

The Effects of Medications Used for the Management of Diabetes and Obesity on Postprandial Lipid Metabolism

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Abstract: Postprandial lipemia has emerged as an independent risk factor for coronary artery disease. In this systematic review we examined the effect of the medications used for the management of diabetes, obesity and dyslipidemia on postprandial lipemia. It should be mentioned that no standardization exists for a test meal and for the duration of observation postprandially to allow for direct comparisons between the published studies. Type 2 diabetes mellitus and insulin resistance are associated with enhanced postprandial lipemia. Insulin is effective in reducing both fasting and postprandial total triglyceride levels as well as triglycerides contained in the triglyceride-rich lipoprotein sub-fractions. Additionally, the newer rapid-acting insulin analogues seem to be more effective in the reduction of postprandial lipemia than the short-acting human insulins. Acarbose ameliorates postprandial lipemia and reduces the atherogenic chylomicron and very low density lipoprotein remnants. Metformin reduces both fasting and postprandial triglyceridemia, fasting and postprandial free fatty acids and may increase the concentrations of the high density lipoprotein cholesterol. Sulfonylureas reduce fasting and postprandial triglyceride levels while data on the effect on high density lipoprotein levels are inconsistent. The effect of meglitinides on postprandial lipid metabolism is neutral. Rosiglitazone decreases fasting and postprandial free fatty acids but has no significant effect on fasting and postprandial triglycerides. Pioglitazone has additional beneficial effects on lipid metabolism because it reduces postprandial free fatty acids, fasting and postprandial triglycerides and increases high density lipoprotein cholesterol levels. Limited available data suggest that glucagon-like peptide-1 analogues and vildagliptin reduce postprandial lipemia through reduction of intestinally-derived triglycerides. No data exist on the effect of sitagliptin on postprandial lipemia. Orlistat improves postprandial lipemia by reducing the absorption of the dietary fat; no data exist on the effect of sibutramine and rimonabant on the metabolism of lipids in the postprandial state.

Keywords: Postprandial lipemia, Chylomicron, Chylomicron remnant, Triglyceride-rich lipoprotein, Remnant-like particle, Apolipoproteins, Insulin, Metformin, Sulfonylureas, Glinides, Glitazones, Acarbose, Glucagon-like peptide-1 analogues, Vildagliptin, Sitagliptin, Orlistat, Sibutramine, Rimonabant.

INTRODUCTION

Postprandial lipemia is a physiological phenomenon occurring several times a day after ingestion of dietary fat. Lipoproteins transport triglycerides and cholesterol from one part of the body to another. Triglycerides are transported by chylomicrons (CM) from the intestine and by very low density lipoproteins (VLDL) from the liver.

Dietary triglycerides are digested in the gut by the enzyme pancreatic lipase to fatty acids and monoglycerides. Fatty acids and monoglycerides are absorbed into the enterocytes where they are re-synthesized in triglycerides and packaged into CM. Subsequently, CM enter the circulation and receive apolipoprotein (apo)C-II and apoE from the high density lipoprotein (HDL) in exchange for apoA-I. Then they reach the enzyme lipoprotein lipase (LPL) at the surface of the capillary endothelial cells which breaks down triglycerides within CM and release large amounts of fatty acids. Part of the fatty acids is taken up by skeletal and cardiac muscle for oxidation and by adipose tissue for storage and part is bound to albumin and circulates in plasma as free fatty acids (FFAs). FFAs are taken up by adipose tissue are

re-synthesized into triglycerides and when energy is required are hydrolyzed by the enzyme hormone-sensitive lipase (HSL). Chylomicron-remnant (CR) particles are formed, which are rich in cholesterol but poor in triglycerides and have apoE as their predominant protein. They are removed from the circulation by the liver by receptor-mediated mechanisms [low density lipoprotein (LDL) receptor, LDL receptor-related protein, apoE receptor], a process stimulated by the enzyme hepatic lipase (HL) [1-5] "Fig. (1)."

VLDL particles are produced by the liver and share with CM a common removal pathway mediated by LPL. At the level of LPL, increased competition occurs between CM and VLDL particles. VLDL remnants (cholesterol-rich and triglyceride-poor particles) are the intermediate density lipoprotein (IDL) cholesterol, which are further catabolized to LDL cholesterol under the action of HL and LPL. IDL and LDL particles are removed by the liver by LDL receptor and LDL receptor-related protein. At the level of the receptor-mediated uptake pathway, VLDL remnants compete with CR [1-5] "Fig. (2)".

HDL particles (cholesterol-rich particles) transport cholesterol from peripheral tissues to the liver and to other lipoproteins (VLDL and LDL), a process that is known as reverse cholesterol transport. Small and protein-rich HDL particles (HDL3) receive free cholesterol which is converted to

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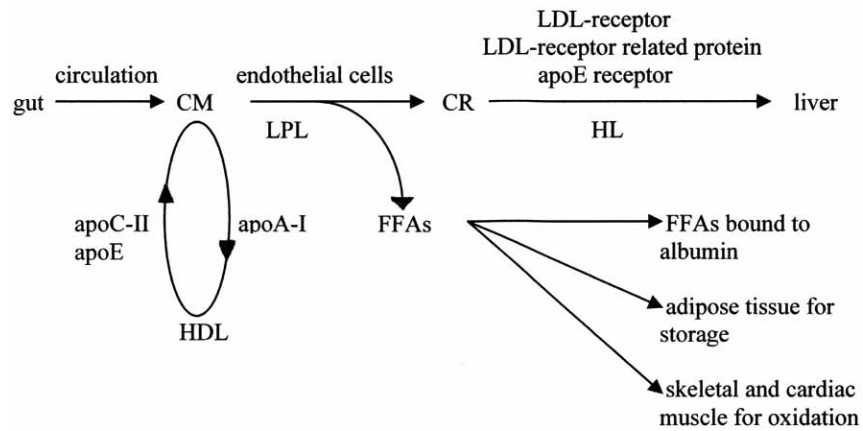


Fig. (1). The metabolism of chylomicrons.

Dietary triglycerides (TG) are digested in the gut by the enzyme pancreatic lipase to fatty acids and monoglycerides. Fatty acids and monoglycerides are absorbed into the enterocytes where they are re-synthesized in TGs and packaged into chylomicrons (CM). Subsequently, CM enter the circulation and receive apolipoprotein (apo)C-II and apoE from the high density lipoprotein (HDL) in exchange for apoA-I. Then they reach the enzyme lipoprotein lipase (LPL) at the surface of the capillary endothelial cells which breaks down TGs within CM and release large amounts of fatty acids. Part of the fatty acids is taken up by skeletal and cardiac muscle for oxidation and by adipose tissue for storage and part is bound to albumin and circulates in plasma as free fatty acids (FFAs). Chylomicron-remnant (CR) particles are formed, which are rich in cholesterol but poor in TGs and have apoE as their predominant protein. They are removed from the circulation by the liver by receptor-mediated mechanisms [low density lipoprotein (LDL) receptor, LDL receptor-related protein, apoE receptor], a process stimulated by the enzyme hepatic lipase (HL).

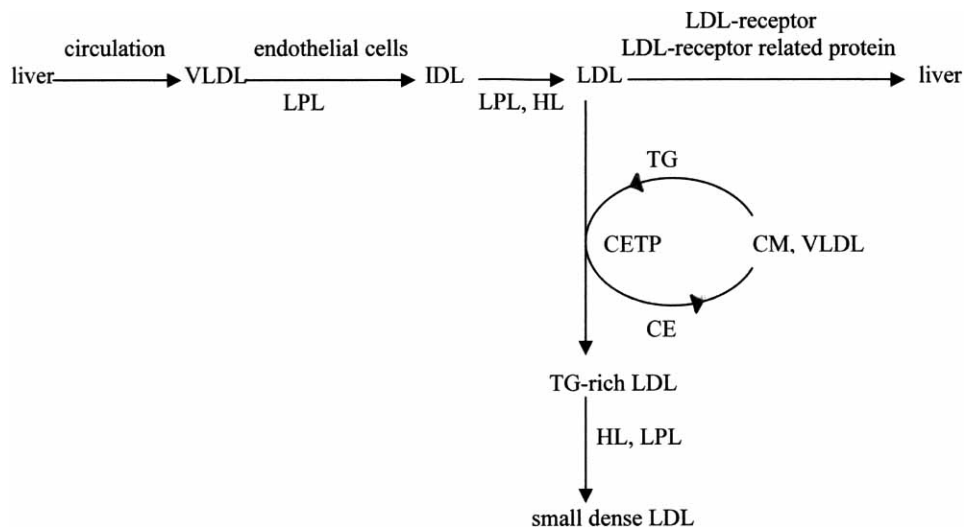


Fig. (2). The metabolism of VLDL.

Very low density lipoprotein (VLDL) particles are produced by the liver and share with chylomicrons (CM) a common removal pathway mediated by lipoprotein lipase (LPL). At the level of LPL, increased competition occurs between CM and VLDL particles. VLDL remnants (cholesterol-rich and triglyceride-poor particles) are the intermediate density lipoprotein (IDL) cholesterol, which are further catabolized to low density lipoprotein (LDL) cholesterol under the action of hepatic lipase (HL) and LPL. IDL and LDL particles are removed by the liver by LDL receptor and LDL receptor-related protein.

Cholesteryl ester (CE) can be transferred from LDL to CM and VLDL by cholesteryl ester transfer protein (CETP) in exchange for triglycerides (TG). The TGs contained in the TG-rich LDL particle are then hydrolyzed by HL or LPL to produce smaller and denser LDL particles.

cholesterol esters (CE) by the enzyme lecithin cholesterol acyl transferase (LCAT). Cholesterol can be taken up by the liver by the hepatic scavenger receptor class B type 1 (SRBI), which removes cholesterol without catabolizing the HDL particles. On the other hand, CE from HDL cholesterol can be transferred to VLDL or LDL cholesterol in exchange for triglycerides, a process mediated by the enzyme cholesterol ester transfer protein CETP resulting in the formation of triglyceride-rich HDL particles (HDL2). The enzyme HL hydrolyses the triglycerides contained in the triglyceride-rich

HDL particles, resulting in the formation of small and dense HDL particles [1, 3, 4, 6, 7]. CE can also be transferred from LDL to triglyceride-rich lipoproteins (TRLs) (CM and VLDL) by CETP in exchange for triglycerides. The triglycerides contained in the triglyceride-rich LDL particle are then hydrolyzed by HL or LPL to produce smaller and denser LDL particles [3, 4, 7, 8] “Fig. (3)”.

CM and CR are intestinally-derived lipoproteins and contain one molecule of apoB-48 while VLDL and their rem-

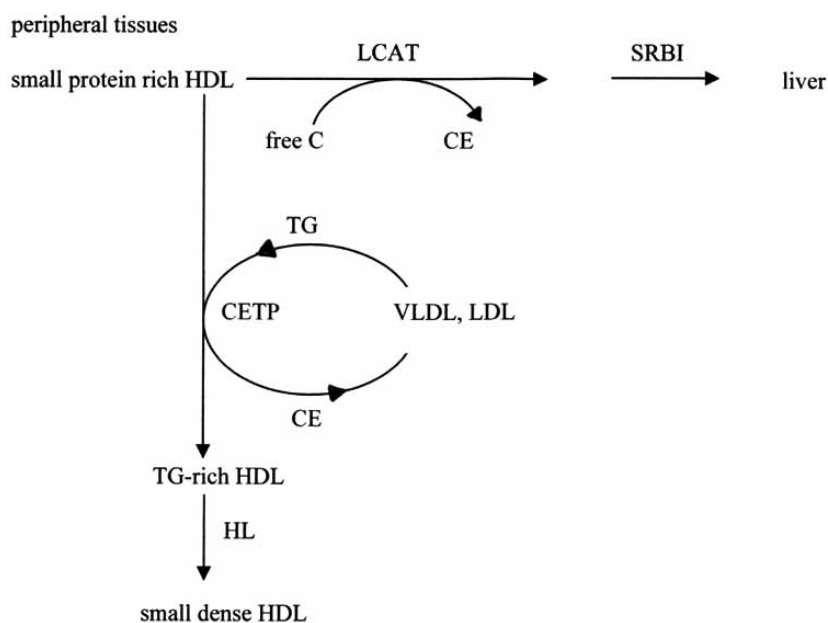


Fig. (3). The reverse cholesterol transport.

High density lipoprotein (HDL) particles transport cholesterol (C) from peripheral tissues to the liver and to very low density lipoproteins (VLDL) and low density lipoproteins (LDL), a process that is known as reverse cholesterol transport. Small and protein-rich HDL particles receive free C which is converted to cholesterol esters (CE) by the enzyme lecithin cholesterol acyl transferase (LCAT). C can be taken up by the liver by the hepatic scavenger receptor class B type 1 (SRBI), which removes C without catabolizing the HDL particles.

CE from HDL-C can be transferred to VLDL- or LDL-C in exchange for triglycerides (TG), a process mediated by the enzyme cholesteryl ester transfer protein (CETP) resulting in the formation of TG-rich HDL particles. The enzyme hepatic lipase (HL) hydrolyses the TGs contained in the TG-rich HDL particles, resulting in the formation of small and dense HDL particles.

nants are hepatically-derived lipoproteins containing one molecule of apoB-100. HDL particles contain apoA-I and often apoA-II.

LPL plays a central role in lipid metabolism since it is the rate-limiting enzyme hydrolyzing the triglycerides contained in CM and VLDL. ApoC-II activates LPL while apoC-III inhibits the activity of the enzyme. In addition, LPL acts as a bridge allowing for lipoproteins to bind with the LDL receptor, the LDL receptor-related protein or the apoE receptor which is necessary for the hepatic uptake of lipoproteins. The activity of LPL is stimulated by insulin. Noteworthy, LPL hydrolyses faster triglycerides contained in the larger than in smaller lipoprotein particles [4, 5, 9].

HL plays a divergent role in lipid metabolism. This enzyme hydrolyses triglycerides in the IDL particles and stimulates the receptor-mediated hepatic uptake pathway of CR and VLDL remnants. On the other hand, HL hydrolyses triglycerides contained in triglyceride-rich HDL and LDL particles, resulting in the formation of smaller and denser particles [3].

Exaggerated postprandial lipemia may contribute to the increased risk of coronary heart disease since there is evidence that accumulation of the remnant particles is highly atherogenic [10]. In addition, TRLs are toxic for the endothelial cells. The large, but especially the small triglyceride-rich remnants can penetrate into subendothelial space where they are taken up by macrophages, resulting in the formation of the foam cells which is the primary event in atherosclerosis [11, 12]. HDL particles protect cells from this cytotoxic effect. Furthermore, prolonged postprandial lipemia results in enhanced CE transfer from LDL and HDL particles to

VLDL particles in exchange for triglycerides. Triglyceride-rich LDL and HDL particles undergo lipolysis by HL, resulting in the formation of smaller and denser particles. Small and dense LDL particles are atherogenic because they are more liable to oxidation and can penetrate easier the vessel intimal wall than the larger particles. In addition, the small and dense HDL particles have reduced ability to prevent LDL oxidation and a more rapid clearance from plasma than the larger HDL particles. As a consequence, plasma concentrations of HDL cholesterol are low and the reverse cholesterol transport is impaired. Eventually these alterations in the HDL cholesterol lead to loss of a protective mechanism against atherosclerosis [1, 2, 6, 7, 13-15].

The objective of the present systematic review is to present available data on the effects of commonly used medications for the management of diabetes and obesity on postprandial lipid metabolism. Because test meals and the duration of observation in the postprandial state differ among the studies, we define at which time point postprandially the determination of concentrations of lipoproteins was performed. In the case this is not stated, the overall response of plasma lipoproteins is expressed as area under the curve.

MEDICATIONS USED FOR THE MANAGEMENT OF DIABETES

Insulin

Hypertriglyceridemia is the major change in lipid metabolism in patients with type 2 diabetes mellitus (DM) along with low HDL cholesterol and increased levels of small and dense LDL particles [1, 6, 7, 16, 17].

In insulin resistance states, there is reduced ability of insulin to suppress lipolysis in adipocytes through its action on HSL and the recently described enzyme adipose triglyceride lipase (ATGL). Therefore, increased amounts of FFAs are released from adipose tissue. At the same time triglycerides catabolism is reduced due to the blunted activity of LPL. The increased FFAs flux to the liver stimulates the assembly and secretion of VLDL, which is further facilitated by lack of the direct inhibitory effect of insulin on hepatic large VLDL production by inhibiting the secretion of the structural protein apoB-100 [15, 18]. Insulin also promotes hepatic triglyceride storage after meal when TRLs production is high. Insulin resistance or deficiency in DM fails to suppress VLDL secretion postprandially. Moreover, prolonged residence in the circulation of triglyceride-rich VLDL particles stimulate the CE transfer mediated by CETP from HDL and LDL cholesterol and promotes the enrichment of HDL with triglycerides. This alteration results in faster catabolic rates of the triglyceride-rich HDL in comparison with the normal HDL under the action of HL. Furthermore, triglyceride-rich LDL particles undergo size reduction through the action of LPL and HL resulting eventually in the formation of small and dense LDL particles [1, 6, 7, 16, 19].

Clinical studies have shown that insulin treatment in patients with type 2 DM is associated with a less atherogenic lipid profile in comparison with oral hypoglycemic drugs, an effect seen independently of blood glucose control. Specifically, insulin reduces fasting plasma total triglycerides and VLDL, increases the activity of LPL and reduces the activity of HL [20-23]. Data on the effect of insulin treatment on fasting HDL cholesterol levels are divergent; some studies have shown that insulin increases HDL cholesterol, whereas others have shown a neutral effect [1, 24, 25].

Boquist *et al.* (2000) [26] investigated the relationship between fasting plasma insulin concentrations and fasting and postprandial lipid levels in healthy men. Subjects were grouped in four quartiles according to the fasting plasma insulin concentrations and received a test meal. Fasting insulin concentrations were associated independently of body mass index, waist-to-hip ratio and blood glucose with fasting VLDL cholesterol and triglycerides as well as with HDL cholesterol. The independent association between baseline insulin with VLDL lipids was mainly accounted for by large VLDLs [Svedberg flotation rate (Sf) > 60 apoB-100]. Additionally, fasting insulin concentrations were associated with the increase in plasma triglycerides after the test meal. Moreover, the postprandial levels of the small CR (Sf 20-60) were significantly higher in the subjects in the upper quartile of fasting insulin levels. The postprandial concentrations of FFAs tended also to be higher in this group. Subjects in the upper quartile are likely to be more insulin resistant and the inhibitory effect of insulin on VLDL production, mainly of the large VLDL production, is reduced. High levels of VLDL result in an increased competition of VLDL and CM for hydrolysis by LPL.

Harbis *et al.* (2001) [27] examined the effects of postprandial hyperinsulinemia per se on postprandial lipid metabolism and especially on TRLs both hepatically and intestinally derived in healthy men after consumption of three isolipid test meals with different glycemic indexes (GI) and

one test meal free of carbohydrates. Postprandial triglyceride concentrations increased significantly after the test meals over baseline with no significant difference among them. Postprandial apoB-48 levels also increased significantly after all test meals over baseline; however, ApoB-48 concentrations peaked earlier after consumption of the test meals with lower GI than the meals with higher GI implying that intestinally derived lipoproteins accumulate earlier after low GI meals and later after meals with high GI. VLDL and CM triglyceride concentrations as well as LPL and HL activity were comparable after all test meals.

In a second experiment Harbis *et al.* [27] examined healthy subjects after they had consumed a carbohydrate free meal followed by either a 3-hour hyperinsulinemic euglycemic clamp or without insulin infusion. Total triglyceride levels were higher following insulin infusion. The increase in apoB-48 was lower in the early postprandial period and increased later with insulin infusion. The postprandial apoB-100 concentrations were not different between the two groups. Following insulin infusion meal the increase in CM triglycerides was higher compared to the phase without insulin administration. It is likely that acute postprandial hyperinsulinemia delays the accumulation of the intestinally derived apoB-48 containing particles, but does not affect the hepatic production of lipoproteins.

Geltner *et al.* (2002) [28] studied the effect of substitution of therapy with sulfonyleureas with a mixture of rapid and intermediate acting human insulins on fasting and postprandial lipid levels in patients with type 2 DM. Patients received an oral fat load at baseline and 4 months after insulin therapy. Fasting total, HDL and HDL3 triglycerides (small dense HDL particles) decreased following treatment with insulin, while total HDL and the HDL3 cholesterol increased; HDL2 cholesterol did not change. Maximum postprandial total and HDL triglycerides reduced with insulin; additionally, total as well as HDL triglycerides reduced at each time point throughout the postprandial period. Plasma levels of apoA-I, apoA-II, apoB and lipoprotein a [Lp(a)] remained unchanged. Insulin administration increased the activity of LPL and CETP, while the activity of HL activity remained unaltered. These findings suggest that insulin treatment improves triglyceride metabolism and the composition of HDL particles by reducing their triglyceride content despite an increase in CETP activity.

Evans *et al.* (2003) [29] investigated the effect of addition of the rapid-acting insulin lispro on postprandial lipemia in patients with type 2 DM who have been treated with oral hypoglycemic agents aiming at near-normal postprandial glycemia. Subjects received a fatty meal at baseline and after 6 weeks of intervention. Postprandial triglyceridemia decreased significantly following insulin treatment. Furthermore, this intervention reduced postprandial VLDL, LDL and HDL triglycerides.

Gallagher *et al.* (2005) [30] examined in a randomized, double-blind, crossover study the effect of the short-acting human insulin and the rapid-acting insulin aspart on postprandial lipid metabolism in patients with type 2 DM. Subjects had been treated with bedtime isophane insulin combined with either premeal short-acting human insulin or rapid-acting insulin aspart for 6 weeks, aiming at achieving

preprandial glucose levels 4.0-6.0 mmol/l and postprandial glucose levels 5.0-7.5 mmol/l in both instances. The difference in HbA1c between the two treatments at 6 weeks was not different. However, postprandial glycemia was significantly lower with insulin aspart. Total triglycerides increased with both premeal insulins postprandially, but they peaked earlier with human insulin. Plasma total and HDL cholesterol concentrations did not increase postmeal and did not differ significantly between the two arms of the study. These results suggest that the lower glucose levels postmeal are not associated with improvement in postprandial lipemia.

Schmoelzer *et al.* (2005) [31] compared in a randomized, crossover trial the acute effect of premixed insulin aspart or premixed human insulins on postprandial lipemia in patients with type 2 DM. The first day patients received a standard breakfast after administration of premixed insulin aspart and on another day they received the same meal after administration of premixed human insulins. Postprandial total triglycerides tended to be lower after premixed insulin aspart than premixed human insulins, but no statistical significance was reached at the examined time-points. However, maximum postprandial total triglyceride levels were lower with the premixed insulin aspart as well as the overall increase in total triglycerides as compared to the human insulins. Postprandial retinyl-palmitate (RP) concentrations, which provide an accurate estimation of TRLs of intestinal origin, were lower following treatment with premixed insulin aspart than premixed of human insulins, although again no statistical significance was reached. These data suggest that insulin aspart may be superior to human insulins concerning its effects on postprandial lipid metabolism.

Ceriello *et al.* (2007) [32] compared in a randomized, crossover study the effect of the combination of the rapid-acting insulin lispro with isophane insulin and isophane insulin alone on postprandial lipemia in patients with type 2 DM treated with oral hypoglycemic agents. Patients received premeal insulin lispro and bedtime isophane insulin first for 12 weeks; subsequently they switched to isophane insulin in the morning and evening for the same time period and vice versa. Subjects received a test meal at baseline and at the end of each test period. Addition of insulin lispro improved postprandial glucose excursions compared with those treated with isophane insulin alone. Postprandial FFAs decreased significantly and earlier in subjects received the combination of insulin lispro and isophane insulin. Postprandial total triglycerides tended to be lower 4 hours after meal following treatment with the combination of insulin lispro and isophane insulin, but the difference was not statistically significant. Postprandial total, LDL and HDL cholesterol concentrations were significantly lower 5 hours after meal following administration of the combination of insulins than isophane insulin alone. The findings of this study suggest that addition of the rapid-acting insulin lispro to isophane insulin is associated with improvement in postprandial lipemia.

In conclusion, insulin treatment has beneficial effects on fasting and postprandial lipid metabolism. Clinical studies have shown that treatment with insulin reduces fasting and postprandial total triglycerides as well as the triglycerides contained in VLDL, LDL and HDL particles. Moreover, the newer rapid-acting insulin analogues may have more favor-

able effects on postprandial lipemia than the short-acting human insulins.

Acarbose

Acarbose is an α -glucosidase inhibitor inhibiting α -glucosidases of the brush border membrane of the small intestine, a group of key intestinal enzymes involved in the digestion of complex carbohydrates [33]. This enables carbohydrates to move into the ileum undigested, thus delaying carbohydrate absorption, attenuating the postprandial increase in plasma glucose level and reducing postprandial hyperinsulinemia. Long-term treatment with acarbose improves insulin resistance as well as glucose tolerance [1]. In clinical studies involving patients with type 2 DM, acarbose decreases HbA1c and postprandial glucose and insulin excursions [34, 35]. It has also been shown in some studies that treatment with acarbose reduces fasting total triglycerides and total cholesterol as well as LDL cholesterol and increases HDL cholesterol levels [36-40].

Hillebrand *et al.* (1979) [41] examined in a double-blind, crossover study the acute effect of acarbose on postprandial lipemia in healthy volunteers. They received before a standard test meal 50 mg, 100 mg, or 200 mg of acarbose or placebo. Acarbose ameliorated postprandial increases in plasma glucose and insulin levels. There was also a dose-dependent effectiveness in the reduction of postprandial total triglyceride levels and the 200 mg dose was more effective. This finding suggests that acarbose sufficiently reduces postprandial triglyceridemia in a dose-dependent manner and the maximal inhibitory effect of acarbose occurs almost two hours after meal.

Hanefeld *et al.* (1991) [42] investigated in a randomized, double-blind, placebo-controlled trial the efficacy of acarbose in reduction of postprandial lipemia in drug-naïve patients with type 2 DM. Subjects received acarbose (100 mg three times daily) or placebo for 24 weeks and a test meal was given at baseline and at the end of the study. Treatment with acarbose resulted in a significant reduction in fasting and postprandial glucose as well as in insulin levels. Moreover, acarbose significantly reduced total triglycerides 1 hour postprandially, while no significant effect was observed in total cholesterol levels. The correction of both hyperglycemia and hyperinsulinemia by acarbose may contribute to the lower hepatic synthesis of triglycerides.

Kado *et al.* (1998) [43] studied in a crossover, placebo-controlled trial the acute effect of acarbose on postprandial lipid metabolism in patients with type 2 DM who had been treated either with diet alone or sulfonylureas. The first day patients consumed a test meal after receiving 100 mg of acarbose and on the next day they consumed the same test meal without acarbose. Acarbose reduced postprandial glucose and insulin levels. Moreover, acarbose ameliorated the postprandial (one and two hours after meal) increase in total triglycerides and remnant-like particle (RLP) cholesterol, a marker of remnant-like apoB-48 and apoB-100 contained in TRLs. The authors concluded that the lower insulin levels after treatment with acarbose may reduce triglycerides and RLP cholesterol concentrations. Acarbose also inhibited the postprandial decline of apoC-II and decreased significantly apoC-III levels. The modulation of LPL activity by apoC-II

and apoC-III may contribute further to the triglyceride- and RLP cholesterol-lowering effect of acarbose.

Ogawa *et al.* (2004) [44] tested in a randomized, placebo-controlled study the effect of a single dose of 100 mg of acarbose and of chronic treatment (300 mg/day for 8 weeks) on lipid metabolism in drug-naïve patients with type 2 DM with either normal or high fasting triglyceride levels. Acute and chronic acarbose administration resulted in reduction in postprandial glucose and insulin in both patients with and without hypertriglyceridemia. One-dose administration of acarbose in patients with normotriglyceridemia resulted in lower FFAs, postprandial total triglycerides and CM levels (at two, four and six hours following meal), while VLDL concentrations did not change. Acarbose administration for 8 weeks reduced fasting FFAs in patients with normal triglyceride levels but had no effect on postprandial FFAs. Postprandial total triglycerides and CM decreased, whereas VLDL remained unchanged. A single dose of acarbose in patients with hypertriglyceridemia reduced postprandial FFAs, total triglycerides and CM concentrations, while VLDL levels were unaltered. Treatment for 8 weeks with acarbose resulted in significant reduction in fasting and postprandial FFAs concentrations and in postprandial total triglyceride and CM levels in patients with hypertriglyceridemia. Moreover, postprandial VLDL concentrations decreased significantly in these patients. It is likely that the long-term treatment with acarbose by improving insulin resistance reduces FFAs; this effect may be due to inhibition of lipolysis and VLDL secretion.

In conclusion, acarbose attenuates the postprandial increase of total triglyceride, CM, VLDL and lipoprotein remnants concentrations. Acarbose may also contribute to the regulation of LPL activity by modifying apoC-II and apoC-III levels. These findings suggest that acarbose may have a beneficial effect on prevention of atherogenesis in type 2 DM by improving both postprandial glucose and lipid metabolism.

Metformin

Metformin is a biguanide derivative widely used as an oral antidiabetic agent. Metformin improves glycemic control primarily by inhibiting hepatic glucose production, especially gluconeogenesis and improving insulin sensitivity in liver and muscle [45]. Although the exact mechanism of action of metformin is not clear, metformin interrupts mitochondrial oxidative processes in the liver and corrects abnormalities of intracellular calcium metabolism in insulin-sensitive tissues and the cardiovascular tissue [46]. In clinical studies involving patients with type 2 DM, metformin decreases fasting and postprandial glucose levels, HbA1c and postprandial insulin levels [47]. Some studies have shown that metformin reduces fasting plasma total cholesterol, total triglyceride and VLDL cholesterol concentrations and increases HDL cholesterol levels [48-51].

Wu *et al.* (1990) [52] investigated the effect of metformin on carbohydrate and lipoprotein metabolism in patients with type 2 DM. Subjects received test meals at the beginning of the study and 4 months after treatment with metformin (500 mg/day gradually increased up to 2.5 g/day). Treatment with metformin lowered both fasting and post-

prandial glucose levels and reduced insulin concentrations. Fasting total cholesterol and total triglyceride levels decreased; this reduction was due to reduction in VLDL cholesterol and VLDL triglycerides respectively, while HDL cholesterol increased. Plasma levels of FFAs and total triglyceride levels were lower from morning until noon hours in the metformin-treated patients. Probably, the improved insulin sensitivity resulted in lower FFAs and VLDL secretion. The increase in HDL cholesterol may be a secondary phenomenon following the reduction of both insulin and triglycerides after treatment with metformin.

Hollenbeck *et al.* (1991) [53] studied the effect of metformin on lipid metabolism in patients with type 2 DM and mild hypertriglyceridemia. Subjects were studied before and after 3 months of treatment with metformin. Metformin induced reductions in daylong glucose and insulin concentrations. VLDL triglycerides and total cholesterol concentrations were lower, while HDL cholesterol levels increased with metformin. Additionally, treatment with metformin reduced mean hourly daylong FFAs and total triglyceride concentrations.

Reaven *et al.* (1992) [54] examined the effect of addition of metformin to sulfonylureas in poorly controlled patients with type 2 DM. Subjects received test meals at the beginning of the study and 3 months after metformin administration (500 mg/day gradually increased up to 2.5 g/day). Metformin induced significant reductions in fasting and postprandial glucose as well as in daylong insulin concentrations. Fasting total cholesterol, total triglyceride, VLDL cholesterol and VLDL triglyceride levels decreased with metformin whereas HDL cholesterol concentrations increased. As a result, the ratio of the total-to-HDL cholesterol decreased significantly. Plasma levels of FFAs and total triglycerides were lower throughout the day after treatment with metformin and the reduction tended to be of greater magnitude in the afternoon.

Jeppensen *et al.* (1994) [55] examined the effect of metformin on the metabolism of TRLs of intestinal origin in patients with type 2 DM treated with glipizide. Subjects consumed test meals at the beginning of the study and 8 weeks after treatment with metformin (starting at 850 mg/day at increased up to 2.55 g/day). Metformin induced significant reductions in daylong glucose and insulin concentrations. Both fasting total cholesterol and total triglyceride levels reduced following treatment with metformin and this effect was entirely attributed to the decrease in VLDL cholesterol and VLDL triglyceride concentrations. Metformin decreased daylong plasma FFAs. Postprandial daylong total triglycerides were significantly lower in the Sf > 400 fraction (predominantly CM) and in the Sf 20-400 fraction (containing both VLDL and CR) after treatment with metformin. Postprandial daylong TRLs of intestinal origin also reduced with metformin. The improved CM metabolism with metformin was attributed to the lower fasting and postprandial triglycerides; this effect reduces the competition of the intestinally and hepatically derived lipoproteins for lipolysis and clearance from plasma.

Weintraub *et al.* (1998) [56] investigated the effect of metformin on postprandial lipemia in nondiabetic obese subjects with impaired glucose tolerance. Subjects consumed a

fat-rich meal at baseline and 3 months after metformin administration (850 mg twice daily). Treatment with metformin reduced postprandial insulin levels. Additionally, postprandial RP concentrations in the CM (Sf > 1000) and in the non-CM fraction (Sf < 1000) decreased with metformin.

Emral *et al.* (2005) [57] investigated the effect of short-term glycemic regulation with either metformin or gliclazide or both on postprandial lipemia in patients with type 2 DM. Subjects were studied in two different occasions; at the beginning of the study when glycemic control was poor and after improvement in glycemic control with the mentioned medications. At the beginning and the end of the study patients consumed a standard mixed meal. Fasting total cholesterol reduced, while no change was observed in fasting HDL and LDL cholesterol levels. Both fasting and postprandial triglycerides decreased after the intervention in comparison with the baseline values. The main finding of this study was that the improvement of glycemia reduces both fasting and postprandial triglyceridemia.

James *et al.* (2005) [58] examined whether the insulin-sensitizing agents metformin and rosiglitazone improved lipoprotein metabolism in obese insulin-resistant individuals. Subjects were randomized to receive either metformin (1 g/day), rosiglitazone (4 mg/day) or placebo (control) for a period of 8 weeks. An oral fat load was given before and at the end of the intervention. Both metformin and rosiglitazone increased insulin sensitivity, but fasting glucose levels were not different between the two groups. No change was observed in fasting FFAs, total triglycerides, apoB-48, total, LDL and HDL cholesterol concentrations after either treatment. The postprandial changes of apoB-48 and CM were not significantly different between the metformin and the control group. The postprandial increase of apoB-48 was higher after treatment with rosiglitazone than after the placebo. Postprandial levels of total triglycerides were not different between metformin and rosiglitazone. Treatment with metformin resulted in a slight decline in the ratio of triglyceride-to-apoB-48 postmeal, whereas after treatment with rosiglitazone this ratio decreased significantly in comparison with the control group. A decrease in this ratio may reflect a smaller size of CM particles.

In conclusion, metformin improves glycemic control and lipoprotein metabolism in patients with type 2 DM. Metformin lowers postprandial glucose, insulin and FFAs levels. Moreover, metformin reduces postprandial total triglycerides and RP in the CM and in the non-CM fraction and may increase HDL cholesterol. These favorable effects of metformin on lipids may be associated with reduced risk for macrovascular complications in patients with type 2 DM.

Sulfonylureas

Sulfonylureas stimulate insulin secretion from the pancreatic β -cells. The most common members of this class are glibenclamide (gliburide), glipizide, gliclazide and glimepiride. Clinical studies involving patients with type 2 DM have shown that sulfonylureas decrease fasting plasma glucose, HbA1c, fasting total triglyceride and total cholesterol concentrations [59, 60]. Concerning the effect of sulfonylureas on HDL cholesterol, clinical data are divergent; some studies have shown that sulfonylureas increase while others

have shown a small or a neutral effect on HDL cholesterol levels [1, 61, 62].

Jeppesen *et al.* (1994) [63] investigated the effect of glipizide on postprandial concentrations of TRLs of intestinal origin in patients with type 2 DM treated with diet alone or sulfonylurea. Subjects received glipizide (the dose titrated until either excellent glycemic control was achieved or the maximum dose of 20 mg twice daily was reached) for 8 weeks. Subjects were given standard test meals at baseline and at the end of the study. Glipizide induced reductions in fasting and postprandial glucose concentrations, whereas daylong insulin levels increased. Fasting total cholesterol and triglyceride levels decreased after treatment with glipizide; these effects were mainly due to reductions in VLDL cholesterol and VLDL triglycerides, respectively. HDL cholesterol increased and the ratio of the total-to-HDL cholesterol decreased. Treatment with glipizide was associated with a decrease in daylong FFAs. Postprandial total triglycerides and triglycerides contained in the Sf 20-400 fraction were lower after treatment, while triglyceride contained in the Sf > 400 fraction remained unaltered. Postprandial RP in the Sf > 400 and in the Sf 20-400 fractions were also lower with glipizide. Additionally, glipizide increased the activity of the LPL and HL. It is possible that the decrease in FFAs resulted in a reduction in the VLDL production by the liver, while the increased activity of LPL and HL in an increased clearance of VLDL triglycerides. Moreover, the increased LPL activity may contribute to the lower levels of intestinally derived TRLs.

Skrapari *et al.* (2001) [64] examined the acute effects of glibenclamide on postprandial lipemia in drug-naïve patients with type 2 DM on two occasions; one day participants received a test meal after taking 5 mg of glibenclamide and on second day they received the same test meal after taking placebo. Treatment with glibenclamide resulted in lower glucose and higher insulin concentrations postprandially in comparison with the placebo. No significant changes were observed in FFAs, total, LDL and HDL cholesterol levels between the two phases of the study. The postprandial increase in total triglycerides and in triglycerides contained in the CM fraction were significantly lower after glibenclamide than placebo, while no significant difference between glibenclamide and placebo was observed in the triglycerides contained in the CM-deficient plasma nor in the VLDL1, VLDL2 and IDL particles. These findings suggest that the lower postprandial lipemia after glibenclamide is mainly due to a decline in triglycerides of intestinal origin. It is also likely that acute hyperinsulinemia secondary to glibenclamide administration leads to activation of LPL and an increased clearance of CM from plasma.

Vakkilainen *et al.* (2002) [65] examined in a randomized, double-blind study the effect of glibenclamide and nateglinide on postprandial lipid metabolism in patients with type 2 DM. Subjects in this study received glibenclamide 5 mg once or twice daily for 12 weeks or nateglinide 120 mg three times daily. Fat tolerance tests were performed at baseline and at the end of the study. Glibenclamide administration induced higher reductions in fasting and postprandial glucose levels and higher insulin concentrations postprandially than nateglinide. No significant difference was observed in

the fasting lipid levels. Treatment with glibenclamide resulted in a greater reduction in postprandial FFAs, but the difference from nateglinide was not statistically significant. The effect of both medications on postprandial CM and VLDL1 triglycerides was minor and not different between the two arms of the study. The same was valid for CM apoB-48, VLDL1 apoB-100, CM, VLDL2 and IDL as well as HDL cholesterol. In addition, the size of the LDL cholesterol in the postprandial state was not significantly different between glibenclamide and nateglinide. These findings suggest that acute hyperinsulinemia induced by either nateglinide or glibenclamide does not suppress sufficiently FFAs postprandially to attenuate hepatic VLDL production.

Mori *et al.* (2006) [66] examined the effect of glibenclamide and pioglitazone on postprandial hyperlipidemia in Japanese patients with type 2 DM. Subjects received a meal tolerance test at the beginning of the study and 6 months after treatment with either glibenclamide or pioglitazone. Both pioglitazone and glibenclamide induced significant reductions in fasting glycemia and HbA1c; however, only pioglitazone reduced significantly fasting total triglycerides compared to baseline. Treatment with pioglitazone was associated with increased activity of LPL and increase in HDL cholesterol and adiponectin levels in comparison with the baseline values. However, no such changes were observed with glibenclamide. Additionally, pioglitazone induced lower concentrations of FFAs, total triglycerides and triglycerides of intestinal origin up to six hours postprandially compared to baseline while glibenclamide administration had no effect on these parameters. Moreover, treatment with pioglitazone resulted in a significant reduction in the RLP triglycerides.

In conclusion, data of the effect of sulfonylureas on postprandial lipid metabolism are inconsistent. However, most of the studies suggest that sulfonylureas improve postprandial lipemia ameliorating the postprandial increase in CM and VLDL triglycerides. This effect is possibly due to the increased activity of LPL and HL and to the reduction of glycemia and FFAs postprandially. The reduction of intestinally-derived lipoproteins by sulfonylureas is of clinical importance because small CM remnants are highly atherogenic.

Meglitinides

Nateglinide (D-phenylalanine derivative) and repaglinide (carbamoylmethyl benzoic acid derivative) act by directly stimulating the release of insulin from pancreatic β -cells in a glucose-sensitive manner, through closure of the ATP-sensitive potassium channel of the β -cells [67]. Meglitinides are insulin secretagogues like sulphonylureas, but act in a more rapid and shorter-lasting manner [68]. In several studies it has been shown that meglitinides restore early insulin secretion and decrease postprandial hyperglycemia [69]. However, data from different studies do not consistently demonstrate any effect of meglitinides on the lipid profile [70].

Mohanlal *et al.* (2002) [71] investigated in a double-blind, crossover, placebo-controlled study the effect on postprandial lipemia of acute nateglinide administration subjects with type 2 DM. The first day patients received a standardized meal after taking 120 mg of nateglinide and on second

day patients received the same meal after taking placebo. Nateglinide induced significant reductions in postprandial glucose concentrations and significant increases in postprandial insulin levels. However, nateglinide administration had no any effect on postprandial total triglyceride or FFAs concentrations.

Vakkilainen *et al.* (2002) [65] examined in a randomized, double-blind study the effect of nateglinide and glibenclamide on postprandial lipid metabolism in patients with type 2 DM treated with either diet alone, sulfonylurea or metformin. Subjects received glibenclamide 5 mg once or twice daily or nateglinide 120 mg three times daily for 12 weeks. A fat-rich meal was given at baseline and at the end of the study. Nateglinide induced a significant reduction in fasting and postprandial glucose concentrations and a significantly increase in insulin levels postmeal. No change was observed in fasting lipid levels. Nateglinide decreased significantly postprandial FFA levels. Postprandial CM and VLDL1 triglyceride concentrations were not altered by nateglinide. The same was valid for CM apoB-48 and VLDL1 apoB-100. Furthermore, treatment with nateglinide had no effect on CM, VLDL2, IDL and HDL cholesterol levels. The size of LDL cholesterol did not change significantly in the postprandial period. These findings suggest that the hyperinsulinemia secondary to nateglinide administration does not affect postprandial lipemia in patients with type 2 DM.

Tentolouris *et al.* (2003) [72] examined in a randomized, crossover, placebo-controlled study the effect of acute repaglinide administration on postprandial lipemia in drug-naïve patients with type 2 DM. One day subjects received repaglinide (2 mg) and then they ingested a test meal and another day subjects received placebo followed by the same test meal. Repaglinide induced reduction in postprandial glucose levels and increase in postprandial insulin concentrations compared with placebo. Although the postprandial increases in plasma, CM and non-CM triglyceride concentrations were higher after placebo than after repaglinide, the differences between the two phases of the study were not statistically significant. No significant changes were found in the concentrations in the postprandial state of the total, LDL and HDL cholesterol levels and FFAs after either repaglinide or placebo. These findings suggest that acute hyperinsulinemia induced by repaglinide cannot overcome insulin resistance in the liver in order to suppress VLDL production.

Tentolouris *et al.* (2005) [73] in another study tested the effect of acute nateglinide administration on postprandial lipemia in drug-naïve patients with type 2 DM. Participants in the first day received a test meal after taking 120 mg of nateglinide and another day they received the same test meal with placebo. Nateglinide reduced postprandial glycemia and increased postprandial insulin levels. No significant effect was observed on postprandial total triglycerides, triglycerides of intestinal or of hepatic origin. Total and HDL cholesterol concentrations did not change significantly in the postprandial period compared with fasting values after either nateglinide or placebo. Concentrations of LDL cholesterol decreased postprandially after nateglinide in comparison with the baseline values while no such significant change was observed after placebo; however, the differences between the two phases of the study were not significantly dif-

ferent. These findings are in agreement with the results from the two previous studies.

Ai *et al.* (2006) [74] investigated the effect of acute nateglinide administration on postprandial lipemia in newly diagnosed drug-naïve patients with type 2 DM. Subjects received a fat-rich meal on two occasions; one day they received a fat-rich meal after taking 90 mg of nateglinide and another day they received the same test meal without nateglinide. Nateglinide administration resulted in lower levels of total triglycerides and RLP-C in comparison with the phase of the study when nateglinide was not given. Probably acute hyperinsulinemia secondary to nateglinide improves partially postprandial lipemia in newly diagnosed patients with T2DM.

In conclusion, meglitinides increase postprandial insulin secretion and decrease postprandial glycemia, but according to most of the studies they do not have any impact on postprandial lipemia in patients with type 2 DM.

Thiazolidinediones

Rosiglitazone and pioglitazone are a new class of medications for the management of type 2 DM. They reduce insulin resistance mainly in the muscle and adipose tissue and decrease hepatic glucose production (gluconeogenesis). Thiazolidinediones (or glitazones) are potent synthetic ligands for peroxisome proliferator-activated receptor gamma (PPAR γ) activation and directly influence the transcription of genes regulating insulin sensitivity. PPAR γ is a member of the nuclear receptor superfamily that regulates the expression of numerous proteins, including those related to inflammation [16, 75, 76]. Clinical studies have shown that glitazones reduce fasting and postprandial glucose concentrations, HbA1c levels and fasting as well as postprandial insulin concentrations [77-79]. Rosiglitazone and pioglitazone have similar effects on glycemic regulation but differ in their effects on fasting and postprandial lipid metabolism [80]. It seems that rosiglitazone increases fasting total and LDL cholesterol levels but has no significant effect on fasting total triglycerides [81]. Pioglitazone on the other hand increases HDL cholesterol and decreases fasting and postprandial triglyceride concentrations [82-85].

Raskin *et al.* (2000) [86] investigated the effect of rosiglitazone on postprandial metabolism in patients with type 2 DM. Subjects were given a standardized breakfast at baseline and 8 weeks after treatment with rosiglitazone at doses of 2 mg, 4 mg or 6 mg twice daily or placebo. Rosiglitazone induced significant reductions in fasting and postprandial glucose and in fasting insulin concentration. Fasting FFAs reduced following treatment with rosiglitazone, but fasting total and LDL cholesterol levels increased significantly compared to placebo. No significant change was observed in fasting HDL cholesterol levels, in the ratio total-to-HDL cholesterol and in fasting total triglycerides. Rosiglitazone had no differential effect on postprandial lipemia in comparison with the placebo.

Tan *et al.* (2005) [87] investigated in a double-blind, placebo-controlled, crossover study the effects of rosiglitazone on postprandial FFAs and triglyceride metabolism in drug-naïve patients with type 2 DM. Subjects received rosiglitazone (4 mg twice daily) for 12 weeks followed by placebo

for the same time period and vice versa. A standardized mixed meal was given at baseline and at the end of each treatment period. Rosiglitazone induced significant reductions in fasting and postprandial glucose and insulin concentrations. Fasting FFAs remained unchanged but postprandial concentrations decreased significantly after rosiglitazone; this effect was seen mainly in the late postprandial period. Rosiglitazone had no effect on fasting total triglycerides but lowered significantly postprandial total triglyceride levels compared with placebo. Rosiglitazone did not change postprandial RLP cholesterol levels. These findings suggest that there are two possible mechanisms for the lowering effect of the medication in postprandial triglyceridemia; the first is the reduction in postprandial FFAs associated with lower hepatic VLDL triglyceride secretion, and the other is the increased insulin sensitivity secondary to rosiglitazone, which inhibits VLDL triglyceride production.

Van Wijk *et al.* (2005) [88] conducted a double-blind, placebo-controlled, crossover trial to investigate the effect of rosiglitazone on postprandial triglycerides and FFAs metabolism in patients with type 2 DM treated with oral antidiabetic agents. Subjects received rosiglitazone (4 mg/day) for 8 weeks followed by placebo for 8 weeks and vice versa. At the beginning and at the end of each treatment period patients received a fat-rich meal. Rosiglitazone induced significant reductions in fasting glucose concentrations; however a significant increase in fasting total cholesterol levels was observed due to an increase in LDL cholesterol. Rosiglitazone had no effect on fasting triglycerides but postprandial triglyceridemia was lower with rosiglitazone than with placebo. Rosiglitazone also reduced the triglycerides contained in the CM fraction and the VLDL1 fraction postmeal; however, no difference from placebo was observed in the triglycerides contained in the VLDL2 fraction. Moreover, rosiglitazone reduced significantly postprandial FFAs but had no any effect on the fasting FFAs. It is possible that the beneficial effects of rosiglitazone on postprandial triglyceridemia are due to decreased postprandial FFAs and improved glycemic control, leading to reduced hepatic VLDL production. Moreover, improved insulin sensitivity by rosiglitazone may result in reduced production of the hepatic large VLDL1.

Shimono *et al.* (2001) [89] examined the effect of pioglitazone on postprandial triglyceridemia in type 2 diabetic patients. Subjects were treated with pioglitazone (30 mg/day) in combination with sulfonylurea or sulfonylurea alone for 6 months. Patients were given a standardized breakfast at baseline and at the end of the study. Pioglitazone induced significant reductions in HbA1c in comparison with the sulfonylurea-treated group, while no significant change was observed in total cholesterol concentrations. Pioglitazone had no effect on postprandial triglycerides.

Al Majali *et al.* (2006) [90] studied the effect of pioglitazone vs. glibenclamide on postprandial lipid metabolism in patients with type 2 DM and moderate hypertriglyceridemia. Subjects received pioglitazone (45 mg/day) or glibenclamide (5 mg/day) for 20 weeks. Ten healthy control subjects were also recruited. At baseline and the end of the study participants received a test meal with RP. Pioglitazone induced significant reductions in fasting and postprandial glucose and fasting insulin concentrations, while glibenclamide had no

such effect on glucose. However, glibenclamide induced higher fasting insulin concentrations. Fasting total cholesterol and FFAs levels remained unaltered following either treatment. Treatment with pioglitazone, but not with glibenclamide, resulted in a significant reduction in fasting total triglycerides. Treatment with pioglitazone was associated with a reduction in fasting VLDL triglycerides and VLDL2 (Sf 20-60) triglycerides but not with fasting VLDL cholesterol. No significant effects were observed on these parameters following glibenclamide administration. IDL, LDL and HDL cholesterol concentrations remained unaltered after either treatment. Pioglitazone but not glibenclamide resulted in a reduction in postprandial total triglycerides. Postprandial CM (Sf > 400) and CR (Sf 20-400) RP concentrations decreased significantly with pioglitazone but remained unchanged with glibenclamide. Neither pioglitazone nor glibenclamide decreased postprandial FFAs. Treatment with pioglitazone reduced the activity of HL, while no such effect was seen with glibenclamide. Neither pioglitazone nor glibenclamide affected LPL, LCAT or CETP activity. Pioglitazone but not glibenclamide reduced the activity of phospholipid transfer protein postprandially. It is likely that the improved insulin sensitivity after treatment with pioglitazone reduces hepatic triglyceride synthesis; a direct effect of pioglitazone on hepatic triglyceride synthesis cannot be ruled out. The decreased postprandial CM and CR concentrations are likely to be due to decreased competition for clearance with the hepatically derived lipoproteins.

Mori *et al.* (2006) [66] see sulfonylureas.

Mieszczanska *et al.* (2007) [91] conducted a randomized, double-blind, placebo-controlled, crossover study to examine the effect of pioglitazone on postprandial lipid metabolism in overweight non-diabetic patients with coronary artery disease, all treated with atorvastatin. Subjects received pioglitazone (45 mg/day) for 12 weeks followed by placebo for another 12 weeks and vice versa. A standardized test meal was given at baseline and 12 weeks after each treatment. Insulin sensitivity increased significantly with pioglitazone in comparison with the baseline values. There was a trend towards a reduction in fasting triglycerides and apoB concentrations and an increase of HDL cholesterol levels after pioglitazone. Postprandial triglyceridemia reduced with pioglitazone, while postprandial HDL cholesterol levels increased significantly.

Chappuis *et al.* (2007) [92] conducted a comparative randomized, crossover study to examine the effect of rosiglitazone and pioglitazone on postprandial lipemia in patients with type 2 DM. Subjects received rosiglitazone (4 mg/day for 4 weeks and 4 mg twice daily for another 8 weeks) for a total of 12 weeks followed by pioglitazone (30 mg/day for 4 weeks and 45 mg/day for another 8 weeks) for a total of 12 weeks and vice versa with an 8 week wash-out period in between. A standardized breakfast was given to the patients at baseline and 12 weeks after intervention. Treatment with both rosiglitazone and pioglitazone resulted in a similar glycaemic control (similar reductions in HbA1c, fasting and postprandial plasma glucose, fasting and postprandial insulin concentrations). Fasting FFAs decreased to the same degree after both treatments. Postprandial FFAs reduced with rosiglitazone but remained unaltered with pioglitazone.

Rosiglitazone resulted in increase, while pioglitazone tended to lower fasting triglycerides and the difference between the two glitazones was statistically significant. This difference was mainly attributed to an increase of VLDL3 (Sf 20-60) triglycerides after rosiglitazone. Postprandial triglycerides tended to increase after rosiglitazone but decreased significantly after pioglitazone. Fasting total cholesterol levels increased with rosiglitazone but remained unchanged with pioglitazone. The difference between the two glitazones was mainly due to an increase in VLDL2 and VLDL3 cholesterol following rosiglitazone administration. Rosiglitazone tended to increase the protein content of VLDL2, while pioglitazone had no effect on VLDL protein content. Postprandial total triglycerides, total cholesterol concentrations and protein content of VLDL3 increased with rosiglitazone and remained unaltered with pioglitazone. Triglyceride, cholesterol and protein content of all three VLDL subfractions tended to increase with rosiglitazone and to decrease with pioglitazone. Rosiglitazone increased apoC-II and apoC-III concentrations, whereas both apoC-II and apoC-III levels tended to decrease with pioglitazone. However the ratio apoC-II-to-apoC-III remained unaltered after either therapy. Rosiglitazone reduced CETP activity, while pioglitazone tended to increase its activity, resulting in a statistically significant difference between the two drugs. Rosiglitazone and pioglitazone did not differ with regards to their effect on LPL and HL activity. These findings suggest that rosiglitazone and pioglitazone have differential effects of hepatic VLDL production.

In summary, both rosiglitazone and pioglitazone have beneficial effect on fasting and postprandial glucose metabolism, but differential effect on lipid metabolism. Rosiglitazone decreases fasting and postprandial FFAs, while has no significant effect on fasting and postprandial triglycerides. Pioglitazone seems to have additional beneficial effects on lipid metabolism. Pioglitazone reduces postprandial FFAs, fasting and postprandial triglycerides and increases HDL cholesterol levels. These effects may have clinical implications because they may contribute to a reduction in cardiovascular risk in patients with type 2 DM.

GLP-1 Analogues

Glucagon-like peptide-1 (7-36 amide) or GLP-1 is a gastro-intestinal peptide and is considered to be one of the major enteral hormone of the entero-insular axis (incretin). GLP-1 enhances glucose-induced insulin secretion and lowers glucagon release and therefore is considered an alternative drug for the treatment of type 2 DM [93-95]. Clinical studies have shown that GLP-1 administration not only abolishes postprandial glucose increase but also decreases significantly postprandial glucose and increases postprandial insulin concentrations [96-98]. Furthermore, GLP-1 inhibits gastric acid secretion and gastric emptying and thereby diminishes meal-induced glucose excursions, delays absorption of dietary triglycerides and it is likely to ameliorate postprandial lipemia [99, 100]. Moreover, lipolysis may be increased after GLP-1 administration because GLP-1 increases LPL activity in adipose tissue.

Juntti-Berggren *et al.* (1996) [101] investigated the effect of GLP-1 on glucose and lipid metabolism during a 7 day treatment in patients with type 2 DM. The first 7 days pa-

tients were treated with regular insulin before meals and isophane insulin at night. Then patients were randomized into two groups. The one group was treated with GLP-1 before meals in addition to insulins and the control group continued treatment with insulins but instead of GLP-1 a subcutaneous injection of saline (placebo) was given before meals. Treatment with GLP-1 was associated with lower glucose and higher insulin levels postprandially. Treatment with GLP-1 reduced VLDL triglycerides. LDL and HDL cholesterol concentrations remained unaltered. Additionally, GLP-1 increased LDL particle diameter in comparison with the control group.

Meier *et al.* (2006) [102] studied the effects of acute GLP-1 administration on postprandial hypertriglyceridemia in healthy volunteers. The first day subjects received a standardized test meal after i.v. infusion of GLP-1 and on another day they received the same meal after placebo administration. Fasting and postprandial glucose concentrations decreased with GLP-1. GLP-1 had no effect on fasting total triglycerides but reduced postprandial triglycerides. Fasting and postprandial FFAs decreased with GLP-1 but not with placebo. GLP-1 delayed gastric emptying and almost 50% of the initial content remained in the stomach six hours following meal. The delay in gastric emptying is probably the mechanism for the attenuation of postprandial lipemia after treatment with GLP-1.

The exact effect of GLP-1 on postprandial lipemia has not yet been elucidated. However, several clinical studies have shown a beneficial effect of GLP-1 on postprandial glucose metabolism, which may improve lipid metabolism as well. Further studies are needed to elucidate the effect of GLP-1 on postprandial lipid metabolism.

Dipeptidyl-Peptidase-4 Inhibitors

Sitagliptin and vildagliptin are selective inhibitors of dipeptidyl peptidase-4 (DPP-4) which improves glycemic control by increasing levels of GLP-1 and islet alpha-cell (α -cell) and beta-cell (β -cell) responsiveness to glucose. Sitagliptin and vildagliptin reduce glucagon and increases insulin secretion in patients with type 2 DM [103]. Clinical studies have shown that vildagliptin reduces fasting and postprandial glucose levels, HbA1c and increases insulin secretion in patients with type 2 DM. Hepatic glucose production is also decreased by vildagliptin, resulting in lower fasting glucose levels [104-106].

Matikainen *et al.* (2006) [107] investigated in a randomized, double-blind, placebo-controlled study the effect of vildagliptin on postprandial lipoprotein particles in patients with type 2 DM. Subjects received a fat meal at baseline and 4 weeks after treatment with vildagliptin (50 mg twice daily) or placebo. Vildagliptin had no effect on fasting triglycerides and total cholesterol concentrations or on apoB-48 and apoB-100 contained in the CM (Sf > 400) and in the VLDL-IDL (Sf 12-400) fractions. However, vildagliptin reduced postprandial total triglycerides and triglycerides, cholesterol and apoB-48 contained in the CM fraction compared to placebo. There was also a trend towards lower postprandial triglycerides contained in the VLDL-IDL fraction. Treatment with vildagliptin had no effect on fasting or postprandial FFAs. The improved postprandial metabolism with vilda-

gliptin could reflect either improved glycemic control or improvement in insulin resistance. However, a direct effect of GLP-1 on lipoprotein metabolism is also likely because vildagliptin increases plasma levels of GLP-1.

This study suggests that vildagliptin reduces postprandial triglyceridemia mainly due to a reduction in intestinally derived apoB-48 particles. Further studies are needed to examine the effect of vildagliptin and other DPP-4 inhibitors on postprandial lipemia in DM. No data are available on the effect of sitagliptin on postprandial lipemia.

The effects of medications used for the management of diabetes on postprandial lipid metabolism are summarized in Table 1.

MEDICATIONS USED FOR THE MANAGEMENT OF OBESITY

Orlistat

Orlistat is an anti-obesity drug of the compound of tetrahydrolipstatin. Orlistat is a pancreatic lipase inhibitor that inhibits both pancreatic and gastric lipase in the lumen of the gastrointestinal track by its ability to bind irreversibly to these enzymes and limits dietary fat absorption by approximately 30% [108, 109]. Moreover, when combined with a mildly hypocaloric diet and low fat intake, orlistat can induce an average weight loss of 10% of the initial weight after 1 year of treatment [110]. Clinical studies have shown that orlistat reduces fasting total and LDL cholesterol levels and attenuates postprandial triglyceridemia [111, 112].

Reitsma *et al.* (1994) [113] investigated in a randomized, double-blind, placebo-controlled study the effect of orlistat on postprandial lipoprotein metabolism, especially CR, in patients with hypercholesterolemia. Subjects received 10, 30, 60, 120 mg orlistat or placebo 3 times daily for 8 weeks and placebo 3 times daily for a 2-week follow-up period. During the entire study period the patients were on a low-fat, low-cholesterol diet. A fat-rich meal was given on the last day of the active treatment period (week 8) and one after the 2-week follow-up period (week 10). Orlistat induced reduction in fasting total and LDL cholesterol as well as in apoB levels after 8 weeks of treatment compared with baseline, whereas total triglycerides and HDL cholesterol concentrations remained unchanged. Postprandial triglycerides decreased after treatment with orlistat (week 8) compared to the off-treatment period (week 10). Postprandial RP concentrations also decreased in patients receiving orlistat compared with the follow-up period. It is likely that the diminished absorption of dietary fat with orlistat leads to decreased formation of CM and of CR. The reduced number of circulating CM and CR may decrease the flux of cholesterol- and triglyceride-rich particles in the liver. This in turn may result in upregulation of hepatic LDL receptors and increased CM clearance.

Shepard *et al.* (2000) [114] examined in a randomized, double-blind, placebo-controlled study the effect of orlistat on postprandial pre- and postheparin LPL and HL activity and on postprandial lipoprotein concentrations in healthy volunteers. Subjects received orlistat (120 mg three times daily) or placebo with meals for 10 days. On days 5 and 10 subjects they ingested a fat-rich breakfast. No significant differences were observed in fasting and postprandial trigly-

Table 1. The Effect of Antidiabetic Medications on Postprandial Lipid Metabolism

Medication	Dose (mg/d)	Ref.	Fractions Altered	Other Effects
Acarbose	50, 100, 200	[41]	↓ total TG	↓ glu, ↓ ins
Acarbose	100	[43]	↓ total TG, ↓ RLP-C	↓ glu, ↓ ins, ↓ apoC-III, ↓ postprandial decline of apoC-II
Acarbose	100, 300	[44]	↓ total TG	↓ glu, ↓ ins, ↓ CM, ↓ FFA and VLDL levels in hypertriglyceridemic patients
Acarbose	300	[42]	↓ total TG, (-) TC	↓ glu, ↓ ins
Metformin	(NA)	[53]	↓ total TG	↓ glu, ↓ ins, ↓ FFAs
Metformin	(NA)	[57]	↓ total TG	
Metformin	500-2500	[52, 54]	↓ total TG	↓ glu, ↓ ins, ↓ FFAs
Metformin	850-2550	[55]	↓ CM (Sf >400)- and (VLDL-CR) (Sf <400)-TG, ↓ CM- and (VLDL-CR)-RP	↓ glu, ↓ ins, ↓ FFAs,
Metformin	1000	[58]	(-) total TG	(-) apoB-48, (-) CM levels, (-) ratio TG-to-apoB-48
Metformin	1700	[56]	↓ CM (Sf >1000)- and non-CM (Sf <1000)-RP	↓ ins
Glipizide	max 40	[63]	↓ total TG, ↓ (Sf 20-400)-TG, (-) (Sf >400)-TG, ↓ (Sf 20-400)- and (Sf >400)-RP	↓ glu, ↑ ins, ↓ FFAs, ↑ LPL and HL activity
Glibenclamide	(NA)	[66]	(-) total TG, (-) RLP-TG	↓ glu, (-) FFAs
Glibenclamide	5	[64]	↓ total TG, ↓ CM-TG, (-) CM-deficient plasma-, VLDL1-, VLDL2- and IDL-TG	↓ glu, ↑ ins
Glibenclamide	5	[90]	(-) total TG, (-) CM (Sf >400)- and CR (Sf 20-400)-RP	(-) FFAs
Glibenclamide	5-10	[65]	(-) total TG, (-) CM- and VLDL1-TG	(-) FFAs, (-) CM-apoB-48, (-) VLDL1-apoB-100, (-) LDL size
Nateglinide	90	[74]	↓ total TG, ↓ RLP-C	
Nateglinide	120	[71]	(-) total TG	↓ glu, ↑ ins, (-) FFAs
Nateglinide	120	[73]	(-) total TG, (-) CM- and non-CM-TG, (-) TC, (-) LDL- and HDL-C	↓ glu, ↑ ins
Nateglinide	360	[65]	(-) CM- and VLDL1-TG	↓ glu, ↑ ins, ↓ FFAs, (-) CM-apoB-48, (-) VLDL1-apoB-100, (-) LDL size
Repaglinide	2	[72]	(-) total TG, (-) CM- and non-CM-TG, (-) TC, (-) LDL- and HDL-C	↓ glu, ↑ ins, (-) FFAs
Rosiglitazone	4	[58]	(-) total TG	↑ apoB-48, ↓ ratio TG-to-apoB-48
Rosiglitazone	4	[87]	↓ total TG, (-) RLP-C	↓ glu, ↓ ins, ↓ FFAs
Rosiglitazone	4	[88]	↓ total TG, ↓ CM- and VLDL1-TG, (-) VLDL2-TG	↓ FFAs
Rosiglitazone	4, 8	[92]	(-) total TG, ↑ VLDL3-TG, ↑ VLDL3-C	↓ glu, ↓ ins, ↓ FFAs
Rosiglitazone	4, 8, 12	[86]	(-) total TG	↓ glu
Pioglitazone	(NA)	[66]	↓ total TG, ↓ RLP-TG	↓ glu, ↓ ins, ↓ FFAs
Pioglitazone	30	[89]	(-) total TG	
Pioglitazone	30, 45	[92]	↓ total TG, (-) VLDL3-TG, (-) VLDL3-C	↓ glu, ↓ ins, (-) FFAs

Table 1. contd....

Medication	Dose (mg/d)	Ref.	Fractions Altered	Other Effects
Pioglitazone	45	[90]	↓ total TG, ↓ CM (Sf >400)- and CR (Sf 20-400)-RP	↓ glu, (-) FFAs, ↓ activity of phospholipid transfer protein
Pioglitazone	45	[91]	↓ total TG, ↑ HDL-C	
GLP-1	(NA)	[101]		↓ glu, ↑ ins, ↑ LDL diameter
GLP-1	(NA)	[102]	↓ total TG	↓ FFAs
DPP-4, vildagliptin	100	[107]	↓ total TG, ↓ CM-TG, (-) (VLDL-IDL)-TG, ↓ CM-C	↓ CM-apoB-48, (-) FFAs

CM: chylomicrons, CR: chylomicron remnant, TG: triglyceride, TC: total cholesterol, C: cholesterol, Glu: glucose, Ins: insulin, VLDL: very low density lipoprotein, IDL: intermediate density lipoprotein, LDL: low density lipoprotein, HDL: high density lipoprotein, FFA: free fatty acid, RP: retinyl palmitate, RLP: remnant-like particle, TRL: triglyceride-rich lipoprotein, Apo: apolipoprotein, LPL: lipoprotein lipase, HL: hepatic lipase; Sf: Svedberg flotation rate
 ↑: increase, ↓: decrease, (-): neutral effect, (NA): not available

cerides, FFAs, LDL, HDL and VLDL cholesterol levels between the two treatments on day 5. There were no differences between the orlistat and the placebo group in pre-heparin LPL or HL activity in the fasting or the postprandial state on day 5. The measurements of postheparin LPL and HL activities on day 10 were also not different between the two groups. These results suggest that short-term administration of orlistat does not affect lipid metabolism or the activity of LPL and HL.

Tan *et al.* (2002) [115] evaluated in a randomized, double-blind, placebo-controlled study the acute effect of a single dose of 120 mg of orlistat on postprandial lipids, remnant lipoproteins and FFAs in overweight patients with type 2 DM. The first day patients received a test meal with a single dose of orlistat and on another day patients received the same test meal with placebo. Postprandial total triglycerides, RLP cholesterol and FFAs were lower following orlistat. The favorable effect of orlistat on postprandial lipemia is probably mediated through the reduction in intestinal absorption of triglycerides and to decreased formation of CM.

Suter *et al.* (2005) [116] investigated in a double-blind randomized crossover study the acute effect of orlistat on postprandial lipemia after moderate- and high-fat meals in healthy volunteers. All subjects were studied in three separate days and received in a random order one of the three treatment regimens: orlistat 120 mg plus a high-fat meal, orlistat 120 mg plus a moderate-fat meal, or placebo plus a high-fat meal. Postprandial total triglycerides were not significantly different between the two orlistat regimens but they were significantly lower compared to placebo. The maximal postprandial triglyceridemia occurred earlier with the two orlistat regimens compared to placebo. In addition, the time-point at which postprandial lipemia returned to baseline levels was significantly delayed after placebo in comparison with orlistat. No differences were observed in the postprandial concentrations of FFAs, total cholesterol, apoA-I and apoB levels among the three treatment regimens. Postprandial lipemia was not significantly different after the high-fat plus orlistat vs. the moderate-fat plus orlistat regimens. This finding may be due to the higher inhibition of fat absorption after consumption of larger than moderate amount of fat when subjects are treated with orlistat.

In conclusion, these data suggest that orlistat improves postprandial lipemia ameliorating postprandial increase in total triglycerides, CM and TRL remnants. Thus, orlistat may represent another relatively unexplored pharmacological approach to cardiovascular risk modulation in overweight patients.

Sibutramine

Sibutramine is a centrally acting weight management agent that was first developed as an antidepressant. Sibutramine is a serotonin (5-hydroxytryptamine) and noradrenalin (norepinephrine) reuptake inhibitor (SNRI) that acts increasing satiety and stimulating thermogenesis [108, 117]. Sibutramine enhances weight loss and improves weight maintenance [118]. In studies involving patients with type 2 DM, sibutramine decreases HbA1c levels and blood glucose levels and increases insulin sensitivity. Furthermore, clinical trials have shown that sibutramine reduces fasting total triglycerides and increases HDL cholesterol, while has a neutral effect on LDL cholesterol levels [119-121]. No data exist on the effect of sibutramine on postprandial lipemia.

Rimonabant

Rimonabant is a CB₁-receptor blocker, one of the two major receptors of the endocannabinoid system. The CB₁-receptor activation in the central nervous system (mesolimbic system and central melanocortin system) increases food intake and peripherally increases hepatic and adipocyte lipogenesis and reduces thermogenesis in skeletal muscle. The blockade of this system with rimonabant has opposite effects [108, 122]. Rimonabant is a new anti-obesity agent that reduces fat intake and body weight [123, 124]. Clinical studies have shown that rimonabant has a beneficial effect on LDL particle size and a neutral effect on total and LDL cholesterol concentrations. It has also been shown to reduce fasting total triglycerides and non-HDL cholesterol levels and to increase HDL cholesterol concentrations [125]. No data are available concerning a potential effect of rimonabant on postprandial lipemia.

The effects of medications used for the management of obesity on postprandial lipid metabolism are summarized in Table 2.

Table 2. The Effect of Medications Used for the Management of Obesity on Postprandial Lipid Metabolism

Medication	Dose (mg/d)	Ref.	Fractions Altered	Other Effects
Orlistat	30, 90, 180, 360	[113]	↓ total TG, ↓ RP	
Orlistat	120	[115]	↓ total TG, ↓ RLP-C	↓ FFAs
Orlistat	120	[116]	↓ total TG, (-) TC	(-) FFAs, (-) apoA-I and apoB levels
Orlistat	360	[114]	(-) total TG, (-) LDL-, HDL- and VLDL-C	(-) FFAs, (-) LPL and HL activity
Sibutramine			(NA)	
Rimonabant			(NA)	

TG: triglyceride, TC: total cholesterol, C: cholesterol, VLDL: very low density lipoprotein, IDL: intermediate density lipoprotein, LDL: low density lipoprotein, HDL: high density lipoprotein, FFA: free fatty acid, RP: retinyl palmitate, RLP: remnant-like particle, Apo: apolipoprotein, LPL: lipoprotein lipase, HL: hepatic lipase
 †: increase, ‡: decrease, (-): neutral effect, (NA): not available

LIMITATIONS

Different problems arise for the evaluation of postprandial lipemia and discrepancies among several studies may be related to these problems. The first problem is the choice of the test meal used for the evaluation of postprandial lipemia. A second problem is the selection of the study population on which the test meal is applied. A third problem is the time after meal when blood samples are obtained for lipids determination, since there is not a standardized postprandial time point widely acceptable. Most studies though express plasma lipid concentrations in the postprandial state as area under the curve or their changes from baseline as incremental area under the curve. Moreover, different doses of medications have been used and potential differences or lack of differences may have contributed to the diverged results on the effect of medications on postprandial lipemia among some of the studies. Finally, discrepancies among studies may result from differences in biochemical methods and procedures used for determination of lipoproteins [126]. Such methodological issues do not allow for direct comparisons between the published studies [127].

SUMMARY

However, we can reach essential conclusions about the effect of medications used in the treatment of diabetes and obesity. Available data concerning the effect of insulin, acarbose, metformin and sulfonylureas, GLP-1 analogues and vildagliptin on postprandial lipemia suggest that these drugs ameliorate the increase in lipid parameters following meal, whereas meglitinides do not affect postprandial lipid metabolism. Glitazones influence postprandial lipemia differentially, with pioglitazone having a more beneficial and rosiglitazone a weaker effect on lipid parameters. Orlistat ameliorates postprandial lipemia, but no clinical trials exist about the effects of sibutramine and rimonabant on postprandial lipid metabolism.

ABBREVIATIONS

- Apo = Apolipoprotein
- CM = Chylomicron
- CR = Chylomicron remnant

- VLDL = Very low density lipoprotein
- IDL = Intermediate density lipoprotein
- LDL = Low density lipoprotein
- HDL = High density lipoprotein
- FFA = Free fatty acid
- TRL = Triglyceride-rich lipoprotein
- Lp(a) = Lipoprotein (a)
- LPL = Lipoprotein lipase
- HL = Hepatic lipase
- CETP = Cholesteryl ester transfer protein
- LCAT = Lecithin cholesterol acyl transferase
- Sf = Svedberg flotation rate
- CE = Cholesteryl ester
- RP = Retinyl palmitate
- RLP = Remnant-like particle
- HbA1c = Glycosylated (glycated) hemoglobin
- DM = Diabetes mellitus
- GLP-1 = Glucagon-like peptide-1

REFERENCES

- [1] De Man FH, Cabezas MC, Van Barlingen HH, Erkelens DW, de Bruin TW. Triglyceride-rich lipoproteins in non-insulin-dependent diabetes mellitus: post-prandial metabolism and relation to premature atherosclerosis. *Eur J Clin Invest* 1996; 26: 89-108.
- [2] Hyson D, Rutledge JC, Berglund L. Postprandial lipemia and cardiovascular disease. *Curr Atheroscler Rep* 2003; 5: 437-44.
- [3] Jansen H. Hepatic lipase: friend or foe and under what circumstances? *Curr Atheroscler Rep* 2004; 6: 343-7.
- [4] Otarod JK, Goldberg IJ. Lipoprotein lipase and its role in regulation of plasma lipoproteins and cardiac risk. *Curr Atheroscler Rep* 2004; 6: 335-42.
- [5] Cooper AD. Hepatic uptake of chylomicron remnants. *J Lipid Res* 1997; 38: 2173-92.
- [6] Krentz AJ. Lipoprotein abnormalities and their consequences for patients with type 2 diabetes. *Diabetes Obes Metab* 2003; 5(Suppl 1): S19-27.
- [7] Taskinen MR. LDL-cholesterol, HDL-cholesterol or triglycerides--which is the culprit? *Diabetes Res Clin Pract* 2003; 61(Suppl 1): S19-26.

- [8] Tan KC, Cooper MB, Ling KL, *et al.* Fasting and postprandial determinants for the occurrence of small dense LDL species in non-insulin-dependent diabetic patients with and without hypertriglyceridaemia: the involvement of insulin, insulin precursor species and insulin resistance. *Atherosclerosis* 1995; 113: 273-87.
- [9] Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. *J Mol Med* 2002; 80: 753-69.
- [10] Karpe F, Steiner G, Uffelman K, Olivecrona T, Hamsten A. Postprandial lipoproteins and progression of coronary atherosclerosis. *Atherosclerosis* 1994; 106: 83-97.
- [11] Zilversmit DB. Atherogenesis: a postprandial phenomenon. *Circulation* 1979; 60: 473-85.
- [12] Hodis HN. Triglyceride-rich lipoprotein remnant particles and risk of atherosclerosis. *Circulation* 1999; 99: 2852-4.
- [13] Karpe F. Postprandial lipemia--effect of lipid-lowering drugs. *Atheroscler Suppl* 2002; 3: 41-6.
- [14] Patsch JR, Miesenbock G, Hopferwieser T, *et al.* Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. *Arterioscler Thromb* 1992; 12: 1336-45.
- [15] Karpe F. Postprandial lipoprotein metabolism and atherosclerosis. *J Intern Med* 1999; 246: 341-55.
- [16] Cottrell DA, Marshall BJ, Falko JM. Therapeutic approaches to dyslipidemia in diabetes mellitus and metabolic syndrome. *Curr Opin Cardiol* 2003; 18: 301-8.
- [17] Steinmetz A. Treatment of diabetic dyslipoproteinemia. *Exp Clin Endocrinol Diabetes* 2003; 111: 239-45.
- [18] Rivellese AA, De Natale C, Di Marino L, *et al.* Exogenous and endogenous postprandial lipid abnormalities in type 2 diabetic patients with optimal blood glucose control and optimal fasting triglyceride levels. *J Clin Endocrinol Metab* 2004; 89: 2153-9.
- [19] Pastromas S, Terzi AB, Tousoulis D, Koulouris S. Postprandial lipemia: An under-recognized atherogenic factor in patients with diabetes mellitus. *Int J Cardiol* 2008; 126: 3-12.
- [20] Lewis GF, Uffelman KD, Szeto LW, Steiner G. Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals. *Diabetes* 1993; 42: 833-42.
- [21] Malmstrom R, Packard CJ, Watson TD, *et al.* Metabolic basis of hypotriglyceridemic effects of insulin in normal men. *Arterioscler Thromb Vasc Biol* 1997; 17: 1454-64.
- [22] Cummings MH, Watts GF, Umpheby AM, *et al.* Acute hyperinsulinemia decreases the hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 in NIDDM. *Diabetes* 1995; 44: 1059-65.
- [23] Lewis GF, Uffelman KD, Szeto LW, Weller B, Steiner G. Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. *J Clin Invest* 1995; 95: 158-66.
- [24] Romano G, Patti L, Innelli F, *et al.* Insulin and sulfonylurea therapy in NIDDM patients. Are the effects on lipoprotein metabolism different even with similar blood glucose control? *Diabetes* 1997; 46: 1601-6.
- [25] Taskinen MR, Kuusi T, Helve E, Nikkila EA, Yki-Jarvinen H. Insulin therapy induces antiatherogenic changes of serum lipoproteins in noninsulin-dependent diabetes. *Arteriosclerosis* 1988; 8: 168-77.
- [26] Boquist S, Hamsten A, Karpe F, Ruotolo G. Insulin and non-esterified fatty acid relations to alimentary lipaemia and plasma concentrations of postprandial triglyceride-rich lipoproteins in healthy middle-aged men. *Diabetologia* 2000; 43: 185-93.
- [27] Harbis A, Defoort C, Narbonne H, *et al.* Acute hyperinsulinism modulates plasma apolipoprotein B-48 triglyceride-rich lipoproteins in healthy subjects during the postprandial period. *Diabetes* 2001; 50: 462-9.
- [28] Geltner C, Lechleitner M, Foger B, *et al.* Insulin improves fasting and postprandial lipemia in type 2 diabetes. *Eur J Intern Med* 2002; 13: 256-63.
- [29] Evans M, Anderson RA, Smith JC, *et al.* Effects of insulin lispro and chronic vitamin C therapy on postprandial lipaemia, oxidative stress and endothelial function in patients with type 2 diabetes mellitus. *Eur J Clin Invest* 2003; 33: 231-8.
- [30] Gallagher A, Home PD. The effect of improved post-prandial blood glucose control on post-prandial metabolism and markers of vascular risk in people with Type 2 diabetes. *Diabetes Res Clin Pract* 2005; 67: 196-203.
- [31] Schmoelzer I, de Campo A, Pressl H, *et al.* Biphasic insulin aspart compared to biphasic human insulin reduces postprandial hyperlipidemia in patients with Type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2005; 113: 176-81.
- [32] Ceriello A, Del Prato S, Bue-Valleskey J, *et al.* Premeal insulin lispro plus bedtime NPH or twice-daily NPH in patients with type 2 diabetes: acute postprandial and chronic effects on glycemic control and cardiovascular risk factors. *J Diabetes Complications* 2007; 21: 20-7.
- [33] Puls W, Keup U, Krause HP, Thomas G, Hoffmeister F. Glucosidase inhibition. A new approach to the treatment of diabetes, obesity, and hyperlipoproteinaemia. *Naturwissenschaften* 1977; 64: 536-7.
- [34] Lardinois CK, Greenfield MS, Schwartz HC, Vreman HJ, Reaven GM. Acarbose treatment of non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1984; 144: 345-7.
- [35] Scott R, Lintott CJ, Zimmet P, *et al.* Will acarbose improve the metabolic abnormalities of insulin-resistant type 2 diabetes mellitus? *Diabetes Res Clin Pract* 1999; 43: 179-85.
- [36] Baron AD, Eckel RH, Schmeiser L, Kolterman OG. The effect of short-term alpha-glucosidase inhibition on carbohydrate and lipid metabolism in type II (noninsulin-dependent) diabetics. *Metabolism* 1987; 36: 409-15.
- [37] Walter-Sack IE, Wolfram G, Zollner N. Effects of acarbose on serum lipoproteins in healthy individuals during prolonged administration of a fiber-free formula diet. *Ann Nutr Metab* 1989; 33: 100-7.
- [38] Reaven GM, Lardinois CK, Greenfield MS, Schwartz HC, Vreman HJ. Effect of acarbose on carbohydrate and lipid metabolism in NIDDM patients poorly controlled by sulfonylureas. *Diabetes Care* 1990; 13(Suppl 3): 32-6.
- [39] Malaguarnera M, Giugno I, Ruello P, Maugeri D, Pistone G. Treatment of familial hypertriglyceridaemia with acarbose. *Diabetes Obes Metab* 2000; 2: 33-8.
- [40] Leonhardt W, Hanefeld M, Fischer S, Schulze J. Efficacy of alpha-glucosidase inhibitors on lipids in NIDDM subjects with moderate hyperlipidaemia. *Eur J Clin Invest* 1994; 24 (Suppl 3): 45-9.
- [41] Hillebrand I, Boehme K, Frank G, Fink H, Berchtold P. The effects of the alpha-glucosidase inhibitor BAY g 5421 (Acarbose) on postprandial blood glucose, serum insulin, and triglyceride levels: dose-time-response relationships in man. *Res Exp Med (Berl)* 1979; 175: 87-94.
- [42] Hanefeld M, Fischer S, Schulze J, *et al.* Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. *Diabetes Care* 1991; 14: 732-7.
- [43] Kado S, Murakami T, Aoki A, *et al.* Effect of acarbose on postprandial lipid metabolism in type 2 diabetes mellitus. *Diabetes Res Clin Pract* 1998; 41: 49-55.
- [44] Ogawa S, Takeuchi K, Ito S. Acarbose lowers serum triglyceride and postprandial chylomicron levels in type 2 diabetes. *Diabetes Obes Metab* 2004; 6: 384-90.
- [45] Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992; 15: 755-72.
- [46] Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med* 2002; 137: 25-33.
- [47] Inzucchi SE, Maggs DG, Spollett GR, *et al.* Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 1998; 338: 867-72.
- [48] Sirtori CR, Tremoli E, Sirtori M, Conti F, Paoletti R. Treatment of hypertriglyceridemia with metformin. Effectiveness and analysis of results. *Atherosclerosis* 1977; 26: 583-92.
- [49] Giugliano D, De Rosa N, Di Maro G, *et al.* Metformin improves glucose, lipid metabolism, and reduces blood pressure in hypertensive, obese women. *Diabetes Care* 1993; 16: 1387-90.
- [50] DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* 1995; 333: 541-9.
- [51] Charles MA, Eschwege E, Grandmottet P, *et al.* Treatment with metformin of non-diabetic men with hypertension, hypertriglyceridaemia and central fat distribution: the BIGPRO 1.2 trial. *Diabetes Metab Res Rev* 2000; 16: 2-7.
- [52] Wu MS, Johnston P, Sheu WH, *et al.* Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 1990; 13: 1-8.
- [53] Hollenbeck CB, Johnston P, Varasteh BB, Chen YD, Reaven GM. Effects of metformin on glucose, insulin and lipid metabolism in

- patients with mild hypertriglyceridaemia and non-insulin dependent diabetes by glucose tolerance test criteria. *Diabet Metab* 1991; 17: 483-9.
- [54] Reaven GM, Johnston P, Hollenbeck CB, *et al.* Combined metformin-sulfonylurea treatment of patients with noninsulin-dependent diabetes in fair to poor glycemic control. *J Clin Endocrinol Metab* 1992; 74: 1020-6.
- [55] Jeppesen J, Zhou MY, Chen YD, Reaven GM. Effect of metformin on postprandial lipemia in patients with fairly to poorly controlled NIDDM. *Diabetes Care* 1994; 17: 1093-9.
- [56] Weintraub MS, Charach G, Grosskopf I. Effects of fibric acid derivatives and metformin on postprandial lipemia. *Atherosclerosis* 1998; 141(Suppl 1): S71-5.
- [57] Emral R, Koseogullari O, Tonyukuk V, *et al.* The effect of short-term glycemic regulation with gliclazide and metformin on postprandial lipemia. *Exp Clin Endocrinol Diabetes* 2005; 113: 80-4.
- [58] James AP, Watts GF, Mamo JC. The effect of metformin and rosiglitazone on postprandial lipid metabolism in obese insulin-resistant subjects. *Diabetes Obes Metab* 2005; 7: 381-9.
- [59] Hughes TA, Kramer JO, Segrest JP. Effects of glyburide therapy on lipoproteins in non-insulin-dependent diabetes mellitus. *Am J Med* 1985; 79: 86-91.
- [60] Taskinen MR, Beltz WF, Harper I, *et al.* Effects of NIDDM on very-low-density lipoprotein triglyceride and apolipoprotein B metabolism. Studies before and after sulfonylurea therapy. *Diabetes* 1986; 35: 1268-77.
- [61] Greenfield MS, Doberne L, Rosenthal M, Vreman HJ, Reaven GM. Lipid metabolism in non-insulin-dependent diabetes mellitus: effect of glipizide therapy. *Arch Intern Med* 1982; 142: 1498-500.
- [62] Baynes C, Elkeles RS, Henderson AD, Richmond W, Johnston DG. The effects of glibenclamide on glucose homeostasis and lipoprotein metabolism in poorly controlled type 2 diabetes. *Horm Metab Res* 1993; 25: 96-101.
- [63] Jeppesen J, Zhou MY, Chen YD, Reaven GM. Effect of glipizide treatment on postprandial lipaemia in patients with NIDDM. *Diabetologia* 1994; 37: 781-7.
- [64] Skrapari I, Perrea D, Ioannidis I, *et al.* Glibenclamide improves postprandial hypertriglyceridaemia in type 2 diabetic patients by reducing chylomicrons but not the very low-density lipoprotein subfraction levels. *Diabet Med* 2001; 18: 781-5.
- [65] Vakkilainen J, Mero N, Schweizer A, Foley JE, Taskinen MR. Effects of nateglinide and glibenclamide on postprandial lipid and glucose metabolism in type 2 diabetes. *Diabetes Metab Res Rev* 2002; 18: 484-90.
- [66] Mori Y, Itoh Y, Obata T, Tajima N. Effects of pioglitazone vs glibenclamide on postprandial increases in glucose and triglyceride levels and on oxidative stress in Japanese patients with type 2 diabetes. *Endocrine* 2006; 29: 143-8.
- [67] Malaisse WJ. Mechanism of action of a new class of insulin secretagogues. *Exp Clin Endocrinol Diabetes* 1999; 107(Suppl 4): S140-3.
- [68] Dornhorst A. Insulinotropic meglitinide analogues. *Lancet* 2001; 358: 1709-16.
- [69] Hollander PA, Schwartz SL, Gatlin MR, *et al.* Importance of early insulin secretion: comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care* 2001; 24: 983-8.
- [70] Wolffenbuttel BH, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Dutch and German Repaglinide Study Group. *Diabetes Care* 1999; 22: 463-7.
- [71] Mohanlal N, Holman R. The effect of nateglinide stimulated insulin secretion on post challenge glucose and lipid metabolism in type 2 diabetes mellitus. *Diabetologia* 2002; 45: A768.
- [72] Tentolouris N, Kolia M, Tselepis AD, *et al.* Lack of effect of acute repaglinide administration on postprandial lipaemia in patients with type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2003; 111: 370-3.
- [73] Tentolouris N, Boutati E, Karambakalis N, *et al.* Acute nateglinide administration in subjects with type 2 diabetes: effects on postprandial metabolism, coagulation, and fibrinolysis. *Nutr Metab Cardiovasc Dis* 2005; 15: 6-12.
- [74] Ai M, Tanaka A, Ogita K, Shimokado K. Favorable effects of early insulin secretion by nateglinide on postprandial hyperlipidemia in patients with type 2 diabetes. *Diabetes Care* 2006; 29: 1180.
- [75] Lehmann JM, Moore LB, Smith-Oliver TA, *et al.* An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 1995; 270: 12953-6.
- [76] Olefsky JM, Saltiel AR. PPAR gamma and the treatment of insulin resistance. *Trends Endocrinol Metab* 2000; 11: 362-8.
- [77] Patel J, Anderson RJ, Rappaport EB. Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-week, randomized, placebo-controlled study. *Diabetes Obes Metab* 1999; 1: 165-72.
- [78] Nolan JJ, Jones NP, Patwardhan R, Deacon LF. Rosiglitazone taken once daily provides effective glycaemic control in patients with Type 2 diabetes mellitus. *Diabet Med* 2000; 17: 287-94.
- [79] Miyazaki Y, Mahankali A, Matsuda M, *et al.* Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 2001; 24: 710-9.
- [80] Buse JB, Tan MH, Prince MJ, Erickson PP. The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. *Diabetes Obes Metab* 2004; 6: 133-56.
- [81] Wolffenbuttel BH, Gomis R, Squatrito S, Jones NP, Patwardhan RN. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients. *Diabet Med* 2000; 17: 40-7.
- [82] Nagashima K, Lopez C, Donovan D, *et al.* Effects of the PPAR-gamma agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus. *J Clin Invest* 2005; 115: 1323-32.
- [83] Aronoff S, Rosenblatt S, Braithwaite S, *et al.* Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. *Diabetes Care* 2000; 23: 1605-11.
- [84] Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs* 2003; 63: 1373-405.
- [85] van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 2003; 23: 1744-9.
- [86] Raskin P, Rappaport EB, Cole ST, *et al.* Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia* 2000; 43: 278-84.
- [87] Tan GD, Fielding BA, Currie JM, *et al.* The effects of rosiglitazone on fatty acid and triglyceride metabolism in type 2 diabetes. *Diabetologia* 2005; 48: 83-95.
- [88] van Wijk JP, de Koning EJ, Castro Cabezas M, Rabelink TJ. Rosiglitazone improves postprandial triglyceride and free fatty acid metabolism in type 2 diabetes. *Diabetes Care* 2005; 28: 844-9.
- [89] Shimono D, Kuwamura N, Nakamura Y, Koshiyama H. Lack of effect of pioglitazone on postprandial triglyceride levels in type 2 diabetes. *Diabetes Care* 2001; 24: 971.
- [90] Al Majali K, Cooper MB, Staels B, *et al.* The effect of sensitisation to insulin with pioglitazone on fasting and postprandial lipid metabolism, lipoprotein modification by lipases, and lipid transfer activities in type 2 diabetic patients. *Diabetologia* 2006; 49: 527-37.
- [91] Mieszczańska H, Kaba NK, Francis CW, *et al.* Effects of pioglitazone on fasting and postprandial levels of lipid and hemostatic variables in overweight non-diabetic patients with coronary artery disease. *J Thromb Haemost* 2007; 5: 942-9.
- [92] Chappuis B, Braun M, Stettler C, *et al.* Differential effect of pioglitazone (PGZ) and rosiglitazone (RGZ) on postprandial glucose and lipid metabolism in patients with type 2 diabetes mellitus: a prospective, randomized crossover study. *Diabetes Metab Res Rev* 2007; 23: 392-9.
- [93] Orskov C. Glucagon-like peptide-1, a new hormone of the entero-insular axis. *Diabetologia* 1992; 35: 701-11.
- [94] Toft-Nielsen MB, Madsbad S, Holst JJ. Continuous subcutaneous infusion of glucagon-like peptide 1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. *Diabetes Care* 1999; 22: 1137-43.
- [95] Buse JB, Henry RR, Han J, *et al.* Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004; 27: 2628-35.
- [96] Gutniak M, Orskov C, Holst JJ, Ahren B, Efendic S. Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus. *N Engl J Med* 1992; 326: 1316-22.
- [97] Nauck MA, Kleine N, Orskov C, *et al.* Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 am-

- ide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1993; 36: 741-4.
- [98] Gutniak MK, Linde B, Holst JJ, Efendic S. Subcutaneous injection of the incretin hormone glucagon-like peptide 1 abolishes postprandial glycemia in NIDDM. *Diabetes Care* 1994; 17: 1039-44.
- [99] Willms B, Werner J, Holst JJ, *et al.* Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. *J Clin Endocrinol Metab* 1996; 81: 327-32.
- [100] Meier JJ, Gallwitz B, Salmen S, *et al.* Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2003; 88: 2719-25.
- [101] Juntti-Berggren L, Pigon J, Karpe F, *et al.* The antidiabetogenic effect of GLP-1 is maintained during a 7-day treatment period and improves diabetic dyslipoproteinemia in NIDDM patients. *Diabetes Care* 1996; 19: 1200-6.
- [102] Meier JJ, Gethmann A, Gotze O, *et al.* Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. *Diabetologia* 2006; 49: 452-8.
- [103] Panina G. The DPP-4 inhibitor vildagliptin: robust glycaemic control in type 2 diabetes and beyond. *Diabetes Obes Metab* 2007; 9(Suppl 1): 32-9.
- [104] Ahren B, Landin-Olsson M, Jansson PA, *et al.* Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab* 2004; 89: 2078-84.
- [105] Mari A, Sallas WM, He YL, *et al.* Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2005; 90: 4888-94.
- [106] Rosenstock J, Baron MA, Dejager S, Mills D, Schweizer A. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Care* 2007; 30: 217-23.
- [107] Matikainen N, Manttari S, Schweizer A, *et al.* Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia* 2006; 49: 2049-57.
- [108] Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *Lancet* 2007; 369: 71-7.
- [109] Hogan S, Fleury A, Hadvary P, *et al.* Studies on the antiobesity activity of tetrahydrolipstatin, a potent and selective inhibitor of pancreatic lipase. *Int J Obes* 1987; 11 (Suppl 3): 35-42.
- [110] Sjostrom L, Rissanen A, Andersen T, *et al.* Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998; 352: 167-72.
- [111] Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. *Pharmacotherapy* 2000; 20: 270-9.
- [112] Hollander PA, Elbein SC, Hirsch IB, *et al.* Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care* 1998; 21: 1288-94.
- [113] Reitsma JB, Castro Cabezas M, de Bruin TW, Erkelens DW. Relationship between improved postprandial lipemia and low-density lipoprotein metabolism during treatment with tetrahydrolipstatin, a pancreatic lipase inhibitor. *Metabolism* 1994; 43: 293-8.
- [114] Shepard TY, Jensen DR, Blotner S, *et al.* Orlistat fails to alter postprandial plasma lipid excursions or plasma lipases in normal-weight male volunteers. *Int J Obes Relat Metab Disord* 2000; 24: 187-94.
- [115] Tan KC, Tso AW, Tam SC, Pang RW, Lam KS. Acute effect of orlistat on post-prandial lipaemia and free fatty acids in overweight patients with Type 2 diabetes mellitus. *Diabet Med* 2002; 19: 944-8.
- [116] Suter PM, Marmier G, Veya-Linder C, *et al.* Effect of orlistat on postprandial lipemia, NMR lipoprotein subclass profiles and particle size. *Atherosclerosis* 2005; 180: 127-35.
- [117] Lean ME. How does sibutramine work? *Int J Obes Relat Metab Disord* 2001; 25 (Suppl 4): S8-11.
- [118] McNeely W, Goa KL. Sibutramine. A review of its contribution to the management of obesity. *Drugs* 1998; 56: 1093-124.
- [119] Vettor R, Serra R, Fabris R, Pagano C, Federspil G. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* 2005; v 28: 942-9.
- [120] Sabuncu T, Ucar E, Birden F, Yasar O. The effect of 1-yr sibutramine treatment on glucose tolerance, insulin sensitivity and serum lipid profiles in obese subjects. *Diabetes Nutr Metab* 2004; 17: 103-7.
- [121] Filippatos TD, Kiortsis DN, Liberopoulos EN, Mikhailidis DP, Elisaf MS. A review of the metabolic effects of sibutramine. *Curr Med Res Opin* 2005; 21: 457-68.
- [122] Lafontan M, Piazza PV, Girard J. Effects of CB1 antagonist on the control of metabolic functions in obese type 2 diabetic patients. *Diabetes Metab* 2007; 33: 85-95.
- [123] Jensen MD. What is the potential role of cannabinoid-1 receptor blockade in glucose and lipid management? *Am J Med* 2007; 120: S25-31; discussion S31-2.
- [124] Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006; 295: 761-75.
- [125] Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 2005; 353: 2121-34.
- [126] Cohn JS, Marcoux C, Davignon J. Detection, quantification, and characterization of potentially atherogenic triglyceride-rich remnant lipoproteins. *Arterioscler Thromb Vasc Biol* 1999; 19: 2474-86.
- [127] Katsilambros N. Postprandial triglyceridaemia. *Diabet Med* 1995; 12: 451-2.