidation process due to decreased LPL activity and to competition between chylomicrons and VLDL particles for the contact with LPL [54].

Several qualitative abnormalities of VLDL have been described in patients with type 2 diabetes. The overproduction of VLDL is characterized by an increased synthesis of large VLDL particles (VLDL1), relatively richer in triglycerides than the smaller VLDL2 particles. VLDL1 are easily taken up by scavenger receptors of macrophages,
promoting lipid accumulation within macrophages and leading to the formation of foam cells in vessel walls [55]. Glycation of apolipoproteins in VLDL (apoB, apoCs, apoE) may occur in diabetes. This may reduce VLDL binding to the B/E receptor and hence impair its catabolism [56]. Furthermore, it has been suggested that glycation of apoCII, a cofactor of lipoprotein lipase, could contribute to lesser activation of this enzyme [57].

**LDL**

Although plasma LDL-cholesterol level is usually normal in type 2 diabetic patients, important modifications of its metabolism are observed. Indeed, it has been shown *in vivo* in type 2 diabetic patients featuring LDL-cholesterol values similar to normolipidemic non-diabetic controls, a significant 28% reduction of LDL catabolism associated with a reduced LDL production (secondary to decreased LDL catabolism) [47]. Thus, although having normal plasma LDL-cholesterol levels, patients with type 2 diabetes show reduced turn-over of their LDL particles with a reduction of catabolism leading automatically to increase LDL plasma residence time. Augmented LDL residence time in plasma is likely to promote cholesterol deposition in the arterial wall. Our group has shown that insulin treatment, in type 2 diabetic patients, completely normalize LDL catabolism [58]. The impaired LDL catabolism, in type 2 diabetes, could be due to a reduction of the number of LDL B/E receptors. Indeed, type 2 diabetic patients show a significant reduction of LDL B/E receptors on cell surface [59]. Moreover, insulin treatment restores a normal number of LDL B/E receptors on cell surface, in type 2 diabetic patients [59]. It has also been suggested that reduced LDL catabolism could be partly attributed to a decreased affinity of LDLs for their receptors secondary to apoB glycation [60].

Important qualitative abnormalities of LDLs, potentially atherogenic, are observed in type 2 diabetic patients. Small dense, triglyceride-rich, LDL particles (known as subclass B) are more prevalent in type 2 diabetes [61, 62]. The presence of small dense LDLs appears to be mainly related to hypertriglyceridemia [63] and it has been found that VLDL1 triglyceride is the major predictor of LDL size in type 2 diabetic patients as in non-diabetic subjects [52]. It seems likely, in type 2 diabetes, that the increase of triglyceride-rich lipoproteins stimulates CETP activity, promoting the transfer of triglycerides to LDLs leading to the formation of triglyceride-rich LDL particles, which are preferential substrate for hepatic lipase. Thus, the stimulated hepatic lipase activity favors the formation of small dense LDL particles. Several studies have shown that the presence of small dense LDL particles is associated with increased cardiovascular risk [64-66]. Many data indicate that small dense LDL particles have atherogenic properties. Indeed, small dense LDL particles have reduced affinity for the LDL B/E receptor and are preferentially taken up by macrophages, through the scavenger receptor, leading to the formation of foam cells. Small dense LDL particles have higher affinity for intimal proteoglycans than large LDL particles which may favor the penetration of LDL particles into the arterial wall [67, 68]. It has been shown that subjects with small dense LDL particles show an impaired response to the endothelium dependent vasodilator acetylcholine [69, 70]. Moreover, small dense LDL particles show an increased susceptibility to oxidation [70, 71]. Another lipoprotein modification with marked atherogenic potential, observed in type 2 diabetes, is increased LDL oxidation [24, 25]. *In vitro* studies, have shown an increased oxydability of LDL particles from type 2 diabetic patients [72]. Moreover, an increased number of plasma oxidized LDL particles is observed in type 2 diabetic patients [73]. Oxidative modification of LDL results in rapid uptake by macrophages, leading to foam cell formation. Oxidized LDLs produce chemotactic effects on monocytes by increasing the formation of adhesion molecules, such as ICAM-1 (intercellular adhesion Molecule 1) by endothelial cells. Oxidized LDLs stimulate the formation by macrophages of cytokines, such as TNFα or IL1, which amplify the inflammatory atherosclerotic process. Glycation of LDL (glycation of apoB within LDL particles) is an additional qualitative lipoprotein abnormality noted in diabetic patients. Glycation of apoB may significantly modify LDL metabolism [74, 75]. Indeed, glycated LDL have reduced affinity for LDL B/E receptor [76] and are preferentially taken up by macrophages leading to the formation of foam cells [77]. Furthermore, glycated LDL are easily oxidized [78, 79].

**HDL**

Type 2 diabetes is associated with decreased plasma HDL-cholesterol levels related to reduction of the HDL2 subfraction [80]. Reduced HDL2 level, in type 2 diabetes, has been shown to be correlated with both hypertriglyceridaemia and obesity [81]. The decrease in HDL-cholesterol, noted in patients with type 2 diabetes, is due to increased catabolism of HDL particles, which has been demonstrated by *in vivo* kinetic studies using radio-isotopes [82] and more recently using stable isotopes [83]. An increased activity of hepatic lipase, which is in charge of HDL catabolism, is observed in type 2 diabetes [82, 84]. The increased HDL catabolism is related to the insulin-resistant state. Indeed, a similar increase of HDL catabolism is observed in obese insulinresistant non-diabetic patients [85, 86]. One of the main reasons for increased catabolism of HDL particles in insulin-resistant states and type 2 diabetes is the increased pool of triglyceride-rich lipoproteins (mainly VLDL). The augmented level of plasma triglyceride-rich lipoproteins drives, through CETP, the transfer of triglycerides from triglyceride-rich lipoproteins to HDL leading to the forma-
tion of triglyceride-rich HDL particles [87]. HDL enriched in triglycerides become very good substrate for hepatic lipase whose activity is augmented in insulin resistant states and type 2 diabetes, leading to increased catabolism of HDL particles.

Several qualitative abnormalities of HDL particles are described in type 2 diabetes. HDLs of patients with type 2 diabetes are enriched in triglycerides which is responsible for increased catabolism of HDL particles (see above). Furthermore, HDL particles are glycated in type 2 diabetes and a direct correlation has been observed between plasma glucose level and glycation of apoA-I [88]. It has been suggested that apoA-I glycation may reduce HDL binding to its receptor [89]. The qualitative abnormalities of HDL particles may impair HDL mediated cholesterol efflux and reverse cholesterol transport as suggested by in vitro studies [90-92].

**Lipid transfer proteins**

The qualitative abnormalities of lipoproteins observed in type 2 diabetes, such as increased triglyceride content of LDL and HDL particles, indicate an increased activity of CETP which is responsible for the transfer of triglycerides and cholesterol esters between lipoproteins. However, ex vivo CETP activity has been shown to be either increased [93, 94] or decreased [95] in diabetic patients. These discrepancies are likely to be due to the different methods used to assess CETP activity. Nevertheless, regarding the qualitative abnormalities of lipoproteins, it is considered that in vivo CETP activity is increased in type 2 diabetic patients. The main factor responsible for increased CETP activity in type 2 diabetes is the augmented pool of triglyceride-rich lipoproteins (mainly VLDL), which directly stimulate CETP. However, hyperglycaemia per se could also activate CETP since glycation of lipoproteins has been shown to increase CETP activity [96].

Increased PLTP mass and PLTP activity have been reported in type 2 diabetes [94, 97]. However, the exact consequences of such an increased PLTP activity remain unclear.

**A putative role of adipocytokines in the pathophysiology of lipid abnormalities in type 2 diabetes?**

Beyond its capacity for fat storage, white adipose tissue is now well recognized as an endocrine tissue producing several adipocytokines whose plasma levels are altered in type 2 diabetes. Data have shown that some adipocytokines, such as adiponectin or TNFα, influence lipid metabolism [98]. Thus, it is not excluded that adipocytokines could play a role in the pathophysiology of lipid abnormalities in type 2 diabetes.

Adiponectin increases muscle free fatty acid uptake and oxidation, decreases muscle and liver triglyceride content and reduces plasma free fatty acid level [98-100]. Patients with type 2 diabetes and insulin-resistant obese subjects have reduced circulating adiponectin levels and expression in white adipose tissue [101, 102]. In non-diabetic individuals as in type 2 diabetic patients, plasma adiponectin has been shown to be negatively correlated with plasma triglycerides and positively with plasma HDL-cholesterol [103-106]. Moreover, the associations between adiponectin and plasma lipids have been shown to be independent of indexes of insulin-resistance [103-105]. Recently, plasma adiponectin level has been shown to be positively correlated with VLDL apoB catabolism independently of HOMA index [107]. These data suggest a possible direct action of adiponectin on lipid metabolism independent of its effects on insulin sensitivity. However, the mechanisms by which decreased adiponectin may affect lipid metabolism, in type 2 diabetes, remain unclear. Adiponectin may decrease plasma triglyceride level by enhancing free fatty acid oxidation through activation of acetylCoA oxidase and carnitine palmitoyltransferase-1 and AMP kinase [108]. Adiponectin may also indirectly stimulate lipoprotein lipase [109], by increasing the expression of PPAR-α in the liver and the adipocytes [100].

The production of TNFα by the white adipose tissue is increased in insulin resistance and type 2 diabetes [98, 110, 111]. TNFα has several effects on lipid metabolism. TNFα reduces free fatty acid uptake in the adipose tissue, promotes lipolysis and free fatty acid efflux [98]. It also suppresses the production of factors involved in triglyceride accumulation such as lipoprotein lipase, fatty acid transport protein and acetylCoA synthetase [98, 105]. However, a role of TNFα in the pathophysiology of lipid abnormalities in type 2 diabetes is not certain. Indeed, no correlations have been found between circulating TNFα and plasma lipids in patients with diabetes or at risk to develop diabetes [106]. Furthermore, TNFα has not been found to be associated with TG-rich lipoprotein metabolism [107, 112].

Resistin, another adipocytokine is found to be negatively correlated with HDL-cholesterol, in diabetic subjects, after adjustment for BMI and HbA1c [106]. However no correlations have been found between resistin and TG-rich lipoprotein metabolism [107, 112]. Further studies are still needed to precise the putative role of adipocytokines on lipid abnormalities in type 2 diabetes.

In conclusion, lipid abnormalities in patients with type 2 diabetes are likely to play an important role in the development of atherogenesis. These lipid disorders include potentially atherogenic quantitative and qualitative lipid abnormalities. The main lipid quantitative abnormalities are hypertriglyceridaemia and low HDL-cholesterol levels. The major qualitative abnormalities include large VLDL particles (VLDL1), small dense LDLS, increase of triglyceride content of LDLS and HDLS, glycation of apolipoproteins and increased LDL oxidation. The pathophysiology
of lipid abnormalities in type 2 diabetes is complex and not yet totally explained. Some more studies are still needed to get further insight into the precise mechanisms of diabetic dyslipidemia. The improvement of our understanding of lipid disorders in type 2 diabetes will lead to a better treatment of diabetic dyslipidemia.

References

10. Fried SK, Russell CD, Grauso NL, Brolin RE. Lipoprotein lipase regulation of diabetic dyslipidemia. The improvement of our understanding of lipid disorders in type 2 diabetes will lead to a better treatment of diabetic dyslipidemia.

References

10. Fried SK, Russell CD, Grauso NL, Brolin RE. Lipoprotein lipase regulation of diabetic dyslipidemia. The improvement of our understanding of lipid disorders in type 2 diabetes will lead to a better treatment of diabetic dyslipidemia.

References

10. Fried SK, Russell CD, Grauso NL, Brolin RE. Lipoprotein lipase regulation of diabetic dyslipidemia. The improvement of our understanding of lipid disorders in type 2 diabetes will lead to a better treatment of diabetic dyslipidemia.


52. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. Diabetesologia 2003;46:733-49


B Vergès, Galland F, Duvalillard L, et al. Direct measurement of plasma oxidized LDL levels in type 2 diabetic patients before and after insulin therapy. Diabetologia 2003;46(suppl 2):71 [Abstract]


Bagdale JD, Lane JT, Subbaiah PV, Otto ME, Ritter MC. Accelerated cholesteryl ester transfer in non-insulin-dependent diabetes mellitus. Atherosclerosis 1993;104:69-77


Passarelli M, Catanozzi S, Nakandakare ER, Rocha JC, Morton RE, Shimabukuro AF, Quintao EC. Plasma lipoproteins from patients with poorly controlled diabetes mellitus and "in vitro" glycation of lipoproteins enhance the transfer rate of cholesteryl ester from HDL to apo-B-containing lipoproteins. Diabetologia 1997;40:1085-93


Ng T, Watts G, Farvid M, Chan D, Barrett PH. Adipocytokines and VLDL metabolism. Independent regulatory effects of adiponectin,


